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The following report contains a description of the request, request specifications, and results from the modular program run(s).

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## Overview for Request: cder\_mpl2p\_wp046\_nsd1\_v01 (Report 1, ITS)

**Request ID:** cder\_mpl2p\_wp046\_nsd1\_v01

**Request Description:** This report contains the estimates of prevalent utilization of hydrochlorothiazide (HCTZ)-containing diuretics, non HCTZ-containing diuretics, and antihypertensives in the Sentinel Distributed Database (SDD) to understand the impact of labeling changes that were made on August 8, 2020.

**Sentinel Routine Querying Module:** Cohort Identification and Descriptive Analysis (CIDA) module, version 12.1.0

**Data Source:** We distributed this query to 5 Data Partners on September 29, 2023. The study period included data from January 1, 2017 through June 30, 2023. Please see Appendix A for a list of dates of available data for each Data Partner.

**Study Design:** This query assessed the prevalence of outpatient exposure to HCTZ-containing diuretics, non HCTZ-containing diuretics, and antihypertensives among individuals within the SDD, overall and by calendar year-month. Results were reported overall and stratified by age group; sex; race; and both age group and race. This query is part one of a two-part analysis, where part two contains inclusion or exclusion criteria for history of skin cancer. This report presents the results from the Interrupted time series (ITS) analyses performed using data from Report 1. Please refer to Report 1 for the Appendices.

This was a Type 2 analysis in the Query Request Package (QRP) documentation.

**Exposure(s) of Interest:** The exposures of interest were any HCTZ-containing product (including HCTZ monotherapy, any HCTZ combination product, HCTZ-angiotensin converting enzyme inhibitor [ACEi] combination product, HCTZ-angiotensin receptor blocker [ARB] combination product, HCTZ-potassium sparing diuretic combination product, HCTZ-beta blocker combination product, HCTZ-ARB-calcium channel blocker [CCB] combination product, HCTZ-direct renin inhibitor combination product, and HCTZ-central alpha 2 agonist combination product), any HCTZ containing product with HCTZ strength < 25 mg, any HCTZ containing product with HCTZ strength ≥ 25 mg, any HCTZ combination product with HCTZ strength < 25 mg, any HCTZ combination product with HCTZ strength ≥ 25 mg, any non HCTZ-containing diuretic (including chlorothiazide, bendroflumethiazide, and thiazide-like diuretics), ACEi, CCB, potassium sparing diuretic, and loop diuretic. Additionally, two groups of exposures were defined as denominators for calculating proportions by calendar year-month: limited denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide, or thiazide-like diuretic) and full denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide, thiazide-like diuretic, or any antihypertensive). All qualifying exposures during the study period were evaluated. The exposures of interest were defined using National Drug Code (NDCs). See Appendix B for non-proprietary and brand names of medical products used to define exposures of interest.

**Cohort Eligibility Criteria:** We identified cohorts which included patients of all ages. The following age groups were defined: 0-40, 41-54, 55-64, 65-74, 75-84, and 85 years of age or greater. No pre-index enrollment requirement was applied.

**Follow-Up Time:** We determined follow-up time based on the length of exposure episodes, which was defined using days supply information recorded in the outpatient pharmacy dispensings to create any period of continuous exposure. No exposure episode gaps or extensions were considered in the creation of the episode. Dispensings in each cohort were stockpiled with all other exposure-defining dispensings within the cohort, regardless of the original drug class. Follow-up began on the index date and continued until the last day of supply of the last dispensing, or until the first occurrence of any of the following: 1) disenrollment; 2) death; 3) the end date of the data provided by each Data Partner; or 4) the end of the query period (June 30, 2023).

**Analysis:** We fitted an autoregression piecewise linear model describing the change of an observed rate over exposure time in months with an autoregression lag of 12 months and an intervention date on August 8, 2020, which is the date of the HCTZ drug safety communication (DSC)<sup>1</sup> issued by the US Food and Drug Administration (FDA). Numerator and denominator counts used to calculate observed rates were taken to be the number of patients with any duration of the exposure episode during the corresponding month interval. The rate modeled is described below:

## Overview for Request: cder\_mpl2p\_wp046\_nsd1\_v01 (Report 1, ITS)

Cohort 1) The rate used for the ITS regression model is the number of patients with use of any HCTZ-containing product among users in the limited denominator cohort.

Cohort 2) The rate used for the ITS regression model is the number of patients with use of HCTZ single ingredient among users in the limited denominator cohort.

Cohort 3) The rate used for the ITS regression model is the number of patients with use of ACEI + HCTZ combo product among users in the limited denominator cohort.

Cohort 4) The rate used for the ITS regression model is the number of patients with use of ARB + HCTZ combo product among users in the limited denominator cohort.

Cohort 5) The rate used for the ITS regression model is the number of patients with use of potassium-sparing diuretic + HCTZ combo product among users in the limited denominator cohort.

Cohort 6) The rate used for the ITS regression model is the number of patients with use of beta blocker + HCTZ combo product among users in the limited denominator cohort.

Cohort 7) The rate used for the ITS regression model is the number of patients with use of ARB + CCB + HCTZ combo product among users in the limited denominator cohort.

Cohort 8) The rate used for the ITS regression model is the number of patients with use of direct renin inhibitor + HCTZ combo product among users in the limited denominator cohort.

Cohort 9) The rate used for the ITS regression model is the number of patients with use of central alpha 2 agonist + HCTZ combo product among users in the limited denominator cohort.

Cohort 10) The rate used for the ITS regression model is the number of patients with use of any HCTZ-containing products among users in the full denominator cohort.

Cohort 11) The rate used for the ITS regression model is the number of patients with use of chlorothiazide, bendroflumethiazide or thiazide-like diuretic product among users in the full denominator cohort.

Cohort 12) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination ACEI product among users in the full denominator cohort.

Cohort 13) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination CCB product among users in the full denominator cohort.

Cohort 14) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination potassium-sparing diuretic product among users in the full denominator cohort.

Cohort 15) The rate used for the ITS regression model is the number of patients with use of loop diuretic product among users in the full denominator cohort.

ITS regression was performed for overall population.

We also fitted these same models using an anticipatory and lag period from July 1, 2020 to September 30, 2020 during which observations were not included in the autoregression model.

**Please see the Appendix C for the specifications of parameters used in the analyses for this request.**

**Limitations:** Algorithms to define exposures, inclusion, and exclusion criteria are imperfect and may result in misclassification. Therefore, data should be interpreted with this limitation in mind.

**Notes:** Please contact the Sentinel Operations Center ([info@sentinel-system.org](mailto:info@sentinel-system.org)) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (<https://dev.sentinel-system.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse>).

| Table of Contents                   |                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Results without Anticipatory Period |                                                                                                                                                                                                                                                                                                                                             |
| <b>Glossary</b>                     | Cohort Identification and Descriptive Analysis (CIDA)                                                                                                                                                                                                                                                                                       |
| <b>Table 1</b>                      | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                          |
| <b>Table 2</b>                      | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                   |
| <b>Figure 1</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                  |
| <b>Table 3</b>                      | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                        |
| <b>Table 4</b>                      | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend |
| <b>Figure 2</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                |
| <b>Table 5</b>                      | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                                      |
| <b>Table 6</b>                      | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                               |
| <b>Figure 3</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                              |
| <b>Table 7</b>                      | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                                                            |
| <b>Table 8</b>                      | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                                     |
| <b>Figure 4</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                                                    |
| <b>Table 9</b>                      | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                                                 |
| <b>Table 10</b>                     | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                          |
| <b>Figure 5</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                                         |
| <b>Table 11</b>                     | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                                           |
| <b>Table 12</b>                     | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                                    |
| <b>Figure 6</b>                     | Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                                                   |
| <b>Table 13</b>                     | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                                                                          |
| <b>Table 14</b>                     | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                                                   |

## Table of Contents

|                  |                                                                                                                                                                                                                                                                                                       |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Figure 7</b>  | Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                            |
| <b>Table 15</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                            |
| <b>Table 16</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend     |
| <b>Figure 8</b>  | Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                    |
| <b>Table 17</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                         |
| <b>Table 18</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                  |
| <b>Figure 9</b>  | Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                 |
| <b>Table 19</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                        |
| <b>Table 20</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend |
| <b>Figure 10</b> | Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                |
| <b>Table 21</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                    |
| <b>Table 22</b>  | Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend             |
| <b>Figure 11</b> | Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                            |
| <b>Table 23</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                    |
| <b>Table 24</b>  | Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                             |
| <b>Figure 12</b> | Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                            |
| <b>Table 25</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                                    |
| <b>Table 26</b>  | Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                             |
| <b>Figure 13</b> | Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                                            |
| <b>Table 27</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                       |
| <b>Table 28</b>  | Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                |
| <b>Figure 14</b> | Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                               |

## Table of Contents

**Table 29** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020

**Table 30** Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 15** Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020

## Results with Anticipatory Period

**Table 31** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020

**Table 32** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 16** Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020

**Table 33** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020

**Table 34** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 17** Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020

**Table 35** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020

**Table 36** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 18** Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020

**Table 37** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020

**Table 38** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 19** Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020

**Table 39** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020

**Table 40** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 20** Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020

**Table 41** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020

**Table 42** Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 21** Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020

## Table of Contents

|                  |                                                                                                                                                                                                                                                                                                       |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Table 43</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                                    |
| <b>Table 44</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                             |
| <b>Figure 22</b> | Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                            |
| <b>Table 45</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                            |
| <b>Table 46</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend     |
| <b>Figure 23</b> | Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                    |
| <b>Table 47</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                                         |
| <b>Table 48</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                  |
| <b>Figure 24</b> | Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                                 |
| <b>Table 49</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020                        |
| <b>Table 50</b>  | Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend |
| <b>Figure 25</b> | Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020                                                                                |
| <b>Table 51</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                    |
| <b>Table 52</b>  | Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend             |
| <b>Figure 26</b> | Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                            |
| <b>Table 53</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                    |
| <b>Table 54</b>  | Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                             |
| <b>Figure 27</b> | Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                            |
| <b>Table 55</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                                    |
| <b>Table 56</b>  | Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend                                             |
| <b>Figure 28</b> | Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020                                                                                                                            |
| <b>Table 57</b>  | Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020                                                       |

## Table of Contents

**Table 58** Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 29** Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020

**Table 59** Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020

**Table 60** Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

**Figure 30** Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020

**Appendix A** Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (August 30, 2023)

**Appendix B** Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

**Appendix C** Specifications Defining Parameters for this Request

## **Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Module\***

**Amount Supplied** - number of units (pills, tablets, vials) dispensed. Net amount per National Drug Code (NDC) per dispensing.

**Blackout Period** - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

**Care Setting** - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

**Ambulatory Visit (AV)** - includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.

**Emergency Department (ED)** - includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.

**Inpatient Hospital Stay (IP)** - includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.

**Non-Acute Institutional Stay (IS)** - includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.

**Other Ambulatory Visit (OA)** - includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

**Charlson/Elixhauser Combined Comorbidity Score** - calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

**Code Days** - the minimum number of times the diagnosis must be found during the evaluation period in order to fulfill the algorithm to identify the corresponding patient characteristic.

**Cohort Definition (drug/exposure)** - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

**Computed Start Marketing Date** - represents the first observed dispensing date among all valid users within a GROUP (scenario) within each Data Partner site.

**Days Supplied** - number of days supplied for all dispensings in qualifying treatment episodes.

**Eligible Members** - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

**Enrollment Gap** - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

**Episodes** - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

**Episode Gap** - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

**Event Deduplication** - specifies how events are counted by the Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

**Exposure Episode Length** - number of days after exposure initiation that is considered "exposed time."

**Exposure Extension Period** - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions are added after any episode gaps have been bridged.

### **Glossary of Terms for Analyses Using**

#### **Cohort Identification and Descriptive Analysis (CIDA) Module\***

**Lookback Period** - number of days wherein a member is required to have evidence of pre-existing condition

**Maximum Episode Duration** - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

**Member-Years** - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

**Minimum Days Supplied** - specifies a minimum number of days in length of the days supplied for the episode to be considered.

**Minimum Episode Duration** - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

**Monitoring Period** - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

**Principal Diagnosis (PDX)** - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

**Query Period** - period in which the modular program looks for exposures and outcomes of interest.

**Switch Evaluation Step Value** - value used to differentiate evaluation step. Each switch pattern can support up to 2 evaluation steps (0 = switch pattern evaluation start; 1 = first evaluation; 2 = second evaluation).

**Switch Gap Inclusion Indicator** - indicator for whether gaps in treatment episodes that are included in a switch episode will be counted as part of the switch episode duration.

**Switch Pattern Cohort Inclusion Date** - indicates which date to use for inclusion into the switch pattern cohort of interest as well as optionally as the index date of the treatment episode initiating the switch pattern. Valid options are the product approval date, product marketing date, other requester defined date, or computed start marketing date.

**Switch Pattern Cohort Inclusion Strategy** - indicates how the switch pattern cohort inclusion date will be used: 01: used only as a switch cohort entry date. First treatment episode dispensing date is used as index for computing time to first switch; 02: used as switch cohort entry date and as initial switch step index date for computing time to first switch.

**Treatment Episode Truncation Indicator** - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

**Washout Period (drug/exposure)** - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

**Washout Period (event/outcome)** - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

**Years at Risk** - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

\*all terms may not be used in this report

**Table 1. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.194680  | (0.193365, 0.195996)   | <.001               |
| Baseline trend                                                          | -0.000330 | (-0.000378, -0.000282) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000793 | (-0.001727, 0.000141)  | 0.095               |
| Trend Change (After Intervention 1)                                     | -0.000201 | (-0.000321, -0.000082) | 0.001               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.194680  | (0.193365, 0.195996)   | <.001               |
| Baseline trend                                                          | -0.000330 | (-0.000378, -0.000282) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000793 | (-0.001727, 0.000141)  | 0.095               |
| Trend Change (After Intervention 1)                                     | -0.000201 | (-0.000321, -0.000082) | 0.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 2. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

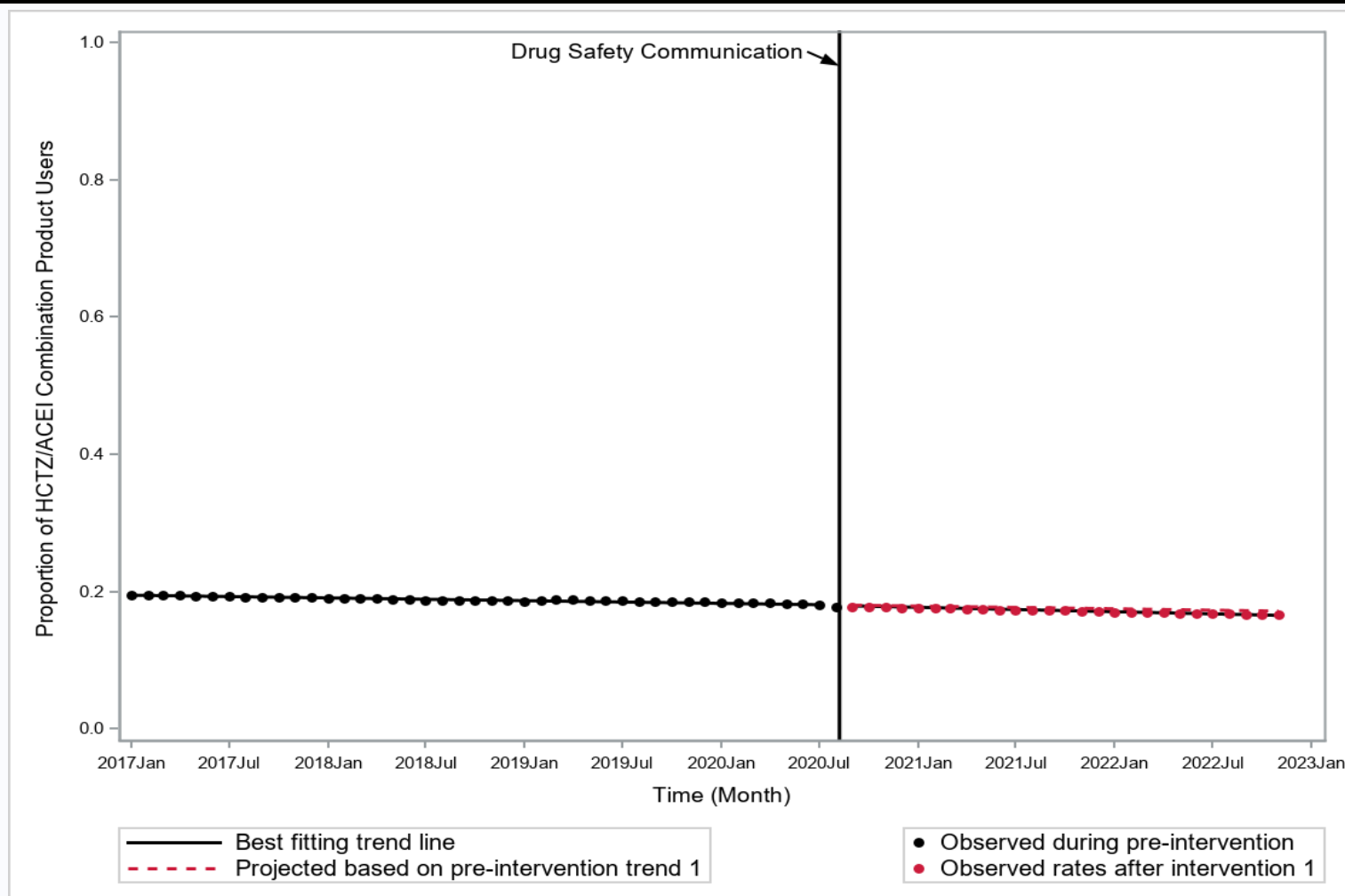
| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|---------------------------------------------------|
|                                                       |           |                        |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | -0.000995 | (-0.001956, -0.000034) | 0.178832                                 | 0.179826                                          |
| Relative Change (%) at 1 Months after Intervention 1  | -0.55     | (-1.09, -0.02)         | 0.178832                                 | 0.179826                                          |
| Absolute Change at 2 Months after Intervention 1      | -0.001196 | (-0.002160, -0.000232) | 0.178300                                 | 0.179496                                          |
| Relative Change (%) at 2 Months after Intervention 1  | -0.67     | (-1.20, -0.13)         | 0.178300                                 | 0.179496                                          |
| Absolute Change at 3 Months after Intervention 1      | -0.001397 | (-0.002379, -0.000415) | 0.177769                                 | 0.179166                                          |
| Relative Change (%) at 3 Months after Intervention 1  | -0.78     | (-1.32, -0.24)         | 0.177769                                 | 0.179166                                          |
| Absolute Change at 4 Months after Intervention 1      | -0.001598 | (-0.002614, -0.000583) | 0.177238                                 | 0.178836                                          |
| Relative Change (%) at 4 Months after Intervention 1  | -0.89     | (-1.46, -0.33)         | 0.177238                                 | 0.178836                                          |
| Absolute Change at 5 Months after Intervention 1      | -0.001800 | (-0.002862, -0.000737) | 0.176706                                 | 0.178506                                          |
| Relative Change (%) at 5 Months after Intervention 1  | -1.01     | (-1.60, -0.42)         | 0.176706                                 | 0.178506                                          |
| Absolute Change at 6 Months after Intervention 1      | -0.002001 | (-0.003122, -0.000880) | 0.176175                                 | 0.178176                                          |
| Relative Change (%) at 6 Months after Intervention 1  | -1.12     | (-1.75, -0.50)         | 0.176175                                 | 0.178176                                          |
| Absolute Change at 7 Months after Intervention 1      | -0.002202 | (-0.003392, -0.001012) | 0.175643                                 | 0.177846                                          |
| Relative Change (%) at 7 Months after Intervention 1  | -1.24     | (-1.90, -0.58)         | 0.175643                                 | 0.177846                                          |
| Absolute Change at 8 Months after Intervention 1      | -0.002404 | (-0.003671, -0.001136) | 0.175112                                 | 0.177516                                          |
| Relative Change (%) at 8 Months after Intervention 1  | -1.35     | (-2.06, -0.65)         | 0.175112                                 | 0.177516                                          |
| Absolute Change at 9 Months after Intervention 1      | -0.002605 | (-0.003957, -0.001253) | 0.174581                                 | 0.177186                                          |
| Relative Change (%) at 9 Months after Intervention 1  | -1.47     | (-2.22, -0.72)         | 0.174581                                 | 0.177186                                          |
| Absolute Change at 10 Months after Intervention 1     | -0.002806 | (-0.004248, -0.001365) | 0.174049                                 | 0.176855                                          |
| Relative Change (%) at 10 Months after Intervention 1 | -1.59     | (-2.39, -0.78)         | 0.174049                                 | 0.176855                                          |
| Absolute Change at 11 Months after Intervention 1     | -0.003008 | (-0.004544, -0.001471) | 0.173518                                 | 0.176525                                          |
| Relative Change (%) at 11 Months after Intervention 1 | -1.70     | (-2.56, -0.85)         | 0.173518                                 | 0.176525                                          |
| Absolute Change at 12 Months after Intervention 1     | -0.003209 | (-0.004844, -0.001574) | 0.172986                                 | 0.176195                                          |
| Relative Change (%) at 12 Months after Intervention 1 | -1.82     | (-2.73, -0.91)         | 0.172986                                 | 0.176195                                          |
| Absolute Change at 13 Months after Intervention 1     | -0.003410 | (-0.005147, -0.001673) | 0.172455                                 | 0.175865                                          |
| Relative Change (%) at 13 Months after Intervention 1 | -1.94     | (-2.91, -0.97)         | 0.172455                                 | 0.175865                                          |
| Absolute Change at 14 Months after Intervention 1     | -0.003611 | (-0.005454, -0.001769) | 0.171924                                 | 0.175535                                          |
| Relative Change (%) at 14 Months after Intervention 1 | -2.06     | (-3.09, -1.03)         | 0.171924                                 | 0.175535                                          |
| Absolute Change at 15 Months after Intervention 1     | -0.003813 | (-0.005762, -0.001864) | 0.171392                                 | 0.175205                                          |
| Relative Change (%) at 15 Months after Intervention 1 | -2.18     | (-3.27, -1.08)         | 0.171392                                 | 0.175205                                          |
| Absolute Change at 16 Months after Intervention 1     | -0.004014 | (-0.006072, -0.001956) | 0.170861                                 | 0.174875                                          |
| Relative Change (%) at 16 Months after Intervention 1 | -2.30     | (-3.45, -1.14)         | 0.170861                                 | 0.174875                                          |
| Absolute Change at 17 Months after Intervention 1     | -0.004215 | (-0.006384, -0.002047) | 0.170329                                 | 0.174545                                          |
| Relative Change (%) at 17 Months after Intervention 1 | -2.42     | (-3.63, -1.20)         | 0.170329                                 | 0.174545                                          |
| Absolute Change at 18 Months after Intervention 1     | -0.004417 | (-0.006697, -0.002136) | 0.169798                                 | 0.174215                                          |
| Relative Change (%) at 18 Months after Intervention 1 | -2.54     | (-3.82, -1.25)         | 0.169798                                 | 0.174215                                          |
| Absolute Change at 19 Months after Intervention 1     | -0.004618 | (-0.007012, -0.002224) | 0.169267                                 | 0.173885                                          |
| Relative Change (%) at 19 Months after Intervention 1 | -2.66     | (-4.00, -1.31)         | 0.169267                                 | 0.173885                                          |
| Absolute Change at 20 Months after Intervention 1     | -0.004819 | (-0.007327, -0.002311) | 0.168735                                 | 0.173555                                          |
| Relative Change (%) at 20 Months after Intervention 1 | -2.78     | (-4.19, -1.36)         | 0.168735                                 | 0.173555                                          |
| Absolute Change at 21 Months after Intervention 1     | -0.005021 | (-0.007644, -0.002397) | 0.168204                                 | 0.173224                                          |
| Relative Change (%) at 21 Months after Intervention 1 | -2.90     | (-4.38, -1.42)         | 0.168204                                 | 0.173224                                          |
| Absolute Change at 22 Months after Intervention 1     | -0.005222 | (-0.007961, -0.002483) | 0.167673                                 | 0.172894                                          |
| Relative Change (%) at 22 Months after Intervention 1 | -3.02     | (-4.57, -1.47)         | 0.167673                                 | 0.172894                                          |
| Absolute Change at 23 Months after Intervention 1     | -0.005423 | (-0.008279, -0.002567) | 0.167141                                 | 0.172564                                          |
| Relative Change (%) at 23 Months after Intervention 1 | -3.14     | (-4.76, -1.52)         | 0.167141                                 | 0.172564                                          |
| Absolute Change at 24 Months after Intervention 1     | -0.005624 | (-0.008597, -0.002651) | 0.166610                                 | 0.172234                                          |
| Relative Change (%) at 24 Months after Intervention 1 | -3.27     | (-4.95, -1.58)         | 0.166610                                 | 0.172234                                          |
| Absolute Change at 25 Months after Intervention 1     | -0.005826 | (-0.008917, -0.002735) | 0.166078                                 | 0.171904                                          |

**Table 2. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|-----------|------------------------|---------------------|-----------------------------|
|                                                       |           |                        | (With Intervention) | Rate (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | -3.39     | (-5.15, -1.63)         | 0.166078            | 0.171904                    |
| Absolute Change at 26 Months after Intervention 1     | -0.006027 | (-0.009236, -0.002818) | 0.165547            | 0.171574                    |
| Relative Change (%) at 26 Months after Intervention 1 | -3.51     | (-5.34, -1.69)         | 0.165547            | 0.171574                    |
| Absolute Change at 27 Months after Intervention 1     | -0.006228 | (-0.009556, -0.002901) | 0.165016            | 0.171244                    |
| Absolute Change at 27 Months after Intervention 1     | -0.006228 | (-0.009556, -0.002901) | 0.165016            | 0.171244                    |
| Relative Change (%) at 27 Months after Intervention 1 | -3.64     | (-5.53, -1.74)         | 0.165016            | 0.171244                    |
| Relative Change (%) at 27 Months after Intervention 1 | -3.64     | (-5.53, -1.74)         | 0.165016            | 0.171244                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 1. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 3. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.005901  | (0.005578, 0.006225)   | <.001               |
| Baseline trend                                                          | -0.000035 | (-0.000047, -0.000024) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000010  | (-0.000093, 0.000113)  | 0.848               |
| Trend Change (After Intervention 1)                                     | -0.000009 | (-0.000038, 0.000020)  | 0.542               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.005836  | (0.005534, 0.006137)   | <.001               |
| Baseline trend                                                          | -0.000032 | (-0.000043, -0.000022) | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000017 | (-0.000044, 0.000009)  | 0.191               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 4. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

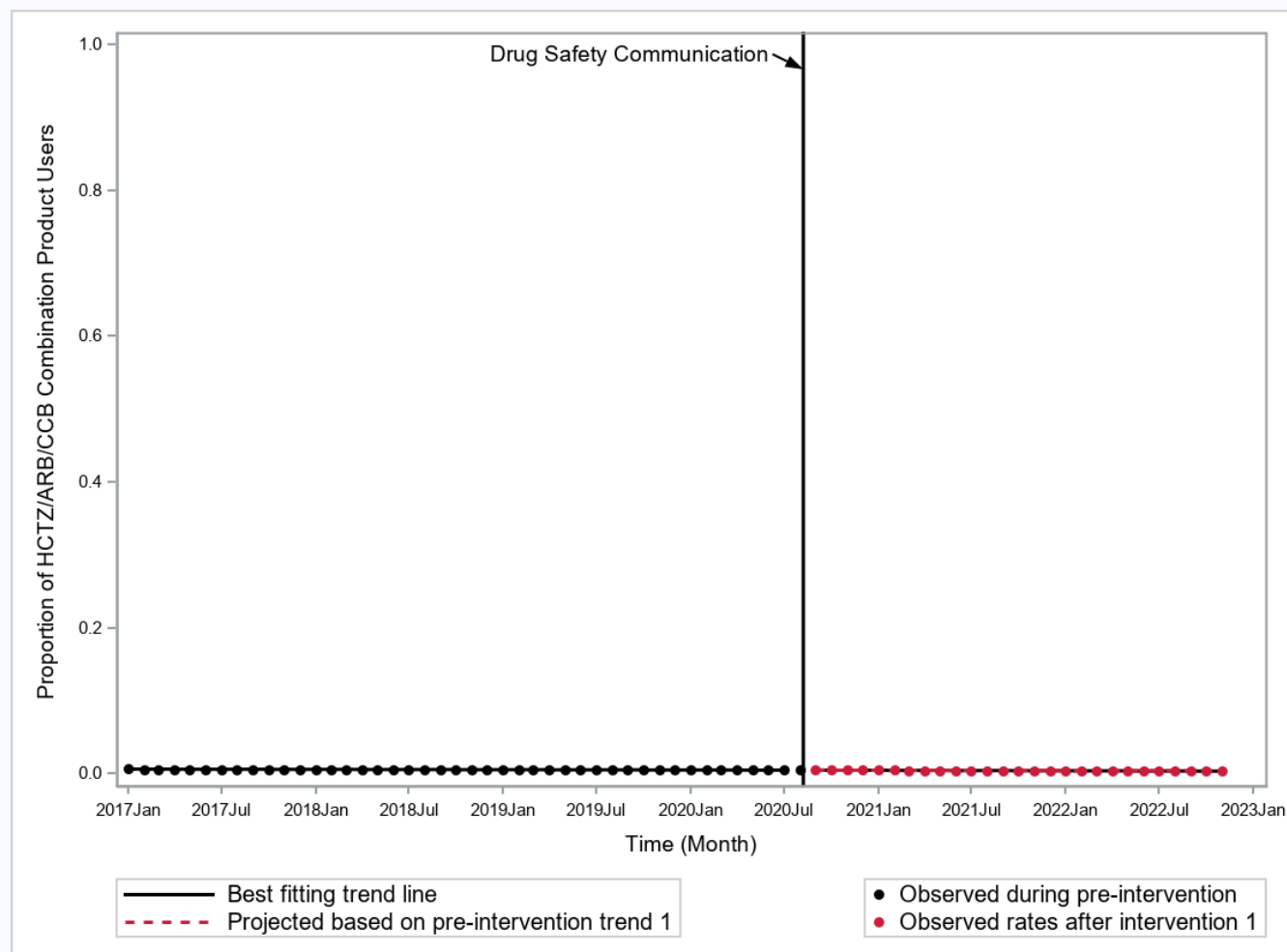
| Outcome Measure                                       | Estimate  | 95% CI                | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|-----------|-----------------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | -0.000017 | (-0.000049, 0.000014) | 0.004364                              | 0.004381                                    |
| Relative Change (%) at 1 Months after Intervention 1  | -0.40     | (-1.09, 0.30)         | 0.004364                              | 0.004381                                    |
| Absolute Change at 2 Months after Intervention 1      | -0.000035 | (-0.000098, 0.000028) | 0.004314                              | 0.004349                                    |
| Relative Change (%) at 2 Months after Intervention 1  | -0.80     | (-2.20, 0.61)         | 0.004314                              | 0.004349                                    |
| Absolute Change at 3 Months after Intervention 1      | -0.000052 | (-0.000147, 0.000043) | 0.004264                              | 0.004316                                    |
| Relative Change (%) at 3 Months after Intervention 1  | -1.21     | (-3.33, 0.91)         | 0.004264                              | 0.004316                                    |
| Absolute Change at 4 Months after Intervention 1      | -0.000069 | (-0.000196, 0.000057) | 0.004215                              | 0.004284                                    |
| Relative Change (%) at 4 Months after Intervention 1  | -1.62     | (-4.47, 1.22)         | 0.004215                              | 0.004284                                    |
| Absolute Change at 5 Months after Intervention 1      | -0.000087 | (-0.000245, 0.000071) | 0.004165                              | 0.004252                                    |
| Relative Change (%) at 5 Months after Intervention 1  | -2.04     | (-5.62, 1.53)         | 0.004165                              | 0.004252                                    |
| Absolute Change at 6 Months after Intervention 1      | -0.000104 | (-0.000294, 0.000085) | 0.004115                              | 0.004219                                    |
| Relative Change (%) at 6 Months after Intervention 1  | -2.47     | (-6.79, 1.85)         | 0.004115                              | 0.004219                                    |
| Absolute Change at 7 Months after Intervention 1      | -0.000122 | (-0.000343, 0.000100) | 0.004066                              | 0.004187                                    |
| Relative Change (%) at 7 Months after Intervention 1  | -2.90     | (-7.97, 2.16)         | 0.004066                              | 0.004187                                    |
| Absolute Change at 8 Months after Intervention 1      | -0.000139 | (-0.000392, 0.000114) | 0.004016                              | 0.004155                                    |
| Relative Change (%) at 8 Months after Intervention 1  | -3.34     | (-9.17, 2.48)         | 0.004016                              | 0.004155                                    |
| Absolute Change at 9 Months after Intervention 1      | -0.000156 | (-0.000441, 0.000128) | 0.003966                              | 0.004122                                    |
| Relative Change (%) at 9 Months after Intervention 1  | -3.79     | (-10.38, 2.80)        | 0.003966                              | 0.004122                                    |
| Absolute Change at 10 Months after Intervention 1     | -0.000174 | (-0.000490, 0.000142) | 0.003916                              | 0.004090                                    |
| Relative Change (%) at 10 Months after Intervention 1 | -4.25     | (-11.62, 3.12)        | 0.003916                              | 0.004090                                    |
| Absolute Change at 11 Months after Intervention 1     | -0.000191 | (-0.000539, 0.000156) | 0.003867                              | 0.004058                                    |
| Relative Change (%) at 11 Months after Intervention 1 | -4.71     | (-12.86, 3.45)        | 0.003867                              | 0.004058                                    |
| Absolute Change at 12 Months after Intervention 1     | -0.000208 | (-0.000588, 0.000171) | 0.003817                              | 0.004026                                    |
| Relative Change (%) at 12 Months after Intervention 1 | -5.18     | (-14.13, 3.77)        | 0.003817                              | 0.004026                                    |
| Absolute Change at 13 Months after Intervention 1     | -0.000226 | (-0.000636, 0.000185) | 0.003767                              | 0.003993                                    |
| Relative Change (%) at 13 Months after Intervention 1 | -5.66     | (-15.41, 4.10)        | 0.003767                              | 0.003993                                    |
| Absolute Change at 14 Months after Intervention 1     | -0.000243 | (-0.000685, 0.000199) | 0.003718                              | 0.003961                                    |
| Relative Change (%) at 14 Months after Intervention 1 | -6.14     | (-16.71, 4.43)        | 0.003718                              | 0.003961                                    |
| Absolute Change at 15 Months after Intervention 1     | -0.000261 | (-0.000734, 0.000213) | 0.003668                              | 0.003929                                    |
| Relative Change (%) at 15 Months after Intervention 1 | -6.63     | (-18.03, 4.77)        | 0.003668                              | 0.003929                                    |
| Absolute Change at 16 Months after Intervention 1     | -0.000278 | (-0.000783, 0.000227) | 0.003618                              | 0.003896                                    |
| Relative Change (%) at 16 Months after Intervention 1 | -7.13     | (-19.37, 5.10)        | 0.003618                              | 0.003896                                    |
| Absolute Change at 17 Months after Intervention 1     | -0.000295 | (-0.000832, 0.000242) | 0.003569                              | 0.003864                                    |
| Relative Change (%) at 17 Months after Intervention 1 | -7.64     | (-20.73, 5.44)        | 0.003569                              | 0.003864                                    |
| Absolute Change at 18 Months after Intervention 1     | -0.000313 | (-0.000881, 0.000256) | 0.003519                              | 0.003832                                    |
| Relative Change (%) at 18 Months after Intervention 1 | -8.16     | (-22.10, 5.78)        | 0.003519                              | 0.003832                                    |
| Absolute Change at 19 Months after Intervention 1     | -0.000330 | (-0.000930, 0.000270) | 0.003469                              | 0.003799                                    |
| Relative Change (%) at 19 Months after Intervention 1 | -8.69     | (-23.50, 6.12)        | 0.003469                              | 0.003799                                    |
| Absolute Change at 20 Months after Intervention 1     | -0.000347 | (-0.000979, 0.000284) | 0.003419                              | 0.003767                                    |
| Relative Change (%) at 20 Months after Intervention 1 | -9.22     | (-24.91, 6.47)        | 0.003419                              | 0.003767                                    |
| Absolute Change at 21 Months after Intervention 1     | -0.000365 | (-0.001028, 0.000299) | 0.003370                              | 0.003735                                    |
| Relative Change (%) at 21 Months after Intervention 1 | -9.77     | (-26.35, 6.81)        | 0.003370                              | 0.003735                                    |
| Absolute Change at 22 Months after Intervention 1     | -0.000382 | (-0.001077, 0.000313) | 0.003320                              | 0.003702                                    |
| Relative Change (%) at 22 Months after Intervention 1 | -10.32    | (-27.81, 7.16)        | 0.003320                              | 0.003702                                    |
| Absolute Change at 23 Months after Intervention 1     | -0.000400 | (-0.001126, 0.000327) | 0.003270                              | 0.003670                                    |
| Relative Change (%) at 23 Months after Intervention 1 | -10.89    | (-29.29, 7.51)        | 0.003270                              | 0.003670                                    |
| Absolute Change at 24 Months after Intervention 1     | -0.000417 | (-0.001175, 0.000341) | 0.003221                              | 0.003638                                    |
| Relative Change (%) at 24 Months after Intervention 1 | -11.46    | (-30.79, 7.86)        | 0.003221                              | 0.003638                                    |

**Table 4. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>         | <b>Predicted Rate<br/>(With Intervention)</b> | <b>Extrapolated Rate<br/>(Without Intervention)</b> |
|-------------------------------------------------------|-----------------|-----------------------|-----------------------------------------------|-----------------------------------------------------|
| Absolute Change at 25 Months after Intervention 1     | -0.000434       | (-0.001224, 0.000355) | 0.003171                                      | 0.003605                                            |
| Relative Change (%) at 25 Months after Intervention 1 | -12.05          | (-32.31, 8.22)        | 0.003171                                      | 0.003605                                            |
| Absolute Change at 26 Months after Intervention 1     | -0.000452       | (-0.001273, 0.000370) | 0.003121                                      | 0.003573                                            |
| Relative Change (%) at 26 Months after Intervention 1 | -12.64          | (-33.86, 8.57)        | 0.003121                                      | 0.003573                                            |
| Absolute Change at 27 Months after Intervention 1     | -0.000469       | (-0.001322, 0.000384) | 0.003072                                      | 0.003541                                            |
| Absolute Change at 27 Months after Intervention 1     | -0.000469       | (-0.001322, 0.000384) | 0.003072                                      | 0.003541                                            |
| Relative Change (%) at 27 Months after Intervention 1 | -13.25          | (-35.42, 8.93)        | 0.003072                                      | 0.003541                                            |
| Relative Change (%) at 27 Months after Intervention 1 | -13.25          | (-35.42, 8.93)        | 0.003072                                      | 0.003541                                            |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 2. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 5. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.267039  | (0.250288, 0.283790)   | <.001               |
| Baseline trend                                                          | -0.001469 | (-0.002066, -0.000872) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000738 | (-0.003482, 0.002005)  | 0.593               |
| Trend Change (After Intervention 1)                                     | 0.001506  | (0.000041, 0.002971)   | 0.044               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.266258  | (0.249392, 0.283123)   | <.001               |
| Baseline trend                                                          | -0.001433 | (-0.002030, -0.000836) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.001373  | (-0.000042, 0.002788)  | 0.057               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 6. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

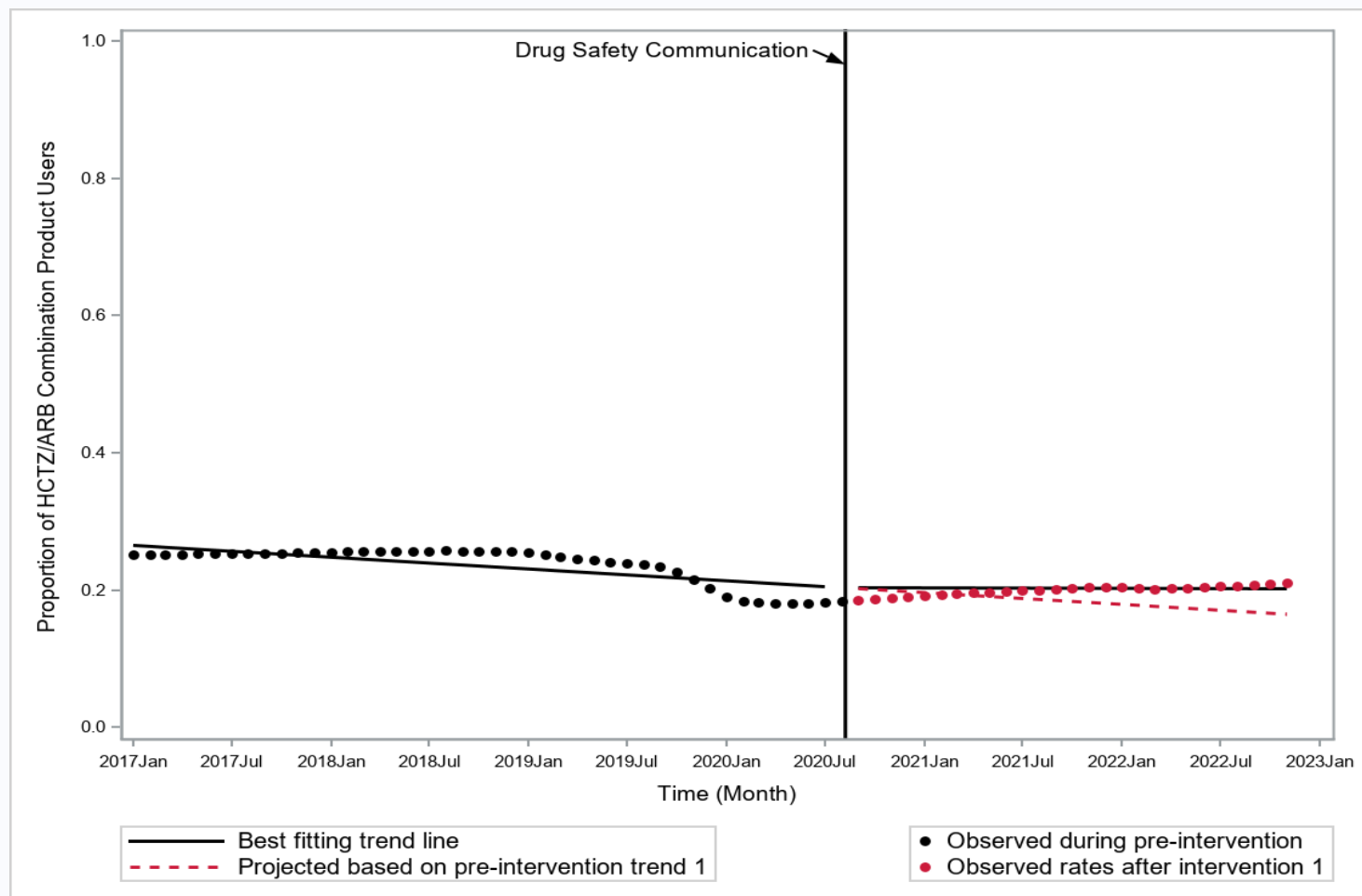
| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|-----------------------|---------------------|------------------------|
|                                                       |          |                       | (With Intervention) | (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | 0.001373 | (-0.000083, 0.002829) | 0.203158            | 0.201785               |
| Relative Change (%) at 1 Months after Intervention 1  | 0.68     | (-0.09, 1.45)         | 0.203158            | 0.201785               |
| Absolute Change at 2 Months after Intervention 1      | 0.002746 | (-0.000166, 0.005657) | 0.203098            | 0.200352               |
| Relative Change (%) at 2 Months after Intervention 1  | 1.37     | (-0.18, 2.92)         | 0.203098            | 0.200352               |
| Absolute Change at 3 Months after Intervention 1      | 0.004119 | (-0.000248, 0.008486) | 0.203038            | 0.198920               |
| Relative Change (%) at 3 Months after Intervention 1  | 2.07     | (-0.27, 4.42)         | 0.203038            | 0.198920               |
| Absolute Change at 4 Months after Intervention 1      | 0.005492 | (-0.000331, 0.011315) | 0.202979            | 0.197487               |
| Relative Change (%) at 4 Months after Intervention 1  | 2.78     | (-0.38, 5.94)         | 0.202979            | 0.197487               |
| Absolute Change at 5 Months after Intervention 1      | 0.006865 | (-0.000414, 0.014144) | 0.202919            | 0.196054               |
| Relative Change (%) at 5 Months after Intervention 1  | 3.50     | (-0.49, 7.49)         | 0.202919            | 0.196054               |
| Absolute Change at 6 Months after Intervention 1      | 0.008238 | (-0.000497, 0.016972) | 0.202859            | 0.194621               |
| Relative Change (%) at 6 Months after Intervention 1  | 4.23     | (-0.60, 9.07)         | 0.202859            | 0.194621               |
| Absolute Change at 7 Months after Intervention 1      | 0.009611 | (-0.000579, 0.019801) | 0.202800            | 0.193189               |
| Relative Change (%) at 7 Months after Intervention 1  | 4.97     | (-0.72, 10.67)        | 0.202800            | 0.193189               |
| Absolute Change at 8 Months after Intervention 1      | 0.010984 | (-0.000662, 0.022630) | 0.202740            | 0.191756               |
| Relative Change (%) at 8 Months after Intervention 1  | 5.73     | (-0.85, 12.31)        | 0.202740            | 0.191756               |
| Absolute Change at 9 Months after Intervention 1      | 0.012357 | (-0.000745, 0.025459) | 0.202680            | 0.190323               |
| Relative Change (%) at 9 Months after Intervention 1  | 6.49     | (-0.99, 13.97)        | 0.202680            | 0.190323               |
| Absolute Change at 10 Months after Intervention 1     | 0.013730 | (-0.000828, 0.028287) | 0.202620            | 0.188890               |
| Relative Change (%) at 10 Months after Intervention 1 | 7.27     | (-1.13, 15.67)        | 0.202620            | 0.188890               |
| Absolute Change at 11 Months after Intervention 1     | 0.015103 | (-0.000910, 0.031116) | 0.202561            | 0.187458               |
| Relative Change (%) at 11 Months after Intervention 1 | 8.06     | (-1.28, 17.39)        | 0.202561            | 0.187458               |
| Absolute Change at 12 Months after Intervention 1     | 0.016476 | (-0.000993, 0.033945) | 0.202501            | 0.186025               |
| Relative Change (%) at 12 Months after Intervention 1 | 8.86     | (-1.44, 19.15)        | 0.202501            | 0.186025               |
| Absolute Change at 13 Months after Intervention 1     | 0.017849 | (-0.001076, 0.036773) | 0.202441            | 0.184592               |
| Relative Change (%) at 13 Months after Intervention 1 | 9.67     | (-1.60, 20.94)        | 0.202441            | 0.184592               |
| Absolute Change at 14 Months after Intervention 1     | 0.019222 | (-0.001159, 0.039602) | 0.202381            | 0.183160               |
| Relative Change (%) at 14 Months after Intervention 1 | 10.49    | (-1.78, 22.77)        | 0.202381            | 0.183160               |
| Absolute Change at 15 Months after Intervention 1     | 0.020595 | (-0.001241, 0.042431) | 0.202322            | 0.181727               |
| Relative Change (%) at 15 Months after Intervention 1 | 11.33    | (-1.96, 24.63)        | 0.202322            | 0.181727               |
| Absolute Change at 16 Months after Intervention 1     | 0.021968 | (-0.001324, 0.045260) | 0.202262            | 0.180294               |
| Relative Change (%) at 16 Months after Intervention 1 | 12.18    | (-2.16, 26.52)        | 0.202262            | 0.180294               |
| Absolute Change at 17 Months after Intervention 1     | 0.023341 | (-0.001407, 0.048088) | 0.202202            | 0.178861               |
| Relative Change (%) at 17 Months after Intervention 1 | 13.05    | (-2.36, 28.46)        | 0.202202            | 0.178861               |
| Absolute Change at 18 Months after Intervention 1     | 0.024714 | (-0.001490, 0.050917) | 0.202142            | 0.177429               |
| Relative Change (%) at 18 Months after Intervention 1 | 13.93    | (-2.57, 30.43)        | 0.202142            | 0.177429               |
| Absolute Change at 19 Months after Intervention 1     | 0.026087 | (-0.001572, 0.053746) | 0.202083            | 0.175996               |
| Relative Change (%) at 19 Months after Intervention 1 | 14.82    | (-2.80, 32.44)        | 0.202083            | 0.175996               |
| Absolute Change at 20 Months after Intervention 1     | 0.027460 | (-0.001655, 0.056574) | 0.202023            | 0.174563               |
| Relative Change (%) at 20 Months after Intervention 1 | 15.73    | (-3.03, 34.49)        | 0.202023            | 0.174563               |
| Absolute Change at 21 Months after Intervention 1     | 0.028833 | (-0.001738, 0.059403) | 0.201963            | 0.173130               |
| Relative Change (%) at 21 Months after Intervention 1 | 16.65    | (-3.28, 36.58)        | 0.201963            | 0.173130               |
| Absolute Change at 22 Months after Intervention 1     | 0.030206 | (-0.001821, 0.062232) | 0.201903            | 0.171698               |
| Relative Change (%) at 22 Months after Intervention 1 | 17.59    | (-3.53, 38.72)        | 0.201903            | 0.171698               |
| Absolute Change at 23 Months after Intervention 1     | 0.031579 | (-0.001903, 0.065061) | 0.201844            | 0.170265               |
| Relative Change (%) at 23 Months after Intervention 1 | 18.55    | (-3.80, 40.90)        | 0.201844            | 0.170265               |
| Absolute Change at 24 Months after Intervention 1     | 0.032952 | (-0.001986, 0.067889) | 0.201784            | 0.168832               |
| Relative Change (%) at 24 Months after Intervention 1 | 19.52    | (-4.09, 43.12)        | 0.201784            | 0.168832               |
| Absolute Change at 25 Months after Intervention 1     | 0.034325 | (-0.002069, 0.070718) | 0.201724            | 0.167400               |

**Table 6. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|-----------------------|---------------------|------------------------|
|                                                       |          |                       | (With Intervention) | (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 20.50    | (-4.38, 45.39)        | 0.201724            | 0.167400               |
| Absolute Change at 26 Months after Intervention 1     | 0.035698 | (-0.002152, 0.073547) | 0.201664            | 0.165967               |
| Relative Change (%) at 26 Months after Intervention 1 | 21.51    | (-4.70, 47.71)        | 0.201664            | 0.165967               |
| Absolute Change at 27 Months after Intervention 1     | 0.037071 | (-0.002234, 0.076376) | 0.201605            | 0.164534               |
| Absolute Change at 27 Months after Intervention 1     | 0.037071 | (-0.002234, 0.076376) | 0.201605            | 0.164534               |
| Relative Change (%) at 27 Months after Intervention 1 | 22.53    | (-5.02, 50.08)        | 0.201605            | 0.164534               |
| Relative Change (%) at 27 Months after Intervention 1 | 22.53    | (-5.02, 50.08)        | 0.201605            | 0.164534               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 3. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 7. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.021574  | (0.021504, 0.021644)   | <.001               |
| Baseline trend                                                          | -0.000071 | (-0.000074, -0.000069) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000047  | (-0.000024, 0.000118)  | 0.193               |
| Trend Change (After Intervention 1)                                     | 0.000014  | (0.000008, 0.000020)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.021574  | (0.021504, 0.021644)   | <.001               |
| Baseline trend                                                          | -0.000071 | (-0.000074, -0.000069) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000047  | (-0.000024, 0.000118)  | 0.193               |
| Trend Change (After Intervention 1)                                     | 0.000014  | (0.000008, 0.000020)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 8. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

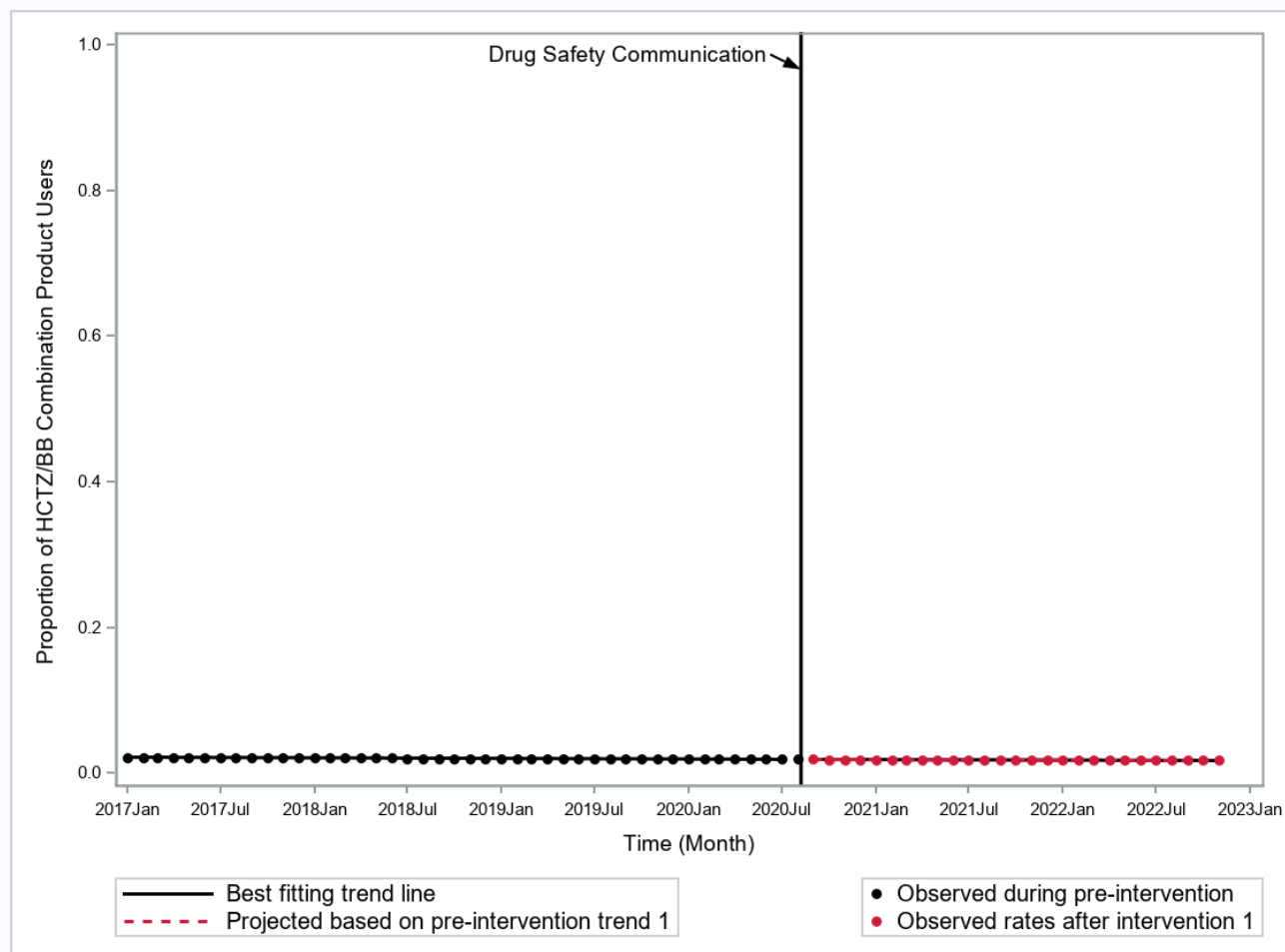
| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|-----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |          |                       |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | 0.000061 | (-0.000011, 0.000132) | 0.018427                                 | 0.018366                                          |
| Relative Change (%) at 1 Months after Intervention 1  | 0.33     | (-0.06, 0.72)         | 0.018427                                 | 0.018366                                          |
| Absolute Change at 2 Months after Intervention 1      | 0.000074 | (0.000004, 0.000145)  | 0.018369                                 | 0.018295                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 0.41     | (0.02, 0.79)          | 0.018369                                 | 0.018295                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000088 | (0.000019, 0.000158)  | 0.018312                                 | 0.018224                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 0.49     | (0.10, 0.87)          | 0.018312                                 | 0.018224                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000102 | (0.000033, 0.000172)  | 0.018255                                 | 0.018152                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 0.56     | (0.18, 0.95)          | 0.018255                                 | 0.018152                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.000116 | (0.000046, 0.000187)  | 0.018197                                 | 0.018081                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 0.64     | (0.25, 1.03)          | 0.018197                                 | 0.018081                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.000130 | (0.000059, 0.000202)  | 0.018140                                 | 0.018010                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 0.72     | (0.32, 1.12)          | 0.018140                                 | 0.018010                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.000144 | (0.000071, 0.000217)  | 0.018083                                 | 0.017939                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 0.80     | (0.39, 1.21)          | 0.018083                                 | 0.017939                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.000158 | (0.000082, 0.000234)  | 0.018025                                 | 0.017867                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 0.88     | (0.46, 1.31)          | 0.018025                                 | 0.017867                                          |
| Absolute Change at 9 Months after Intervention 1      | 0.000172 | (0.000094, 0.000250)  | 0.017968                                 | 0.017796                                          |
| Relative Change (%) at 9 Months after Intervention 1  | 0.97     | (0.52, 1.41)          | 0.017968                                 | 0.017796                                          |
| Absolute Change at 10 Months after Intervention 1     | 0.000186 | (0.000105, 0.000267)  | 0.017910                                 | 0.017725                                          |
| Relative Change (%) at 10 Months after Intervention 1 | 1.05     | (0.59, 1.51)          | 0.017910                                 | 0.017725                                          |
| Absolute Change at 11 Months after Intervention 1     | 0.000200 | (0.000115, 0.000284)  | 0.017853                                 | 0.017653                                          |
| Relative Change (%) at 11 Months after Intervention 1 | 1.13     | (0.65, 1.61)          | 0.017853                                 | 0.017653                                          |
| Absolute Change at 12 Months after Intervention 1     | 0.000214 | (0.000126, 0.000302)  | 0.017796                                 | 0.017582                                          |
| Relative Change (%) at 12 Months after Intervention 1 | 1.22     | (0.71, 1.72)          | 0.017796                                 | 0.017582                                          |
| Absolute Change at 13 Months after Intervention 1     | 0.000228 | (0.000136, 0.000320)  | 0.017738                                 | 0.017511                                          |
| Relative Change (%) at 13 Months after Intervention 1 | 1.30     | (0.77, 1.83)          | 0.017738                                 | 0.017511                                          |
| Absolute Change at 14 Months after Intervention 1     | 0.000241 | (0.000145, 0.000338)  | 0.017681                                 | 0.017440                                          |
| Relative Change (%) at 14 Months after Intervention 1 | 1.38     | (0.83, 1.94)          | 0.017681                                 | 0.017440                                          |
| Absolute Change at 15 Months after Intervention 1     | 0.000255 | (0.000155, 0.000356)  | 0.017624                                 | 0.017368                                          |
| Relative Change (%) at 15 Months after Intervention 1 | 1.47     | (0.88, 2.06)          | 0.017624                                 | 0.017368                                          |
| Absolute Change at 16 Months after Intervention 1     | 0.000269 | (0.000164, 0.000374)  | 0.017566                                 | 0.017297                                          |
| Relative Change (%) at 16 Months after Intervention 1 | 1.56     | (0.94, 2.17)          | 0.017566                                 | 0.017297                                          |
| Absolute Change at 17 Months after Intervention 1     | 0.000283 | (0.000174, 0.000393)  | 0.017509                                 | 0.017226                                          |
| Relative Change (%) at 17 Months after Intervention 1 | 1.64     | (1.00, 2.29)          | 0.017509                                 | 0.017226                                          |
| Absolute Change at 18 Months after Intervention 1     | 0.000297 | (0.000183, 0.000412)  | 0.017452                                 | 0.017154                                          |
| Relative Change (%) at 18 Months after Intervention 1 | 1.73     | (1.06, 2.41)          | 0.017452                                 | 0.017154                                          |
| Absolute Change at 19 Months after Intervention 1     | 0.000311 | (0.000192, 0.000431)  | 0.017394                                 | 0.017083                                          |
| Relative Change (%) at 19 Months after Intervention 1 | 1.82     | (1.11, 2.53)          | 0.017394                                 | 0.017083                                          |
| Absolute Change at 20 Months after Intervention 1     | 0.000325 | (0.000200, 0.000450)  | 0.017337                                 | 0.017012                                          |
| Relative Change (%) at 20 Months after Intervention 1 | 1.91     | (1.17, 2.65)          | 0.017337                                 | 0.017012                                          |
| Absolute Change at 21 Months after Intervention 1     | 0.000339 | (0.000209, 0.000469)  | 0.017279                                 | 0.016941                                          |
| Relative Change (%) at 21 Months after Intervention 1 | 2.00     | (1.22, 2.78)          | 0.017279                                 | 0.016941                                          |
| Absolute Change at 22 Months after Intervention 1     | 0.000353 | (0.000218, 0.000488)  | 0.017222                                 | 0.016869                                          |
| Relative Change (%) at 22 Months after Intervention 1 | 2.09     | (1.28, 2.90)          | 0.017222                                 | 0.016869                                          |
| Absolute Change at 23 Months after Intervention 1     | 0.000367 | (0.000226, 0.000507)  | 0.017165                                 | 0.016798                                          |
| Relative Change (%) at 23 Months after Intervention 1 | 2.18     | (1.33, 3.03)          | 0.017165                                 | 0.016798                                          |
| Absolute Change at 24 Months after Intervention 1     | 0.000381 | (0.000235, 0.000526)  | 0.017107                                 | 0.016727                                          |
| Relative Change (%) at 24 Months after Intervention 1 | 2.28     | (1.39, 3.16)          | 0.017107                                 | 0.016727                                          |
| Absolute Change at 25 Months after Intervention 1     | 0.000395 | (0.000243, 0.000546)  | 0.017050                                 | 0.016655                                          |

**Table 8. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|----------|----------------------|---------------------|-----------------------------|
|                                                       |          |                      | (With Intervention) | Rate (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 2.37     | (1.45, 3.29)         | 0.017050            | 0.016655                    |
| Absolute Change at 26 Months after Intervention 1     | 0.000408 | (0.000252, 0.000565) | 0.016993            | 0.016584                    |
| Relative Change (%) at 26 Months after Intervention 1 | 2.46     | (1.50, 3.42)         | 0.016993            | 0.016584                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000422 | (0.000260, 0.000585) | 0.016935            | 0.016513                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000422 | (0.000260, 0.000585) | 0.016935            | 0.016513                    |
| Relative Change (%) at 27 Months after Intervention 1 | 2.56     | (1.56, 3.56)         | 0.016935            | 0.016513                    |
| Relative Change (%) at 27 Months after Intervention 1 | 2.56     | (1.56, 3.56)         | 0.016935            | 0.016513                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 4. Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 9. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 66)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.000032  | (0.000026, 0.000039)   | <.001               |
| Baseline trend                                                          | -0.000001 | (-0.000001, -0.000000) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000002 | (-0.000004, -0.000000) | 0.017               |
| Trend Change (After Intervention 1)                                     | 0.000001  | (0.000000, 0.000001)   | 0.005               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.000032  | (0.000026, 0.000039)   | <.001               |
| Baseline trend                                                          | -0.000001 | (-0.000001, -0.000000) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000002 | (-0.000004, -0.000000) | 0.017               |
| Trend Change (After Intervention 1)                                     | 0.000001  | (0.000000, 0.000001)   | 0.005               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 10. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|-----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |           |                       |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | -0.000001 | (-0.000003, 0.000000) | 0.000003                                 | 0.000005                                          |
| Relative Change (%) at 1 Months after Intervention 1  | -32.13    | (-89.61, 25.36)       | 0.000003                                 | 0.000005                                          |
| Absolute Change at 2 Months after Intervention 1      | -0.000001 | (-0.000003, 0.000001) | 0.000003                                 | 0.000004                                          |
| Relative Change (%) at 2 Months after Intervention 1  | -23.77    | (-72.90, 25.36)       | 0.000003                                 | 0.000004                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000000  | (-0.000002, 0.000002) | 0.000003                                 | 0.000003                                          |
| Relative Change (%) at 3 Months after Intervention 1  | -12.29    | (-61.91, 37.33)       | 0.000003                                 | 0.000003                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000000  | (-0.000002, 0.000002) | 0.000003                                 | 0.000003                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 4.49      | (-91.77, 100.75)      | 0.000003                                 | 0.000003                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.000001  | (-0.000002, 0.000003) | 0.000003                                 | 0.000002                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 31.35     | (-209.43, 272.13)     | 0.000003                                 | 0.000002                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.000001  | (-0.000002, 0.000004) | 0.000003                                 | 0.000001                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 81.24     | (-585.43, 747.90)     | 0.000003                                 | 0.000001                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.000002  | (-0.000002, 0.000005) | 0.000003                                 | 0.000001                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 205.98    | (-2365.58, 2777.54)   | 0.000003                                 | 0.000001                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.000002  | (-0.000002, 0.000006) | 0.000002                                 | 0.000000                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 1080.45   | (-48298.6, 50459.49)  | 0.000002                                 | 0.000000                                          |
| Absolute Change at 9 Months after Intervention 1      | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 9 Months after Intervention 1  | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 10 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 10 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 11 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 11 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 12 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 12 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 13 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 13 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 14 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 14 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 15 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 15 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 16 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 16 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 17 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 17 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 18 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 18 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 19 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 19 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 20 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 20 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 21 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 21 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 22 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 22 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 23 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 23 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Absolute Change at 24 Months after Intervention 1     | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |
| Relative Change (%) at 24 Months after Intervention 1 | N/A       | (N/A, N/A)            | N/A                                      | N/A                                               |

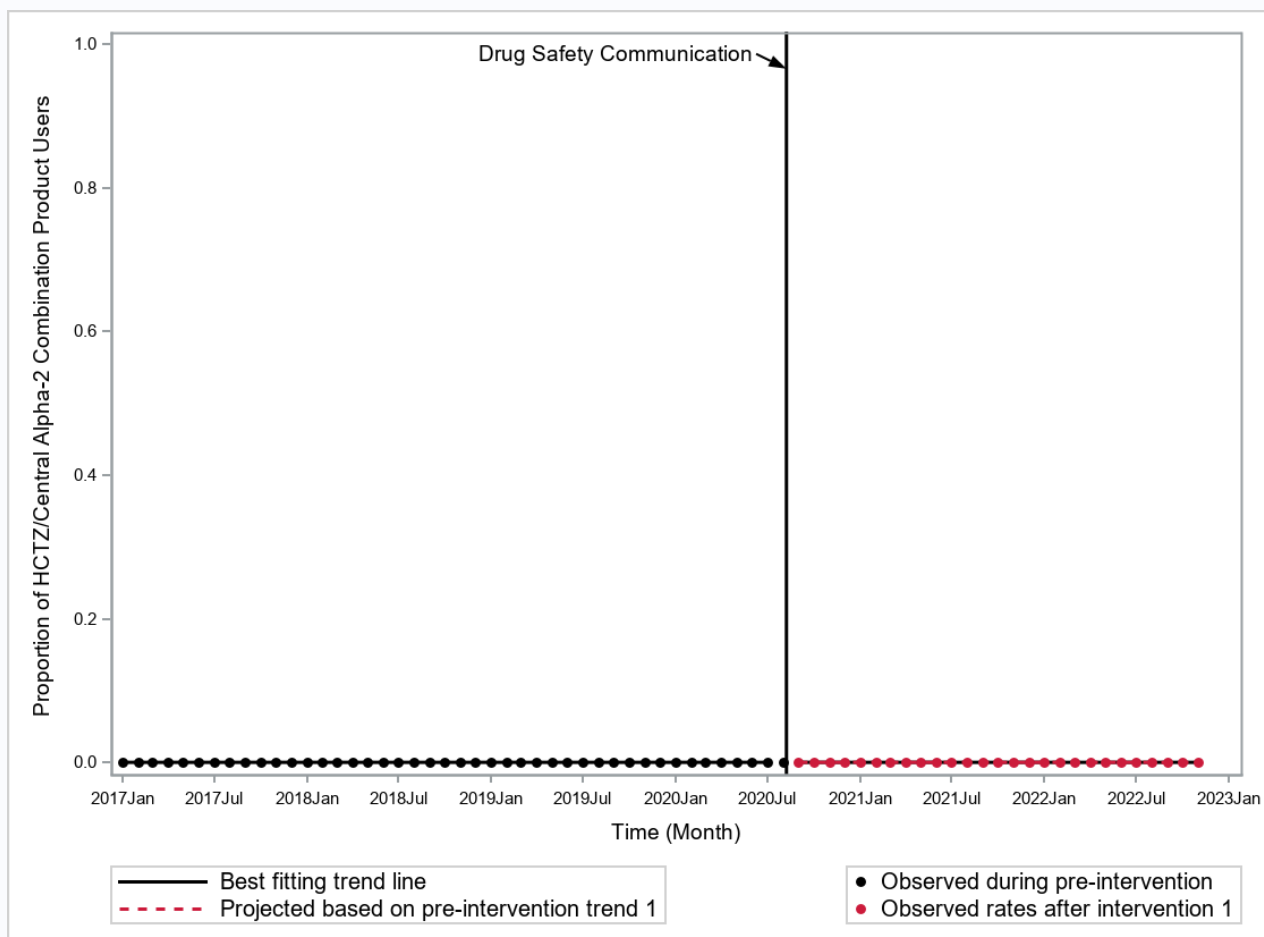
**Table 10. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI     | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|------------|---------------------|------------------------|
|                                                       |          |            | (With Intervention) | (Without Intervention) |
| Absolute Change at 25 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Relative Change (%) at 25 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Absolute Change at 26 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Relative Change (%) at 26 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                 | N/A                    |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                 | N/A                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

N/A: Not Applicable.

**Figure 5. Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 11. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 64)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.361998  | (0.359998, 0.363998)   | <.001               |
| Baseline trend                                                          | -0.000646 | (-0.000717, -0.000576) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001288  | (-0.000033, 0.002608)  | 0.056               |
| Trend Change (After Intervention 1)                                     | -0.000048 | (-0.000216, 0.000119)  | 0.567               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.362291  | (0.360600, 0.363982)   | <.001               |
| Baseline trend                                                          | -0.000661 | (-0.000707, -0.000616) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001193  | (-0.000095, 0.002482)  | 0.069               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 12. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

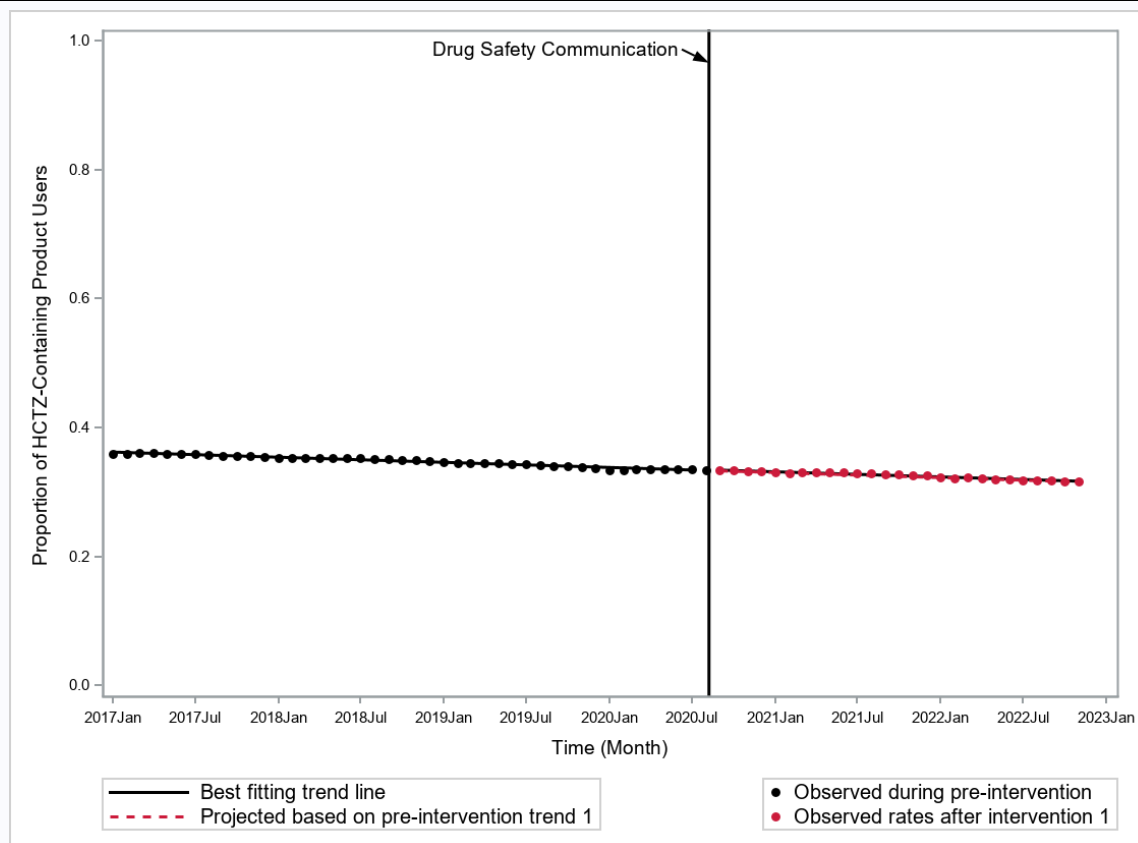
| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|----------|-----------------------|---------------------|-----------------------------|
|                                                       |          |                       | (With Intervention) | Rate (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.333719            | 0.332526                    |
| Relative Change (%) at 1 Months after Intervention 1  | 0.36     | (-0.05, 0.77)         | 0.333719            | 0.332526                    |
| Absolute Change at 2 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.333057            | 0.331864                    |
| Relative Change (%) at 2 Months after Intervention 1  | 0.36     | (-0.05, 0.77)         | 0.333057            | 0.331864                    |
| Absolute Change at 3 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.332396            | 0.331203                    |
| Relative Change (%) at 3 Months after Intervention 1  | 0.36     | (-0.05, 0.77)         | 0.332396            | 0.331203                    |
| Absolute Change at 4 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.331735            | 0.330541                    |
| Relative Change (%) at 4 Months after Intervention 1  | 0.36     | (-0.05, 0.77)         | 0.331735            | 0.330541                    |
| Absolute Change at 5 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.331073            | 0.329880                    |
| Relative Change (%) at 5 Months after Intervention 1  | 0.36     | (-0.05, 0.78)         | 0.331073            | 0.329880                    |
| Absolute Change at 6 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.330412            | 0.329218                    |
| Relative Change (%) at 6 Months after Intervention 1  | 0.36     | (-0.05, 0.78)         | 0.330412            | 0.329218                    |
| Absolute Change at 7 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.329750            | 0.328557                    |
| Relative Change (%) at 7 Months after Intervention 1  | 0.36     | (-0.05, 0.78)         | 0.329750            | 0.328557                    |
| Absolute Change at 8 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.329089            | 0.327895                    |
| Relative Change (%) at 8 Months after Intervention 1  | 0.36     | (-0.05, 0.78)         | 0.329089            | 0.327895                    |
| Absolute Change at 9 Months after Intervention 1      | 0.001193 | (-0.000168, 0.002555) | 0.328427            | 0.327234                    |
| Relative Change (%) at 9 Months after Intervention 1  | 0.36     | (-0.05, 0.78)         | 0.328427            | 0.327234                    |
| Absolute Change at 10 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.327766            | 0.326572                    |
| Relative Change (%) at 10 Months after Intervention 1 | 0.37     | (-0.05, 0.78)         | 0.327766            | 0.326572                    |
| Absolute Change at 11 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.327104            | 0.325911                    |
| Relative Change (%) at 11 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.327104            | 0.325911                    |
| Absolute Change at 12 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.326443            | 0.325250                    |
| Relative Change (%) at 12 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.326443            | 0.325250                    |
| Absolute Change at 13 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.325781            | 0.324588                    |
| Relative Change (%) at 13 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.325781            | 0.324588                    |
| Absolute Change at 14 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.325120            | 0.323927                    |
| Relative Change (%) at 14 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.325120            | 0.323927                    |
| Absolute Change at 15 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.324459            | 0.323265                    |
| Relative Change (%) at 15 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.324459            | 0.323265                    |
| Absolute Change at 16 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.323797            | 0.322604                    |
| Relative Change (%) at 16 Months after Intervention 1 | 0.37     | (-0.05, 0.79)         | 0.323797            | 0.322604                    |
| Absolute Change at 17 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.323136            | 0.321942                    |
| Relative Change (%) at 17 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.323136            | 0.321942                    |
| Absolute Change at 18 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.322474            | 0.321281                    |
| Relative Change (%) at 18 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.322474            | 0.321281                    |
| Absolute Change at 19 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.321813            | 0.320619                    |
| Relative Change (%) at 19 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.321813            | 0.320619                    |
| Absolute Change at 20 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.321151            | 0.319958                    |
| Relative Change (%) at 20 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.321151            | 0.319958                    |
| Absolute Change at 21 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.320490            | 0.319296                    |
| Relative Change (%) at 21 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.320490            | 0.319296                    |
| Absolute Change at 22 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.319828            | 0.318635                    |
| Relative Change (%) at 22 Months after Intervention 1 | 0.37     | (-0.05, 0.80)         | 0.319828            | 0.318635                    |
| Absolute Change at 23 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.319167            | 0.317974                    |
| Relative Change (%) at 23 Months after Intervention 1 | 0.38     | (-0.05, 0.81)         | 0.319167            | 0.317974                    |
| Absolute Change at 24 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.318505            | 0.317312                    |
| Relative Change (%) at 24 Months after Intervention 1 | 0.38     | (-0.05, 0.81)         | 0.318505            | 0.317312                    |

**Table 12. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|----------|-----------------------|---------------------|-----------------------------|
|                                                       |          |                       | (With Intervention) | Rate (Without Intervention) |
| Absolute Change at 25 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.317844            | 0.316651                    |
| Relative Change (%) at 25 Months after Intervention 1 | 0.38     | (-0.05, 0.81)         | 0.317844            | 0.316651                    |
| Absolute Change at 26 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.317183            | 0.315989                    |
| Relative Change (%) at 26 Months after Intervention 1 | 0.38     | (-0.06, 0.81)         | 0.317183            | 0.315989                    |
| Absolute Change at 27 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.316521            | 0.315328                    |
| Absolute Change at 27 Months after Intervention 1     | 0.001193 | (-0.000168, 0.002555) | 0.316521            | 0.315328                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.38     | (-0.06, 0.81)         | 0.316521            | 0.315328                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.38     | (-0.06, 0.81)         | 0.316521            | 0.315328                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 6. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 13. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.942274  | (0.941563, 0.942986)   | <.001               |
| Baseline trend                                                          | -0.000411 | (-0.000437, -0.000386) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000309  | (-0.000202, 0.000820)  | 0.232               |
| Trend Change (After Intervention 1)                                     | 0.000183  | (0.000121, 0.000245)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.942174  | (0.941362, 0.942986)   | <.001               |
| Baseline trend                                                          | -0.000406 | (-0.000435, -0.000377) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000185  | (0.000115, 0.000254)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 14. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

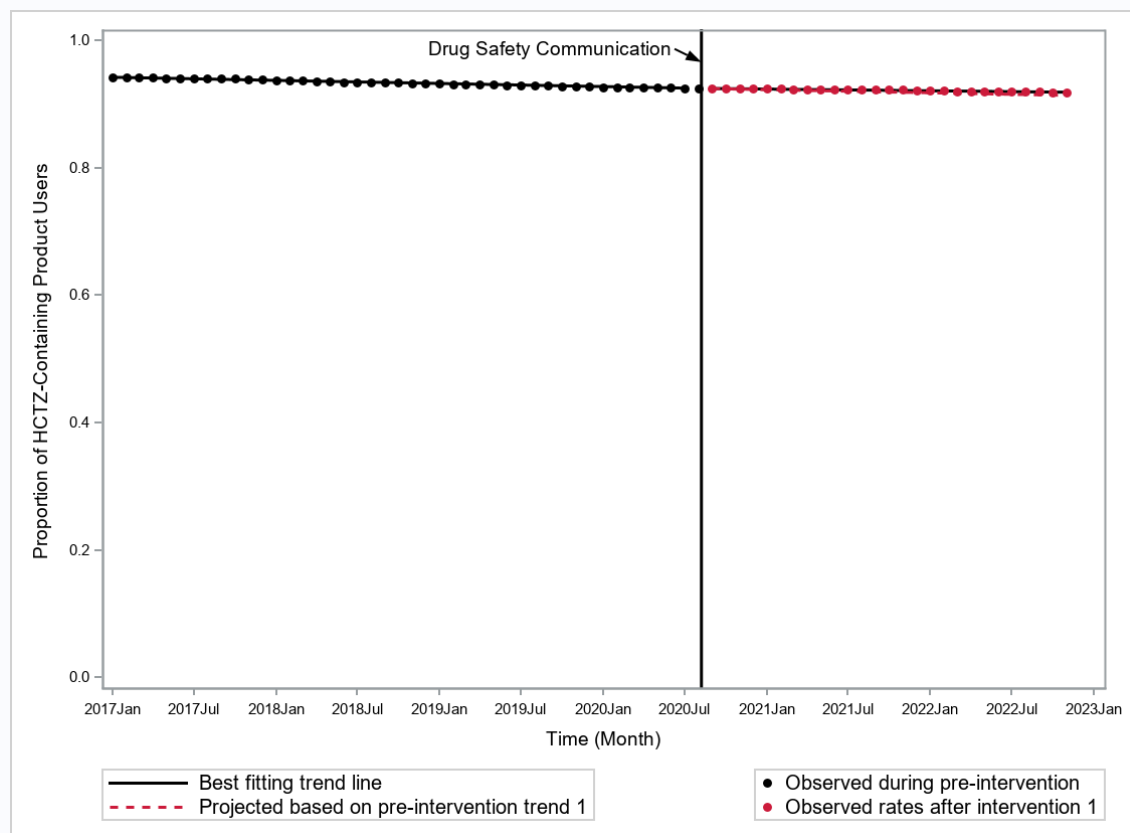
| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|----------|----------------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | 0.000185 | (0.000113, 0.000256) | 0.924089                              | 0.923905                                    |
| Relative Change (%) at 1 Months after Intervention 1  | 0.02     | (0.01, 0.03)         | 0.924089                              | 0.923905                                    |
| Absolute Change at 2 Months after Intervention 1      | 0.000369 | (0.000227, 0.000512) | 0.923868                              | 0.923499                                    |
| Relative Change (%) at 2 Months after Intervention 1  | 0.04     | (0.02, 0.06)         | 0.923868                              | 0.923499                                    |
| Absolute Change at 3 Months after Intervention 1      | 0.000554 | (0.000340, 0.000767) | 0.923647                              | 0.923093                                    |
| Relative Change (%) at 3 Months after Intervention 1  | 0.06     | (0.04, 0.08)         | 0.923647                              | 0.923093                                    |
| Absolute Change at 4 Months after Intervention 1      | 0.000738 | (0.000454, 0.001023) | 0.923425                              | 0.922687                                    |
| Relative Change (%) at 4 Months after Intervention 1  | 0.08     | (0.05, 0.11)         | 0.923425                              | 0.922687                                    |
| Absolute Change at 5 Months after Intervention 1      | 0.000923 | (0.000567, 0.001279) | 0.923204                              | 0.922281                                    |
| Relative Change (%) at 5 Months after Intervention 1  | 0.10     | (0.06, 0.14)         | 0.923204                              | 0.922281                                    |
| Absolute Change at 6 Months after Intervention 1      | 0.001108 | (0.000681, 0.001535) | 0.922983                              | 0.921875                                    |
| Relative Change (%) at 6 Months after Intervention 1  | 0.12     | (0.07, 0.17)         | 0.922983                              | 0.921875                                    |
| Absolute Change at 7 Months after Intervention 1      | 0.001292 | (0.000794, 0.001790) | 0.922761                              | 0.921469                                    |
| Relative Change (%) at 7 Months after Intervention 1  | 0.14     | (0.09, 0.19)         | 0.922761                              | 0.921469                                    |
| Absolute Change at 8 Months after Intervention 1      | 0.001477 | (0.000908, 0.002046) | 0.922540                              | 0.921063                                    |
| Relative Change (%) at 8 Months after Intervention 1  | 0.16     | (0.10, 0.22)         | 0.922540                              | 0.921063                                    |
| Absolute Change at 9 Months after Intervention 1      | 0.001661 | (0.001021, 0.002302) | 0.922318                              | 0.920657                                    |
| Relative Change (%) at 9 Months after Intervention 1  | 0.18     | (0.11, 0.25)         | 0.922318                              | 0.920657                                    |
| Absolute Change at 10 Months after Intervention 1     | 0.001846 | (0.001135, 0.002558) | 0.922097                              | 0.920251                                    |
| Relative Change (%) at 10 Months after Intervention 1 | 0.20     | (0.12, 0.28)         | 0.922097                              | 0.920251                                    |
| Absolute Change at 11 Months after Intervention 1     | 0.002031 | (0.001248, 0.002813) | 0.921876                              | 0.919845                                    |
| Relative Change (%) at 11 Months after Intervention 1 | 0.22     | (0.14, 0.31)         | 0.921876                              | 0.919845                                    |
| Absolute Change at 12 Months after Intervention 1     | 0.002215 | (0.001362, 0.003069) | 0.921654                              | 0.919439                                    |
| Relative Change (%) at 12 Months after Intervention 1 | 0.24     | (0.15, 0.33)         | 0.921654                              | 0.919439                                    |
| Absolute Change at 13 Months after Intervention 1     | 0.002400 | (0.001475, 0.003325) | 0.921433                              | 0.919033                                    |
| Relative Change (%) at 13 Months after Intervention 1 | 0.26     | (0.16, 0.36)         | 0.921433                              | 0.919033                                    |
| Absolute Change at 14 Months after Intervention 1     | 0.002585 | (0.001589, 0.003581) | 0.921212                              | 0.918627                                    |
| Relative Change (%) at 14 Months after Intervention 1 | 0.28     | (0.17, 0.39)         | 0.921212                              | 0.918627                                    |
| Absolute Change at 15 Months after Intervention 1     | 0.002769 | (0.001702, 0.003836) | 0.920990                              | 0.918221                                    |
| Relative Change (%) at 15 Months after Intervention 1 | 0.30     | (0.19, 0.42)         | 0.920990                              | 0.918221                                    |
| Absolute Change at 16 Months after Intervention 1     | 0.002954 | (0.001815, 0.004092) | 0.920769                              | 0.917815                                    |
| Relative Change (%) at 16 Months after Intervention 1 | 0.32     | (0.20, 0.45)         | 0.920769                              | 0.917815                                    |
| Absolute Change at 17 Months after Intervention 1     | 0.003138 | (0.001929, 0.004348) | 0.920547                              | 0.917409                                    |
| Relative Change (%) at 17 Months after Intervention 1 | 0.34     | (0.21, 0.47)         | 0.920547                              | 0.917409                                    |
| Absolute Change at 18 Months after Intervention 1     | 0.003323 | (0.002042, 0.004604) | 0.920326                              | 0.917003                                    |
| Relative Change (%) at 18 Months after Intervention 1 | 0.36     | (0.22, 0.50)         | 0.920326                              | 0.917003                                    |
| Absolute Change at 19 Months after Intervention 1     | 0.003508 | (0.002156, 0.004859) | 0.920105                              | 0.916597                                    |
| Relative Change (%) at 19 Months after Intervention 1 | 0.38     | (0.23, 0.53)         | 0.920105                              | 0.916597                                    |
| Absolute Change at 20 Months after Intervention 1     | 0.003692 | (0.002269, 0.005115) | 0.919883                              | 0.916191                                    |
| Relative Change (%) at 20 Months after Intervention 1 | 0.40     | (0.25, 0.56)         | 0.919883                              | 0.916191                                    |
| Absolute Change at 21 Months after Intervention 1     | 0.003877 | (0.002383, 0.005371) | 0.919662                              | 0.915785                                    |
| Relative Change (%) at 21 Months after Intervention 1 | 0.42     | (0.26, 0.59)         | 0.919662                              | 0.915785                                    |
| Absolute Change at 22 Months after Intervention 1     | 0.004061 | (0.002496, 0.005627) | 0.919441                              | 0.915379                                    |
| Relative Change (%) at 22 Months after Intervention 1 | 0.44     | (0.27, 0.62)         | 0.919441                              | 0.915379                                    |
| Absolute Change at 23 Months after Intervention 1     | 0.004246 | (0.002610, 0.005882) | 0.919219                              | 0.914973                                    |
| Relative Change (%) at 23 Months after Intervention 1 | 0.46     | (0.28, 0.64)         | 0.919219                              | 0.914973                                    |
| Absolute Change at 24 Months after Intervention 1     | 0.004431 | (0.002723, 0.006138) | 0.918998                              | 0.914567                                    |
| Relative Change (%) at 24 Months after Intervention 1 | 0.48     | (0.30, 0.67)         | 0.918998                              | 0.914567                                    |

**Table 14. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>        | <b>Predicted Rate<br/>(With Intervention)</b> | <b>Extrapolated Rate<br/>(Without Intervention)</b> |
|-------------------------------------------------------|-----------------|----------------------|-----------------------------------------------|-----------------------------------------------------|
| Absolute Change at 25 Months after Intervention 1     | 0.004615        | (0.002837, 0.006394) | 0.918776                                      | 0.914161                                            |
| Relative Change (%) at 25 Months after Intervention 1 | 0.50            | (0.31, 0.70)         | 0.918776                                      | 0.914161                                            |
| Absolute Change at 26 Months after Intervention 1     | 0.004800        | (0.002950, 0.006650) | 0.918555                                      | 0.913755                                            |
| Relative Change (%) at 26 Months after Intervention 1 | 0.53            | (0.32, 0.73)         | 0.918555                                      | 0.913755                                            |
| Absolute Change at 27 Months after Intervention 1     | 0.004984        | (0.003064, 0.006905) | 0.918334                                      | 0.913349                                            |
| Absolute Change at 27 Months after Intervention 1     | 0.004984        | (0.003064, 0.006905) | 0.918334                                      | 0.913349                                            |
| Relative Change (%) at 27 Months after Intervention 1 | 0.55            | (0.33, 0.76)         | 0.918334                                      | 0.913349                                            |
| Relative Change (%) at 27 Months after Intervention 1 | 0.55            | (0.33, 0.76)         | 0.918334                                      | 0.913349                                            |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 7. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 15. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 66)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.000499  | (0.000448, 0.000550)   | <.001               |
| Baseline trend                                                          | -0.000007 | (-0.000009, -0.000006) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000001  | (-0.000011, 0.000014)  | 0.829               |
| Trend Change (After Intervention 1)                                     | 0.000003  | (0.000001, 0.000006)   | 0.022               |
| <b>Most Parsimonious Final Model Parameters (df = 67)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.000499  | (0.000448, 0.000550)   | <.001               |
| Baseline trend                                                          | -0.000007 | (-0.000009, -0.000006) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000003  | (0.000001, 0.000006)   | 0.019               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 16. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|-----------------------|---------------------|------------------------|
|                                                       |          |                       | (With Intervention) | (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | 0.000003 | (0.000000, 0.000007)  | 0.000181            | 0.000178               |
| Relative Change (%) at 1 Months after Intervention 1  | 1.85     | (-0.79, 4.48)         | 0.000181            | 0.000178               |
| Absolute Change at 2 Months after Intervention 1      | 0.000007 | (-0.000001, 0.000014) | 0.000178            | 0.000171               |
| Relative Change (%) at 2 Months after Intervention 1  | 3.84     | (-1.73, 9.42)         | 0.000178            | 0.000171               |
| Absolute Change at 3 Months after Intervention 1      | 0.000010 | (-0.000001, 0.000021) | 0.000174            | 0.000164               |
| Relative Change (%) at 3 Months after Intervention 1  | 6.02     | (-2.84, 14.88)        | 0.000174            | 0.000164               |
| Absolute Change at 4 Months after Intervention 1      | 0.000013 | (-0.000002, 0.000028) | 0.000170            | 0.000157               |
| Relative Change (%) at 4 Months after Intervention 1  | 8.39     | (-4.18, 20.96)        | 0.000170            | 0.000157               |
| Absolute Change at 5 Months after Intervention 1      | 0.000016 | (-0.000002, 0.000035) | 0.000166            | 0.000150               |
| Relative Change (%) at 5 Months after Intervention 1  | 10.99    | (-5.79, 27.76)        | 0.000166            | 0.000150               |
| Absolute Change at 6 Months after Intervention 1      | 0.000020 | (-0.000003, 0.000042) | 0.000162            | 0.000142               |
| Relative Change (%) at 6 Months after Intervention 1  | 13.84    | (-7.73, 35.42)        | 0.000162            | 0.000142               |
| Absolute Change at 7 Months after Intervention 1      | 0.000023 | (-0.000003, 0.000049) | 0.000158            | 0.000135               |
| Relative Change (%) at 7 Months after Intervention 1  | 17.00    | (-10.08, 44.09)       | 0.000158            | 0.000135               |
| Absolute Change at 8 Months after Intervention 1      | 0.000026 | (-0.000004, 0.000056) | 0.000154            | 0.000128               |
| Relative Change (%) at 8 Months after Intervention 1  | 20.51    | (-12.95, 53.98)       | 0.000154            | 0.000128               |
| Absolute Change at 9 Months after Intervention 1      | 0.000030 | (-0.000004, 0.000063) | 0.000151            | 0.000121               |
| Relative Change (%) at 9 Months after Intervention 1  | 24.44    | (-16.49, 65.37)       | 0.000151            | 0.000121               |
| Absolute Change at 10 Months after Intervention 1     | 0.000033 | (-0.000004, 0.000070) | 0.000147            | 0.000114               |
| Relative Change (%) at 10 Months after Intervention 1 | 28.85    | (-20.88, 78.59)       | 0.000147            | 0.000114               |
| Absolute Change at 11 Months after Intervention 1     | 0.000036 | (-0.000005, 0.000077) | 0.000143            | 0.000107               |
| Relative Change (%) at 11 Months after Intervention 1 | 33.86    | (-26.39, 94.11)       | 0.000143            | 0.000107               |
| Absolute Change at 12 Months after Intervention 1     | 0.000039 | (-0.000005, 0.000084) | 0.000139            | 0.000100               |
| Relative Change (%) at 12 Months after Intervention 1 | 39.58    | (-33.38, 112.54)      | 0.000139            | 0.000100               |
| Absolute Change at 13 Months after Intervention 1     | 0.000043 | (-0.000006, 0.000091) | 0.000135            | 0.000093               |
| Relative Change (%) at 13 Months after Intervention 1 | 46.18    | (-42.36, 134.73)      | 0.000135            | 0.000093               |
| Absolute Change at 14 Months after Intervention 1     | 0.000046 | (-0.000006, 0.000098) | 0.000131            | 0.000085               |
| Relative Change (%) at 14 Months after Intervention 1 | 53.89    | (-54.09, 161.87)      | 0.000131            | 0.000085               |
| Absolute Change at 15 Months after Intervention 1     | 0.000049 | (-0.000007, 0.000105) | 0.000128            | 0.000078               |
| Relative Change (%) at 15 Months after Intervention 1 | 63.00    | (-69.71, 195.71)      | 0.000128            | 0.000078               |
| Absolute Change at 16 Months after Intervention 1     | 0.000053 | (-0.000007, 0.000112) | 0.000124            | 0.000071               |
| Relative Change (%) at 16 Months after Intervention 1 | 73.94    | (-90.97, 238.85)      | 0.000124            | 0.000071               |
| Absolute Change at 17 Months after Intervention 1     | 0.000056 | (-0.000007, 0.000119) | 0.000120            | 0.000064               |
| Relative Change (%) at 17 Months after Intervention 1 | 87.32    | (-120.69, 295.32)     | 0.000120            | 0.000064               |
| Absolute Change at 18 Months after Intervention 1     | 0.000059 | (-0.000008, 0.000126) | 0.000116            | 0.000057               |
| Relative Change (%) at 18 Months after Intervention 1 | 104.05   | (-163.67, 371.77)     | 0.000116            | 0.000057               |
| Absolute Change at 19 Months after Intervention 1     | 0.000062 | (-0.000008, 0.000133) | 0.000112            | 0.000050               |
| Relative Change (%) at 19 Months after Intervention 1 | 125.58   | (-228.48, 479.64)     | 0.000112            | 0.000050               |
| Absolute Change at 20 Months after Intervention 1     | 0.000066 | (-0.000009, 0.000140) | 0.000108            | 0.000043               |
| Relative Change (%) at 20 Months after Intervention 1 | 154.33   | (-331.71, 640.37)     | 0.000108            | 0.000043               |
| Absolute Change at 21 Months after Intervention 1     | 0.000069 | (-0.000009, 0.000147) | 0.000104            | 0.000035               |
| Relative Change (%) at 21 Months after Intervention 1 | 194.63   | (-508.76, 898.02)     | 0.000104            | 0.000035               |
| Absolute Change at 22 Months after Intervention 1     | 0.000072 | (-0.000010, 0.000154) | 0.000101            | 0.000028               |
| Relative Change (%) at 22 Months after Intervention 1 | 255.23   | (-846.03, 1356.49)    | 0.000101            | 0.000028               |
| Absolute Change at 23 Months after Intervention 1     | 0.000076 | (-0.000010, 0.000161) | 0.000097            | 0.000021               |
| Relative Change (%) at 23 Months after Intervention 1 | 356.61   | (-1601.44, 2314.65)   | 0.000097            | 0.000021               |
| Absolute Change at 24 Months after Intervention 1     | 0.000079 | (-0.000011, 0.000168) | 0.000093            | 0.000014               |
| Relative Change (%) at 24 Months after Intervention 1 | 560.78   | (-3850.22, 4971.78)   | 0.000093            | 0.000014               |

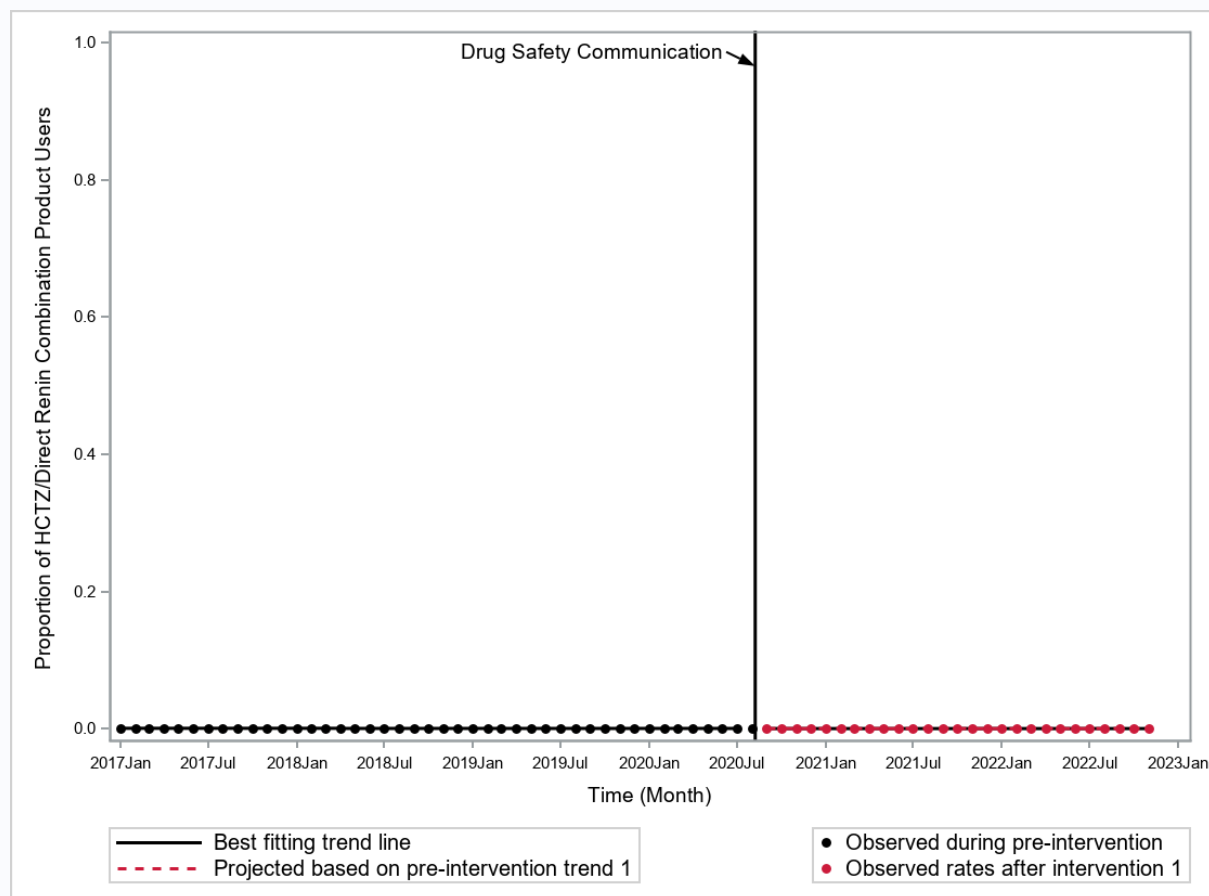
**Table 16. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI                | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|-----------------------|---------------------|------------------------|
|                                                       |          |                       | (With Intervention) | (Without Intervention) |
| Absolute Change at 25 Months after Intervention 1     | 0.000082 | (-0.000011, 0.000175) | 0.000089            | 0.000007               |
| Relative Change (%) at 25 Months after Intervention 1 | 1184.94  | (-16756.9, 19126.78)  | 0.000089            | 0.000007               |
| Absolute Change at 26 Months after Intervention 1     | N/A      | (N/A, N/A)            | N/A                 | N/A                    |
| Relative Change (%) at 26 Months after Intervention 1 | N/A      | (N/A, N/A)            | N/A                 | N/A                    |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A)            | N/A                 | N/A                    |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A)            | N/A                 | N/A                    |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A)            | N/A                 | N/A                    |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A)            | N/A                 | N/A                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

N/A means Not Applicable.

**Figure 8. Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 17. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.352164  | (0.336120, 0.368207)   | <.001               |
| Baseline trend                                                          | 0.002126  | (0.001554, 0.002698)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.000934  | (-0.002316, 0.004185)  | 0.568               |
| Trend Change (After Intervention 1)                                     | -0.002054 | (-0.003469, -0.000638) | 0.005               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.352898  | (0.336794, 0.369003)   | <.001               |
| Baseline trend                                                          | 0.002096  | (0.001523, 0.002669)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.001930 | (-0.003306, -0.000553) | 0.007               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 18. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

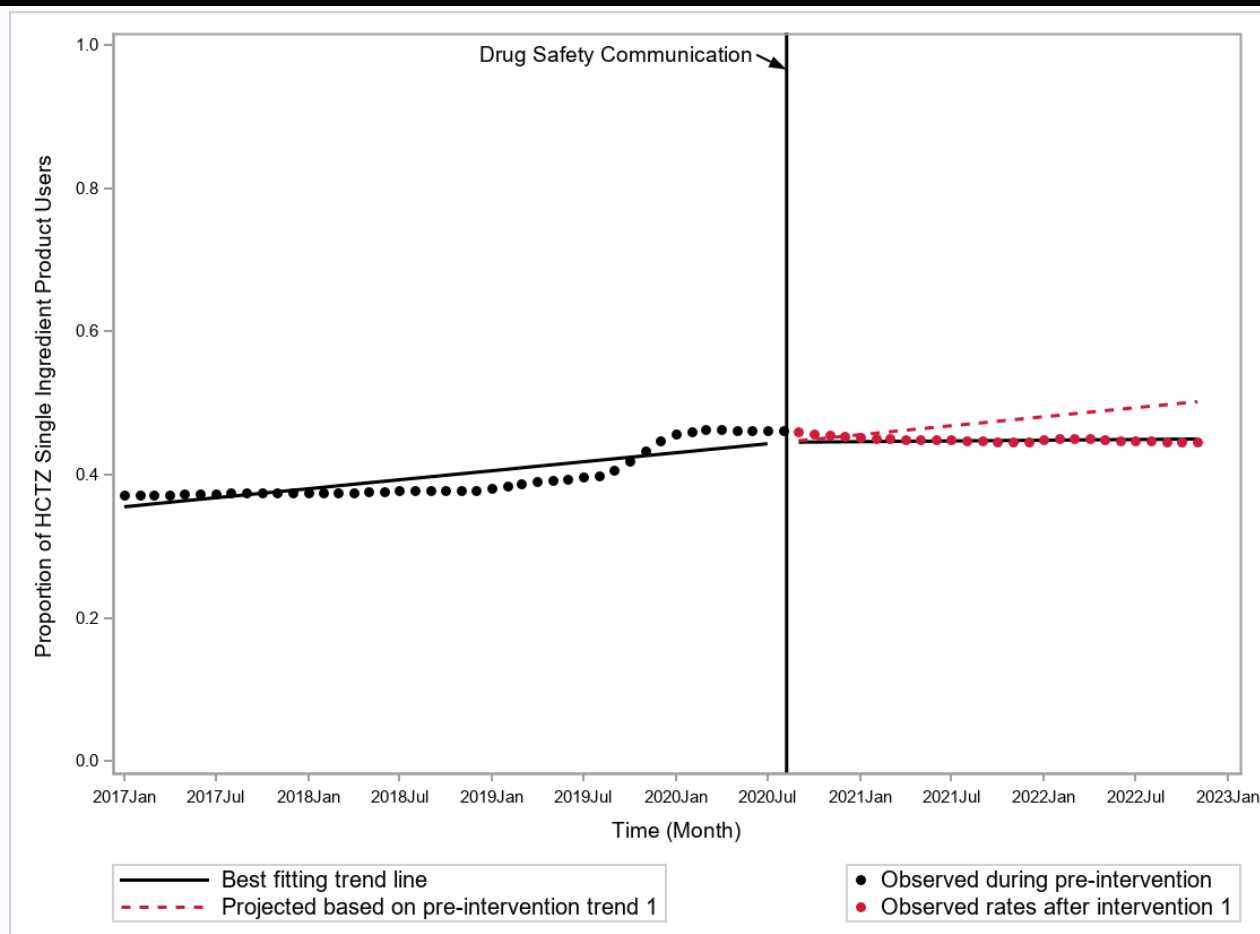
| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted<br>Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|---------------------------------------------|---------------------------------------------------|
|                                                       |           |                        |                                             |                                                   |
| Absolute Change at 1 Months after Intervention 1      | -0.001930 | (-0.003305, -0.000554) | 0.445290                                    | 0.447219                                          |
| Relative Change (%) at 1 Months after Intervention 1  | -0.43     | (-0.73, -0.14)         | 0.445290                                    | 0.447219                                          |
| Absolute Change at 2 Months after Intervention 1      | -0.003859 | (-0.006610, -0.001108) | 0.445456                                    | 0.449315                                          |
| Relative Change (%) at 2 Months after Intervention 1  | -0.86     | (-1.45, -0.27)         | 0.445456                                    | 0.449315                                          |
| Absolute Change at 3 Months after Intervention 1      | -0.005789 | (-0.009915, -0.001662) | 0.445623                                    | 0.451411                                          |
| Relative Change (%) at 3 Months after Intervention 1  | -1.28     | (-2.16, -0.41)         | 0.445623                                    | 0.451411                                          |
| Absolute Change at 4 Months after Intervention 1      | -0.007718 | (-0.013220, -0.002216) | 0.445789                                    | 0.453507                                          |
| Relative Change (%) at 4 Months after Intervention 1  | -1.70     | (-2.86, -0.54)         | 0.445789                                    | 0.453507                                          |
| Absolute Change at 5 Months after Intervention 1      | -0.009648 | (-0.016525, -0.002770) | 0.445956                                    | 0.455603                                          |
| Relative Change (%) at 5 Months after Intervention 1  | -2.12     | (-3.56, -0.67)         | 0.445956                                    | 0.455603                                          |
| Absolute Change at 6 Months after Intervention 1      | -0.011577 | (-0.019830, -0.003324) | 0.446122                                    | 0.457699                                          |
| Relative Change (%) at 6 Months after Intervention 1  | -2.53     | (-4.25, -0.81)         | 0.446122                                    | 0.457699                                          |
| Absolute Change at 7 Months after Intervention 1      | -0.013507 | (-0.023135, -0.003878) | 0.446289                                    | 0.459795                                          |
| Relative Change (%) at 7 Months after Intervention 1  | -2.94     | (-4.94, -0.94)         | 0.446289                                    | 0.459795                                          |
| Absolute Change at 8 Months after Intervention 1      | -0.015436 | (-0.026440, -0.004432) | 0.446455                                    | 0.461891                                          |
| Relative Change (%) at 8 Months after Intervention 1  | -3.34     | (-5.61, -1.07)         | 0.446455                                    | 0.461891                                          |
| Absolute Change at 9 Months after Intervention 1      | -0.017366 | (-0.029745, -0.004986) | 0.446622                                    | 0.463987                                          |
| Relative Change (%) at 9 Months after Intervention 1  | -3.74     | (-6.28, -1.20)         | 0.446622                                    | 0.463987                                          |
| Absolute Change at 10 Months after Intervention 1     | -0.019295 | (-0.033050, -0.005540) | 0.446788                                    | 0.466083                                          |
| Relative Change (%) at 10 Months after Intervention 1 | -4.14     | (-6.94, -1.34)         | 0.446788                                    | 0.466083                                          |
| Absolute Change at 11 Months after Intervention 1     | -0.021225 | (-0.036355, -0.006094) | 0.446955                                    | 0.468179                                          |
| Relative Change (%) at 11 Months after Intervention 1 | -4.53     | (-7.60, -1.47)         | 0.446955                                    | 0.468179                                          |
| Absolute Change at 12 Months after Intervention 1     | -0.023154 | (-0.039660, -0.006649) | 0.447121                                    | 0.470275                                          |
| Relative Change (%) at 12 Months after Intervention 1 | -4.92     | (-8.25, -1.60)         | 0.447121                                    | 0.470275                                          |
| Absolute Change at 13 Months after Intervention 1     | -0.025084 | (-0.042965, -0.007203) | 0.447288                                    | 0.472371                                          |
| Relative Change (%) at 13 Months after Intervention 1 | -5.31     | (-8.89, -1.73)         | 0.447288                                    | 0.472371                                          |
| Absolute Change at 14 Months after Intervention 1     | -0.027013 | (-0.046270, -0.007757) | 0.447454                                    | 0.474467                                          |
| Relative Change (%) at 14 Months after Intervention 1 | -5.69     | (-9.53, -1.86)         | 0.447454                                    | 0.474467                                          |
| Absolute Change at 15 Months after Intervention 1     | -0.028943 | (-0.049575, -0.008311) | 0.447621                                    | 0.476564                                          |
| Relative Change (%) at 15 Months after Intervention 1 | -6.07     | (-10.16, -1.98)        | 0.447621                                    | 0.476564                                          |
| Absolute Change at 16 Months after Intervention 1     | -0.030872 | (-0.052880, -0.008865) | 0.447787                                    | 0.478660                                          |
| Relative Change (%) at 16 Months after Intervention 1 | -6.45     | (-10.79, -2.11)        | 0.447787                                    | 0.478660                                          |
| Absolute Change at 17 Months after Intervention 1     | -0.032802 | (-0.056185, -0.009419) | 0.447954                                    | 0.480756                                          |
| Relative Change (%) at 17 Months after Intervention 1 | -6.82     | (-11.41, -2.24)        | 0.447954                                    | 0.480756                                          |
| Absolute Change at 18 Months after Intervention 1     | -0.034731 | (-0.059490, -0.009973) | 0.448120                                    | 0.482852                                          |
| Relative Change (%) at 18 Months after Intervention 1 | -7.19     | (-12.02, -2.37)        | 0.448120                                    | 0.482852                                          |
| Absolute Change at 19 Months after Intervention 1     | -0.036661 | (-0.062795, -0.010527) | 0.448287                                    | 0.484948                                          |
| Relative Change (%) at 19 Months after Intervention 1 | -7.56     | (-12.63, -2.49)        | 0.448287                                    | 0.484948                                          |
| Absolute Change at 20 Months after Intervention 1     | -0.038590 | (-0.066100, -0.011081) | 0.448453                                    | 0.487044                                          |
| Relative Change (%) at 20 Months after Intervention 1 | -7.92     | (-13.23, -2.62)        | 0.448453                                    | 0.487044                                          |
| Absolute Change at 21 Months after Intervention 1     | -0.040520 | (-0.069405, -0.011635) | 0.448620                                    | 0.489140                                          |
| Relative Change (%) at 21 Months after Intervention 1 | -8.28     | (-13.82, -2.74)        | 0.448620                                    | 0.489140                                          |
| Absolute Change at 22 Months after Intervention 1     | -0.042449 | (-0.072710, -0.012189) | 0.448786                                    | 0.491236                                          |
| Relative Change (%) at 22 Months after Intervention 1 | -8.64     | (-14.41, -2.87)        | 0.448786                                    | 0.491236                                          |
| Absolute Change at 23 Months after Intervention 1     | -0.044379 | (-0.076014, -0.012743) | 0.448953                                    | 0.493332                                          |
| Relative Change (%) at 23 Months after Intervention 1 | -9.00     | (-15.00, -2.99)        | 0.448953                                    | 0.493332                                          |
| Absolute Change at 24 Months after Intervention 1     | -0.046308 | (-0.079319, -0.013297) | 0.449119                                    | 0.495428                                          |
| Relative Change (%) at 24 Months after Intervention 1 | -9.35     | (-15.58, -3.12)        | 0.449119                                    | 0.495428                                          |
| Absolute Change at 25 Months after Intervention 1     | -0.048238 | (-0.082624, -0.013851) | 0.449286                                    | 0.497524                                          |

**Table 18. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate (With Intervention)</b> | <b>Extrapolated Rate (Without Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|-------------------------------------------|-------------------------------------------------|
| Relative Change (%) at 25 Months after Intervention 1 | -9.70           | (-16.15, -3.24)        | 0.449286                                  | 0.497524                                        |
| Absolute Change at 26 Months after Intervention 1     | -0.050167       | (-0.085929, -0.014405) | 0.449452                                  | 0.499620                                        |
| Relative Change (%) at 26 Months after Intervention 1 | -10.04          | (-16.72, -3.36)        | 0.449452                                  | 0.499620                                        |
| Absolute Change at 27 Months after Intervention 1     | -0.052097       | (-0.089234, -0.014959) | 0.449619                                  | 0.501716                                        |
| Absolute Change at 27 Months after Intervention 1     | -0.052097       | (-0.089234, -0.014959) | 0.449619                                  | 0.501716                                        |
| Relative Change (%) at 27 Months after Intervention 1 | -10.38          | (-17.28, -3.49)        | 0.449619                                  | 0.501716                                        |
| Relative Change (%) at 27 Months after Intervention 1 | -10.38          | (-17.28, -3.49)        | 0.449619                                  | 0.501716                                        |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 9. Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 19. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 66)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.107670  | (0.106408, 0.108931)   | <.001               |
| Baseline trend                                                          | -0.000334 | (-0.000370, -0.000299) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000071  | (-0.000250, 0.000391)  | 0.661               |
| Trend Change (After Intervention 1)                                     | 0.000013  | (-0.000057, 0.000084)  | 0.704               |
| <b>Most Parsimonious Final Model Parameters (df = 68)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.107636  | (0.106368, 0.108904)   | <.001               |
| Baseline trend                                                          | -0.000328 | (-0.000353, -0.000304) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 20. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

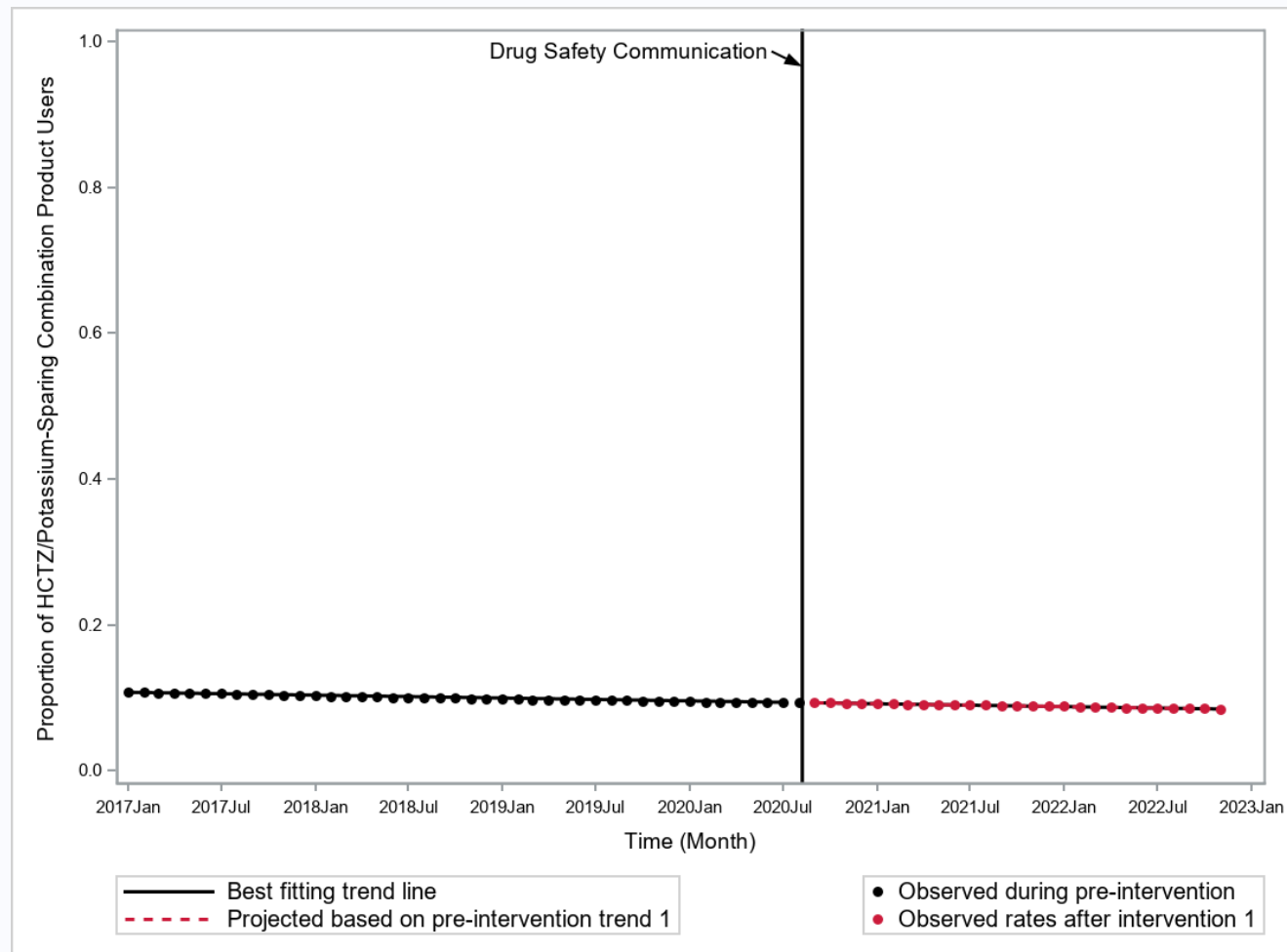
| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |          |                      |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.092862                                 | 0.092862                                          |
| Relative Change (%) at 1 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.092862                                 | 0.092862                                          |
| Absolute Change at 2 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.092533                                 | 0.092533                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.092533                                 | 0.092533                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.092205                                 | 0.092205                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.092205                                 | 0.092205                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091877                                 | 0.091877                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091877                                 | 0.091877                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091548                                 | 0.091548                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091548                                 | 0.091548                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091220                                 | 0.091220                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091220                                 | 0.091220                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090892                                 | 0.090892                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090892                                 | 0.090892                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090564                                 | 0.090564                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090564                                 | 0.090564                                          |
| Absolute Change at 9 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090235                                 | 0.090235                                          |
| Relative Change (%) at 9 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090235                                 | 0.090235                                          |
| Absolute Change at 10 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089907                                 | 0.089907                                          |
| Relative Change (%) at 10 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089907                                 | 0.089907                                          |
| Absolute Change at 11 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089579                                 | 0.089579                                          |
| Relative Change (%) at 11 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089579                                 | 0.089579                                          |
| Absolute Change at 12 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089250                                 | 0.089250                                          |
| Relative Change (%) at 12 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089250                                 | 0.089250                                          |
| Absolute Change at 13 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088922                                 | 0.088922                                          |
| Relative Change (%) at 13 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088922                                 | 0.088922                                          |
| Absolute Change at 14 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088594                                 | 0.088594                                          |
| Relative Change (%) at 14 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088594                                 | 0.088594                                          |
| Absolute Change at 15 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088265                                 | 0.088265                                          |
| Relative Change (%) at 15 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088265                                 | 0.088265                                          |
| Absolute Change at 16 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087937                                 | 0.087937                                          |
| Relative Change (%) at 16 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087937                                 | 0.087937                                          |
| Absolute Change at 17 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087609                                 | 0.087609                                          |
| Relative Change (%) at 17 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087609                                 | 0.087609                                          |
| Absolute Change at 18 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087280                                 | 0.087280                                          |
| Relative Change (%) at 18 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087280                                 | 0.087280                                          |
| Absolute Change at 19 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086952                                 | 0.086952                                          |
| Relative Change (%) at 19 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086952                                 | 0.086952                                          |
| Absolute Change at 20 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086624                                 | 0.086624                                          |
| Relative Change (%) at 20 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086624                                 | 0.086624                                          |
| Absolute Change at 21 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086295                                 | 0.086295                                          |
| Relative Change (%) at 21 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086295                                 | 0.086295                                          |
| Absolute Change at 22 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085967                                 | 0.085967                                          |
| Relative Change (%) at 22 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085967                                 | 0.085967                                          |
| Absolute Change at 23 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085639                                 | 0.085639                                          |
| Relative Change (%) at 23 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085639                                 | 0.085639                                          |
| Absolute Change at 24 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085310                                 | 0.085310                                          |
| Relative Change (%) at 24 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085310                                 | 0.085310                                          |
| Absolute Change at 25 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084982                                 | 0.084982                                          |

**Table 20. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|----------|----------------------|---------------------|-----------------------------|
|                                                       |          |                      | (With Intervention) | Rate (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084982            | 0.084982                    |
| Absolute Change at 26 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084654            | 0.084654                    |
| Relative Change (%) at 26 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084654            | 0.084654                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084326            | 0.084326                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084326            | 0.084326                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084326            | 0.084326                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084326            | 0.084326                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 10. Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 21. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 61)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.400037  | (0.399096, 0.400978)   | <.001               |
| Baseline trend                                                          | -0.000627 | (-0.000662, -0.000592) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001951  | (0.000895, 0.003008)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000271 | (-0.000359, -0.000183) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 61)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.400037  | (0.399096, 0.400978)   | <.001               |
| Baseline trend                                                          | -0.000627 | (-0.000662, -0.000592) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001951  | (0.000895, 0.003008)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000271 | (-0.000359, -0.000183) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 22. Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

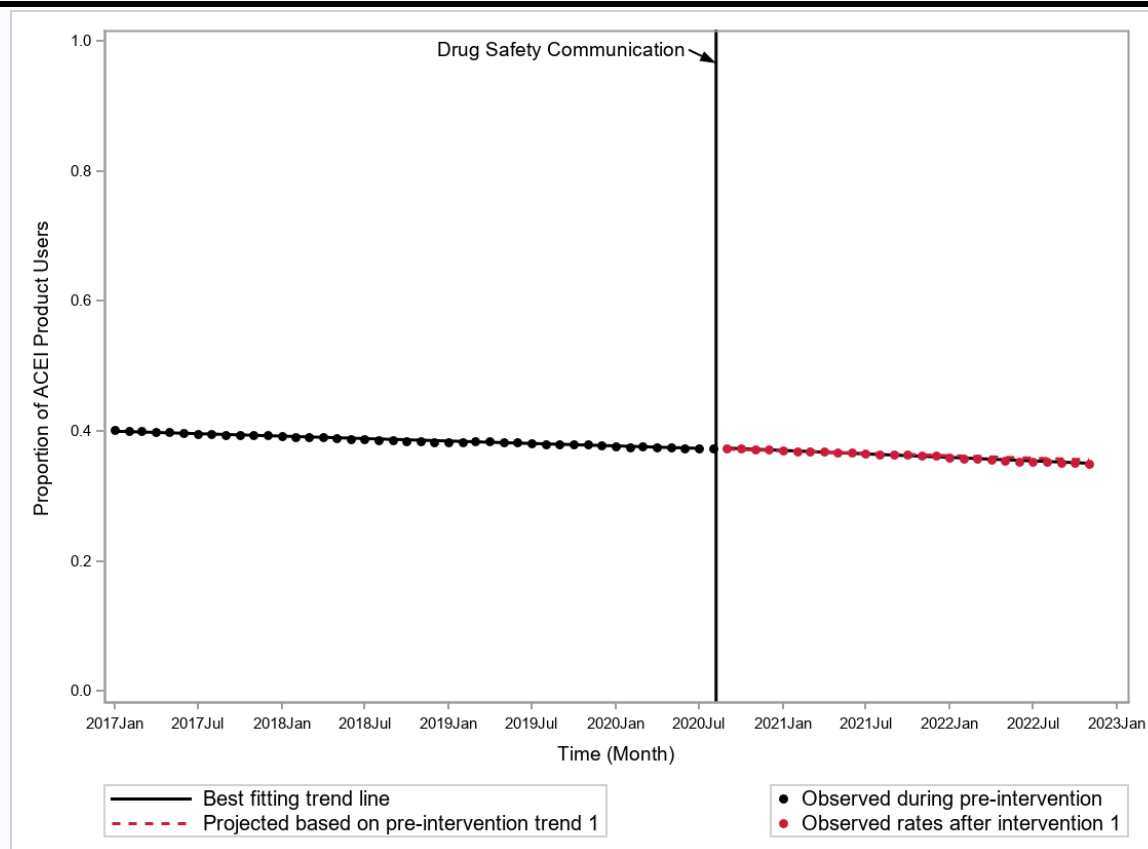
| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|-----------|------------------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | 0.001680  | (0.000590, 0.002770)   | 0.373494                              | 0.371814                                    |
| Relative Change (%) at 1 Months after Intervention 1  | 0.45      | (0.16, 0.75)           | 0.373494                              | 0.371814                                    |
| Absolute Change at 2 Months after Intervention 1      | 0.001409  | (0.000339, 0.002479)   | 0.372596                              | 0.371187                                    |
| Relative Change (%) at 2 Months after Intervention 1  | 0.38      | (0.09, 0.67)           | 0.372596                              | 0.371187                                    |
| Absolute Change at 3 Months after Intervention 1      | 0.001138  | (0.000081, 0.002195)   | 0.371697                              | 0.370560                                    |
| Relative Change (%) at 3 Months after Intervention 1  | 0.31      | (0.02, 0.59)           | 0.371697                              | 0.370560                                    |
| Absolute Change at 4 Months after Intervention 1      | 0.000867  | (-0.000185, 0.001918)  | 0.370799                              | 0.369932                                    |
| Relative Change (%) at 4 Months after Intervention 1  | 0.23      | (-0.05, 0.52)          | 0.370799                              | 0.369932                                    |
| Absolute Change at 5 Months after Intervention 1      | 0.000595  | (-0.000459, 0.001649)  | 0.369901                              | 0.369305                                    |
| Relative Change (%) at 5 Months after Intervention 1  | 0.16      | (-0.12, 0.45)          | 0.369901                              | 0.369305                                    |
| Absolute Change at 6 Months after Intervention 1      | 0.000324  | (-0.000740, 0.001389)  | 0.369002                              | 0.368678                                    |
| Relative Change (%) at 6 Months after Intervention 1  | 0.09      | (-0.20, 0.38)          | 0.369002                              | 0.368678                                    |
| Absolute Change at 7 Months after Intervention 1      | 0.000053  | (-0.001029, 0.001135)  | 0.368104                              | 0.368051                                    |
| Relative Change (%) at 7 Months after Intervention 1  | 0.01      | (-0.28, 0.31)          | 0.368104                              | 0.368051                                    |
| Absolute Change at 8 Months after Intervention 1      | -0.000218 | (-0.001325, 0.000889)  | 0.367206                              | 0.367424                                    |
| Relative Change (%) at 8 Months after Intervention 1  | -0.06     | (-0.36, 0.24)          | 0.367206                              | 0.367424                                    |
| Absolute Change at 9 Months after Intervention 1      | -0.000489 | (-0.001628, 0.000649)  | 0.366307                              | 0.366797                                    |
| Relative Change (%) at 9 Months after Intervention 1  | -0.13     | (-0.44, 0.18)          | 0.366307                              | 0.366797                                    |
| Absolute Change at 10 Months after Intervention 1     | -0.000760 | (-0.001937, 0.000416)  | 0.365409                              | 0.366169                                    |
| Relative Change (%) at 10 Months after Intervention 1 | -0.21     | (-0.53, 0.11)          | 0.365409                              | 0.366169                                    |
| Absolute Change at 11 Months after Intervention 1     | -0.001031 | (-0.002251, 0.000188)  | 0.364511                              | 0.365542                                    |
| Relative Change (%) at 11 Months after Intervention 1 | -0.28     | (-0.62, 0.05)          | 0.364511                              | 0.365542                                    |
| Absolute Change at 12 Months after Intervention 1     | -0.001303 | (-0.002571, -0.000034) | 0.363612                              | 0.364915                                    |
| Relative Change (%) at 12 Months after Intervention 1 | -0.36     | (-0.70, -0.01)         | 0.363612                              | 0.364915                                    |
| Absolute Change at 13 Months after Intervention 1     | -0.001574 | (-0.002895, -0.000253) | 0.362714                              | 0.364288                                    |
| Relative Change (%) at 13 Months after Intervention 1 | -0.43     | (-0.79, -0.07)         | 0.362714                              | 0.364288                                    |
| Absolute Change at 14 Months after Intervention 1     | -0.001845 | (-0.003223, -0.000467) | 0.361816                              | 0.363661                                    |
| Relative Change (%) at 14 Months after Intervention 1 | -0.51     | (-0.88, -0.13)         | 0.361816                              | 0.363661                                    |
| Absolute Change at 15 Months after Intervention 1     | -0.002116 | (-0.003554, -0.000678) | 0.360917                              | 0.363033                                    |
| Relative Change (%) at 15 Months after Intervention 1 | -0.58     | (-0.98, -0.19)         | 0.360917                              | 0.363033                                    |
| Absolute Change at 16 Months after Intervention 1     | -0.002387 | (-0.003889, -0.000886) | 0.360019                              | 0.362406                                    |
| Relative Change (%) at 16 Months after Intervention 1 | -0.66     | (-1.07, -0.25)         | 0.360019                              | 0.362406                                    |
| Absolute Change at 17 Months after Intervention 1     | -0.002658 | (-0.004226, -0.001091) | 0.359121                              | 0.361779                                    |
| Relative Change (%) at 17 Months after Intervention 1 | -0.73     | (-1.17, -0.30)         | 0.359121                              | 0.361779                                    |
| Absolute Change at 18 Months after Intervention 1     | -0.002929 | (-0.004565, -0.001294) | 0.358222                              | 0.361152                                    |
| Relative Change (%) at 18 Months after Intervention 1 | -0.81     | (-1.26, -0.36)         | 0.358222                              | 0.361152                                    |
| Absolute Change at 19 Months after Intervention 1     | -0.003201 | (-0.004907, -0.001494) | 0.357324                              | 0.360525                                    |
| Relative Change (%) at 19 Months after Intervention 1 | -0.89     | (-1.36, -0.42)         | 0.357324                              | 0.360525                                    |
| Absolute Change at 20 Months after Intervention 1     | -0.003472 | (-0.005250, -0.001693) | 0.356426                              | 0.359898                                    |
| Relative Change (%) at 20 Months after Intervention 1 | -0.96     | (-1.46, -0.47)         | 0.356426                              | 0.359898                                    |
| Absolute Change at 21 Months after Intervention 1     | -0.003743 | (-0.005595, -0.001890) | 0.355528                              | 0.359270                                    |
| Relative Change (%) at 21 Months after Intervention 1 | -1.04     | (-1.55, -0.53)         | 0.355528                              | 0.359270                                    |
| Absolute Change at 22 Months after Intervention 1     | -0.004014 | (-0.005942, -0.002086) | 0.354629                              | 0.358643                                    |
| Relative Change (%) at 22 Months after Intervention 1 | -1.12     | (-1.65, -0.59)         | 0.354629                              | 0.358643                                    |
| Absolute Change at 23 Months after Intervention 1     | -0.004285 | (-0.006290, -0.002281) | 0.353731                              | 0.358016                                    |
| Relative Change (%) at 23 Months after Intervention 1 | -1.20     | (-1.75, -0.64)         | 0.353731                              | 0.358016                                    |
| Absolute Change at 24 Months after Intervention 1     | -0.004556 | (-0.006638, -0.002474) | 0.352833                              | 0.357389                                    |
| Relative Change (%) at 24 Months after Intervention 1 | -1.27     | (-1.85, -0.70)         | 0.352833                              | 0.357389                                    |
| Absolute Change at 25 Months after Intervention 1     | -0.004827 | (-0.006988, -0.002666) | 0.351934                              | 0.356762                                    |

**Table 22. Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|-----------|------------------------|---------------------------------------|---------------------------------------------|
| Relative Change (%) at 25 Months after Intervention 1 | -1.35     | (-1.95, -0.75)         | 0.351934                              | 0.356762                                    |
| Absolute Change at 26 Months after Intervention 1     | -0.005099 | (-0.007339, -0.002858) | 0.351036                              | 0.356134                                    |
| Relative Change (%) at 26 Months after Intervention 1 | -1.43     | (-2.06, -0.81)         | 0.351036                              | 0.356134                                    |
| Absolute Change at 27 Months after Intervention 1     | -0.005370 | (-0.007691, -0.003049) | 0.350138                              | 0.355507                                    |
| Absolute Change at 27 Months after Intervention 1     | -0.005370 | (-0.007691, -0.003049) | 0.350138                              | 0.355507                                    |
| Relative Change (%) at 27 Months after Intervention 1 | -1.51     | (-2.16, -0.86)         | 0.350138                              | 0.355507                                    |
| Relative Change (%) at 27 Months after Intervention 1 | -1.51     | (-2.16, -0.86)         | 0.350138                              | 0.355507                                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 11. Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 23. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 63)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.373602  | (0.372442, 0.374761)   | <.001               |
| Baseline trend                                                          | 0.000700  | (0.000658, 0.000741)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.001089  | (0.000116, 0.002062)   | 0.029               |
| Trend Change (After Intervention 1)                                     | -0.000255 | (-0.000355, -0.000156) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 63)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.373602  | (0.372442, 0.374761)   | <.001               |
| Baseline trend                                                          | 0.000700  | (0.000658, 0.000741)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.001089  | (0.000116, 0.002062)   | 0.029               |
| Trend Change (After Intervention 1)                                     | -0.000255 | (-0.000355, -0.000156) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 24. Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

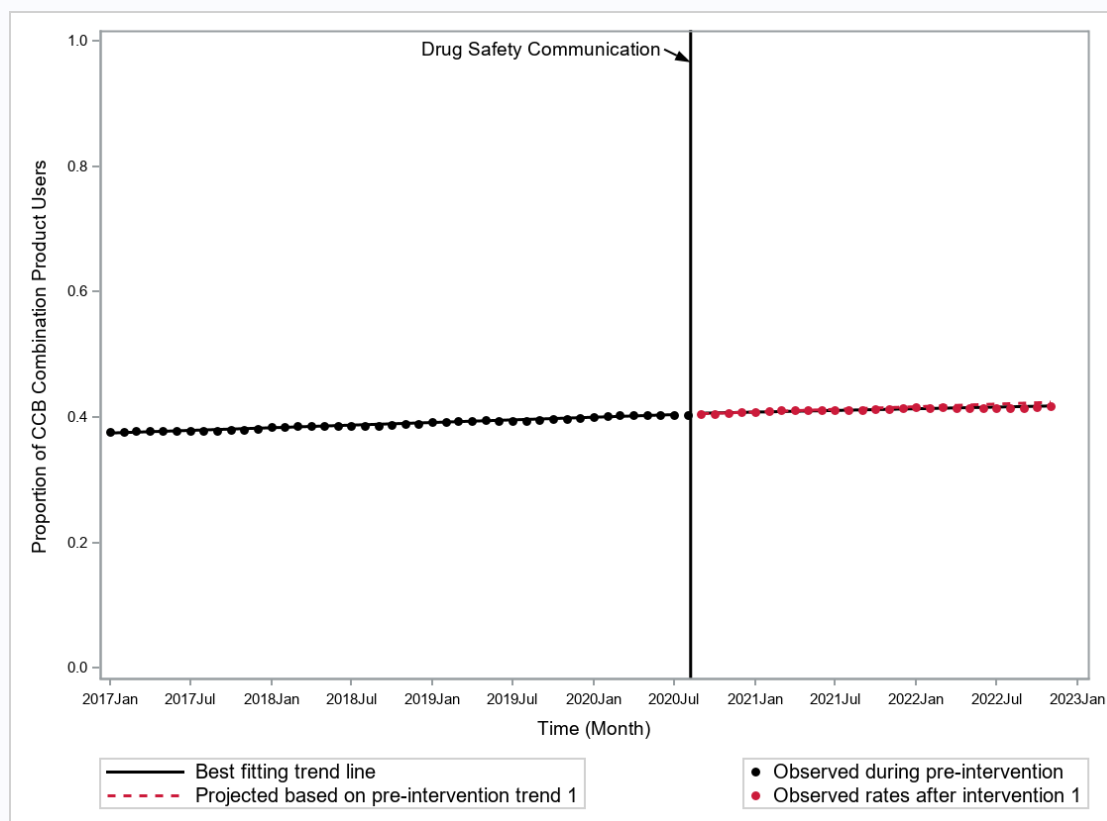
| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|---------------------------------------------------|
|                                                       |           |                        |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | 0.000833  | (-0.000154, 0.001820)  | 0.405924                                 | 0.405090                                          |
| Relative Change (%) at 1 Months after Intervention 1  | 0.21      | (-0.04, 0.45)          | 0.405924                                 | 0.405090                                          |
| Absolute Change at 2 Months after Intervention 1      | 0.000578  | (-0.000409, 0.001565)  | 0.406368                                 | 0.405790                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 0.14      | (-0.10, 0.39)          | 0.406368                                 | 0.405790                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000323  | (-0.000677, 0.001322)  | 0.406813                                 | 0.406490                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 0.08      | (-0.17, 0.33)          | 0.406813                                 | 0.406490                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000067  | (-0.000956, 0.001091)  | 0.407257                                 | 0.407190                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 0.02      | (-0.23, 0.27)          | 0.407257                                 | 0.407190                                          |
| Absolute Change at 5 Months after Intervention 1      | -0.000188 | (-0.001247, 0.000872)  | 0.407702                                 | 0.407889                                          |
| Relative Change (%) at 5 Months after Intervention 1  | -0.05     | (-0.31, 0.21)          | 0.407702                                 | 0.407889                                          |
| Absolute Change at 6 Months after Intervention 1      | -0.000443 | (-0.001548, 0.000662)  | 0.408146                                 | 0.408589                                          |
| Relative Change (%) at 6 Months after Intervention 1  | -0.11     | (-0.38, 0.16)          | 0.408146                                 | 0.408589                                          |
| Absolute Change at 7 Months after Intervention 1      | -0.000698 | (-0.001857, 0.000460)  | 0.408590                                 | 0.409289                                          |
| Relative Change (%) at 7 Months after Intervention 1  | -0.17     | (-0.45, 0.11)          | 0.408590                                 | 0.409289                                          |
| Absolute Change at 8 Months after Intervention 1      | -0.000954 | (-0.002174, 0.000267)  | 0.409035                                 | 0.409989                                          |
| Relative Change (%) at 8 Months after Intervention 1  | -0.23     | (-0.53, 0.06)          | 0.409035                                 | 0.409989                                          |
| Absolute Change at 9 Months after Intervention 1      | -0.001209 | (-0.002498, 0.000080)  | 0.409479                                 | 0.410688                                          |
| Relative Change (%) at 9 Months after Intervention 1  | -0.29     | (-0.61, 0.02)          | 0.409479                                 | 0.410688                                          |
| Absolute Change at 10 Months after Intervention 1     | -0.001464 | (-0.002827, -0.000101) | 0.409924                                 | 0.411388                                          |
| Relative Change (%) at 10 Months after Intervention 1 | -0.36     | (-0.69, -0.03)         | 0.409924                                 | 0.411388                                          |
| Absolute Change at 11 Months after Intervention 1     | -0.001720 | (-0.003161, -0.000278) | 0.410368                                 | 0.412088                                          |
| Relative Change (%) at 11 Months after Intervention 1 | -0.42     | (-0.77, -0.07)         | 0.410368                                 | 0.412088                                          |
| Absolute Change at 12 Months after Intervention 1     | -0.001975 | (-0.003499, -0.000451) | 0.410813                                 | 0.412788                                          |
| Relative Change (%) at 12 Months after Intervention 1 | -0.48     | (-0.85, -0.11)         | 0.410813                                 | 0.412788                                          |
| Absolute Change at 13 Months after Intervention 1     | -0.002230 | (-0.003840, -0.000620) | 0.411257                                 | 0.413487                                          |
| Relative Change (%) at 13 Months after Intervention 1 | -0.54     | (-0.93, -0.15)         | 0.411257                                 | 0.413487                                          |
| Absolute Change at 14 Months after Intervention 1     | -0.002486 | (-0.004184, -0.000787) | 0.411701                                 | 0.414187                                          |
| Relative Change (%) at 14 Months after Intervention 1 | -0.60     | (-1.01, -0.19)         | 0.411701                                 | 0.414187                                          |
| Absolute Change at 15 Months after Intervention 1     | -0.002741 | (-0.004531, -0.000951) | 0.412146                                 | 0.414887                                          |
| Relative Change (%) at 15 Months after Intervention 1 | -0.66     | (-1.09, -0.23)         | 0.412146                                 | 0.414887                                          |
| Absolute Change at 16 Months after Intervention 1     | -0.002996 | (-0.004880, -0.001113) | 0.412590                                 | 0.415587                                          |
| Relative Change (%) at 16 Months after Intervention 1 | -0.72     | (-1.17, -0.27)         | 0.412590                                 | 0.415587                                          |
| Absolute Change at 17 Months after Intervention 1     | -0.003252 | (-0.005230, -0.001273) | 0.413035                                 | 0.416286                                          |
| Relative Change (%) at 17 Months after Intervention 1 | -0.78     | (-1.25, -0.31)         | 0.413035                                 | 0.416286                                          |
| Absolute Change at 18 Months after Intervention 1     | -0.003507 | (-0.005582, -0.001432) | 0.413479                                 | 0.416986                                          |
| Relative Change (%) at 18 Months after Intervention 1 | -0.84     | (-1.34, -0.35)         | 0.413479                                 | 0.416986                                          |
| Absolute Change at 19 Months after Intervention 1     | -0.003762 | (-0.005935, -0.001589) | 0.413924                                 | 0.417686                                          |
| Relative Change (%) at 19 Months after Intervention 1 | -0.90     | (-1.42, -0.38)         | 0.413924                                 | 0.417686                                          |
| Absolute Change at 20 Months after Intervention 1     | -0.004018 | (-0.006290, -0.001745) | 0.414368                                 | 0.418386                                          |
| Relative Change (%) at 20 Months after Intervention 1 | -0.96     | (-1.50, -0.42)         | 0.414368                                 | 0.418386                                          |
| Absolute Change at 21 Months after Intervention 1     | -0.004273 | (-0.006645, -0.001901) | 0.414813                                 | 0.419085                                          |
| Relative Change (%) at 21 Months after Intervention 1 | -1.02     | (-1.58, -0.46)         | 0.414813                                 | 0.419085                                          |
| Absolute Change at 22 Months after Intervention 1     | -0.004528 | (-0.007001, -0.002055) | 0.415257                                 | 0.419785                                          |
| Relative Change (%) at 22 Months after Intervention 1 | -1.08     | (-1.66, -0.49)         | 0.415257                                 | 0.419785                                          |
| Absolute Change at 23 Months after Intervention 1     | -0.004784 | (-0.007359, -0.002208) | 0.415701                                 | 0.420485                                          |
| Relative Change (%) at 23 Months after Intervention 1 | -1.14     | (-1.75, -0.53)         | 0.415701                                 | 0.420485                                          |
| Absolute Change at 24 Months after Intervention 1     | -0.005039 | (-0.007716, -0.002361) | 0.416146                                 | 0.421185                                          |
| Relative Change (%) at 24 Months after Intervention 1 | -1.20     | (-1.83, -0.57)         | 0.416146                                 | 0.421185                                          |
| Absolute Change at 25 Months after Intervention 1     | -0.005294 | (-0.008075, -0.002513) | 0.416590                                 | 0.421884                                          |

**Table 24. Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|-----------|------------------------|---------------------|-----------------------------|
|                                                       |           |                        | (With Intervention) | Rate (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | -1.25     | (-1.91, -0.60)         | 0.416590            | 0.421884                    |
| Absolute Change at 26 Months after Intervention 1     | -0.005549 | (-0.008434, -0.002665) | 0.417035            | 0.422584                    |
| Relative Change (%) at 26 Months after Intervention 1 | -1.31     | (-1.99, -0.64)         | 0.417035            | 0.422584                    |
| Absolute Change at 27 Months after Intervention 1     | -0.005805 | (-0.008793, -0.002816) | 0.417479            | 0.423284                    |
| Absolute Change at 27 Months after Intervention 1     | -0.005805 | (-0.008793, -0.002816) | 0.417479            | 0.423284                    |
| Relative Change (%) at 27 Months after Intervention 1 | -1.37     | (-2.07, -0.67)         | 0.417479            | 0.423284                    |
| Relative Change (%) at 27 Months after Intervention 1 | -1.37     | (-2.07, -0.67)         | 0.417479            | 0.423284                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 12. Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 25. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 64)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.169209  | (0.168584, 0.169833)   | <.001               |
| Baseline trend                                                          | -0.000153 | (-0.000174, -0.000132) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000071  | (-0.000545, 0.000686)  | 0.820               |
| Trend Change (After Intervention 1)                                     | -0.000183 | (-0.000226, -0.000140) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.169199  | (0.168586, 0.169812)   | <.001               |
| Baseline trend                                                          | -0.000152 | (-0.000171, -0.000133) | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000182 | (-0.000223, -0.000141) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 26. Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated<br/>Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|---------------------------------------------------|-------------------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | -0.000182       | (-0.000223, -0.000141) | 0.162171                                          | 0.162353                                                    |
| Relative Change (%) at 1 Months after Intervention 1  | -0.11           | (-0.14, -0.09)         | 0.162171                                          | 0.162353                                                    |
| Absolute Change at 2 Months after Intervention 1      | -0.000363       | (-0.000446, -0.000281) | 0.161837                                          | 0.162200                                                    |
| Relative Change (%) at 2 Months after Intervention 1  | -0.22           | (-0.27, -0.17)         | 0.161837                                          | 0.162200                                                    |
| Absolute Change at 3 Months after Intervention 1      | -0.000545       | (-0.000668, -0.000422) | 0.161503                                          | 0.162048                                                    |
| Relative Change (%) at 3 Months after Intervention 1  | -0.34           | (-0.41, -0.26)         | 0.161503                                          | 0.162048                                                    |
| Absolute Change at 4 Months after Intervention 1      | -0.000727       | (-0.000891, -0.000562) | 0.161170                                          | 0.161896                                                    |
| Relative Change (%) at 4 Months after Intervention 1  | -0.45           | (-0.55, -0.35)         | 0.161170                                          | 0.161896                                                    |
| Absolute Change at 5 Months after Intervention 1      | -0.000908       | (-0.001114, -0.000703) | 0.160836                                          | 0.161744                                                    |
| Relative Change (%) at 5 Months after Intervention 1  | -0.56           | (-0.69, -0.44)         | 0.160836                                          | 0.161744                                                    |
| Absolute Change at 6 Months after Intervention 1      | -0.001090       | (-0.001337, -0.000843) | 0.160502                                          | 0.161592                                                    |
| Relative Change (%) at 6 Months after Intervention 1  | -0.67           | (-0.83, -0.52)         | 0.160502                                          | 0.161592                                                    |
| Absolute Change at 7 Months after Intervention 1      | -0.001271       | (-0.001559, -0.000984) | 0.160168                                          | 0.161440                                                    |
| Relative Change (%) at 7 Months after Intervention 1  | -0.79           | (-0.96, -0.61)         | 0.160168                                          | 0.161440                                                    |
| Absolute Change at 8 Months after Intervention 1      | -0.001453       | (-0.001782, -0.001124) | 0.159834                                          | 0.161288                                                    |
| Relative Change (%) at 8 Months after Intervention 1  | -0.90           | (-1.10, -0.70)         | 0.159834                                          | 0.161288                                                    |
| Absolute Change at 9 Months after Intervention 1      | -0.001635       | (-0.002005, -0.001265) | 0.159501                                          | 0.161135                                                    |
| Relative Change (%) at 9 Months after Intervention 1  | -1.01           | (-1.24, -0.79)         | 0.159501                                          | 0.161135                                                    |
| Absolute Change at 10 Months after Intervention 1     | -0.001816       | (-0.002228, -0.001405) | 0.159167                                          | 0.160983                                                    |
| Relative Change (%) at 10 Months after Intervention 1 | -1.13           | (-1.38, -0.88)         | 0.159167                                          | 0.160983                                                    |
| Absolute Change at 11 Months after Intervention 1     | -0.001998       | (-0.002451, -0.001546) | 0.158833                                          | 0.160831                                                    |
| Relative Change (%) at 11 Months after Intervention 1 | -1.24           | (-1.52, -0.97)         | 0.158833                                          | 0.160831                                                    |
| Absolute Change at 12 Months after Intervention 1     | -0.002180       | (-0.002673, -0.001686) | 0.158499                                          | 0.160679                                                    |

**Table 26. Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

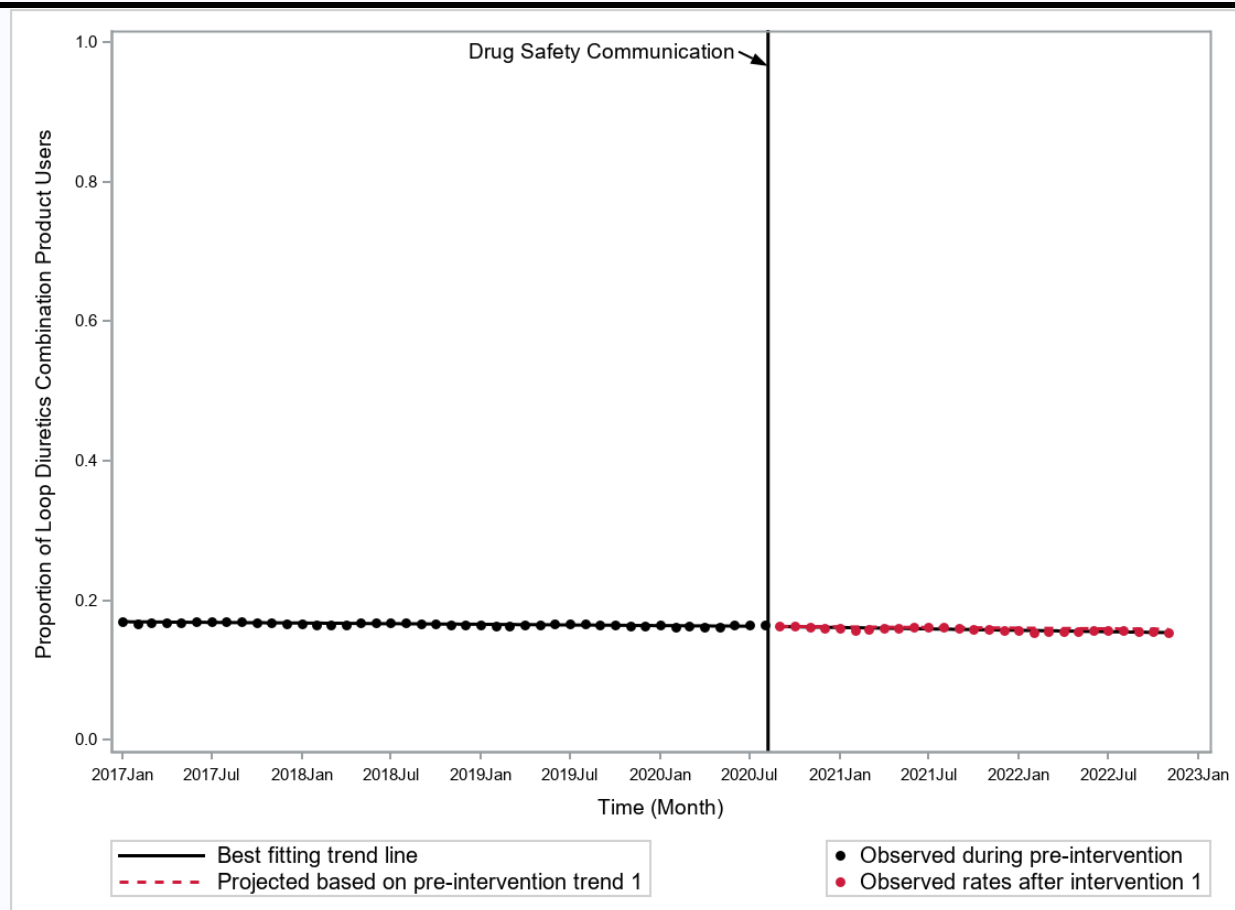
| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated<br/>Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|---------------------------------------------------|-------------------------------------------------------------|
| Relative Change (%) at 12 Months after Intervention 1 | -1.36           | (-1.66, -1.05)         | 0.158499                                          | 0.160679                                                    |
| Absolute Change at 13 Months after Intervention 1     | -0.002361       | (-0.002896, -0.001827) | 0.158165                                          | 0.160527                                                    |
| Relative Change (%) at 13 Months after Intervention 1 | -1.47           | (-1.80, -1.14)         | 0.158165                                          | 0.160527                                                    |
| Absolute Change at 14 Months after Intervention 1     | -0.002543       | (-0.003119, -0.001967) | 0.157832                                          | 0.160375                                                    |
| Relative Change (%) at 14 Months after Intervention 1 | -1.59           | (-1.94, -1.23)         | 0.157832                                          | 0.160375                                                    |
| Absolute Change at 15 Months after Intervention 1     | -0.002725       | (-0.003342, -0.002108) | 0.157498                                          | 0.160223                                                    |
| Relative Change (%) at 15 Months after Intervention 1 | -1.70           | (-2.08, -1.32)         | 0.157498                                          | 0.160223                                                    |
| Absolute Change at 16 Months after Intervention 1     | -0.002906       | (-0.003564, -0.002248) | 0.157164                                          | 0.160070                                                    |
| Relative Change (%) at 16 Months after Intervention 1 | -1.82           | (-2.22, -1.41)         | 0.157164                                          | 0.160070                                                    |
| Absolute Change at 17 Months after Intervention 1     | -0.003088       | (-0.003787, -0.002389) | 0.156830                                          | 0.159918                                                    |
| Relative Change (%) at 17 Months after Intervention 1 | -1.93           | (-2.36, -1.50)         | 0.156830                                          | 0.159918                                                    |
| Absolute Change at 18 Months after Intervention 1     | -0.003270       | (-0.004010, -0.002529) | 0.156497                                          | 0.159766                                                    |
| Relative Change (%) at 18 Months after Intervention 1 | -2.05           | (-2.50, -1.59)         | 0.156497                                          | 0.159766                                                    |
| Absolute Change at 19 Months after Intervention 1     | -0.003451       | (-0.004233, -0.002670) | 0.156163                                          | 0.159614                                                    |
| Relative Change (%) at 19 Months after Intervention 1 | -2.16           | (-2.64, -1.68)         | 0.156163                                          | 0.159614                                                    |
| Absolute Change at 20 Months after Intervention 1     | -0.003633       | (-0.004456, -0.002810) | 0.155829                                          | 0.159462                                                    |
| Relative Change (%) at 20 Months after Intervention 1 | -2.28           | (-2.78, -1.77)         | 0.155829                                          | 0.159462                                                    |
| Absolute Change at 21 Months after Intervention 1     | -0.003814       | (-0.004678, -0.002951) | 0.155495                                          | 0.159310                                                    |
| Relative Change (%) at 21 Months after Intervention 1 | -2.39           | (-2.93, -1.86)         | 0.155495                                          | 0.159310                                                    |
| Absolute Change at 22 Months after Intervention 1     | -0.003996       | (-0.004901, -0.003091) | 0.155161                                          | 0.159158                                                    |
| Relative Change (%) at 22 Months after Intervention 1 | -2.51           | (-3.07, -1.95)         | 0.155161                                          | 0.159158                                                    |
| Absolute Change at 23 Months after Intervention 1     | -0.004178       | (-0.005124, -0.003232) | 0.154828                                          | 0.159005                                                    |
| Relative Change (%) at 23 Months after Intervention 1 | -2.63           | (-3.21, -2.04)         | 0.154828                                          | 0.159005                                                    |

**Table 26. Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated<br/>Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|---------------------------------------------------|-------------------------------------------------------------|
| Absolute Change at 24 Months after Intervention 1     | -0.004359       | (-0.005347, -0.003372) | 0.154494                                          | 0.158853                                                    |
| Relative Change (%) at 24 Months after Intervention 1 | -2.74           | (-3.35, -2.14)         | 0.154494                                          | 0.158853                                                    |
| Absolute Change at 25 Months after Intervention 1     | -0.004541       | (-0.005569, -0.003513) | 0.154160                                          | 0.158701                                                    |
| Relative Change (%) at 25 Months after Intervention 1 | -2.86           | (-3.50, -2.23)         | 0.154160                                          | 0.158701                                                    |
| Absolute Change at 26 Months after Intervention 1     | -0.004723       | (-0.005792, -0.003653) | 0.153826                                          | 0.158549                                                    |
| Relative Change (%) at 26 Months after Intervention 1 | -2.98           | (-3.64, -2.32)         | 0.153826                                          | 0.158549                                                    |
| Absolute Change at 27 Months after Intervention 1     | -0.004904       | (-0.006015, -0.003794) | 0.153493                                          | 0.158397                                                    |
| Absolute Change at 27 Months after Intervention 1     | -0.004904       | (-0.006015, -0.003794) | 0.153493                                          | 0.158397                                                    |
| Relative Change (%) at 27 Months after Intervention 1 | -3.10           | (-3.78, -2.41)         | 0.153493                                          | 0.158397                                                    |
| Relative Change (%) at 27 Months after Intervention 1 | -3.10           | (-3.78, -2.41)         | 0.153493                                          | 0.158397                                                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 13. Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 27. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.047152  | (0.046925, 0.047379)   | <.001               |
| Baseline trend                                                          | 0.000205  | (0.000197, 0.000214)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000398 | (-0.000701, -0.000095) | 0.011               |
| Trend Change (After Intervention 1)                                     | 0.000079  | (0.000059, 0.000100)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.047152  | (0.046925, 0.047379)   | <.001               |
| Baseline trend                                                          | 0.000205  | (0.000197, 0.000214)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000398 | (-0.000701, -0.000095) | 0.011               |
| Trend Change (After Intervention 1)                                     | 0.000079  | (0.000059, 0.000100)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 28. Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

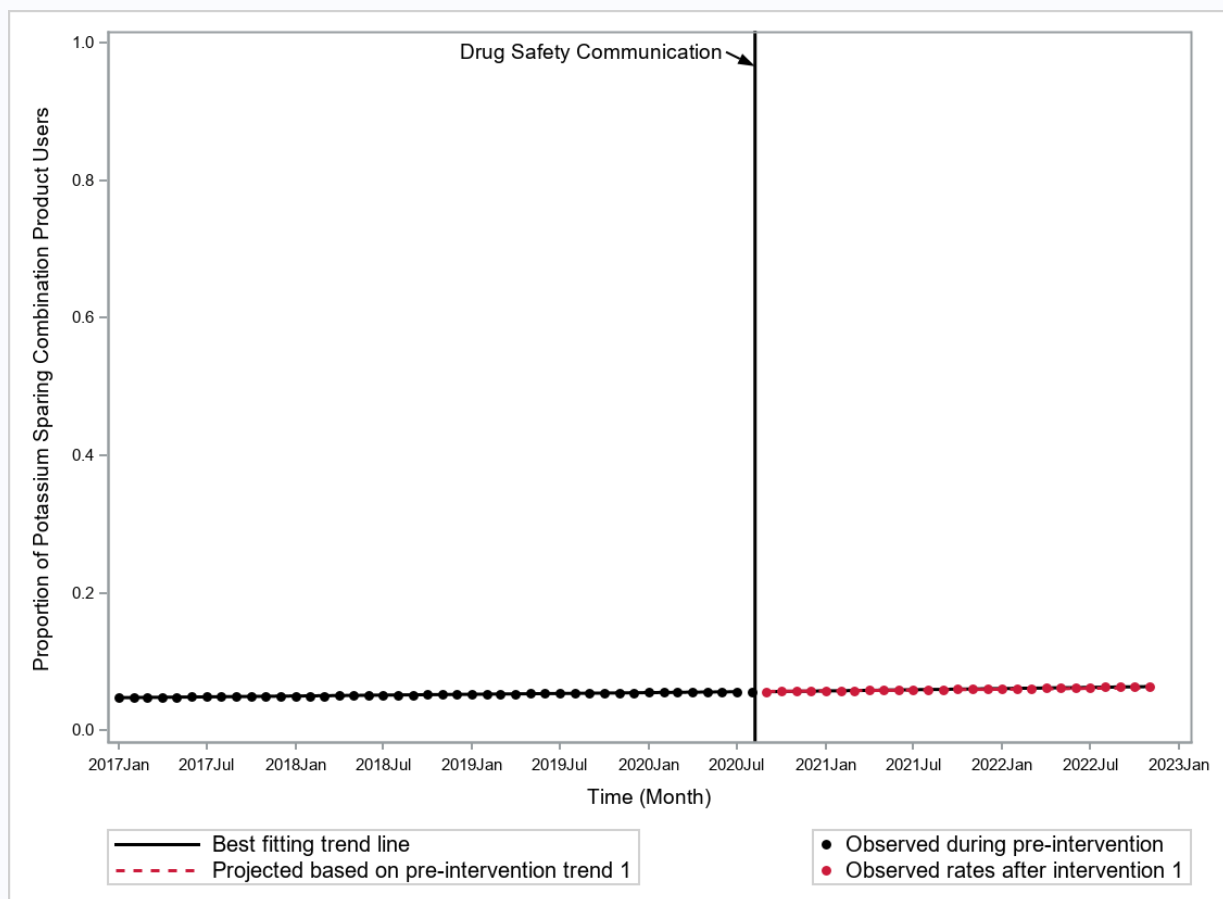
| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate (With Intervention) | Extrapolated Rate (Without Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------|------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | -0.000319 | (-0.000624, -0.000013) | 0.056061                           | 0.056380                                 |
| Relative Change (%) at 1 Months after Intervention 1  | -0.57     | (-1.11, -0.03)         | 0.056061                           | 0.056380                                 |
| Absolute Change at 2 Months after Intervention 1      | -0.000239 | (-0.000540, 0.000062)  | 0.056346                           | 0.056585                                 |
| Relative Change (%) at 2 Months after Intervention 1  | -0.42     | (-0.95, 0.11)          | 0.056346                           | 0.056585                                 |
| Absolute Change at 3 Months after Intervention 1      | -0.000160 | (-0.000458, 0.000138)  | 0.056630                           | 0.056790                                 |
| Relative Change (%) at 3 Months after Intervention 1  | -0.28     | (-0.81, 0.24)          | 0.056630                           | 0.056790                                 |
| Absolute Change at 4 Months after Intervention 1      | -0.000080 | (-0.000377, 0.000216)  | 0.056915                           | 0.056995                                 |
| Relative Change (%) at 4 Months after Intervention 1  | -0.14     | (-0.66, 0.38)          | 0.056915                           | 0.056995                                 |
| Absolute Change at 5 Months after Intervention 1      | -0.000001 | (-0.000298, 0.000296)  | 0.057200                           | 0.057200                                 |
| Relative Change (%) at 5 Months after Intervention 1  | 0.00      | (-0.52, 0.52)          | 0.057200                           | 0.057200                                 |
| Absolute Change at 6 Months after Intervention 1      | 0.000079  | (-0.000219, 0.000376)  | 0.057484                           | 0.057405                                 |
| Relative Change (%) at 6 Months after Intervention 1  | 0.14      | (-0.38, 0.66)          | 0.057484                           | 0.057405                                 |
| Absolute Change at 7 Months after Intervention 1      | 0.000158  | (-0.000142, 0.000459)  | 0.057769                           | 0.057611                                 |
| Relative Change (%) at 7 Months after Intervention 1  | 0.27      | (-0.25, 0.80)          | 0.057769                           | 0.057611                                 |
| Absolute Change at 8 Months after Intervention 1      | 0.000238  | (-0.000067, 0.000542)  | 0.058053                           | 0.057816                                 |
| Relative Change (%) at 8 Months after Intervention 1  | 0.41      | (-0.12, 0.94)          | 0.058053                           | 0.057816                                 |
| Absolute Change at 9 Months after Intervention 1      | 0.000317  | (0.000007, 0.000627)   | 0.058338                           | 0.058021                                 |
| Relative Change (%) at 9 Months after Intervention 1  | 0.55      | (0.01, 1.08)           | 0.058338                           | 0.058021                                 |
| Absolute Change at 10 Months after Intervention 1     | 0.000396  | (0.000080, 0.000712)   | 0.058622                           | 0.058226                                 |
| Relative Change (%) at 10 Months after Intervention 1 | 0.68      | (0.14, 1.23)           | 0.058622                           | 0.058226                                 |
| Absolute Change at 11 Months after Intervention 1     | 0.000476  | (0.000152, 0.000799)   | 0.058907                           | 0.058431                                 |
| Relative Change (%) at 11 Months after Intervention 1 | 0.81      | (0.26, 1.37)           | 0.058907                           | 0.058431                                 |
| Absolute Change at 12 Months after Intervention 1     | 0.000555  | (0.000223, 0.000887)   | 0.059191                           | 0.058636                                 |
| Relative Change (%) at 12 Months after Intervention 1 | 0.95      | (0.38, 1.52)           | 0.059191                           | 0.058636                                 |
| Absolute Change at 13 Months after Intervention 1     | 0.000635  | (0.000293, 0.000976)   | 0.059476                           | 0.058841                                 |
| Relative Change (%) at 13 Months after Intervention 1 | 1.08      | (0.49, 1.66)           | 0.059476                           | 0.058841                                 |
| Absolute Change at 14 Months after Intervention 1     | 0.000714  | (0.000362, 0.001066)   | 0.059760                           | 0.059046                                 |
| Relative Change (%) at 14 Months after Intervention 1 | 1.21      | (0.61, 1.81)           | 0.059760                           | 0.059046                                 |
| Absolute Change at 15 Months after Intervention 1     | 0.000794  | (0.000430, 0.001157)   | 0.060045                           | 0.059251                                 |
| Relative Change (%) at 15 Months after Intervention 1 | 1.34      | (0.72, 1.96)           | 0.060045                           | 0.059251                                 |
| Absolute Change at 16 Months after Intervention 1     | 0.000873  | (0.000498, 0.001249)   | 0.060329                           | 0.059456                                 |
| Relative Change (%) at 16 Months after Intervention 1 | 1.47      | (0.83, 2.11)           | 0.060329                           | 0.059456                                 |
| Absolute Change at 17 Months after Intervention 1     | 0.000953  | (0.000565, 0.001341)   | 0.060614                           | 0.059661                                 |
| Relative Change (%) at 17 Months after Intervention 1 | 1.60      | (0.94, 2.26)           | 0.060614                           | 0.059661                                 |
| Absolute Change at 18 Months after Intervention 1     | 0.001032  | (0.000631, 0.001433)   | 0.060898                           | 0.059866                                 |
| Relative Change (%) at 18 Months after Intervention 1 | 1.72      | (1.04, 2.40)           | 0.060898                           | 0.059866                                 |
| Absolute Change at 19 Months after Intervention 1     | 0.001112  | (0.000696, 0.001527)   | 0.061183                           | 0.060071                                 |
| Relative Change (%) at 19 Months after Intervention 1 | 1.85      | (1.15, 2.55)           | 0.061183                           | 0.060071                                 |
| Absolute Change at 20 Months after Intervention 1     | 0.001191  | (0.000761, 0.001621)   | 0.061468                           | 0.060276                                 |
| Relative Change (%) at 20 Months after Intervention 1 | 1.98      | (1.25, 2.70)           | 0.061468                           | 0.060276                                 |
| Absolute Change at 21 Months after Intervention 1     | 0.001271  | (0.000826, 0.001715)   | 0.061752                           | 0.060482                                 |
| Relative Change (%) at 21 Months after Intervention 1 | 2.10      | (1.35, 2.85)           | 0.061752                           | 0.060482                                 |
| Absolute Change at 22 Months after Intervention 1     | 0.001350  | (0.000890, 0.001810)   | 0.062037                           | 0.060687                                 |
| Relative Change (%) at 22 Months after Intervention 1 | 2.22      | (1.45, 2.99)           | 0.062037                           | 0.060687                                 |
| Absolute Change at 23 Months after Intervention 1     | 0.001429  | (0.000954, 0.001905)   | 0.062321                           | 0.060892                                 |
| Relative Change (%) at 23 Months after Intervention 1 | 2.35      | (1.55, 3.14)           | 0.062321                           | 0.060892                                 |
| Absolute Change at 24 Months after Intervention 1     | 0.001509  | (0.001018, 0.002000)   | 0.062606                           | 0.061097                                 |
| Relative Change (%) at 24 Months after Intervention 1 | 2.47      | (1.65, 3.29)           | 0.062606                           | 0.061097                                 |
| Absolute Change at 25 Months after Intervention 1     | 0.001588  | (0.001081, 0.002096)   | 0.062890                           | 0.061302                                 |

**Table 28. Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate (With Intervention) | Extrapolated Rate (Without Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------|------------------------------------------|
| Relative Change (%) at 25 Months after Intervention 1 | 2.59     | (1.75, 3.43)         | 0.062890                           | 0.061302                                 |
| Absolute Change at 26 Months after Intervention 1     | 0.001668 | (0.001144, 0.002192) | 0.063175                           | 0.061507                                 |
| Relative Change (%) at 26 Months after Intervention 1 | 2.71     | (1.84, 3.58)         | 0.063175                           | 0.061507                                 |
| Absolute Change at 27 Months after Intervention 1     | 0.001747 | (0.001207, 0.002288) | 0.063459                           | 0.061712                                 |
| Absolute Change at 27 Months after Intervention 1     | 0.001747 | (0.001207, 0.002288) | 0.063459                           | 0.061712                                 |
| Relative Change (%) at 27 Months after Intervention 1 | 2.83     | (1.94, 3.72)         | 0.063459                           | 0.061712                                 |
| Relative Change (%) at 27 Months after Intervention 1 | 2.83     | (1.94, 3.72)         | 0.063459                           | 0.061712                                 |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 14. Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 29. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 65)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.023087  | (0.022757, 0.023418)   | <.001               |
| Baseline trend                                                          | 0.000118  | (0.000107, 0.000130)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000117 | (-0.000362, 0.000128)  | 0.345               |
| Trend Change (After Intervention 1)                                     | -0.000096 | (-0.000125, -0.000067) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 66)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.023105  | (0.022752, 0.023457)   | <.001               |
| Baseline trend                                                          | 0.000117  | (0.000105, 0.000130)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000099 | (-0.000129, -0.000069) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 30. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

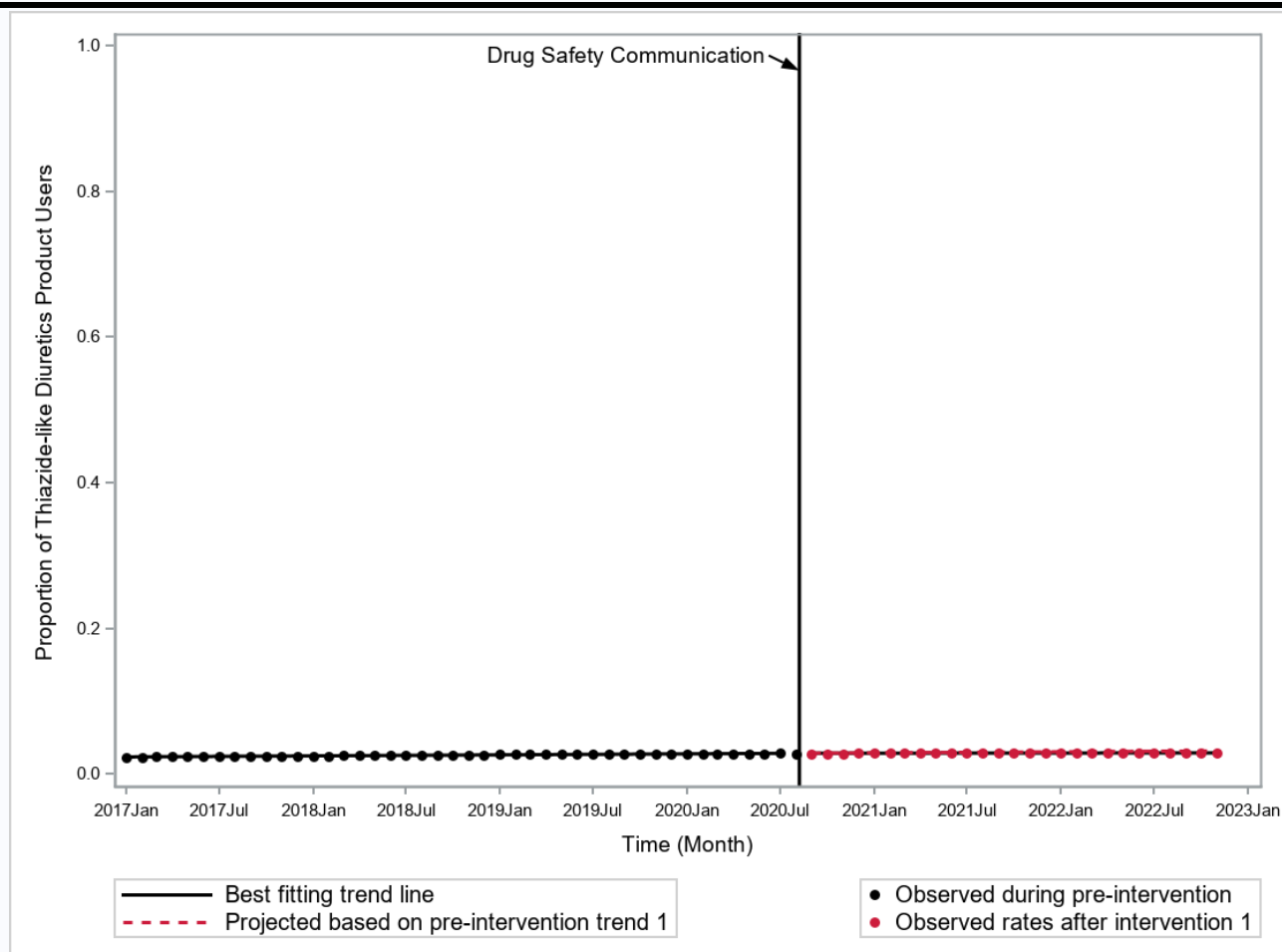
| Outcome Measure                                    | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|----------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1   | -0.000099 | (-0.000129, -0.000069) | 0.028280                                 | 0.028379                                       |
| Relative Change (%) at 1 Months after Intervention | -0.35     | (-0.45, -0.25)         | 0.028280                                 | 0.028379                                       |
| Absolute Change at 2 Months after Intervention 1   | -0.000198 | (-0.000259, -0.000138) | 0.028298                                 | 0.028496                                       |
| Relative Change (%) at 2 Months after Intervention | -0.70     | (-0.90, -0.49)         | 0.028298                                 | 0.028496                                       |
| Absolute Change at 3 Months after Intervention 1   | -0.000297 | (-0.000388, -0.000206) | 0.028316                                 | 0.028613                                       |
| Relative Change (%) at 3 Months after Intervention | -1.04     | (-1.35, -0.73)         | 0.028316                                 | 0.028613                                       |
| Absolute Change at 4 Months after Intervention 1   | -0.000397 | (-0.000518, -0.000275) | 0.028334                                 | 0.028730                                       |
| Relative Change (%) at 4 Months after Intervention | -1.38     | (-1.79, -0.97)         | 0.028334                                 | 0.028730                                       |
| Absolute Change at 5 Months after Intervention 1   | -0.000496 | (-0.000647, -0.000344) | 0.028352                                 | 0.028848                                       |
| Relative Change (%) at 5 Months after Intervention | -1.72     | (-2.23, -1.21)         | 0.028352                                 | 0.028848                                       |
| Absolute Change at 6 Months after Intervention 1   | -0.000595 | (-0.000777, -0.000413) | 0.028370                                 | 0.028965                                       |
| Relative Change (%) at 6 Months after Intervention | -2.05     | (-2.66, -1.45)         | 0.028370                                 | 0.028965                                       |
| Absolute Change at 7 Months after Intervention 1   | -0.000694 | (-0.000906, -0.000481) | 0.028388                                 | 0.029082                                       |
| Relative Change (%) at 7 Months after Intervention | -2.39     | (-3.09, -1.68)         | 0.028388                                 | 0.029082                                       |
| Absolute Change at 8 Months after Intervention 1   | -0.000793 | (-0.001036, -0.000550) | 0.028406                                 | 0.029199                                       |
| Relative Change (%) at 8 Months after Intervention | -2.72     | (-3.52, -1.92)         | 0.028406                                 | 0.029199                                       |
| Absolute Change at 9 Months after Intervention 1   | -0.000892 | (-0.001165, -0.000619) | 0.028424                                 | 0.029316                                       |
| Relative Change (%) at 9 Months after Intervention | -3.04     | (-3.94, -2.15)         | 0.028424                                 | 0.029316                                       |
| Absolute Change at 10 Months after Intervention 1  | -0.000991 | (-0.001295, -0.000688) | 0.028442                                 | 0.029434                                       |
| Relative Change (%) at 10 Months after             | -3.37     | (-4.36, -2.38)         | 0.028442                                 | 0.029434                                       |
| Absolute Change at 11 Months after Intervention 1  | -0.001090 | (-0.001424, -0.000757) | 0.028460                                 | 0.029551                                       |
| Relative Change (%) at 11 Months after             | -3.69     | (-4.77, -2.61)         | 0.028460                                 | 0.029551                                       |
| Absolute Change at 12 Months after Intervention 1  | -0.001190 | (-0.001554, -0.000825) | 0.028478                                 | 0.029668                                       |
| Relative Change (%) at 12 Months after             | -4.01     | (-5.19, -2.83)         | 0.028478                                 | 0.029668                                       |
| Absolute Change at 13 Months after Intervention 1  | -0.001289 | (-0.001683, -0.000894) | 0.028496                                 | 0.029785                                       |
| Relative Change (%) at 13 Months after             | -4.33     | (-5.59, -3.06)         | 0.028496                                 | 0.029785                                       |
| Absolute Change at 14 Months after Intervention 1  | -0.001388 | (-0.001813, -0.000963) | 0.028515                                 | 0.029902                                       |
| Relative Change (%) at 14 Months after             | -4.64     | (-6.00, -3.28)         | 0.028515                                 | 0.029902                                       |
| Absolute Change at 15 Months after Intervention 1  | -0.001487 | (-0.001942, -0.001032) | 0.028533                                 | 0.030020                                       |
| Relative Change (%) at 15 Months after             | -4.95     | (-6.40, -3.50)         | 0.028533                                 | 0.030020                                       |
| Absolute Change at 16 Months after Intervention 1  | -0.001586 | (-0.002072, -0.001101) | 0.028551                                 | 0.030137                                       |
| Relative Change (%) at 16 Months after             | -5.26     | (-6.80, -3.72)         | 0.028551                                 | 0.030137                                       |
| Absolute Change at 17 Months after Intervention 1  | -0.001685 | (-0.002201, -0.001169) | 0.028569                                 | 0.030254                                       |
| Relative Change (%) at 17 Months after             | -5.57     | (-7.20, -3.94)         | 0.028569                                 | 0.030254                                       |
| Absolute Change at 18 Months after Intervention 1  | -0.001784 | (-0.002331, -0.001238) | 0.028587                                 | 0.030371                                       |
| Relative Change (%) at 18 Months after             | -5.88     | (-7.59, -4.16)         | 0.028587                                 | 0.030371                                       |
| Absolute Change at 19 Months after Intervention 1  | -0.001883 | (-0.002460, -0.001307) | 0.028605                                 | 0.030488                                       |
| Relative Change (%) at 19 Months after             | -6.18     | (-7.98, -4.38)         | 0.028605                                 | 0.030488                                       |
| Absolute Change at 20 Months after Intervention 1  | -0.001983 | (-0.002589, -0.001376) | 0.028623                                 | 0.030606                                       |
| Relative Change (%) at 20 Months after             | -6.48     | (-8.36, -4.59)         | 0.028623                                 | 0.030606                                       |
| Absolute Change at 21 Months after Intervention 1  | -0.002082 | (-0.002719, -0.001444) | 0.028641                                 | 0.030723                                       |
| Relative Change (%) at 21 Months after             | -6.78     | (-8.75, -4.81)         | 0.028641                                 | 0.030723                                       |
| Absolute Change at 22 Months after Intervention 1  | -0.002181 | (-0.002848, -0.001513) | 0.028659                                 | 0.030840                                       |
| Relative Change (%) at 22 Months after             | -7.07     | (-9.13, -5.02)         | 0.028659                                 | 0.030840                                       |
| Absolute Change at 23 Months after Intervention 1  | -0.002280 | (-0.002978, -0.001582) | 0.028677                                 | 0.030957                                       |
| Relative Change (%) at 23 Months after             | -7.36     | (-9.50, -5.23)         | 0.028677                                 | 0.030957                                       |
| Absolute Change at 24 Months after Intervention 1  | -0.002379 | (-0.003107, -0.001651) | 0.028695                                 | 0.031074                                       |
| Relative Change (%) at 24 Months after             | -7.66     | (-9.88, -5.44)         | 0.028695                                 | 0.031074                                       |
| Absolute Change at 25 Months after Intervention 1  | -0.002478 | (-0.003237, -0.001720) | 0.028713                                 | 0.031192                                       |

**Table 30. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                   | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|---------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Relative Change (%) at 25 Months after            | -7.95     | (-10.25, -5.64)        | 0.028713                                 | 0.031192                                       |
| Absolute Change at 26 Months after Intervention 1 | -0.002577 | (-0.003366, -0.001788) | 0.028731                                 | 0.031309                                       |
| Relative Change (%) at 26 Months after            | -8.23     | (-10.62, -5.85)        | 0.028731                                 | 0.031309                                       |
| Absolute Change at 27 Months after Intervention 1 | -0.002676 | (-0.003496, -0.001857) | 0.028749                                 | 0.031426                                       |
| Absolute Change at 27 Months after Intervention 1 | -0.002676 | (-0.003496, -0.001857) | 0.028749                                 | 0.031426                                       |
| Relative Change (%) at 27 Months after            | -8.52     | (-10.98, -6.05)        | 0.028749                                 | 0.031426                                       |
| Relative Change (%) at 27 Months after            | -8.52     | (-10.98, -6.05)        | 0.028749                                 | 0.031426                                       |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Figure 15. Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

**Table 31. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 59)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.193926  | (0.193033, 0.194819)   | <.001               |
| Baseline trend                                                          | -0.000283 | (-0.000319, -0.000247) | <.001               |
| Level Change (After Intervention 1)                                     | -0.003485 | (-0.005070, -0.001900) | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000179 | (-0.000262, -0.000097) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 59)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.193926  | (0.193033, 0.194819)   | <.001               |
| Baseline trend                                                          | -0.000283 | (-0.000319, -0.000247) | <.001               |
| Level Change (After Intervention 1)                                     | -0.003485 | (-0.005070, -0.001900) | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000179 | (-0.000262, -0.000097) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 32. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|---------------------------------------------------|---------------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A             | (N/A, N/A)             | N/A                                               | N/A                                                     |
| Relative Change (%) at 1 Months after Intervention 1  | N/A             | (N/A, N/A)             | N/A                                               | N/A                                                     |
| Absolute Change at 2 Months after Intervention 1      | -0.003844       | (-0.005382, -0.002305) | 0.177069                                          | 0.180913                                                |
| Relative Change (%) at 2 Months after Intervention 1  | -2.12           | (-2.97, -1.28)         | 0.177069                                          | 0.180913                                                |
| Absolute Change at 3 Months after Intervention 1      | -0.004023       | (-0.005535, -0.002512) | 0.176607                                          | 0.180630                                                |
| Relative Change (%) at 3 Months after Intervention 1  | -2.23           | (-3.05, -1.40)         | 0.176607                                          | 0.180630                                                |
| Absolute Change at 4 Months after Intervention 1      | -0.004203       | (-0.005691, -0.002714) | 0.176145                                          | 0.180347                                                |
| Relative Change (%) at 4 Months after Intervention 1  | -2.33           | (-3.15, -1.52)         | 0.176145                                          | 0.180347                                                |
| Absolute Change at 5 Months after Intervention 1      | -0.004382       | (-0.005852, -0.002913) | 0.175682                                          | 0.180065                                                |
| Relative Change (%) at 5 Months after Intervention 1  | -2.43           | (-3.24, -1.63)         | 0.175682                                          | 0.180065                                                |
| Absolute Change at 6 Months after Intervention 1      | -0.004562       | (-0.006017, -0.003106) | 0.175220                                          | 0.179782                                                |
| Relative Change (%) at 6 Months after Intervention 1  | -2.54           | (-3.33, -1.74)         | 0.175220                                          | 0.179782                                                |
| Absolute Change at 7 Months after Intervention 1      | -0.004741       | (-0.006187, -0.003296) | 0.174758                                          | 0.179499                                                |
| Relative Change (%) at 7 Months after Intervention 1  | -2.64           | (-3.43, -1.85)         | 0.174758                                          | 0.179499                                                |
| Absolute Change at 8 Months after Intervention 1      | -0.004921       | (-0.006361, -0.003481) | 0.174295                                          | 0.179216                                                |
| Relative Change (%) at 8 Months after Intervention 1  | -2.75           | (-3.53, -1.96)         | 0.174295                                          | 0.179216                                                |
| Absolute Change at 9 Months after Intervention 1      | -0.005100       | (-0.006540, -0.003661) | 0.173833                                          | 0.178933                                                |
| Relative Change (%) at 9 Months after Intervention 1  | -2.85           | (-3.64, -2.06)         | 0.173833                                          | 0.178933                                                |
| Absolute Change at 10 Months after Intervention 1     | -0.005280       | (-0.006723, -0.003836) | 0.173370                                          | 0.178650                                                |
| Relative Change (%) at 10 Months after Intervention 1 | -2.96           | (-3.75, -2.17)         | 0.173370                                          | 0.178650                                                |
| Absolute Change at 11 Months after Intervention 1     | -0.005459       | (-0.006912, -0.004007) | 0.172908                                          | 0.178367                                                |
| Relative Change (%) at 11 Months after Intervention 1 | -3.06           | (-3.86, -2.27)         | 0.172908                                          | 0.178367                                                |
| Absolute Change at 12 Months after Intervention 1     | -0.005639       | (-0.007104, -0.004173) | 0.172446                                          | 0.178084                                                |

**Table 32. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Relative Change (%) at 12 Months after Intervention 1 | -3.17     | (-3.97, -2.36)         | 0.172446                                 | 0.178084                                       |
| Absolute Change at 13 Months after Intervention 1     | -0.005818 | (-0.007302, -0.004335) | 0.171983                                 | 0.177801                                       |
| Relative Change (%) at 13 Months after Intervention 1 | -3.27     | (-4.08, -2.46)         | 0.171983                                 | 0.177801                                       |
| Absolute Change at 14 Months after Intervention 1     | -0.005998 | (-0.007503, -0.004492) | 0.171521                                 | 0.177519                                       |
| Relative Change (%) at 14 Months after Intervention 1 | -3.38     | (-4.20, -2.55)         | 0.171521                                 | 0.177519                                       |
| Absolute Change at 15 Months after Intervention 1     | -0.006177 | (-0.007709, -0.004646) | 0.171058                                 | 0.177236                                       |
| Relative Change (%) at 15 Months after Intervention 1 | -3.49     | (-4.32, -2.65)         | 0.171058                                 | 0.177236                                       |
| Absolute Change at 16 Months after Intervention 1     | -0.006357 | (-0.007918, -0.004795) | 0.170596                                 | 0.176953                                       |
| Relative Change (%) at 16 Months after Intervention 1 | -3.59     | (-4.45, -2.74)         | 0.170596                                 | 0.176953                                       |
| Absolute Change at 17 Months after Intervention 1     | -0.006536 | (-0.008131, -0.004941) | 0.170134                                 | 0.176670                                       |
| Relative Change (%) at 17 Months after Intervention 1 | -3.70     | (-4.57, -2.83)         | 0.170134                                 | 0.176670                                       |
| Absolute Change at 18 Months after Intervention 1     | -0.006716 | (-0.008348, -0.005083) | 0.169671                                 | 0.176387                                       |
| Relative Change (%) at 18 Months after Intervention 1 | -3.81     | (-4.70, -2.91)         | 0.169671                                 | 0.176387                                       |
| Absolute Change at 19 Months after Intervention 1     | -0.006895 | (-0.008568, -0.005223) | 0.169209                                 | 0.176104                                       |
| Relative Change (%) at 19 Months after Intervention 1 | -3.92     | (-4.83, -3.00)         | 0.169209                                 | 0.176104                                       |
| Absolute Change at 20 Months after Intervention 1     | -0.007075 | (-0.008790, -0.005359) | 0.168747                                 | 0.175821                                       |
| Relative Change (%) at 20 Months after Intervention 1 | -4.02     | (-4.97, -3.08)         | 0.168747                                 | 0.175821                                       |
| Absolute Change at 21 Months after Intervention 1     | -0.007254 | (-0.009016, -0.005492) | 0.168284                                 | 0.175538                                       |
| Relative Change (%) at 21 Months after Intervention 1 | -4.13     | (-5.10, -3.16)         | 0.168284                                 | 0.175538                                       |
| Absolute Change at 22 Months after Intervention 1     | -0.007434 | (-0.009244, -0.005623) | 0.167822                                 | 0.175255                                       |
| Relative Change (%) at 22 Months after Intervention 1 | -4.24     | (-5.24, -3.24)         | 0.167822                                 | 0.175255                                       |
| Absolute Change at 23 Months after Intervention 1     | -0.007613 | (-0.009474, -0.005752) | 0.167359                                 | 0.174973                                       |
| Relative Change (%) at 23 Months after Intervention 1 | -4.35     | (-5.38, -3.32)         | 0.167359                                 | 0.174973                                       |

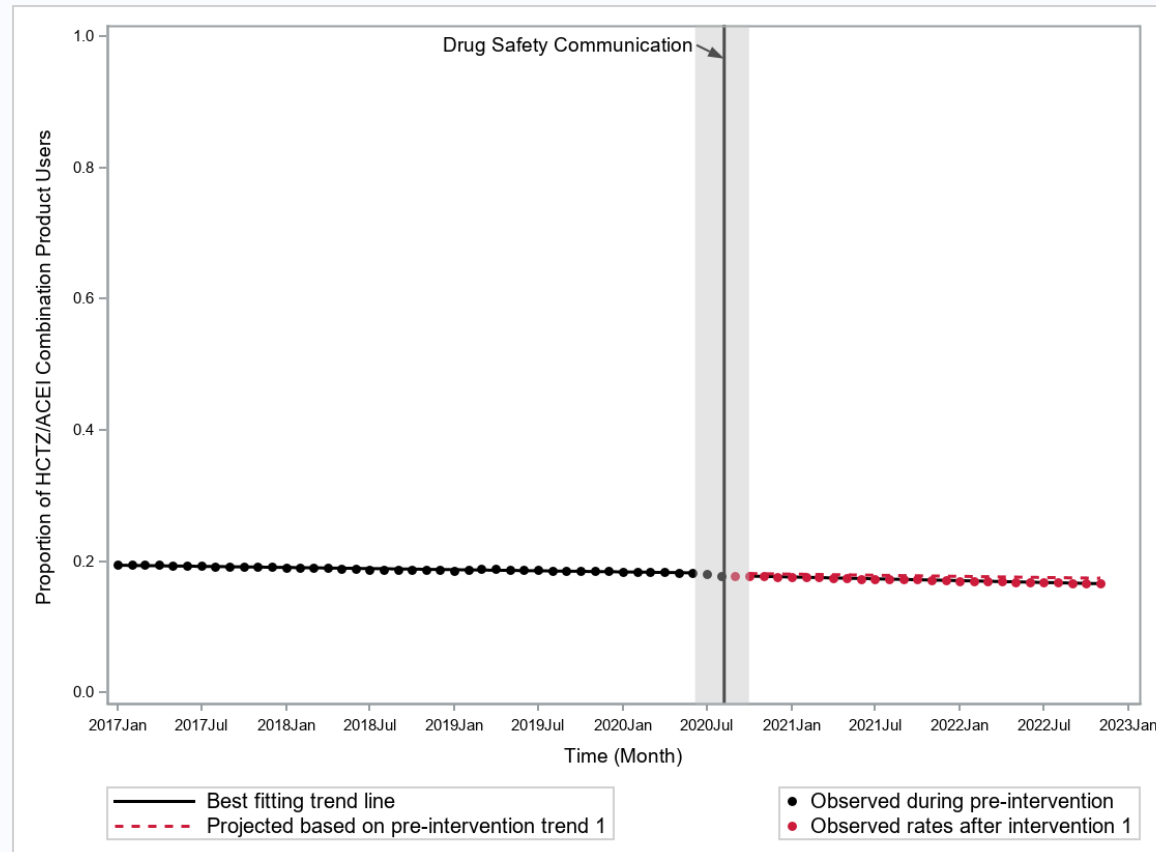
**Table 32. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>          | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|------------------------|---------------------------------------------------|---------------------------------------------------------|
| Absolute Change at 24 Months after Intervention 1     | -0.007793       | (-0.009707, -0.005878) | 0.166897                                          | 0.174690                                                |
| Relative Change (%) at 24 Months after Intervention 1 | -4.46           | (-5.52, -3.40)         | 0.166897                                          | 0.174690                                                |
| Absolute Change at 25 Months after Intervention 1     | -0.007972       | (-0.009941, -0.006003) | 0.166435                                          | 0.174407                                                |
| Relative Change (%) at 25 Months after Intervention 1 | -4.57           | (-5.66, -3.48)         | 0.166435                                          | 0.174407                                                |
| Absolute Change at 26 Months after Intervention 1     | -0.008152       | (-0.010178, -0.006125) | 0.165972                                          | 0.174124                                                |
| Relative Change (%) at 26 Months after Intervention 1 | -4.68           | (-5.80, -3.56)         | 0.165972                                          | 0.174124                                                |
| Absolute Change at 27 Months after Intervention 1     | -0.008331       | (-0.010416, -0.006246) | 0.165510                                          | 0.173841                                                |
| Relative Change (%) at 27 Months after Intervention 1 | -4.79           | (-5.95, -3.64)         | 0.165510                                          | 0.173841                                                |
| Absolute Change at 27 Months after Intervention 1     | -0.008331       | (-0.010416, -0.006246) | 0.165510                                          | 0.173841                                                |
| Relative Change (%) at 27 Months after Intervention 1 | -4.79           | (-5.95, -3.64)         | 0.165510                                          | 0.173841                                                |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 16. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 33. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.005914  | (0.005564, 0.006264)   | <.001               |
| Baseline trend                                                          | -0.000036 | (-0.000049, -0.000023) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000078  | (-0.000169, 0.000326)  | 0.530               |
| Trend Change (After Intervention 1)                                     | -0.000011 | (-0.000042, 0.000021)  | 0.503               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.005967  | (0.005671, 0.006263)   | <.001               |
| Baseline trend                                                          | -0.000038 | (-0.000045, -0.000031) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 34. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                          | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|----------------------------------------------------------|----------|----------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after<br>Intervention 1      | N/A      | (N/A, N/A)           | N/A                                      | N/A                                            |
| Relative Change (%) at 1 Months after<br>Intervention 1  | N/A      | (N/A, N/A)           | N/A                                      | N/A                                            |
| Absolute Change at 2 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004215                                 | 0.004215                                       |
| Relative Change (%) at 2 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004215                                 | 0.004215                                       |
| Absolute Change at 3 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004177                                 | 0.004177                                       |
| Relative Change (%) at 3 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004177                                 | 0.004177                                       |
| Absolute Change at 4 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004139                                 | 0.004139                                       |
| Relative Change (%) at 4 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004139                                 | 0.004139                                       |
| Absolute Change at 5 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004101                                 | 0.004101                                       |
| Relative Change (%) at 5 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004101                                 | 0.004101                                       |
| Absolute Change at 6 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004063                                 | 0.004063                                       |
| Relative Change (%) at 6 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004063                                 | 0.004063                                       |
| Absolute Change at 7 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.004024                                 | 0.004024                                       |
| Relative Change (%) at 7 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.004024                                 | 0.004024                                       |
| Absolute Change at 8 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.003986                                 | 0.003986                                       |
| Relative Change (%) at 8 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.003986                                 | 0.003986                                       |
| Absolute Change at 9 Months after<br>Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.003948                                 | 0.003948                                       |
| Relative Change (%) at 9 Months after<br>Intervention 1  | 0.00     | (0.00, 0.00)         | 0.003948                                 | 0.003948                                       |
| Absolute Change at 10 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003910                                 | 0.003910                                       |
| Relative Change (%) at 10 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003910                                 | 0.003910                                       |
| Absolute Change at 11 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003872                                 | 0.003872                                       |
| Relative Change (%) at 11 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003872                                 | 0.003872                                       |

**Table 34. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 12 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003834                                 | 0.003834                                       |
| Relative Change (%) at 12 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003834                                 | 0.003834                                       |
| Absolute Change at 13 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003796                                 | 0.003796                                       |
| Relative Change (%) at 13 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003796                                 | 0.003796                                       |
| Absolute Change at 14 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003758                                 | 0.003758                                       |
| Relative Change (%) at 14 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003758                                 | 0.003758                                       |
| Absolute Change at 15 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003720                                 | 0.003720                                       |
| Relative Change (%) at 15 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003720                                 | 0.003720                                       |
| Absolute Change at 16 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003682                                 | 0.003682                                       |
| Relative Change (%) at 16 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003682                                 | 0.003682                                       |
| Absolute Change at 17 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003644                                 | 0.003644                                       |
| Relative Change (%) at 17 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003644                                 | 0.003644                                       |
| Absolute Change at 18 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003605                                 | 0.003605                                       |
| Relative Change (%) at 18 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003605                                 | 0.003605                                       |
| Absolute Change at 19 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003567                                 | 0.003567                                       |
| Relative Change (%) at 19 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003567                                 | 0.003567                                       |
| Absolute Change at 20 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003529                                 | 0.003529                                       |
| Relative Change (%) at 20 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003529                                 | 0.003529                                       |
| Absolute Change at 21 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003491                                 | 0.003491                                       |
| Relative Change (%) at 21 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003491                                 | 0.003491                                       |
| Absolute Change at 22 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003453                                 | 0.003453                                       |
| Relative Change (%) at 22 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003453                                 | 0.003453                                       |

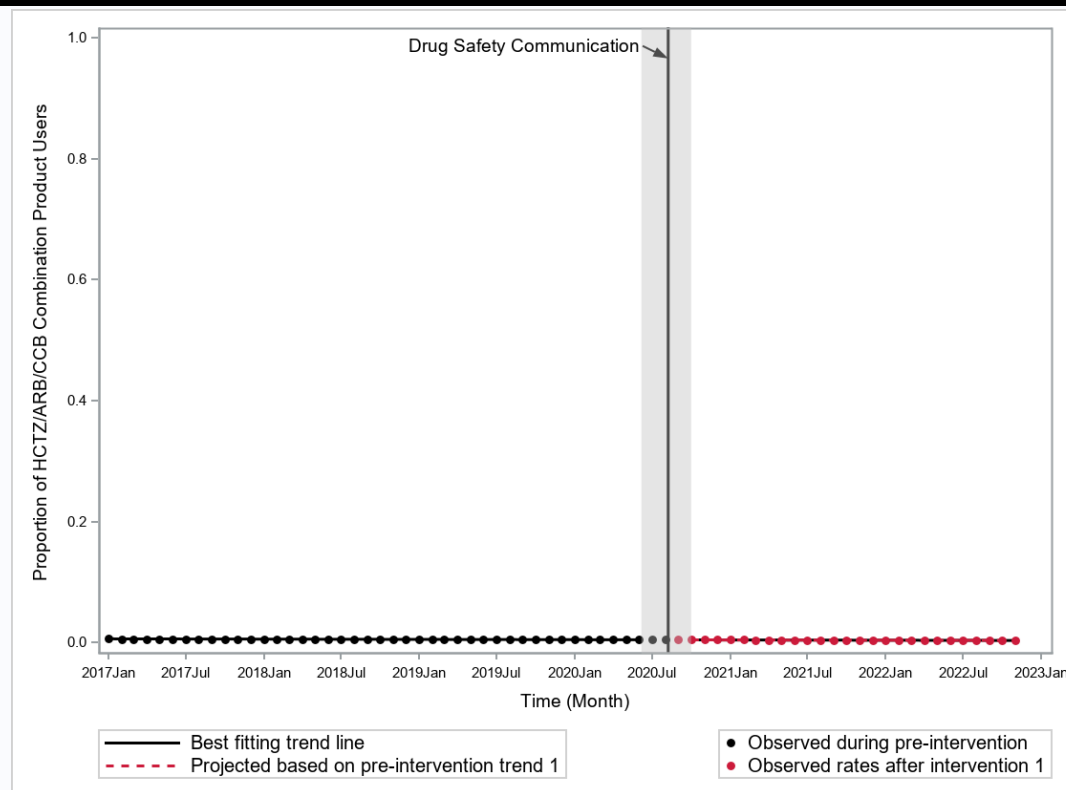
**Table 34. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                          | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|----------------------------------------------------------|----------|----------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 23 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003415                                 | 0.003415                                       |
| Relative Change (%) at 23 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003415                                 | 0.003415                                       |
| Absolute Change at 24 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003377                                 | 0.003377                                       |
| Relative Change (%) at 24 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003377                                 | 0.003377                                       |
| Absolute Change at 25 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003339                                 | 0.003339                                       |
| Relative Change (%) at 25 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003339                                 | 0.003339                                       |
| Absolute Change at 26 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003301                                 | 0.003301                                       |
| Relative Change (%) at 26 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003301                                 | 0.003301                                       |
| Absolute Change at 27 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003263                                 | 0.003263                                       |
| Absolute Change at 27 Months after<br>Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.003263                                 | 0.003263                                       |
| Relative Change (%) at 27 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003263                                 | 0.003263                                       |
| Relative Change (%) at 27 Months after<br>Intervention 1 | 0.00     | (0.00, 0.00)         | 0.003263                                 | 0.003263                                       |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 17. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 35. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 60)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.271190  | (0.257287, 0.285094)   | <.001               |
| Baseline trend                                                          | -0.001610 | (-0.002142, -0.001078) | <.001               |
| Level Change (After Intervention 1)                                     | -0.001643 | (-0.011151, 0.007866)  | 0.731               |
| Trend Change (After Intervention 1)                                     | 0.001746  | (0.000404, 0.003088)   | 0.012               |
| <b>Most Parsimonious Final Model Parameters (df = 63)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.268210  | (0.250970, 0.285450)   | <.001               |
| Baseline trend                                                          | -0.001536 | (-0.002167, -0.000904) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.001662  | (0.000124, 0.003199)   | 0.035               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 36. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |          |                      |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Relative Change (%) at 1 Months after Intervention 1  | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Absolute Change at 2 Months after Intervention 1      | 0.003323 | (0.000176, 0.006470) | 0.200889                                 | 0.197565                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 1.68     | (-0.04, 3.40)        | 0.200889                                 | 0.197565                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.004985 | (0.000265, 0.009705) | 0.201014                                 | 0.196030                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 2.54     | (-0.07, 5.15)        | 0.201014                                 | 0.196030                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.006646 | (0.000353, 0.012940) | 0.201140                                 | 0.194494                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 3.42     | (-0.10, 6.94)        | 0.201140                                 | 0.194494                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.008308 | (0.000441, 0.016175) | 0.201266                                 | 0.192958                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 4.31     | (-0.14, 8.75)        | 0.201266                                 | 0.192958                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.009970 | (0.000529, 0.019410) | 0.201392                                 | 0.191422                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 5.21     | (-0.19, 10.61)       | 0.201392                                 | 0.191422                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.011631 | (0.000618, 0.022645) | 0.201518                                 | 0.189887                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 6.13     | (-0.25, 12.50)       | 0.201518                                 | 0.189887                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.013293 | (0.000706, 0.025880) | 0.201644                                 | 0.188351                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 7.06     | (-0.31, 14.43)       | 0.201644                                 | 0.188351                                          |
| Absolute Change at 9 Months after Intervention 1      | 0.014954 | (0.000794, 0.029115) | 0.201770                                 | 0.186815                                          |
| Relative Change (%) at 9 Months after Intervention 1  | 8.00     | (-0.38, 16.39)       | 0.201770                                 | 0.186815                                          |
| Absolute Change at 10 Months after Intervention 1     | 0.016616 | (0.000882, 0.032350) | 0.201895                                 | 0.185279                                          |
| Relative Change (%) at 10 Months after Intervention 1 | 8.97     | (-0.46, 18.40)       | 0.201895                                 | 0.185279                                          |
| Absolute Change at 11 Months after Intervention 1     | 0.018278 | (0.000971, 0.035585) | 0.202021                                 | 0.183744                                          |
| Relative Change (%) at 11 Months after Intervention 1 | 9.95     | (-0.55, 20.45)       | 0.202021                                 | 0.183744                                          |
| Absolute Change at 12 Months after Intervention 1     | 0.019939 | (0.001059, 0.038820) | 0.202147                                 | 0.182208                                          |
| Relative Change (%) at 12 Months after Intervention 1 | 10.94    | (-0.65, 22.54)       | 0.202147                                 | 0.182208                                          |
| Absolute Change at 13 Months after Intervention 1     | 0.021601 | (0.001147, 0.042055) | 0.202273                                 | 0.180672                                          |
| Relative Change (%) at 13 Months after Intervention 1 | 11.96    | (-0.76, 24.67)       | 0.202273                                 | 0.180672                                          |
| Absolute Change at 14 Months after Intervention 1     | 0.023262 | (0.001235, 0.045289) | 0.202399                                 | 0.179136                                          |
| Relative Change (%) at 14 Months after Intervention 1 | 12.99    | (-0.88, 26.85)       | 0.202399                                 | 0.179136                                          |
| Absolute Change at 15 Months after Intervention 1     | 0.024924 | (0.001324, 0.048524) | 0.202525                                 | 0.177601                                          |
| Relative Change (%) at 15 Months after Intervention 1 | 14.03    | (-1.01, 29.08)       | 0.202525                                 | 0.177601                                          |
| Absolute Change at 16 Months after Intervention 1     | 0.026586 | (0.001412, 0.051759) | 0.202650                                 | 0.176065                                          |
| Relative Change (%) at 16 Months after Intervention 1 | 15.10    | (-1.15, 31.35)       | 0.202650                                 | 0.176065                                          |
| Absolute Change at 17 Months after Intervention 1     | 0.028247 | (0.001500, 0.054994) | 0.202776                                 | 0.174529                                          |
| Relative Change (%) at 17 Months after Intervention 1 | 16.18    | (-1.30, 33.67)       | 0.202776                                 | 0.174529                                          |
| Absolute Change at 18 Months after Intervention 1     | 0.029909 | (0.001588, 0.058229) | 0.202902                                 | 0.172993                                          |
| Relative Change (%) at 18 Months after Intervention 1 | 17.29    | (-1.47, 36.05)       | 0.202902                                 | 0.172993                                          |
| Absolute Change at 19 Months after Intervention 1     | 0.031570 | (0.001677, 0.061464) | 0.203028                                 | 0.171458                                          |
| Relative Change (%) at 19 Months after Intervention 1 | 18.41    | (-1.65, 38.47)       | 0.203028                                 | 0.171458                                          |
| Absolute Change at 20 Months after Intervention 1     | 0.033232 | (0.001765, 0.064699) | 0.203154                                 | 0.169922                                          |
| Relative Change (%) at 20 Months after Intervention 1 | 19.56    | (-1.84, 40.95)       | 0.203154                                 | 0.169922                                          |
| Absolute Change at 21 Months after Intervention 1     | 0.034894 | (0.001853, 0.067934) | 0.203280                                 | 0.168386                                          |
| Relative Change (%) at 21 Months after Intervention 1 | 20.72    | (-2.04, 43.49)       | 0.203280                                 | 0.168386                                          |
| Absolute Change at 22 Months after Intervention 1     | 0.036555 | (0.001941, 0.071169) | 0.203406                                 | 0.166850                                          |
| Relative Change (%) at 22 Months after Intervention 1 | 21.91    | (-2.27, 46.08)       | 0.203406                                 | 0.166850                                          |
| Absolute Change at 23 Months after Intervention 1     | 0.038217 | (0.002030, 0.074404) | 0.203531                                 | 0.165315                                          |
| Relative Change (%) at 23 Months after Intervention 1 | 23.12    | (-2.50, 48.74)       | 0.203531                                 | 0.165315                                          |
| Absolute Change at 24 Months after Intervention 1     | 0.039878 | (0.002118, 0.077639) | 0.203657                                 | 0.163779                                          |
| Relative Change (%) at 24 Months after Intervention 1 | 24.35    | (-2.76, 51.46)       | 0.203657                                 | 0.163779                                          |
| Absolute Change at 25 Months after Intervention 1     | 0.041540 | (0.002206, 0.080874) | 0.203783                                 | 0.162243                                          |

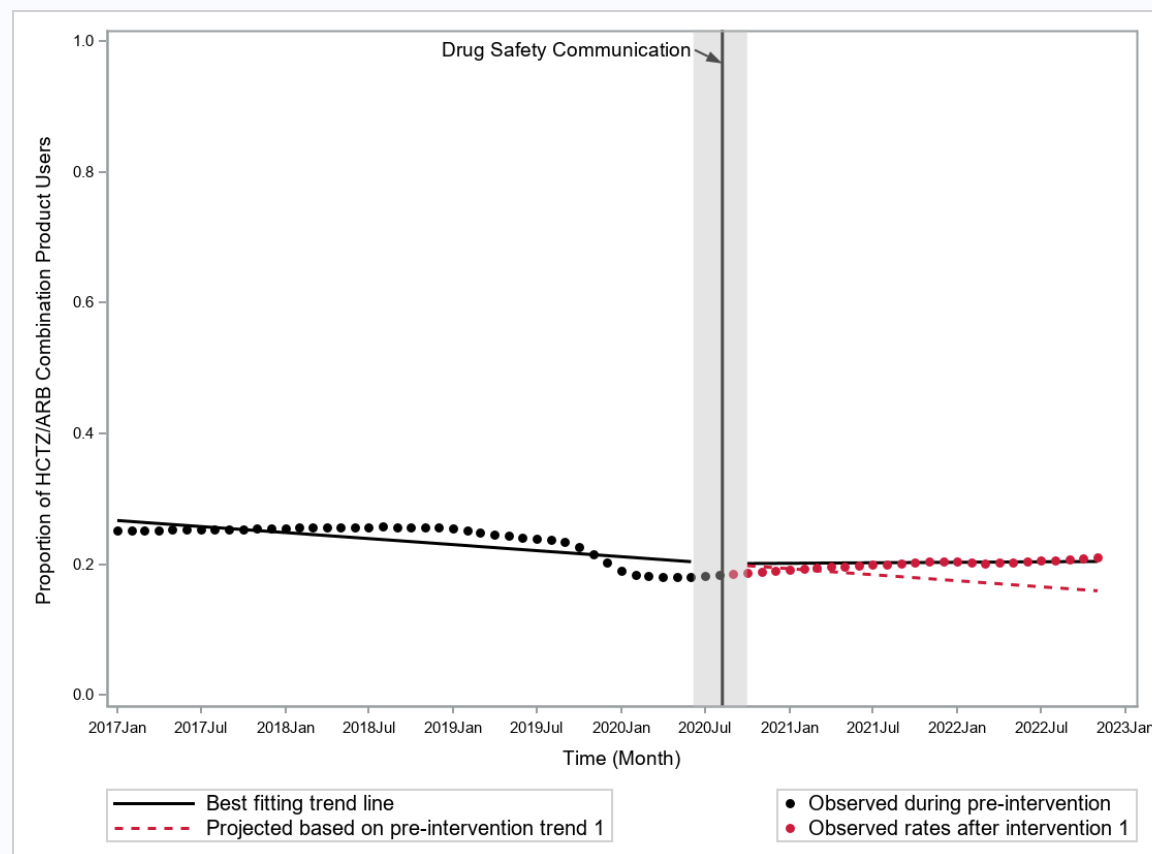
**Table 36. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|----------------------|---------------------|------------------------|
|                                                       |          |                      | (With Intervention) | (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 25.60    | (-3.03, 54.24)       | 0.203783            | 0.162243               |
| Absolute Change at 26 Months after Intervention 1     | 0.043202 | (0.002294, 0.084109) | 0.203909            | 0.160707               |
| Relative Change (%) at 26 Months after Intervention 1 | 26.88    | (-3.32, 57.08)       | 0.203909            | 0.160707               |
| Absolute Change at 27 Months after Intervention 1     | 0.044863 | (0.002383, 0.087344) | 0.204035            | 0.159172               |
| Absolute Change at 27 Months after Intervention 1     | 0.044863 | (0.002383, 0.087344) | 0.204035            | 0.159172               |
| Relative Change (%) at 27 Months after Intervention 1 | 28.19    | (-3.63, 60.00)       | 0.204035            | 0.159172               |
| Relative Change (%) at 27 Months after Intervention 1 | 28.19    | (-3.63, 60.00)       | 0.204035            | 0.159172               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 18. Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB) Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 37. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 60)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.021596  | (0.021529, 0.021663)   | <.001               |
| Baseline trend                                                          | -0.000073 | (-0.000075, -0.000070) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000149  | (0.000035, 0.000263)   | 0.011               |
| Trend Change (After Intervention 1)                                     | 0.000012  | (0.000006, 0.000018)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 60)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.021596  | (0.021529, 0.021663)   | <.001               |
| Baseline trend                                                          | -0.000073 | (-0.000075, -0.000070) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000149  | (0.000035, 0.000263)   | 0.011               |
| Trend Change (After Intervention 1)                                     | 0.000012  | (0.000006, 0.000018)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 38. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |          |                      |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Relative Change (%) at 1 Months after Intervention 1  | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Absolute Change at 2 Months after Intervention 1      | 0.000173 | (0.000054, 0.000292) | 0.018423                                 | 0.018250                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 0.95     | (0.29, 1.60)         | 0.018423                                 | 0.018250                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000185 | (0.000068, 0.000302) | 0.018362                                 | 0.018177                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 1.02     | (0.37, 1.66)         | 0.018362                                 | 0.018177                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000197 | (0.000081, 0.000312) | 0.018301                                 | 0.018104                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 1.09     | (0.44, 1.73)         | 0.018301                                 | 0.018104                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.000209 | (0.000094, 0.000323) | 0.018240                                 | 0.018032                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 1.16     | (0.52, 1.80)         | 0.018240                                 | 0.018032                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.000220 | (0.000107, 0.000334) | 0.018179                                 | 0.017959                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 1.23     | (0.59, 1.87)         | 0.018179                                 | 0.017959                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.000232 | (0.000119, 0.000346) | 0.018119                                 | 0.017886                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 1.30     | (0.66, 1.94)         | 0.018119                                 | 0.017886                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.000244 | (0.000131, 0.000358) | 0.018058                                 | 0.017814                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 1.37     | (0.73, 2.01)         | 0.018058                                 | 0.017814                                          |
| Absolute Change at 9 Months after Intervention 1      | 0.000256 | (0.000143, 0.000370) | 0.017997                                 | 0.017741                                          |
| Relative Change (%) at 9 Months after Intervention 1  | 1.44     | (0.80, 2.09)         | 0.017997                                 | 0.017741                                          |
| Absolute Change at 10 Months after Intervention 1     | 0.000268 | (0.000154, 0.000382) | 0.017936                                 | 0.017668                                          |
| Relative Change (%) at 10 Months after Intervention 1 | 1.52     | (0.87, 2.17)         | 0.017936                                 | 0.017668                                          |
| Absolute Change at 11 Months after Intervention 1     | 0.000280 | (0.000166, 0.000395) | 0.017875                                 | 0.017595                                          |
| Relative Change (%) at 11 Months after Intervention 1 | 1.59     | (0.93, 2.25)         | 0.017875                                 | 0.017595                                          |
| Absolute Change at 12 Months after Intervention 1     | 0.000292 | (0.000176, 0.000408) | 0.017815                                 | 0.017523                                          |
| Relative Change (%) at 12 Months after Intervention 1 | 1.67     | (1.00, 2.33)         | 0.017815                                 | 0.017523                                          |
| Absolute Change at 13 Months after Intervention 1     | 0.000304 | (0.000187, 0.000421) | 0.017754                                 | 0.017450                                          |
| Relative Change (%) at 13 Months after Intervention 1 | 1.74     | (1.06, 2.42)         | 0.017754                                 | 0.017450                                          |
| Absolute Change at 14 Months after Intervention 1     | 0.000316 | (0.000197, 0.000434) | 0.017693                                 | 0.017377                                          |
| Relative Change (%) at 14 Months after Intervention 1 | 1.82     | (1.13, 2.51)         | 0.017693                                 | 0.017377                                          |
| Absolute Change at 15 Months after Intervention 1     | 0.000328 | (0.000207, 0.000448) | 0.017632                                 | 0.017304                                          |
| Relative Change (%) at 15 Months after Intervention 1 | 1.89     | (1.19, 2.60)         | 0.017632                                 | 0.017304                                          |
| Absolute Change at 16 Months after Intervention 1     | 0.000340 | (0.000217, 0.000462) | 0.017571                                 | 0.017232                                          |
| Relative Change (%) at 16 Months after Intervention 1 | 1.97     | (1.25, 2.69)         | 0.017571                                 | 0.017232                                          |
| Absolute Change at 17 Months after Intervention 1     | 0.000352 | (0.000227, 0.000476) | 0.017511                                 | 0.017159                                          |
| Relative Change (%) at 17 Months after Intervention 1 | 2.05     | (1.31, 2.79)         | 0.017511                                 | 0.017159                                          |
| Absolute Change at 18 Months after Intervention 1     | 0.000364 | (0.000236, 0.000491) | 0.017450                                 | 0.017086                                          |
| Relative Change (%) at 18 Months after Intervention 1 | 2.13     | (1.37, 2.89)         | 0.017450                                 | 0.017086                                          |
| Absolute Change at 19 Months after Intervention 1     | 0.000375 | (0.000245, 0.000506) | 0.017389                                 | 0.017013                                          |
| Relative Change (%) at 19 Months after Intervention 1 | 2.21     | (1.43, 2.99)         | 0.017389                                 | 0.017013                                          |
| Absolute Change at 20 Months after Intervention 1     | 0.000387 | (0.000254, 0.000520) | 0.017328                                 | 0.016941                                          |
| Relative Change (%) at 20 Months after Intervention 1 | 2.29     | (1.49, 3.09)         | 0.017328                                 | 0.016941                                          |
| Absolute Change at 21 Months after Intervention 1     | 0.000399 | (0.000263, 0.000536) | 0.017267                                 | 0.016868                                          |
| Relative Change (%) at 21 Months after Intervention 1 | 2.37     | (1.54, 3.19)         | 0.017267                                 | 0.016868                                          |
| Absolute Change at 22 Months after Intervention 1     | 0.000411 | (0.000272, 0.000551) | 0.017206                                 | 0.016795                                          |
| Relative Change (%) at 22 Months after Intervention 1 | 2.45     | (1.60, 3.30)         | 0.017206                                 | 0.016795                                          |
| Absolute Change at 23 Months after Intervention 1     | 0.000423 | (0.000280, 0.000566) | 0.017146                                 | 0.016723                                          |
| Relative Change (%) at 23 Months after Intervention 1 | 2.53     | (1.66, 3.40)         | 0.017146                                 | 0.016723                                          |
| Absolute Change at 24 Months after Intervention 1     | 0.000435 | (0.000288, 0.000582) | 0.017085                                 | 0.016650                                          |
| Relative Change (%) at 24 Months after Intervention 1 | 2.61     | (1.71, 3.51)         | 0.017085                                 | 0.016650                                          |
| Absolute Change at 25 Months after Intervention 1     | 0.000447 | (0.000296, 0.000598) | 0.017024                                 | 0.016577                                          |

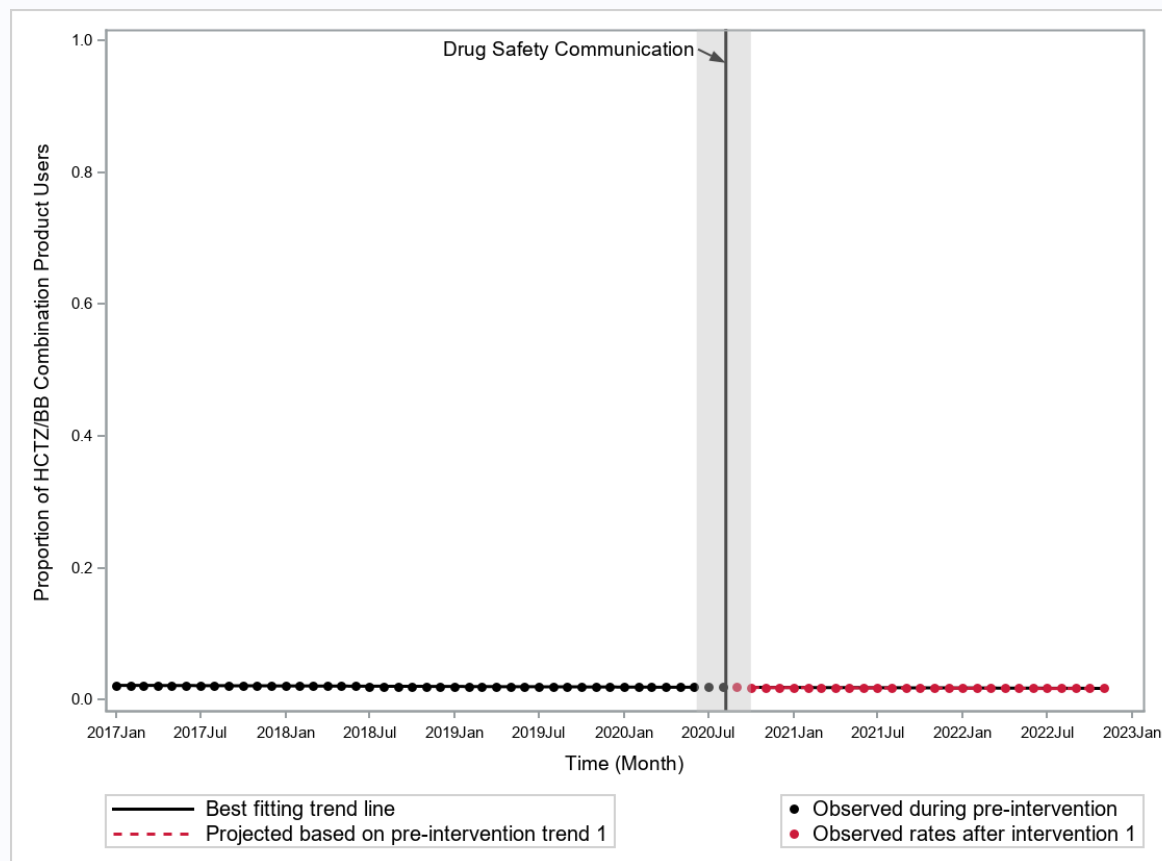
**Table 38. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|----------|----------------------|---------------------|------------------------|
|                                                       |          |                      | (With Intervention) | (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 2.70     | (1.77, 3.62)         | 0.017024            | 0.016577               |
| Absolute Change at 26 Months after Intervention 1     | 0.000459 | (0.000304, 0.000613) | 0.016963            | 0.016504               |
| Relative Change (%) at 26 Months after Intervention 1 | 2.78     | (1.82, 3.74)         | 0.016963            | 0.016504               |
| Absolute Change at 27 Months after Intervention 1     | 0.000471 | (0.000312, 0.000629) | 0.016902            | 0.016432               |
| Absolute Change at 27 Months after Intervention 1     | 0.000471 | (0.000312, 0.000629) | 0.016902            | 0.016432               |
| Relative Change (%) at 27 Months after Intervention 1 | 2.87     | (1.88, 3.85)         | 0.016902            | 0.016432               |
| Relative Change (%) at 27 Months after Intervention 1 | 2.87     | (1.88, 3.85)         | 0.016902            | 0.016432               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A: Not applicable

**Figure 19. Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 39. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.000032  | (0.000029, 0.000034)   | <.001               |
| Baseline trend                                                          | -0.000000 | (-0.000001, -0.000000) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000006 | (-0.000009, -0.000003) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000000  | (0.000000, 0.000001)   | 0.020               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.000032  | (0.000029, 0.000034)   | <.001               |
| Baseline trend                                                          | -0.000000 | (-0.000001, -0.000000) | <.001               |
| Level Change (After Intervention 1)                                     | -0.000006 | (-0.000009, -0.000003) | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000000  | (0.000000, 0.000001)   | 0.020               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 40. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|-----------|------------------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Absolute Change at 2 Months after Intervention 1      | -0.000005 | (-0.000008, -0.000003) | 0.000004                              | 0.000009                                    |
| Relative Change (%) at 2 Months after Intervention 1  | -58.48    | (-82.66, -34.30)       | 0.000004                              | 0.000009                                    |
| Absolute Change at 3 Months after Intervention 1      | -0.000005 | (-0.000008, -0.000002) | 0.000004                              | 0.000008                                    |
| Relative Change (%) at 3 Months after Intervention 1  | -58.34    | (-82.41, -34.27)       | 0.000004                              | 0.000008                                    |
| Absolute Change at 4 Months after Intervention 1      | -0.000005 | (-0.000008, -0.000002) | 0.000003                              | 0.000008                                    |
| Relative Change (%) at 4 Months after Intervention 1  | -58.19    | (-82.43, -33.95)       | 0.000003                              | 0.000008                                    |
| Absolute Change at 5 Months after Intervention 1      | -0.000004 | (-0.000007, -0.000001) | 0.000003                              | 0.000007                                    |
| Relative Change (%) at 5 Months after Intervention 1  | -58.02    | (-82.82, -33.21)       | 0.000003                              | 0.000007                                    |
| Absolute Change at 6 Months after Intervention 1      | -0.000004 | (-0.000007, -0.000001) | 0.000003                              | 0.000007                                    |
| Relative Change (%) at 6 Months after Intervention 1  | -57.82    | (-83.72, -31.91)       | 0.000003                              | 0.000007                                    |
| Absolute Change at 7 Months after Intervention 1      | -0.000004 | (-0.000007, 0.000000)  | 0.000003                              | 0.000006                                    |
| Relative Change (%) at 7 Months after Intervention 1  | -57.59    | (-85.29, -29.89)       | 0.000003                              | 0.000006                                    |
| Absolute Change at 8 Months after Intervention 1      | -0.000003 | (-0.000007, 0.000000)  | 0.000003                              | 0.000006                                    |
| Relative Change (%) at 8 Months after Intervention 1  | -57.32    | (-87.73, -26.92)       | 0.000003                              | 0.000006                                    |
| Absolute Change at 9 Months after Intervention 1      | -0.000003 | (-0.000007, 0.000001)  | 0.000002                              | 0.000005                                    |
| Relative Change (%) at 9 Months after Intervention 1  | -57.01    | (-91.24, -22.78)       | 0.000002                              | 0.000005                                    |
| Absolute Change at 10 Months after Intervention 1     | -0.000003 | (-0.000007, 0.000001)  | 0.000002                              | 0.000005                                    |
| Relative Change (%) at 10 Months after Intervention 1 | -56.63    | (-96.12, -17.14)       | 0.000002                              | 0.000005                                    |
| Absolute Change at 11 Months after Intervention 1     | -0.000003 | (-0.000007, 0.000002)  | 0.000002                              | 0.000004                                    |
| Relative Change (%) at 11 Months after Intervention 1 | -56.17    | (-102.76, -9.59)       | 0.000002                              | 0.000004                                    |
| Absolute Change at 12 Months after Intervention 1     | -0.000002 | (-0.000007, 0.000002)  | 0.000002                              | 0.000004                                    |
| Relative Change (%) at 12 Months after Intervention 1 | -55.60    | (-111.74, 0.54)        | 0.000002                              | 0.000004                                    |
| Absolute Change at 13 Months after Intervention 1     | -0.000002 | (-0.000006, 0.000003)  | 0.000002                              | 0.000004                                    |
| Relative Change (%) at 13 Months after Intervention 1 | -54.86    | (-124.00, 14.27)       | 0.000002                              | 0.000004                                    |
| Absolute Change at 14 Months after Intervention 1     | -0.000002 | (-0.000006, 0.000003)  | 0.000001                              | 0.000003                                    |
| Relative Change (%) at 14 Months after Intervention 1 | -53.89    | (-141.16, 33.39)       | 0.000001                              | 0.000003                                    |
| Absolute Change at 15 Months after Intervention 1     | -0.000001 | (-0.000006, 0.000004)  | 0.000001                              | 0.000003                                    |
| Relative Change (%) at 15 Months after Intervention 1 | -52.52    | (-166.26, 61.22)       | 0.000001                              | 0.000003                                    |
| Absolute Change at 16 Months after Intervention 1     | -0.000001 | (-0.000006, 0.000004)  | 0.000001                              | 0.000002                                    |
| Relative Change (%) at 16 Months after Intervention 1 | -50.49    | (-205.66, 104.68)      | 0.000001                              | 0.000002                                    |
| Absolute Change at 17 Months after Intervention 1     | -0.000001 | (-0.000006, 0.000005)  | 0.000001                              | 0.000002                                    |
| Relative Change (%) at 17 Months after Intervention 1 | -47.13    | (-275.11, 180.85)      | 0.000001                              | 0.000002                                    |
| Absolute Change at 18 Months after Intervention 1     | 0.000000  | (-0.000006, 0.000005)  | 0.000001                              | 0.000001                                    |
| Relative Change (%) at 18 Months after Intervention 1 | -40.53    | (-426.54, 345.48)      | 0.000001                              | 0.000001                                    |
| Absolute Change at 19 Months after Intervention 1     | 0.000000  | (-0.000006, 0.000006)  | 0.000000                              | 0.000001                                    |
| Relative Change (%) at 19 Months after Intervention 1 | -21.63    | (-969.43, 926.18)      | 0.000000                              | 0.000001                                    |
| Absolute Change at 20 Months after Intervention 1     | 0.000000  | (-0.000006, 0.000006)  | 0.000000                              | 0.000000                                    |
| Relative Change (%) at 20 Months after Intervention 1 | 520.66    | (-89772.0, 90813.27)   | 0.000000                              | 0.000000                                    |
| Absolute Change at 21 Months after Intervention 1     | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Relative Change (%) at 21 Months after Intervention 1 | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Absolute Change at 22 Months after Intervention 1     | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Relative Change (%) at 22 Months after Intervention 1 | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Absolute Change at 23 Months after Intervention 1     | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Relative Change (%) at 23 Months after Intervention 1 | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Absolute Change at 24 Months after Intervention 1     | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Relative Change (%) at 24 Months after Intervention 1 | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |
| Absolute Change at 25 Months after Intervention 1     | N/A       | (N/A, N/A)             | N/A                                   | N/A                                         |

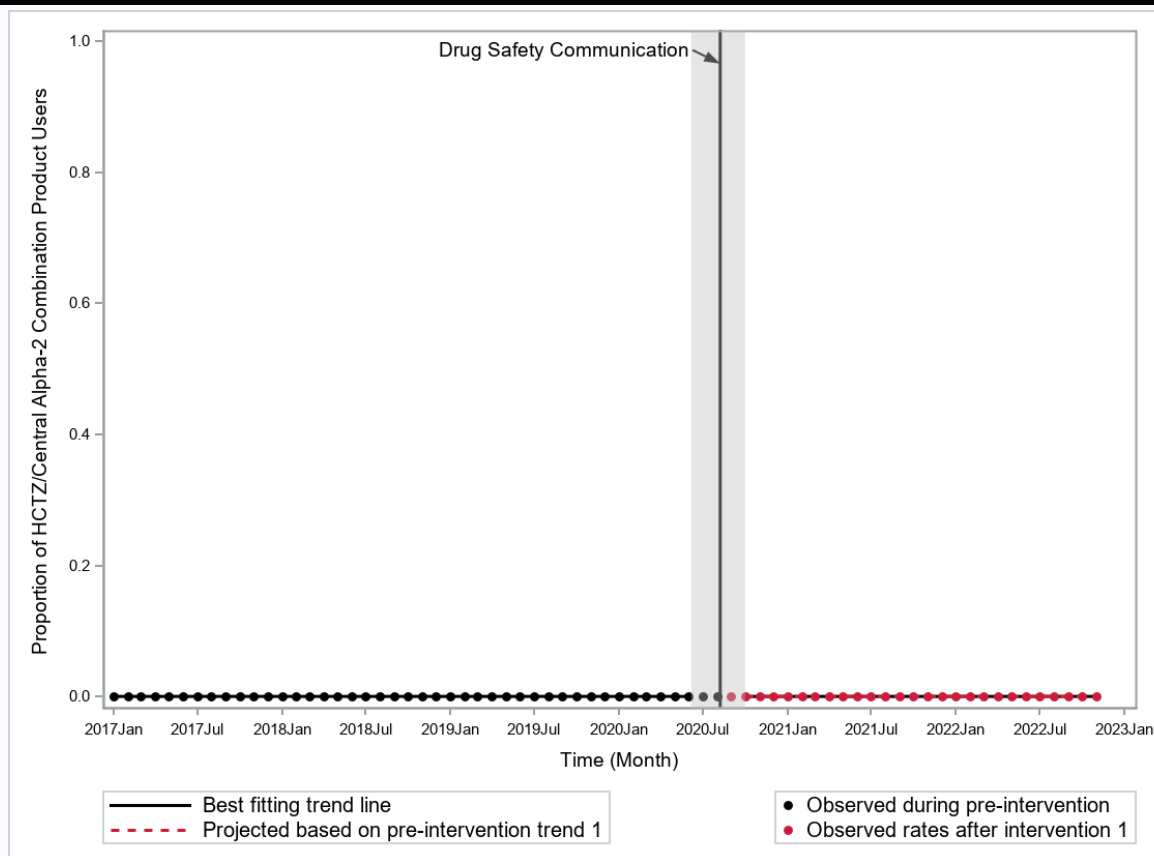
**Table 40. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI     | Predicted Rate (With Intervention) | Extrapolated Rate (Without Intervention) |
|-------------------------------------------------------|----------|------------|------------------------------------|------------------------------------------|
| Relative Change (%) at 25 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Absolute Change at 26 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Relative Change (%) at 26 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Absolute Change at 27 Months after Intervention 1     | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                | N/A                                      |
| Relative Change (%) at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                | N/A                                      |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A: Not applicable

**Figure 20. Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 41. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 60)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.362470  | (0.360700, 0.364240)   | <.001               |
| Baseline trend                                                          | -0.000666 | (-0.000737, -0.000596) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001929  | (-0.000900, 0.004759)  | 0.178               |
| Trend Change (After Intervention 1)                                     | -0.000036 | (-0.000193, 0.000120)  | 0.645               |
| <b>Most Parsimonious Final Model Parameters (df = 54)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.362059  | (0.360434, 0.363683)   | <.001               |
| Baseline trend                                                          | -0.000640 | (-0.000680, -0.000601) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 42. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|----------|----------------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A      | (N/A, N/A)           | N/A                                   | N/A                                         |
| Relative Change (%) at 1 Months after Intervention 1  | N/A      | (N/A, N/A)           | N/A                                   | N/A                                         |
| Absolute Change at 2 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.332612                              | 0.332612                                    |
| Relative Change (%) at 2 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.332612                              | 0.332612                                    |
| Absolute Change at 3 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.331972                              | 0.331972                                    |
| Relative Change (%) at 3 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.331972                              | 0.331972                                    |
| Absolute Change at 4 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.331332                              | 0.331332                                    |
| Relative Change (%) at 4 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.331332                              | 0.331332                                    |
| Absolute Change at 5 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.330691                              | 0.330691                                    |
| Relative Change (%) at 5 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.330691                              | 0.330691                                    |
| Absolute Change at 6 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.330051                              | 0.330051                                    |
| Relative Change (%) at 6 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.330051                              | 0.330051                                    |
| Absolute Change at 7 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.329411                              | 0.329411                                    |
| Relative Change (%) at 7 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.329411                              | 0.329411                                    |
| Absolute Change at 8 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.328771                              | 0.328771                                    |
| Relative Change (%) at 8 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.328771                              | 0.328771                                    |
| Absolute Change at 9 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.328131                              | 0.328131                                    |
| Relative Change (%) at 9 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.328131                              | 0.328131                                    |
| Absolute Change at 10 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.327491                              | 0.327491                                    |
| Relative Change (%) at 10 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.327491                              | 0.327491                                    |
| Absolute Change at 11 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.326851                              | 0.326851                                    |
| Relative Change (%) at 11 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.326851                              | 0.326851                                    |
| Absolute Change at 12 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.326210                              | 0.326210                                    |
| Relative Change (%) at 12 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.326210                              | 0.326210                                    |
| Absolute Change at 13 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.325570                              | 0.325570                                    |
| Relative Change (%) at 13 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.325570                              | 0.325570                                    |
| Absolute Change at 14 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.324930                              | 0.324930                                    |
| Relative Change (%) at 14 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.324930                              | 0.324930                                    |
| Absolute Change at 15 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.324290                              | 0.324290                                    |
| Relative Change (%) at 15 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.324290                              | 0.324290                                    |
| Absolute Change at 16 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.323650                              | 0.323650                                    |
| Relative Change (%) at 16 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.323650                              | 0.323650                                    |
| Absolute Change at 17 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.323010                              | 0.323010                                    |
| Relative Change (%) at 17 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.323010                              | 0.323010                                    |
| Absolute Change at 18 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.322370                              | 0.322370                                    |
| Relative Change (%) at 18 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.322370                              | 0.322370                                    |
| Absolute Change at 19 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.321729                              | 0.321729                                    |
| Relative Change (%) at 19 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.321729                              | 0.321729                                    |
| Absolute Change at 20 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.321089                              | 0.321089                                    |
| Relative Change (%) at 20 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.321089                              | 0.321089                                    |
| Absolute Change at 21 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.320449                              | 0.320449                                    |
| Relative Change (%) at 21 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.320449                              | 0.320449                                    |
| Absolute Change at 22 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.319809                              | 0.319809                                    |
| Relative Change (%) at 22 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.319809                              | 0.319809                                    |
| Absolute Change at 23 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.319169                              | 0.319169                                    |
| Relative Change (%) at 23 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.319169                              | 0.319169                                    |
| Absolute Change at 24 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.318529                              | 0.318529                                    |
| Relative Change (%) at 24 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.318529                              | 0.318529                                    |
| Absolute Change at 25 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.317889                              | 0.317889                                    |

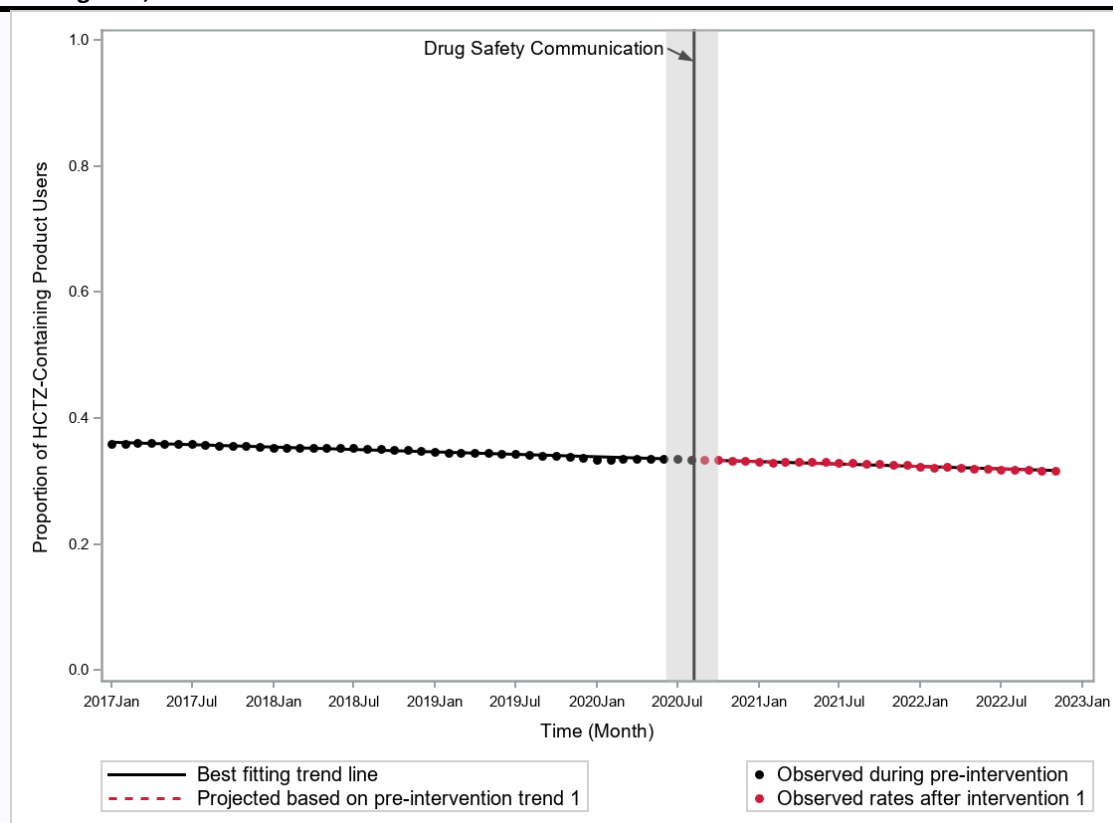
**Table 42. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-------------------------------------------------------|----------|----------------------|---------------------------------------|---------------------------------------------|
| Relative Change (%) at 25 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.317889                              | 0.317889                                    |
| Absolute Change at 26 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.317248                              | 0.317248                                    |
| Relative Change (%) at 26 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.317248                              | 0.317248                                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.316608                              | 0.316608                                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.316608                              | 0.316608                                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.316608                              | 0.316608                                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.316608                              | 0.316608                                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 21. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 43. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.942710  | (0.942285, 0.943134)   | <.001               |
| Baseline trend                                                          | -0.000436 | (-0.000453, -0.000419) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001676  | (0.000934, 0.002418)   | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000170  | (0.000132, 0.000208)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.942710  | (0.942285, 0.943134)   | <.001               |
| Baseline trend                                                          | -0.000436 | (-0.000453, -0.000419) | <.001               |
| Level Change (After Intervention 1)                                     | 0.001676  | (0.000934, 0.002418)   | <.001               |
| Trend Change (After Intervention 1)                                     | 0.000170  | (0.000132, 0.000208)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 44. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|---------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A      | (N/A, N/A)           | N/A                                   | N/A                                            |
| Relative Change (%) at 1 Months after Intervention 1  | N/A      | (N/A, N/A)           | N/A                                   | N/A                                            |
| Absolute Change at 2 Months after Intervention 1      | 0.002017 | (0.001286, 0.002748) | 0.924667                              | 0.922650                                       |
| Relative Change (%) at 2 Months after Intervention 1  | 0.22     | (0.14, 0.30)         | 0.924667                              | 0.922650                                       |
| Absolute Change at 3 Months after Intervention 1      | 0.002187 | (0.001467, 0.002908) | 0.924402                              | 0.922214                                       |
| Relative Change (%) at 3 Months after Intervention 1  | 0.24     | (0.16, 0.32)         | 0.924402                              | 0.922214                                       |
| Absolute Change at 4 Months after Intervention 1      | 0.002358 | (0.001646, 0.003069) | 0.924136                              | 0.921778                                       |
| Relative Change (%) at 4 Months after Intervention 1  | 0.26     | (0.18, 0.33)         | 0.924136                              | 0.921778                                       |
| Absolute Change at 5 Months after Intervention 1      | 0.002528 | (0.001824, 0.003232) | 0.923870                              | 0.921342                                       |
| Relative Change (%) at 5 Months after Intervention 1  | 0.27     | (0.20, 0.35)         | 0.923870                              | 0.921342                                       |
| Absolute Change at 6 Months after Intervention 1      | 0.002698 | (0.002000, 0.003397) | 0.923605                              | 0.920906                                       |
| Relative Change (%) at 6 Months after Intervention 1  | 0.29     | (0.22, 0.37)         | 0.923605                              | 0.920906                                       |
| Absolute Change at 7 Months after Intervention 1      | 0.002869 | (0.002173, 0.003564) | 0.923339                              | 0.920470                                       |
| Relative Change (%) at 7 Months after Intervention 1  | 0.31     | (0.24, 0.39)         | 0.923339                              | 0.920470                                       |
| Absolute Change at 8 Months after Intervention 1      | 0.003039 | (0.002345, 0.003733) | 0.923073                              | 0.920034                                       |
| Relative Change (%) at 8 Months after Intervention 1  | 0.33     | (0.25, 0.41)         | 0.923073                              | 0.920034                                       |
| Absolute Change at 9 Months after Intervention 1      | 0.003210 | (0.002515, 0.003904) | 0.922808                              | 0.919598                                       |
| Relative Change (%) at 9 Months after Intervention 1  | 0.35     | (0.27, 0.42)         | 0.922808                              | 0.919598                                       |
| Absolute Change at 10 Months after Intervention 1     | 0.003380 | (0.002683, 0.004077) | 0.922542                              | 0.919162                                       |
| Relative Change (%) at 10 Months after Intervention 1 | 0.37     | (0.29, 0.44)         | 0.922542                              | 0.919162                                       |
| Absolute Change at 11 Months after Intervention 1     | 0.003550 | (0.002848, 0.004252) | 0.922276                              | 0.918726                                       |
| Relative Change (%) at 11 Months after Intervention 1 | 0.39     | (0.31, 0.46)         | 0.922276                              | 0.918726                                       |
| Absolute Change at 12 Months after Intervention 1     | 0.003721 | (0.003012, 0.004429) | 0.922010                              | 0.918290                                       |
| Relative Change (%) at 12 Months after Intervention 1 | 0.41     | (0.33, 0.48)         | 0.922010                              | 0.918290                                       |
| Absolute Change at 13 Months after Intervention 1     | 0.003891 | (0.003174, 0.004608) | 0.921745                              | 0.917854                                       |
| Relative Change (%) at 13 Months after Intervention 1 | 0.42     | (0.35, 0.50)         | 0.921745                              | 0.917854                                       |
| Absolute Change at 14 Months after Intervention 1     | 0.004061 | (0.003334, 0.004789) | 0.921479                              | 0.917418                                       |
| Relative Change (%) at 14 Months after Intervention 1 | 0.44     | (0.36, 0.52)         | 0.921479                              | 0.917418                                       |
| Absolute Change at 15 Months after Intervention 1     | 0.004232 | (0.003492, 0.004971) | 0.921213                              | 0.916982                                       |
| Relative Change (%) at 15 Months after Intervention 1 | 0.46     | (0.38, 0.54)         | 0.921213                              | 0.916982                                       |
| Absolute Change at 16 Months after Intervention 1     | 0.004402 | (0.003649, 0.005155) | 0.920948                              | 0.916546                                       |
| Relative Change (%) at 16 Months after Intervention 1 | 0.48     | (0.40, 0.56)         | 0.920948                              | 0.916546                                       |
| Absolute Change at 17 Months after Intervention 1     | 0.004573 | (0.003804, 0.005341) | 0.920682                              | 0.916109                                       |
| Relative Change (%) at 17 Months after Intervention 1 | 0.50     | (0.41, 0.58)         | 0.920682                              | 0.916109                                       |
| Absolute Change at 18 Months after Intervention 1     | 0.004743 | (0.003958, 0.005528) | 0.920416                              | 0.915673                                       |
| Relative Change (%) at 18 Months after Intervention 1 | 0.52     | (0.43, 0.60)         | 0.920416                              | 0.915673                                       |
| Absolute Change at 19 Months after Intervention 1     | 0.004913 | (0.004110, 0.005717) | 0.920151                              | 0.915237                                       |
| Relative Change (%) at 19 Months after Intervention 1 | 0.54     | (0.45, 0.63)         | 0.920151                              | 0.915237                                       |
| Absolute Change at 20 Months after Intervention 1     | 0.005084 | (0.004261, 0.005907) | 0.919885                              | 0.914801                                       |
| Relative Change (%) at 20 Months after Intervention 1 | 0.56     | (0.47, 0.65)         | 0.919885                              | 0.914801                                       |
| Absolute Change at 21 Months after Intervention 1     | 0.005254 | (0.004410, 0.006098) | 0.919619                              | 0.914365                                       |
| Relative Change (%) at 21 Months after Intervention 1 | 0.57     | (0.48, 0.67)         | 0.919619                              | 0.914365                                       |
| Absolute Change at 22 Months after Intervention 1     | 0.005424 | (0.004559, 0.006290) | 0.919354                              | 0.913929                                       |
| Relative Change (%) at 22 Months after Intervention 1 | 0.59     | (0.50, 0.69)         | 0.919354                              | 0.913929                                       |
| Absolute Change at 23 Months after Intervention 1     | 0.005595 | (0.004706, 0.006483) | 0.919088                              | 0.913493                                       |
| Relative Change (%) at 23 Months after Intervention 1 | 0.61     | (0.51, 0.71)         | 0.919088                              | 0.913493                                       |
| Absolute Change at 24 Months after Intervention 1     | 0.005765 | (0.004853, 0.006677) | 0.918822                              | 0.913057                                       |
| Relative Change (%) at 24 Months after Intervention 1 | 0.63     | (0.53, 0.73)         | 0.918822                              | 0.913057                                       |
| Absolute Change at 25 Months after Intervention 1     | 0.005936 | (0.004999, 0.006872) | 0.918556                              | 0.912621                                       |
| Relative Change (%) at 25 Months after Intervention 1 | 0.65     | (0.55, 0.75)         | 0.918556                              | 0.912621                                       |
| Absolute Change at 26 Months after Intervention 1     | 0.006106 | (0.005144, 0.007068) | 0.918291                              | 0.912185                                       |

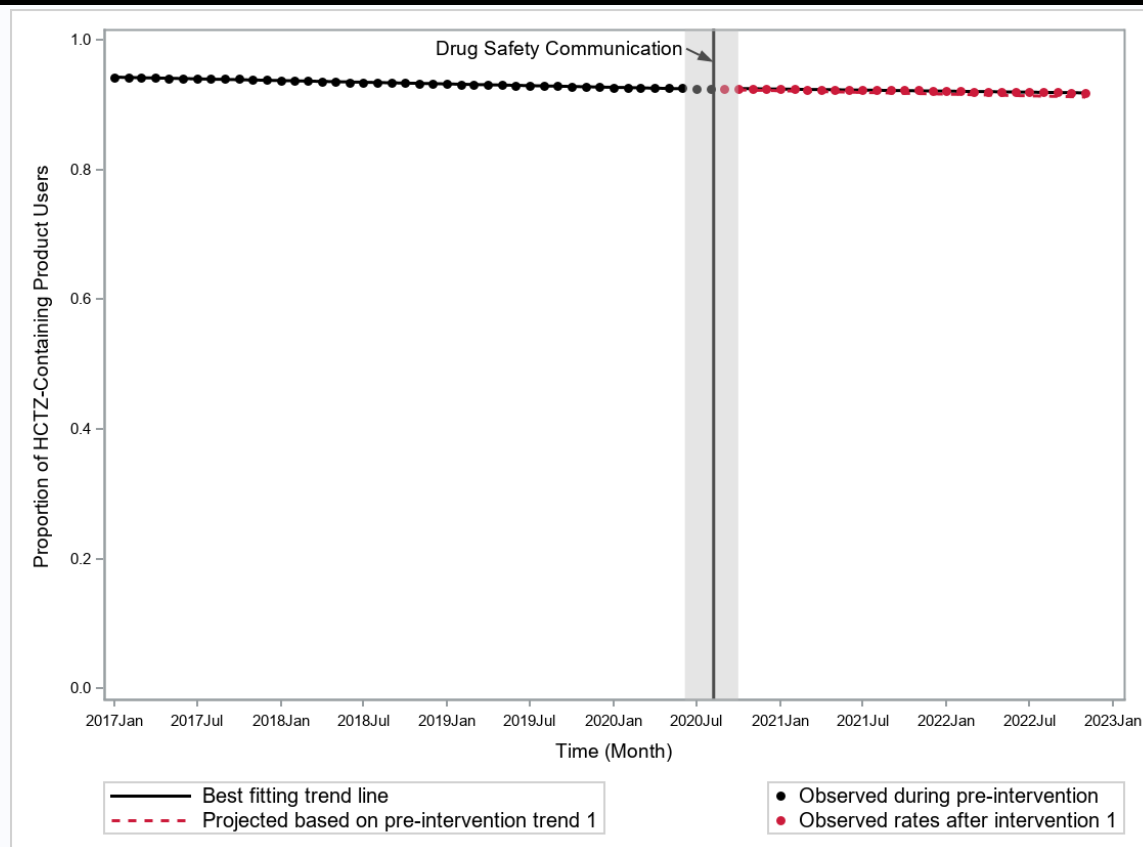
**Table 44. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|---------------------------------------|------------------------------------------------|
| Relative Change (%) at 26 Months after Intervention 1 | 0.67     | (0.56, 0.78)         | 0.918291                              | 0.912185                                       |
| Absolute Change at 27 Months after Intervention 1     | 0.006276 | (0.005288, 0.007265) | 0.918025                              | 0.911749                                       |
| Absolute Change at 27 Months after Intervention 1     | 0.006276 | (0.005288, 0.007265) | 0.918025                              | 0.911749                                       |
| Relative Change (%) at 27 Months after Intervention 1 | 0.69     | (0.58, 0.80)         | 0.918025                              | 0.911749                                       |
| Relative Change (%) at 27 Months after Intervention 1 | 0.69     | (0.58, 0.80)         | 0.918025                              | 0.911749                                       |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 22. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 45. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 63)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.000499  | (0.000452, 0.000546)   | <.001               |
| Baseline trend                                                          | -0.000007 | (-0.000009, -0.000006) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000019  | (-0.000006, 0.000044)  | 0.134               |
| Trend Change (After Intervention 1)                                     | 0.000003  | (0.000001, 0.000006)   | 0.019               |
| <b>Most Parsimonious Final Model Parameters (df = 63)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.000499  | (0.000452, 0.000546)   | <.001               |
| Baseline trend                                                          | -0.000007 | (-0.000009, -0.000006) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000019  | (-0.000006, 0.000044)  | 0.134               |
| Trend Change (After Intervention 1)                                     | 0.000003  | (0.000001, 0.000006)   | 0.019               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 46. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                    | Estimate | 95% CI                | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|----------------------------------------------------|----------|-----------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1   | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |
| Relative Change (%) at 1 Months after Intervention | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |
| Absolute Change at 2 Months after Intervention 1   | 0.000026 | (-0.000001, 0.000052) | 0.000184                                 | 0.000158                                       |
| Relative Change (%) at 2 Months after Intervention | 16.28    | (-3.78, 36.34)        | 0.000184                                 | 0.000158                                       |
| Absolute Change at 3 Months after Intervention 1   | 0.000029 | (0.000002, 0.000057)  | 0.000180                                 | 0.000151                                       |
| Relative Change (%) at 3 Months after Intervention | 19.29    | (-3.82, 42.41)        | 0.000180                                 | 0.000151                                       |
| Absolute Change at 4 Months after Intervention 1   | 0.000032 | (0.000004, 0.000061)  | 0.000176                                 | 0.000144                                       |
| Relative Change (%) at 4 Months after Intervention | 22.62    | (-4.30, 49.53)        | 0.000176                                 | 0.000144                                       |
| Absolute Change at 5 Months after Intervention 1   | 0.000036 | (0.000005, 0.000067)  | 0.000172                                 | 0.000136                                       |
| Relative Change (%) at 5 Months after Intervention | 26.30    | (-5.25, 57.85)        | 0.000172                                 | 0.000136                                       |
| Absolute Change at 6 Months after Intervention 1   | 0.000039 | (0.000006, 0.000072)  | 0.000168                                 | 0.000129                                       |
| Relative Change (%) at 6 Months after Intervention | 30.41    | (-6.75, 67.56)        | 0.000168                                 | 0.000129                                       |
| Absolute Change at 7 Months after Intervention 1   | 0.000043 | (0.000008, 0.000077)  | 0.000164                                 | 0.000121                                       |
| Relative Change (%) at 7 Months after Intervention | 35.01    | (-8.92, 78.95)        | 0.000164                                 | 0.000121                                       |
| Absolute Change at 8 Months after Intervention 1   | 0.000046 | (0.000009, 0.000083)  | 0.000160                                 | 0.000114                                       |
| Relative Change (%) at 8 Months after Intervention | 40.22    | (-11.93, 92.36)       | 0.000160                                 | 0.000114                                       |
| Absolute Change at 9 Months after Intervention 1   | 0.000049 | (0.000009, 0.000089)  | 0.000156                                 | 0.000107                                       |
| Relative Change (%) at 9 Months after Intervention | 46.14    | (-16.02, 108.31)      | 0.000156                                 | 0.000107                                       |
| Absolute Change at 10 Months after Intervention 1  | 0.000053 | (0.000010, 0.000095)  | 0.000152                                 | 0.000099                                       |
| Relative Change (%) at 10 Months after             | 52.95    | (-21.55, 127.45)      | 0.000152                                 | 0.000099                                       |
| Absolute Change at 11 Months after Intervention 1  | 0.000056 | (0.000011, 0.000101)  | 0.000148                                 | 0.000092                                       |
| Relative Change (%) at 11 Months after             | 60.86    | (-29.05, 150.76)      | 0.000148                                 | 0.000092                                       |
| Absolute Change at 12 Months after Intervention 1  | 0.000059 | (0.000011, 0.000107)  | 0.000144                                 | 0.000084                                       |
| Relative Change (%) at 12 Months after             | 70.15    | (-39.29, 179.59)      | 0.000144                                 | 0.000084                                       |
| Absolute Change at 13 Months after Intervention 1  | 0.000063 | (0.000012, 0.000113)  | 0.000140                                 | 0.000077                                       |
| Relative Change (%) at 13 Months after             | 81.23    | (-53.52, 215.97)      | 0.000140                                 | 0.000077                                       |
| Absolute Change at 14 Months after Intervention 1  | 0.000066 | (0.000012, 0.000119)  | 0.000136                                 | 0.000070                                       |
| Relative Change (%) at 14 Months after             | 94.66    | (-73.66, 262.98)      | 0.000136                                 | 0.000070                                       |
| Absolute Change at 15 Months after Intervention 1  | 0.000069 | (0.000013, 0.000126)  | 0.000132                                 | 0.000062                                       |
| Relative Change (%) at 15 Months after             | 111.28   | (-102.99, 325.54)     | 0.000132                                 | 0.000062                                       |
| Absolute Change at 16 Months after Intervention 1  | 0.000073 | (0.000013, 0.000132)  | 0.000127                                 | 0.000055                                       |
| Relative Change (%) at 16 Months after             | 132.39   | (-147.19, 411.97)     | 0.000127                                 | 0.000055                                       |
| Absolute Change at 17 Months after Intervention 1  | 0.000076 | (0.000014, 0.000138)  | 0.000123                                 | 0.000047                                       |
| Relative Change (%) at 17 Months after             | 160.08   | (-217.01, 537.17)     | 0.000123                                 | 0.000047                                       |
| Absolute Change at 18 Months after Intervention 1  | 0.000079 | (0.000014, 0.000145)  | 0.000119                                 | 0.000040                                       |
| Relative Change (%) at 18 Months after             | 198.00   | (-334.42, 730.41)     | 0.000119                                 | 0.000040                                       |
| Absolute Change at 19 Months after Intervention 1  | 0.000083 | (0.000014, 0.000151)  | 0.000115                                 | 0.000033                                       |
| Relative Change (%) at 19 Months after             | 253.10   | (-549.97, 1056.17)    | 0.000115                                 | 0.000033                                       |
| Absolute Change at 20 Months after Intervention 1  | 0.000086 | (0.000014, 0.000158)  | 0.000111                                 | 0.000025                                       |
| Relative Change (%) at 20 Months after             | 340.49   | (-1001.10, 1682.08)   | 0.000111                                 | 0.000025                                       |
| Absolute Change at 21 Months after Intervention 1  | 0.000089 | (0.000015, 0.000164)  | 0.000107                                 | 0.000018                                       |
| Relative Change (%) at 21 Months after             | 500.31   | (-2173.12, 3173.73)   | 0.000107                                 | 0.000018                                       |
| Absolute Change at 22 Months after Intervention 1  | 0.000093 | (0.000015, 0.000170)  | 0.000103                                 | 0.000010                                       |
| Relative Change (%) at 22 Months after             | 886.28   | (-6855.25, 8627.81)   | 0.000103                                 | 0.000010                                       |
| Absolute Change at 23 Months after Intervention 1  | 0.000096 | (0.000015, 0.000177)  | 0.000099                                 | 0.000003                                       |
| Relative Change (%) at 23 Months after             | 3139.82  | (-86494.7, 92774.29)  | 0.000099                                 | 0.000003                                       |
| Absolute Change at 24 Months after Intervention 1  | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |
| Relative Change (%) at 24 Months after             | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |
| Absolute Change at 25 Months after Intervention 1  | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |
| Relative Change (%) at 25 Months after             | N/A      | (N/A, N/A)            | N/A                                      | N/A                                            |

**Table 46. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                   | Estimate | 95% CI     | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|---------------------------------------------------|----------|------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 26 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |
| Relative Change (%) at 26 Months after            | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |
| Absolute Change at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |
| Absolute Change at 27 Months after Intervention 1 | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |
| Relative Change (%) at 27 Months after            | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |
| Relative Change (%) at 27 Months after            | N/A      | (N/A, N/A) | N/A                                      | N/A                                            |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 23. Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 47. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.353199  | (0.337709, 0.368691)   | <.001               |
| Baseline trend                                                          | 0.002048  | (0.001471, 0.002624)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.005397  | (-0.005816, 0.016609)  | 0.340               |
| Trend Change (After Intervention 1)                                     | -0.002058 | (-0.003446, -0.000670) | 0.004               |
| <b>Most Parsimonious Final Model Parameters (df = 63)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.352586  | (0.335982, 0.369189)   | <.001               |
| Baseline trend                                                          | 0.002112  | (0.001508, 0.002716)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.001976 | (-0.003452, -0.000501) | 0.009               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 48. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|-----------|------------------------|---------------------|------------------------|
|                                                       |           |                        | (With Intervention) | (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                 | N/A                    |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                 | N/A                    |
| Absolute Change at 2 Months after Intervention 1      | -0.003953 | (-0.006904, -0.001002) | 0.445782            | 0.449735               |
| Relative Change (%) at 2 Months after Intervention 1  | -0.88     | (-1.51, -0.25)         | 0.445782            | 0.449735               |
| Absolute Change at 3 Months after Intervention 1      | -0.005929 | (-0.010356, -0.001503) | 0.445917            | 0.451847               |
| Relative Change (%) at 3 Months after Intervention 1  | -1.31     | (-2.25, -0.37)         | 0.445917            | 0.451847               |
| Absolute Change at 4 Months after Intervention 1      | -0.007906 | (-0.013808, -0.002004) | 0.446053            | 0.453959               |
| Relative Change (%) at 4 Months after Intervention 1  | -1.74     | (-2.99, -0.50)         | 0.446053            | 0.453959               |
| Absolute Change at 5 Months after Intervention 1      | -0.009882 | (-0.017259, -0.002505) | 0.446188            | 0.456071               |
| Relative Change (%) at 5 Months after Intervention 1  | -2.17     | (-3.71, -0.62)         | 0.446188            | 0.456071               |
| Absolute Change at 6 Months after Intervention 1      | -0.011859 | (-0.020711, -0.003007) | 0.446324            | 0.458183               |
| Relative Change (%) at 6 Months after Intervention 1  | -2.59     | (-4.43, -0.75)         | 0.446324            | 0.458183               |
| Absolute Change at 7 Months after Intervention 1      | -0.013835 | (-0.024163, -0.003508) | 0.446459            | 0.460295               |
| Relative Change (%) at 7 Months after Intervention 1  | -3.01     | (-5.14, -0.87)         | 0.446459            | 0.460295               |
| Absolute Change at 8 Months after Intervention 1      | -0.015812 | (-0.027615, -0.004009) | 0.446595            | 0.462407               |
| Relative Change (%) at 8 Months after Intervention 1  | -3.42     | (-5.85, -0.99)         | 0.446595            | 0.462407               |
| Absolute Change at 9 Months after Intervention 1      | -0.017788 | (-0.031067, -0.004510) | 0.446730            | 0.464519               |
| Relative Change (%) at 9 Months after Intervention 1  | -3.83     | (-6.55, -1.11)         | 0.446730            | 0.464519               |
| Absolute Change at 10 Months after Intervention 1     | -0.019765 | (-0.034519, -0.005011) | 0.446866            | 0.466631               |
| Relative Change (%) at 10 Months after Intervention 1 | -4.24     | (-7.24, -1.23)         | 0.446866            | 0.466631               |
| Absolute Change at 11 Months after Intervention 1     | -0.021741 | (-0.037971, -0.005512) | 0.447001            | 0.468742               |
| Relative Change (%) at 11 Months after Intervention 1 | -4.64     | (-7.92, -1.36)         | 0.447001            | 0.468742               |
| Absolute Change at 12 Months after Intervention 1     | -0.023718 | (-0.041423, -0.006013) | 0.447137            | 0.470854               |
| Relative Change (%) at 12 Months after Intervention 1 | -5.04     | (-8.60, -1.48)         | 0.447137            | 0.470854               |
| Absolute Change at 13 Months after Intervention 1     | -0.025694 | (-0.044874, -0.006514) | 0.447272            | 0.472966               |
| Relative Change (%) at 13 Months after Intervention 1 | -5.43     | (-9.27, -1.60)         | 0.447272            | 0.472966               |
| Absolute Change at 14 Months after Intervention 1     | -0.027671 | (-0.048326, -0.007015) | 0.447407            | 0.475078               |
| Relative Change (%) at 14 Months after Intervention 1 | -5.82     | (-9.93, -1.72)         | 0.447407            | 0.475078               |
| Absolute Change at 15 Months after Intervention 1     | -0.029647 | (-0.051778, -0.007516) | 0.447543            | 0.477190               |
| Relative Change (%) at 15 Months after Intervention 1 | -6.21     | (-10.59, -1.84)        | 0.447543            | 0.477190               |
| Absolute Change at 16 Months after Intervention 1     | -0.031624 | (-0.055230, -0.008018) | 0.447678            | 0.479302               |
| Relative Change (%) at 16 Months after Intervention 1 | -6.60     | (-11.24, -1.96)        | 0.447678            | 0.479302               |
| Absolute Change at 17 Months after Intervention 1     | -0.033600 | (-0.058682, -0.008519) | 0.447814            | 0.481414               |
| Relative Change (%) at 17 Months after Intervention 1 | -6.98     | (-11.88, -2.08)        | 0.447814            | 0.481414               |
| Absolute Change at 18 Months after Intervention 1     | -0.035577 | (-0.062134, -0.009020) | 0.447949            | 0.483526               |
| Relative Change (%) at 18 Months after Intervention 1 | -7.36     | (-12.52, -2.20)        | 0.447949            | 0.483526               |
| Absolute Change at 19 Months after Intervention 1     | -0.037553 | (-0.065586, -0.009521) | 0.448085            | 0.485638               |
| Relative Change (%) at 19 Months after Intervention 1 | -7.73     | (-13.15, -2.31)        | 0.448085            | 0.485638               |
| Absolute Change at 20 Months after Intervention 1     | -0.039530 | (-0.069038, -0.010022) | 0.448220            | 0.487750               |
| Relative Change (%) at 20 Months after Intervention 1 | -8.10     | (-13.78, -2.43)        | 0.448220            | 0.487750               |
| Absolute Change at 21 Months after Intervention 1     | -0.041506 | (-0.072489, -0.010523) | 0.448356            | 0.489862               |
| Relative Change (%) at 21 Months after Intervention 1 | -8.47     | (-14.40, -2.55)        | 0.448356            | 0.489862               |
| Absolute Change at 22 Months after Intervention 1     | -0.043483 | (-0.075941, -0.011024) | 0.448491            | 0.491974               |
| Relative Change (%) at 22 Months after Intervention 1 | -8.84     | (-15.01, -2.67)        | 0.448491            | 0.491974               |
| Absolute Change at 23 Months after Intervention 1     | -0.045459 | (-0.079393, -0.011525) | 0.448627            | 0.494086               |
| Relative Change (%) at 23 Months after Intervention 1 | -9.20     | (-15.62, -2.78)        | 0.448627            | 0.494086               |
| Absolute Change at 24 Months after Intervention 1     | -0.047436 | (-0.082845, -0.012026) | 0.448762            | 0.496198               |
| Relative Change (%) at 24 Months after Intervention 1 | -9.56     | (-16.22, -2.90)        | 0.448762            | 0.496198               |

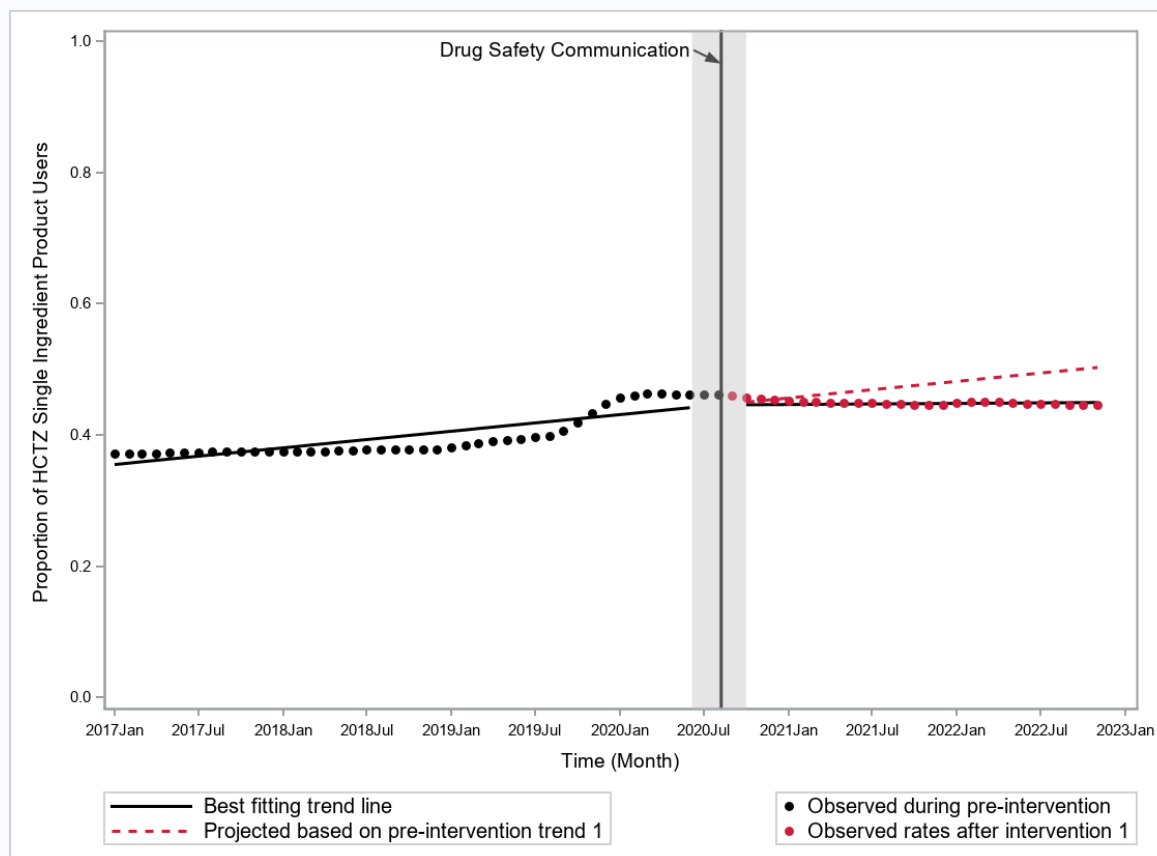
**Table 48. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|-----------|------------------------|---------------------|-----------------------------|
|                                                       |           |                        | (With Intervention) | Rate (Without Intervention) |
| Absolute Change at 25 Months after Intervention 1     | -0.049412 | (-0.086297, -0.012527) | 0.448897            | 0.498310                    |
| Relative Change (%) at 25 Months after Intervention 1 | -9.92     | (-16.82, -3.02)        | 0.448897            | 0.498310                    |
| Absolute Change at 26 Months after Intervention 1     | -0.051389 | (-0.089749, -0.013029) | 0.449033            | 0.500422                    |
| Relative Change (%) at 26 Months after Intervention 1 | -10.27    | (-17.41, -3.13)        | 0.449033            | 0.500422                    |
| Absolute Change at 27 Months after Intervention 1     | -0.053365 | (-0.093201, -0.013530) | 0.449168            | 0.502534                    |
| Absolute Change at 27 Months after Intervention 1     | -0.053365 | (-0.093201, -0.013530) | 0.449168            | 0.502534                    |
| Relative Change (%) at 27 Months after Intervention 1 | -10.62    | (-17.99, -3.25)        | 0.449168            | 0.502534                    |
| Relative Change (%) at 27 Months after Intervention 1 | -10.62    | (-17.99, -3.25)        | 0.449168            | 0.502534                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A: Not applicable

**Figure 24. Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 49. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 63)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.107664  | (0.106575, 0.108752)   | <.001               |
| Baseline trend                                                          | -0.000341 | (-0.000376, -0.000307) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000408  | (-0.000242, 0.001058)  | 0.214               |
| Trend Change (After Intervention 1)                                     | 0.000022  | (-0.000047, 0.000091)  | 0.526               |
| <b>Most Parsimonious Final Model Parameters (df = 65)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.107612  | (0.106336, 0.108888)   | <.001               |
| Baseline trend                                                          | -0.000328 | (-0.000353, -0.000303) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 50. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate<br>(With<br>Intervention) | Extrapolated<br>Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|----------|----------------------|------------------------------------------|---------------------------------------------------|
|                                                       |          |                      |                                          |                                                   |
| Absolute Change at 1 Months after Intervention 1      | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Relative Change (%) at 1 Months after Intervention 1  | N/A      | (N/A, N/A)           | N/A                                      | N/A                                               |
| Absolute Change at 2 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.092527                                 | 0.092527                                          |
| Relative Change (%) at 2 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.092527                                 | 0.092527                                          |
| Absolute Change at 3 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.092199                                 | 0.092199                                          |
| Relative Change (%) at 3 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.092199                                 | 0.092199                                          |
| Absolute Change at 4 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091871                                 | 0.091871                                          |
| Relative Change (%) at 4 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091871                                 | 0.091871                                          |
| Absolute Change at 5 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091543                                 | 0.091543                                          |
| Relative Change (%) at 5 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091543                                 | 0.091543                                          |
| Absolute Change at 6 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.091215                                 | 0.091215                                          |
| Relative Change (%) at 6 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.091215                                 | 0.091215                                          |
| Absolute Change at 7 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090887                                 | 0.090887                                          |
| Relative Change (%) at 7 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090887                                 | 0.090887                                          |
| Absolute Change at 8 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090559                                 | 0.090559                                          |
| Relative Change (%) at 8 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090559                                 | 0.090559                                          |
| Absolute Change at 9 Months after Intervention 1      | 0.000000 | (0.000000, 0.000000) | 0.090231                                 | 0.090231                                          |
| Relative Change (%) at 9 Months after Intervention 1  | 0.00     | (0.00, 0.00)         | 0.090231                                 | 0.090231                                          |
| Absolute Change at 10 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089903                                 | 0.089903                                          |
| Relative Change (%) at 10 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089903                                 | 0.089903                                          |
| Absolute Change at 11 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089575                                 | 0.089575                                          |
| Relative Change (%) at 11 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089575                                 | 0.089575                                          |
| Absolute Change at 12 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.089247                                 | 0.089247                                          |
| Relative Change (%) at 12 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.089247                                 | 0.089247                                          |
| Absolute Change at 13 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088919                                 | 0.088919                                          |
| Relative Change (%) at 13 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088919                                 | 0.088919                                          |
| Absolute Change at 14 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088591                                 | 0.088591                                          |
| Relative Change (%) at 14 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088591                                 | 0.088591                                          |
| Absolute Change at 15 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.088263                                 | 0.088263                                          |
| Relative Change (%) at 15 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.088263                                 | 0.088263                                          |
| Absolute Change at 16 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087936                                 | 0.087936                                          |
| Relative Change (%) at 16 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087936                                 | 0.087936                                          |
| Absolute Change at 17 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087608                                 | 0.087608                                          |
| Relative Change (%) at 17 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087608                                 | 0.087608                                          |
| Absolute Change at 18 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.087280                                 | 0.087280                                          |
| Relative Change (%) at 18 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.087280                                 | 0.087280                                          |
| Absolute Change at 19 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086952                                 | 0.086952                                          |
| Relative Change (%) at 19 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086952                                 | 0.086952                                          |
| Absolute Change at 20 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086624                                 | 0.086624                                          |
| Relative Change (%) at 20 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086624                                 | 0.086624                                          |
| Absolute Change at 21 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.086296                                 | 0.086296                                          |
| Relative Change (%) at 21 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.086296                                 | 0.086296                                          |
| Absolute Change at 22 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085968                                 | 0.085968                                          |
| Relative Change (%) at 22 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085968                                 | 0.085968                                          |
| Absolute Change at 23 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085640                                 | 0.085640                                          |
| Relative Change (%) at 23 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085640                                 | 0.085640                                          |
| Absolute Change at 24 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.085312                                 | 0.085312                                          |
| Relative Change (%) at 24 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.085312                                 | 0.085312                                          |
| Absolute Change at 25 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084984                                 | 0.084984                                          |

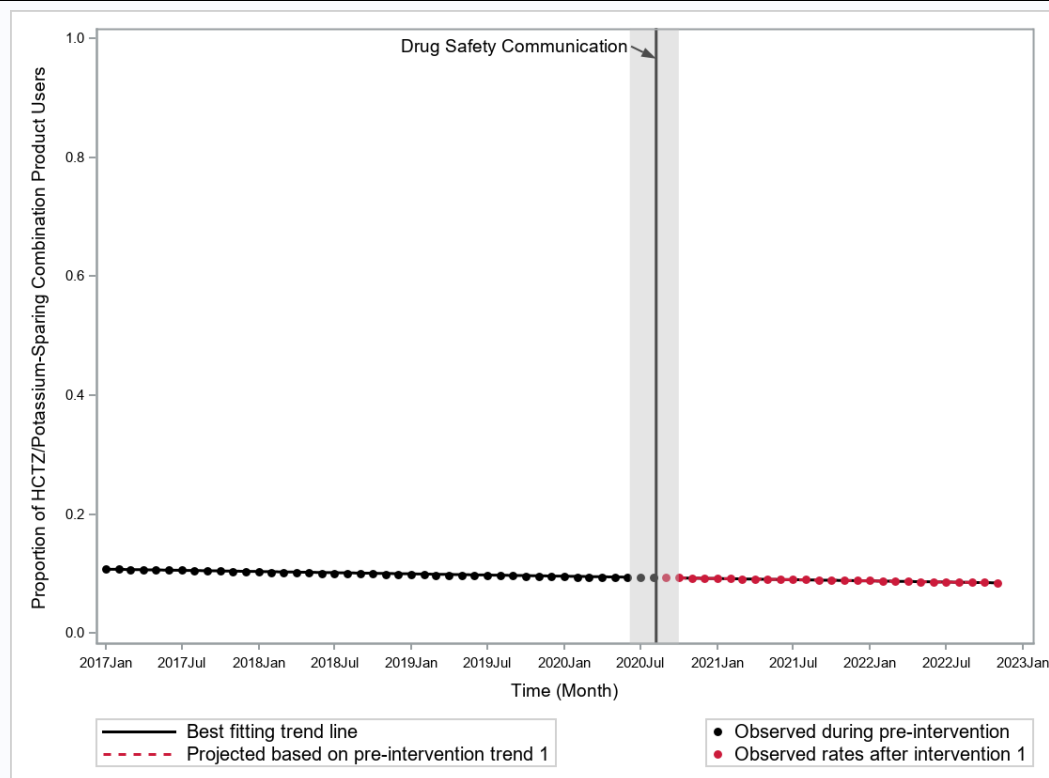
**Table 50. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate | 95% CI               | Predicted Rate      | Extrapolated                |
|-------------------------------------------------------|----------|----------------------|---------------------|-----------------------------|
|                                                       |          |                      | (With Intervention) | Rate (Without Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084984            | 0.084984                    |
| Absolute Change at 26 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084656            | 0.084656                    |
| Relative Change (%) at 26 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084656            | 0.084656                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084328            | 0.084328                    |
| Absolute Change at 27 Months after Intervention 1     | 0.000000 | (0.000000, 0.000000) | 0.084328            | 0.084328                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084328            | 0.084328                    |
| Relative Change (%) at 27 Months after Intervention 1 | 0.00     | (0.00, 0.00)         | 0.084328            | 0.084328                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A: Not applicable

**Figure 25. Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 51. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 61)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.400567  | (0.399464, 0.401671)   | <.001               |
| Baseline trend                                                          | -0.000653 | (-0.000695, -0.000610) | <.001               |
| Level Change (After Intervention 1)                                     | 0.003259  | (0.001699, 0.004820)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000292 | (-0.000385, -0.000199) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 61)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.400567  | (0.399464, 0.401671)   | <.001               |
| Baseline trend                                                          | -0.000653 | (-0.000695, -0.000610) | <.001               |
| Level Change (After Intervention 1)                                     | 0.003259  | (0.001699, 0.004820)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000292 | (-0.000385, -0.000199) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 52. Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted                | Extrapolated Rate      |
|-------------------------------------------------------|-----------|------------------------|--------------------------|------------------------|
|                                                       |           |                        | Rate (With Intervention) | (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                      | N/A                    |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                      | N/A                    |
| Absolute Change at 2 Months after Intervention 1      | 0.002676  | (0.001055, 0.004296)   | 0.373223                 | 0.370547               |
| Relative Change (%) at 2 Months after Intervention 1  | 0.72      | (0.28, 1.16)           | 0.373223                 | 0.370547               |
| Absolute Change at 3 Months after Intervention 1      | 0.002384  | (0.000769, 0.003998)   | 0.372278                 | 0.369894               |
| Relative Change (%) at 3 Months after Intervention 1  | 0.64      | (0.21, 1.08)           | 0.372278                 | 0.369894               |
| Absolute Change at 4 Months after Intervention 1      | 0.002092  | (0.000478, 0.003706)   | 0.371334                 | 0.369242               |
| Relative Change (%) at 4 Months after Intervention 1  | 0.57      | (0.13, 1.01)           | 0.371334                 | 0.369242               |
| Absolute Change at 5 Months after Intervention 1      | 0.001800  | (0.000181, 0.003419)   | 0.370389                 | 0.368589               |
| Relative Change (%) at 5 Months after Intervention 1  | 0.49      | (0.05, 0.93)           | 0.370389                 | 0.368589               |
| Absolute Change at 6 Months after Intervention 1      | 0.001508  | (-0.000121, 0.003137)  | 0.369444                 | 0.367937               |
| Relative Change (%) at 6 Months after Intervention 1  | 0.41      | (-0.03, 0.85)          | 0.369444                 | 0.367937               |
| Absolute Change at 7 Months after Intervention 1      | 0.001216  | (-0.000428, 0.002860)  | 0.368500                 | 0.367284               |
| Relative Change (%) at 7 Months after Intervention 1  | 0.33      | (-0.12, 0.78)          | 0.368500                 | 0.367284               |
| Absolute Change at 8 Months after Intervention 1      | 0.000924  | (-0.000741, 0.002589)  | 0.367555                 | 0.366631               |
| Relative Change (%) at 8 Months after Intervention 1  | 0.25      | (-0.20, 0.71)          | 0.367555                 | 0.366631               |
| Absolute Change at 9 Months after Intervention 1      | 0.000632  | (-0.001058, 0.002322)  | 0.366611                 | 0.365979               |
| Relative Change (%) at 9 Months after Intervention 1  | 0.17      | (-0.29, 0.64)          | 0.366611                 | 0.365979               |
| Absolute Change at 10 Months after Intervention 1     | 0.000340  | (-0.001380, 0.002060)  | 0.365666                 | 0.365326               |
| Relative Change (%) at 10 Months after Intervention 1 | 0.09      | (-0.38, 0.56)          | 0.365666                 | 0.365326               |
| Absolute Change at 11 Months after Intervention 1     | 0.000048  | (-0.001706, 0.001803)  | 0.364722                 | 0.364673               |
| Relative Change (%) at 11 Months after Intervention 1 | 0.01      | (-0.47, 0.49)          | 0.364722                 | 0.364673               |
| Absolute Change at 12 Months after Intervention 1     | -0.000244 | (-0.002037, 0.001550)  | 0.363777                 | 0.364021               |
| Relative Change (%) at 12 Months after Intervention 1 | -0.07     | (-0.56, 0.43)          | 0.363777                 | 0.364021               |
| Absolute Change at 13 Months after Intervention 1     | -0.000536 | (-0.002371, 0.001300)  | 0.362833                 | 0.363368               |
| Relative Change (%) at 13 Months after Intervention 1 | -0.15     | (-0.65, 0.36)          | 0.362833                 | 0.363368               |
| Absolute Change at 14 Months after Intervention 1     | -0.000827 | (-0.002709, 0.001055)  | 0.361888                 | 0.362716               |
| Relative Change (%) at 14 Months after Intervention 1 | -0.23     | (-0.75, 0.29)          | 0.361888                 | 0.362716               |
| Absolute Change at 15 Months after Intervention 1     | -0.001119 | (-0.003051, 0.000812)  | 0.360944                 | 0.362063               |
| Relative Change (%) at 15 Months after Intervention 1 | -0.31     | (-0.84, 0.22)          | 0.360944                 | 0.362063               |
| Absolute Change at 16 Months after Intervention 1     | -0.001411 | (-0.003396, 0.000573)  | 0.359999                 | 0.361410               |
| Relative Change (%) at 16 Months after Intervention 1 | -0.39     | (-0.94, 0.16)          | 0.359999                 | 0.361410               |
| Absolute Change at 17 Months after Intervention 1     | -0.001703 | (-0.003743, 0.000337)  | 0.359055                 | 0.360758               |
| Relative Change (%) at 17 Months after Intervention 1 | -0.47     | (-1.04, 0.09)          | 0.359055                 | 0.360758               |
| Absolute Change at 18 Months after Intervention 1     | -0.001995 | (-0.004093, 0.000103)  | 0.358110                 | 0.360105               |
| Relative Change (%) at 18 Months after Intervention 1 | -0.55     | (-1.13, 0.03)          | 0.358110                 | 0.360105               |
| Absolute Change at 19 Months after Intervention 1     | -0.002287 | (-0.004446, -0.000128) | 0.357165                 | 0.359453               |
| Relative Change (%) at 19 Months after Intervention 1 | -0.64     | (-1.23, -0.04)         | 0.357165                 | 0.359453               |
| Absolute Change at 20 Months after Intervention 1     | -0.002579 | (-0.004801, -0.000357) | 0.356221                 | 0.358800               |
| Relative Change (%) at 20 Months after Intervention 1 | -0.72     | (-1.33, -0.10)         | 0.356221                 | 0.358800               |
| Absolute Change at 21 Months after Intervention 1     | -0.002871 | (-0.005158, -0.000584) | 0.355276                 | 0.358147               |
| Relative Change (%) at 21 Months after Intervention 1 | -0.80     | (-1.44, -0.17)         | 0.355276                 | 0.358147               |
| Absolute Change at 22 Months after Intervention 1     | -0.003163 | (-0.005517, -0.000809) | 0.354332                 | 0.357495               |
| Relative Change (%) at 22 Months after Intervention 1 | -0.88     | (-1.54, -0.23)         | 0.354332                 | 0.357495               |
| Absolute Change at 23 Months after Intervention 1     | -0.003455 | (-0.005877, -0.001032) | 0.353387                 | 0.356842               |
| Relative Change (%) at 23 Months after Intervention 1 | -0.97     | (-1.64, -0.29)         | 0.353387                 | 0.356842               |
| Absolute Change at 24 Months after Intervention 1     | -0.003747 | (-0.006239, -0.001254) | 0.352443                 | 0.356189               |
| Relative Change (%) at 24 Months after Intervention 1 | -1.05     | (-1.75, -0.36)         | 0.352443                 | 0.356189               |
| Absolute Change at 25 Months after Intervention 1     | -0.004039 | (-0.006603, -0.001474) | 0.351498                 | 0.355537               |

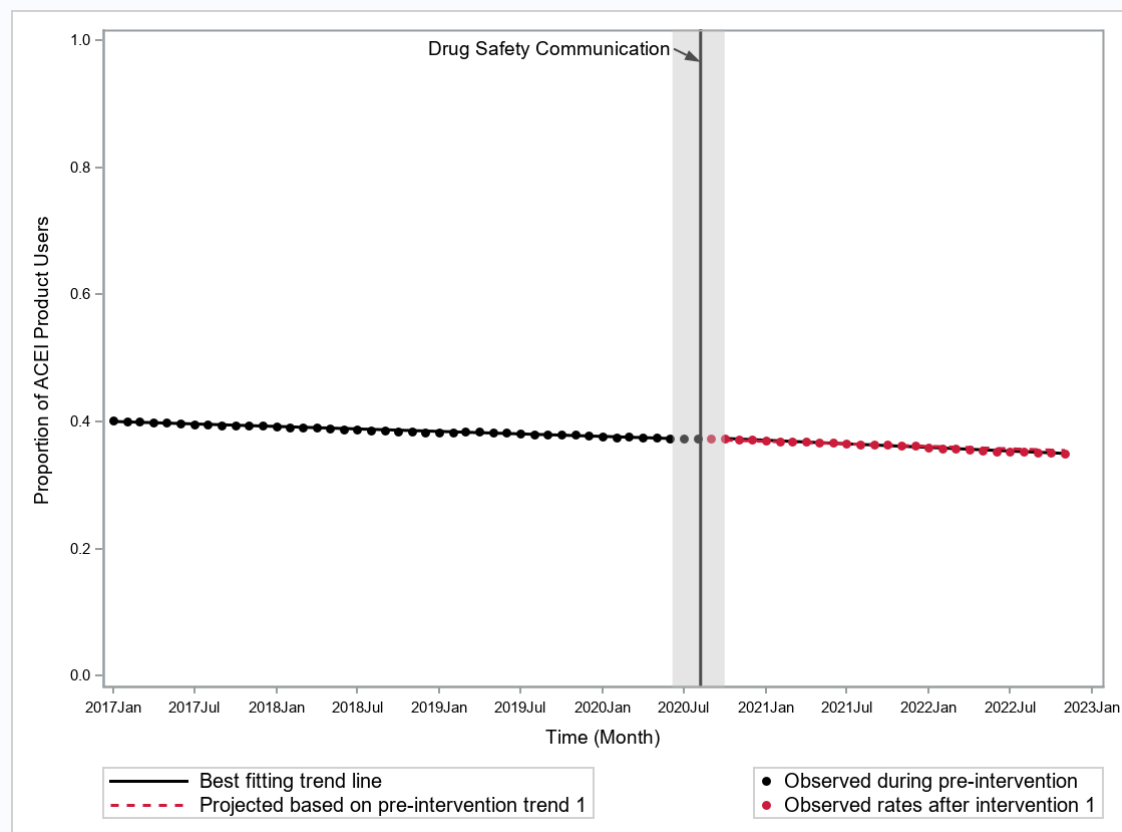
**Table 52. Absolute and Relative Changes in Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted                      | Extrapolated Rate         |
|-------------------------------------------------------|-----------|------------------------|--------------------------------|---------------------------|
|                                                       |           |                        | Rate<br>(With<br>Intervention) | (Without<br>Intervention) |
| Relative Change (%) at 25 Months after Intervention 1 | -1.14     | (-1.85, -0.42)         | 0.351498                       | 0.355537                  |
| Absolute Change at 26 Months after Intervention 1     | -0.004331 | (-0.006968, -0.001693) | 0.350554                       | 0.354884                  |
| Relative Change (%) at 26 Months after Intervention 1 | -1.22     | (-1.96, -0.48)         | 0.350554                       | 0.354884                  |
| Absolute Change at 27 Months after Intervention 1     | -0.004622 | (-0.007334, -0.001911) | 0.349609                       | 0.354232                  |
| Absolute Change at 27 Months after Intervention 1     | -0.004622 | (-0.007334, -0.001911) | 0.349609                       | 0.354232                  |
| Relative Change (%) at 27 Months after Intervention 1 | -1.30     | (-2.06, -0.55)         | 0.349609                       | 0.354232                  |
| Relative Change (%) at 27 Months after Intervention 1 | -1.30     | (-2.06, -0.55)         | 0.349609                       | 0.354232                  |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 26. Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 53. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.373783  | (0.373133, 0.374433)   | <.001               |
| Baseline trend                                                          | 0.000679  | (0.000652, 0.000705)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.003140  | (0.001961, 0.004319)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000297 | (-0.000357, -0.000238) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.373783  | (0.373133, 0.374433)   | <.001               |
| Baseline trend                                                          | 0.000679  | (0.000652, 0.000705)   | <.001               |
| Level Change (After Intervention 1)                                     | 0.003140  | (0.001961, 0.004319)   | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000297 | (-0.000357, -0.000238) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 54. Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|-----------|------------------------|---------------------|------------------------|
|                                                       |           |                        | (With Intervention) | (Without Intervention) |
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                 | N/A                    |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                 | N/A                    |
| Absolute Change at 2 Months after Intervention 1      | 0.002546  | (0.001436, 0.003655)   | 0.407541            | 0.404995               |
| Relative Change (%) at 2 Months after Intervention 1  | 0.63      | (0.35, 0.90)           | 0.407541            | 0.404995               |
| Absolute Change at 3 Months after Intervention 1      | 0.002248  | (0.001159, 0.003338)   | 0.407922            | 0.405674               |
| Relative Change (%) at 3 Months after Intervention 1  | 0.55      | (0.28, 0.82)           | 0.407922            | 0.405674               |
| Absolute Change at 4 Months after Intervention 1      | 0.001951  | (0.000878, 0.003023)   | 0.408303            | 0.406352               |
| Relative Change (%) at 4 Months after Intervention 1  | 0.48      | (0.22, 0.74)           | 0.408303            | 0.406352               |
| Absolute Change at 5 Months after Intervention 1      | 0.001654  | (0.000595, 0.002712)   | 0.408685            | 0.407031               |
| Relative Change (%) at 5 Months after Intervention 1  | 0.41      | (0.15, 0.67)           | 0.408685            | 0.407031               |
| Absolute Change at 6 Months after Intervention 1      | 0.001356  | (0.000309, 0.002404)   | 0.409066            | 0.407709               |
| Relative Change (%) at 6 Months after Intervention 1  | 0.33      | (0.08, 0.59)           | 0.409066            | 0.407709               |
| Absolute Change at 7 Months after Intervention 1      | 0.001059  | (0.000020, 0.002098)   | 0.409447            | 0.408388               |
| Relative Change (%) at 7 Months after Intervention 1  | 0.26      | (0.00, 0.51)           | 0.409447            | 0.408388               |
| Absolute Change at 8 Months after Intervention 1      | 0.000762  | (-0.000273, 0.001797)  | 0.409828            | 0.409067               |
| Relative Change (%) at 8 Months after Intervention 1  | 0.19      | (-0.07, 0.44)          | 0.409828            | 0.409067               |
| Absolute Change at 9 Months after Intervention 1      | 0.000464  | (-0.000569, 0.001498)  | 0.410209            | 0.409745               |
| Relative Change (%) at 9 Months after Intervention 1  | 0.11      | (-0.14, 0.37)          | 0.410209            | 0.409745               |
| Absolute Change at 10 Months after Intervention 1     | 0.000167  | (-0.000869, 0.001203)  | 0.410591            | 0.410424               |
| Relative Change (%) at 10 Months after Intervention 1 | 0.04      | (-0.21, 0.29)          | 0.410591            | 0.410424               |
| Absolute Change at 11 Months after Intervention 1     | -0.000130 | (-0.001172, 0.000911)  | 0.410972            | 0.411102               |
| Relative Change (%) at 11 Months after Intervention 1 | -0.03     | (-0.28, 0.22)          | 0.410972            | 0.411102               |
| Absolute Change at 12 Months after Intervention 1     | -0.000428 | (-0.001478, 0.000623)  | 0.411353            | 0.411781               |
| Relative Change (%) at 12 Months after Intervention 1 | -0.10     | (-0.36, 0.15)          | 0.411353            | 0.411781               |
| Absolute Change at 13 Months after Intervention 1     | -0.000725 | (-0.001787, 0.000338)  | 0.411734            | 0.412459               |
| Relative Change (%) at 13 Months after Intervention 1 | -0.18     | (-0.43, 0.08)          | 0.411734            | 0.412459               |
| Absolute Change at 14 Months after Intervention 1     | -0.001022 | (-0.002100, 0.000055)  | 0.412116            | 0.413138               |
| Relative Change (%) at 14 Months after Intervention 1 | -0.25     | (-0.51, 0.01)          | 0.412116            | 0.413138               |
| Absolute Change at 15 Months after Intervention 1     | -0.001319 | (-0.002415, -0.000224) | 0.412497            | 0.413816               |
| Relative Change (%) at 15 Months after Intervention 1 | -0.32     | (-0.58, -0.05)         | 0.412497            | 0.413816               |
| Absolute Change at 16 Months after Intervention 1     | -0.001617 | (-0.002733, -0.000500) | 0.412878            | 0.414495               |
| Relative Change (%) at 16 Months after Intervention 1 | -0.39     | (-0.66, -0.12)         | 0.412878            | 0.414495               |
| Absolute Change at 17 Months after Intervention 1     | -0.001914 | (-0.003054, -0.000774) | 0.413259            | 0.415173               |
| Relative Change (%) at 17 Months after Intervention 1 | -0.46     | (-0.73, -0.19)         | 0.413259            | 0.415173               |
| Absolute Change at 18 Months after Intervention 1     | -0.002211 | (-0.003378, -0.001045) | 0.413640            | 0.415852               |
| Relative Change (%) at 18 Months after Intervention 1 | -0.53     | (-0.81, -0.25)         | 0.413640            | 0.415852               |
| Absolute Change at 19 Months after Intervention 1     | -0.002509 | (-0.003703, -0.001314) | 0.414022            | 0.416530               |
| Relative Change (%) at 19 Months after Intervention 1 | -0.60     | (-0.89, -0.32)         | 0.414022            | 0.416530               |
| Absolute Change at 20 Months after Intervention 1     | -0.002806 | (-0.004031, -0.001581) | 0.414403            | 0.417209               |
| Relative Change (%) at 20 Months after Intervention 1 | -0.67     | (-0.96, -0.38)         | 0.414403            | 0.417209               |
| Absolute Change at 21 Months after Intervention 1     | -0.003103 | (-0.004361, -0.001846) | 0.414784            | 0.417887               |
| Relative Change (%) at 21 Months after Intervention 1 | -0.74     | (-1.04, -0.44)         | 0.414784            | 0.417887               |
| Absolute Change at 22 Months after Intervention 1     | -0.003401 | (-0.004693, -0.002108) | 0.415165            | 0.418566               |
| Relative Change (%) at 22 Months after Intervention 1 | -0.81     | (-1.12, -0.51)         | 0.415165            | 0.418566               |
| Absolute Change at 23 Months after Intervention 1     | -0.003698 | (-0.005026, -0.002369) | 0.415547            | 0.419244               |
| Relative Change (%) at 23 Months after Intervention 1 | -0.88     | (-1.20, -0.57)         | 0.415547            | 0.419244               |
| Absolute Change at 24 Months after Intervention 1     | -0.003995 | (-0.005362, -0.002629) | 0.415928            | 0.419923               |
| Relative Change (%) at 24 Months after Intervention 1 | -0.95     | (-1.27, -0.63)         | 0.415928            | 0.419923               |
| Absolute Change at 25 Months after Intervention 1     | -0.004293 | (-0.005698, -0.002887) | 0.416309            | 0.420602               |
| Relative Change (%) at 25 Months after Intervention 1 | -1.02     | (-1.35, -0.69)         | 0.416309            | 0.420602               |

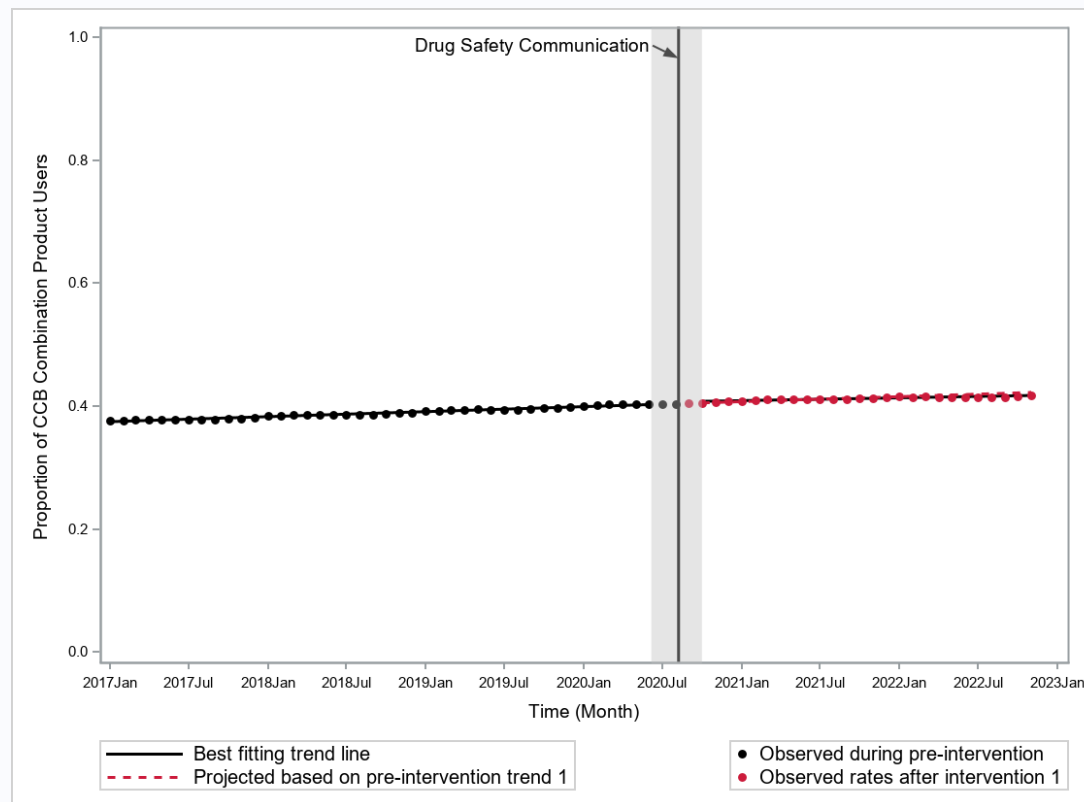
**Table 54. Absolute and Relative Changes in Proportion of Calcium Channel Blockers (CCB) Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate      | Extrapolated Rate      |
|-------------------------------------------------------|-----------|------------------------|---------------------|------------------------|
|                                                       |           |                        | (With Intervention) | (Without Intervention) |
| Absolute Change at 26 Months after Intervention 1     | -0.004590 | (-0.006036, -0.003144) | 0.416690            | 0.421280               |
| Relative Change (%) at 26 Months after Intervention 1 | -1.09     | (-1.43, -0.75)         | 0.416690            | 0.421280               |
| Absolute Change at 27 Months after Intervention 1     | -0.004887 | (-0.006375, -0.003399) | 0.417071            | 0.421959               |
| Absolute Change at 27 Months after Intervention 1     | -0.004887 | (-0.006375, -0.003399) | 0.417071            | 0.421959               |
| Relative Change (%) at 27 Months after Intervention 1 | -1.16     | (-1.51, -0.81)         | 0.417071            | 0.421959               |
| Relative Change (%) at 27 Months after Intervention 1 | -1.16     | (-1.51, -0.81)         | 0.417071            | 0.421959               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 27. Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 55. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 61)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.169194  | (0.168564, 0.169825)   | <.001               |
| Baseline trend                                                          | -0.000152 | (-0.000174, -0.000130) | <.001               |
| Level Change (After Intervention 1)                                     | 0.000097  | (-0.000598, 0.000791)  | 0.782               |
| Trend Change (After Intervention 1)                                     | -0.000187 | (-0.000232, -0.000141) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.169180  | (0.168563, 0.169798)   | <.001               |
| Baseline trend                                                          | -0.000151 | (-0.000171, -0.000131) | <.001               |
| Trend Change (After Intervention 1)                                     | -0.000185 | (-0.000229, -0.000141) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 56. Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                                      | N/A                                            |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                                      | N/A                                            |
| Absolute Change at 2 Months after Intervention 1      | -0.000371 | (-0.000459, -0.000283) | 0.161878                                 | 0.162248                                       |
| Relative Change (%) at 2 Months after Intervention 1  | -0.23     | (-0.28, -0.17)         | 0.161878                                 | 0.162248                                       |
| Absolute Change at 3 Months after Intervention 1      | -0.000556 | (-0.000688, -0.000424) | 0.161542                                 | 0.162098                                       |
| Relative Change (%) at 3 Months after Intervention 1  | -0.34     | (-0.42, -0.26)         | 0.161542                                 | 0.162098                                       |
| Absolute Change at 4 Months after Intervention 1      | -0.000741 | (-0.000918, -0.000565) | 0.161206                                 | 0.161947                                       |
| Relative Change (%) at 4 Months after Intervention 1  | -0.46     | (-0.57, -0.35)         | 0.161206                                 | 0.161947                                       |
| Absolute Change at 5 Months after Intervention 1      | -0.000927 | (-0.001147, -0.000706) | 0.160869                                 | 0.161796                                       |
| Relative Change (%) at 5 Months after Intervention 1  | -0.57     | (-0.71, -0.44)         | 0.160869                                 | 0.161796                                       |
| Absolute Change at 6 Months after Intervention 1      | -0.001112 | (-0.001377, -0.000848) | 0.160533                                 | 0.161646                                       |
| Relative Change (%) at 6 Months after Intervention 1  | -0.69     | (-0.85, -0.53)         | 0.160533                                 | 0.161646                                       |
| Absolute Change at 7 Months after Intervention 1      | -0.001298 | (-0.001606, -0.000989) | 0.160197                                 | 0.161495                                       |
| Relative Change (%) at 7 Months after Intervention 1  | -0.80     | (-0.99, -0.62)         | 0.160197                                 | 0.161495                                       |
| Absolute Change at 8 Months after Intervention 1      | -0.001483 | (-0.001836, -0.001130) | 0.159861                                 | 0.161344                                       |
| Relative Change (%) at 8 Months after Intervention 1  | -0.92     | (-1.13, -0.70)         | 0.159861                                 | 0.161344                                       |
| Absolute Change at 9 Months after Intervention 1      | -0.001668 | (-0.002065, -0.001271) | 0.159525                                 | 0.161194                                       |
| Relative Change (%) at 9 Months after Intervention 1  | -1.03     | (-1.28, -0.79)         | 0.159525                                 | 0.161194                                       |
| Absolute Change at 10 Months after Intervention 1     | -0.001854 | (-0.002295, -0.001413) | 0.159189                                 | 0.161043                                       |
| Relative Change (%) at 10 Months after Intervention 1 | -1.15     | (-1.42, -0.88)         | 0.159189                                 | 0.161043                                       |
| Absolute Change at 11 Months after Intervention 1     | -0.002039 | (-0.002524, -0.001554) | 0.158853                                 | 0.160892                                       |
| Relative Change (%) at 11 Months after Intervention 1 | -1.27     | (-1.56, -0.97)         | 0.158853                                 | 0.160892                                       |
| Absolute Change at 12 Months after Intervention 1     | -0.002224 | (-0.002754, -0.001695) | 0.158517                                 | 0.160741                                       |
| Relative Change (%) at 12 Months after Intervention 1 | -1.38     | (-1.71, -1.06)         | 0.158517                                 | 0.160741                                       |
| Absolute Change at 13 Months after Intervention 1     | -0.002410 | (-0.002983, -0.001837) | 0.158181                                 | 0.160591                                       |
| Relative Change (%) at 13 Months after Intervention 1 | -1.50     | (-1.85, -1.15)         | 0.158181                                 | 0.160591                                       |
| Absolute Change at 14 Months after Intervention 1     | -0.002595 | (-0.003213, -0.001978) | 0.157845                                 | 0.160440                                       |
| Relative Change (%) at 14 Months after Intervention 1 | -1.62     | (-2.00, -1.24)         | 0.157845                                 | 0.160440                                       |
| Absolute Change at 15 Months after Intervention 1     | -0.002781 | (-0.003442, -0.002119) | 0.157509                                 | 0.160289                                       |
| Relative Change (%) at 15 Months after Intervention 1 | -1.73     | (-2.14, -1.33)         | 0.157509                                 | 0.160289                                       |
| Absolute Change at 16 Months after Intervention 1     | -0.002966 | (-0.003672, -0.002260) | 0.157173                                 | 0.160139                                       |
| Relative Change (%) at 16 Months after Intervention 1 | -1.85     | (-2.28, -1.42)         | 0.157173                                 | 0.160139                                       |
| Absolute Change at 17 Months after Intervention 1     | -0.003151 | (-0.003901, -0.002402) | 0.156837                                 | 0.159988                                       |
| Relative Change (%) at 17 Months after Intervention 1 | -1.97     | (-2.43, -1.51)         | 0.156837                                 | 0.159988                                       |
| Absolute Change at 18 Months after Intervention 1     | -0.003337 | (-0.004130, -0.002543) | 0.156501                                 | 0.159837                                       |
| Relative Change (%) at 18 Months after Intervention 1 | -2.09     | (-2.57, -1.60)         | 0.156501                                 | 0.159837                                       |
| Absolute Change at 19 Months after Intervention 1     | -0.003522 | (-0.004360, -0.002684) | 0.156165                                 | 0.159687                                       |
| Relative Change (%) at 19 Months after Intervention 1 | -2.21     | (-2.72, -1.69)         | 0.156165                                 | 0.159687                                       |
| Absolute Change at 20 Months after Intervention 1     | -0.003707 | (-0.004589, -0.002825) | 0.155829                                 | 0.159536                                       |
| Relative Change (%) at 20 Months after Intervention 1 | -2.32     | (-2.87, -1.78)         | 0.155829                                 | 0.159536                                       |
| Absolute Change at 21 Months after Intervention 1     | -0.003893 | (-0.004819, -0.002967) | 0.155492                                 | 0.159385                                       |
| Relative Change (%) at 21 Months after Intervention 1 | -2.44     | (-3.01, -1.87)         | 0.155492                                 | 0.159385                                       |
| Absolute Change at 22 Months after Intervention 1     | -0.004078 | (-0.005048, -0.003108) | 0.155156                                 | 0.159235                                       |
| Relative Change (%) at 22 Months after Intervention 1 | -2.56     | (-3.16, -1.96)         | 0.155156                                 | 0.159235                                       |
| Absolute Change at 23 Months after Intervention 1     | -0.004264 | (-0.005278, -0.003249) | 0.154820                                 | 0.159084                                       |
| Relative Change (%) at 23 Months after Intervention 1 | -2.68     | (-3.30, -2.06)         | 0.154820                                 | 0.159084                                       |
| Absolute Change at 24 Months after Intervention 1     | -0.004449 | (-0.005507, -0.003390) | 0.154484                                 | 0.158933                                       |
| Relative Change (%) at 24 Months after Intervention 1 | -2.80     | (-3.45, -2.15)         | 0.154484                                 | 0.158933                                       |
| Absolute Change at 25 Months after Intervention 1     | -0.004634 | (-0.005737, -0.003532) | 0.154148                                 | 0.158782                                       |
| Relative Change (%) at 25 Months after Intervention 1 | -2.92     | (-3.60, -2.24)         | 0.154148                                 | 0.158782                                       |

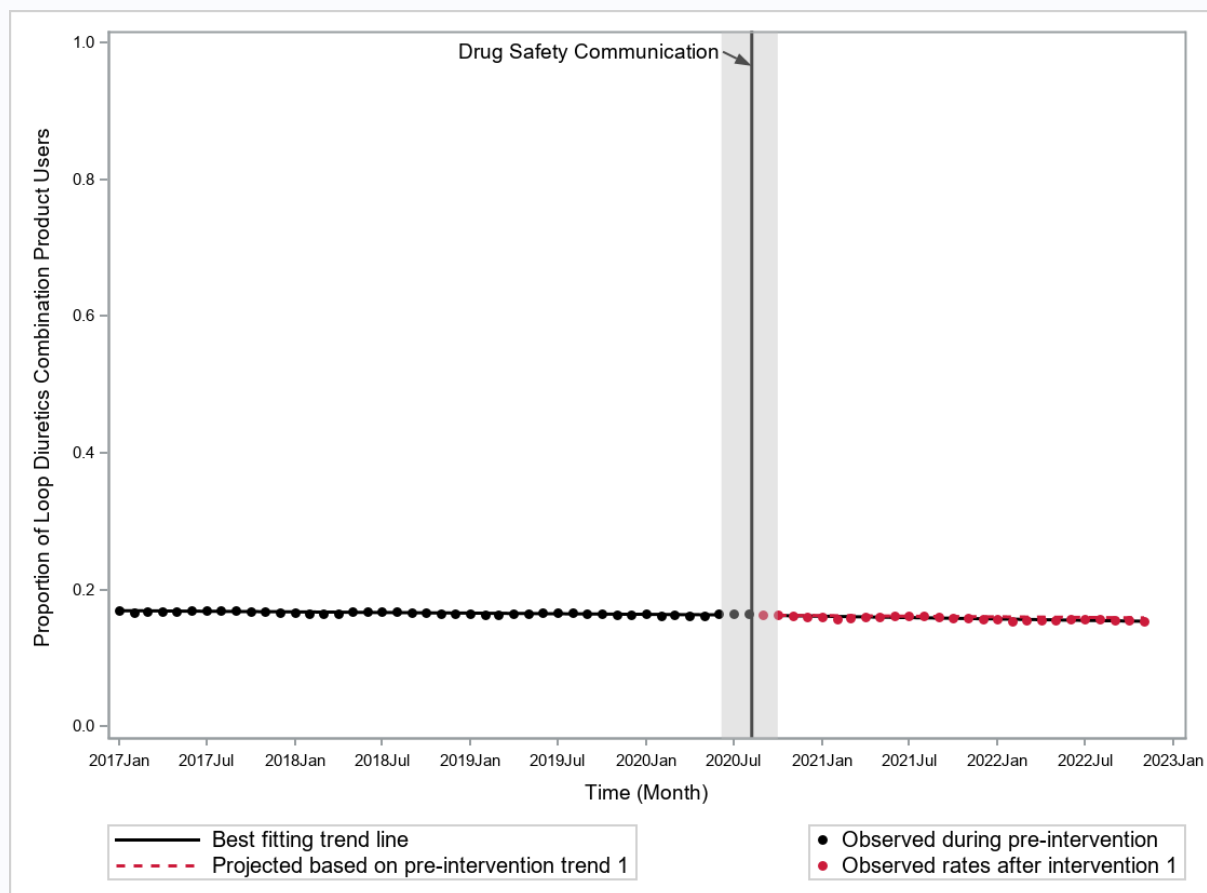
**Table 56. Absolute and Relative Changes in Proportion of Loop Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 26 Months after Intervention 1     | -0.004820 | (-0.005966, -0.003673) | 0.153812                                 | 0.158632                                       |
| Relative Change (%) at 26 Months after Intervention 1 | -3.04     | (-3.75, -2.33)         | 0.153812                                 | 0.158632                                       |
| Absolute Change at 27 Months after Intervention 1     | -0.005005 | (-0.006196, -0.003814) | 0.153476                                 | 0.158481                                       |
| Absolute Change at 27 Months after Intervention 1     | -0.005005 | (-0.006196, -0.003814) | 0.153476                                 | 0.158481                                       |
| Relative Change (%) at 27 Months after Intervention 1 | -3.16     | (-3.89, -2.42)         | 0.153476                                 | 0.158481                                       |
| Relative Change (%) at 27 Months after Intervention 1 | -3.16     | (-3.89, -2.42)         | 0.153476                                 | 0.158481                                       |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 28. Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 57. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 60)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.047091  | (0.046894, 0.047288)   | <.001               |
| Baseline trend                                                          | 0.000209  | (0.000201, 0.000217)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000585 | (-0.000949, -0.000221) | 0.002               |
| Trend Change (After Intervention 1)                                     | 0.000080  | (0.000061, 0.000098)   | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 60)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.047091  | (0.046894, 0.047288)   | <.001               |
| Baseline trend                                                          | 0.000209  | (0.000201, 0.000217)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000585 | (-0.000949, -0.000221) | 0.002               |
| Trend Change (After Intervention 1)                                     | 0.000080  | (0.000061, 0.000098)   | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 58. Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                       | Estimate  | 95% CI                 | Predicted Rate<br>(With<br>Intervention) | Extrapolated Rate<br>(Without<br>Intervention) |
|-------------------------------------------------------|-----------|------------------------|------------------------------------------|------------------------------------------------|
| Absolute Change at 1 Months after Intervention 1      | N/A       | (N/A, N/A)             | N/A                                      | N/A                                            |
| Relative Change (%) at 1 Months after Intervention 1  | N/A       | (N/A, N/A)             | N/A                                      | N/A                                            |
| Absolute Change at 2 Months after Intervention 1      | -0.000426 | (-0.000772, -0.000079) | 0.056262                                 | 0.056688                                       |
| Relative Change (%) at 2 Months after Intervention 1  | -0.75     | (-1.36, -0.14)         | 0.056262                                 | 0.056688                                       |
| Absolute Change at 3 Months after Intervention 1      | -0.000346 | (-0.000687, -0.000006) | 0.056550                                 | 0.056896                                       |
| Relative Change (%) at 3 Months after Intervention 1  | -0.61     | (-1.20, -0.01)         | 0.056550                                 | 0.056896                                       |
| Absolute Change at 4 Months after Intervention 1      | -0.000267 | (-0.000602, 0.000069)  | 0.056839                                 | 0.057105                                       |
| Relative Change (%) at 4 Months after Intervention 1  | -0.47     | (-1.05, 0.12)          | 0.056839                                 | 0.057105                                       |
| Absolute Change at 5 Months after Intervention 1      | -0.000187 | (-0.000518, 0.000144)  | 0.057127                                 | 0.057314                                       |
| Relative Change (%) at 5 Months after Intervention 1  | -0.33     | (-0.90, 0.25)          | 0.057127                                 | 0.057314                                       |
| Absolute Change at 6 Months after Intervention 1      | -0.000107 | (-0.000436, 0.000221)  | 0.057415                                 | 0.057522                                       |
| Relative Change (%) at 6 Months after Intervention 1  | -0.19     | (-0.76, 0.38)          | 0.057415                                 | 0.057522                                       |
| Absolute Change at 7 Months after Intervention 1      | -0.000028 | (-0.000354, 0.000298)  | 0.057703                                 | 0.057731                                       |
| Relative Change (%) at 7 Months after Intervention 1  | -0.05     | (-0.61, 0.52)          | 0.057703                                 | 0.057731                                       |
| Absolute Change at 8 Months after Intervention 1      | 0.000052  | (-0.000273, 0.000377)  | 0.057991                                 | 0.057940                                       |
| Relative Change (%) at 8 Months after Intervention 1  | 0.09      | (-0.47, 0.65)          | 0.057991                                 | 0.057940                                       |
| Absolute Change at 9 Months after Intervention 1      | 0.000131  | (-0.000193, 0.000456)  | 0.058280                                 | 0.058148                                       |
| Relative Change (%) at 9 Months after Intervention 1  | 0.23      | (-0.33, 0.79)          | 0.058280                                 | 0.058148                                       |
| Absolute Change at 10 Months after Intervention 1     | 0.000211  | (-0.000115, 0.000537)  | 0.058568                                 | 0.058357                                       |
| Relative Change (%) at 10 Months after Intervention 1 | 0.36      | (-0.20, 0.92)          | 0.058568                                 | 0.058357                                       |
| Absolute Change at 11 Months after Intervention 1     | 0.000290  | (-0.000037, 0.000618)  | 0.058856                                 | 0.058565                                       |
| Relative Change (%) at 11 Months after Intervention 1 | 0.50      | (-0.07, 1.06)          | 0.058856                                 | 0.058565                                       |
| Absolute Change at 12 Months after Intervention 1     | 0.000370  | (0.000040, 0.000701)   | 0.059144                                 | 0.058774                                       |
| Relative Change (%) at 12 Months after Intervention 1 | 0.63      | (0.06, 1.19)           | 0.059144                                 | 0.058774                                       |
| Absolute Change at 13 Months after Intervention 1     | 0.000450  | (0.000115, 0.000784)   | 0.059432                                 | 0.058983                                       |
| Relative Change (%) at 13 Months after Intervention 1 | 0.76      | (0.19, 1.33)           | 0.059432                                 | 0.058983                                       |
| Absolute Change at 14 Months after Intervention 1     | 0.000529  | (0.000190, 0.000868)   | 0.059721                                 | 0.059191                                       |
| Relative Change (%) at 14 Months after Intervention 1 | 0.89      | (0.32, 1.47)           | 0.059721                                 | 0.059191                                       |
| Absolute Change at 15 Months after Intervention 1     | 0.000609  | (0.000264, 0.000954)   | 0.060009                                 | 0.059400                                       |
| Relative Change (%) at 15 Months after Intervention 1 | 1.02      | (0.44, 1.61)           | 0.060009                                 | 0.059400                                       |
| Absolute Change at 16 Months after Intervention 1     | 0.000688  | (0.000337, 0.001040)   | 0.060297                                 | 0.059609                                       |
| Relative Change (%) at 16 Months after Intervention 1 | 1.15      | (0.56, 1.75)           | 0.060297                                 | 0.059609                                       |
| Absolute Change at 17 Months after Intervention 1     | 0.000768  | (0.000409, 0.001127)   | 0.060585                                 | 0.059817                                       |
| Relative Change (%) at 17 Months after Intervention 1 | 1.28      | (0.68, 1.89)           | 0.060585                                 | 0.059817                                       |
| Absolute Change at 18 Months after Intervention 1     | 0.000848  | (0.000481, 0.001214)   | 0.060873                                 | 0.060026                                       |
| Relative Change (%) at 18 Months after Intervention 1 | 1.41      | (0.79, 2.03)           | 0.060873                                 | 0.060026                                       |
| Absolute Change at 19 Months after Intervention 1     | 0.000927  | (0.000551, 0.001303)   | 0.061162                                 | 0.060234                                       |
| Relative Change (%) at 19 Months after Intervention 1 | 1.54      | (0.91, 2.17)           | 0.061162                                 | 0.060234                                       |
| Absolute Change at 20 Months after Intervention 1     | 0.001007  | (0.000621, 0.001392)   | 0.061450                                 | 0.060443                                       |
| Relative Change (%) at 20 Months after Intervention 1 | 1.67      | (1.02, 2.31)           | 0.061450                                 | 0.060443                                       |
| Absolute Change at 21 Months after Intervention 1     | 0.001086  | (0.000691, 0.001482)   | 0.061738                                 | 0.060652                                       |
| Relative Change (%) at 21 Months after Intervention 1 | 1.79      | (1.13, 2.45)           | 0.061738                                 | 0.060652                                       |
| Absolute Change at 22 Months after Intervention 1     | 0.001166  | (0.000760, 0.001572)   | 0.062026                                 | 0.060860                                       |
| Relative Change (%) at 22 Months after Intervention 1 | 1.92      | (1.24, 2.59)           | 0.062026                                 | 0.060860                                       |
| Absolute Change at 23 Months after Intervention 1     | 0.001245  | (0.000828, 0.001663)   | 0.062314                                 | 0.061069                                       |
| Relative Change (%) at 23 Months after Intervention 1 | 2.04      | (1.35, 2.73)           | 0.062314                                 | 0.061069                                       |
| Absolute Change at 24 Months after Intervention 1     | 0.001325  | (0.000896, 0.001754)   | 0.062603                                 | 0.061278                                       |
| Relative Change (%) at 24 Months after Intervention 1 | 2.16      | (1.45, 2.87)           | 0.062603                                 | 0.061278                                       |
| Absolute Change at 25 Months after Intervention 1     | 0.001405  | (0.000964, 0.001845)   | 0.062891                                 | 0.061486                                       |
| Relative Change (%) at 25 Months after Intervention 1 | 2.28      | (1.55, 3.01)           | 0.062891                                 | 0.061486                                       |

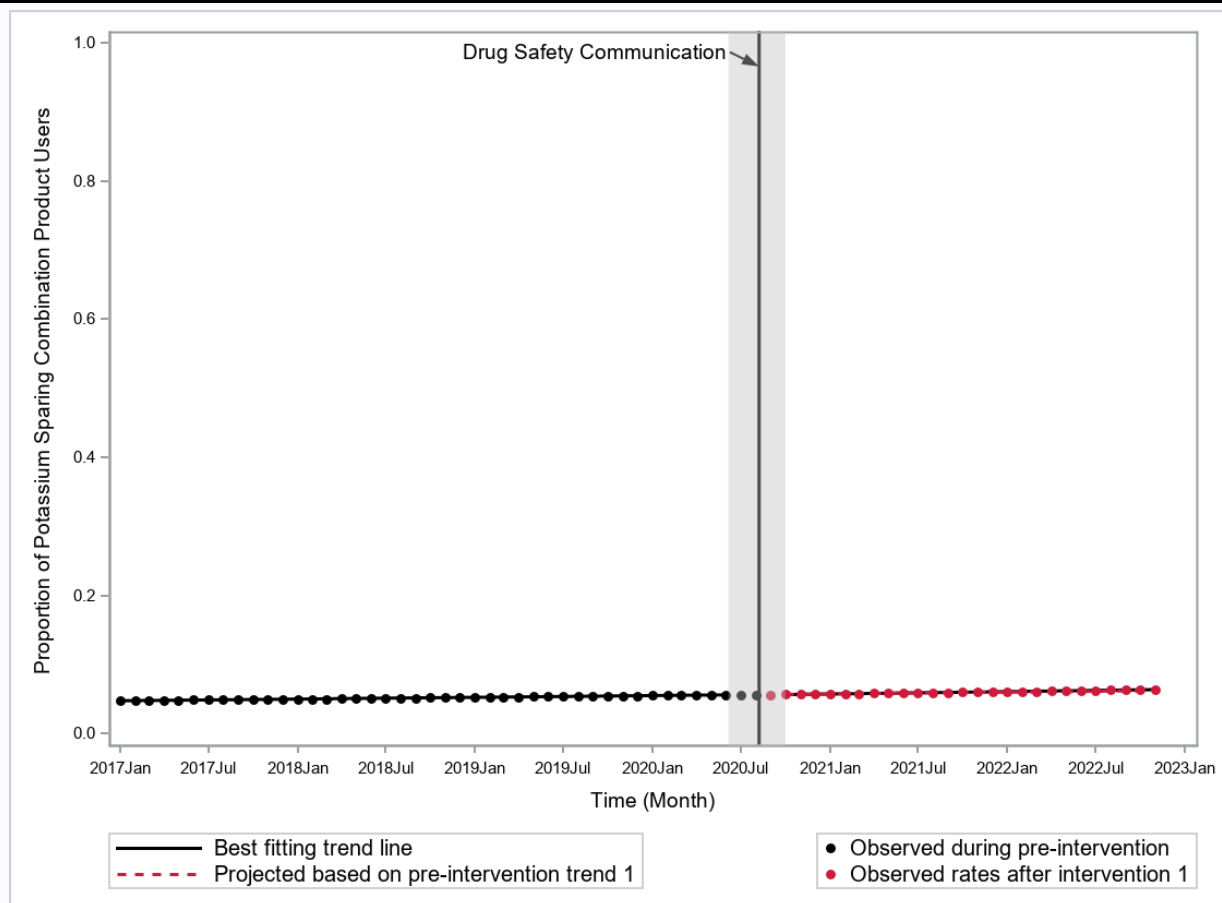
**Table 58. Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| <b>Outcome Measure</b>                                | <b>Estimate</b> | <b>95% CI</b>        | <b>Predicted Rate<br/>(With<br/>Intervention)</b> | <b>Extrapolated Rate<br/>(Without<br/>Intervention)</b> |
|-------------------------------------------------------|-----------------|----------------------|---------------------------------------------------|---------------------------------------------------------|
| Absolute Change at 26 Months after Intervention 1     | 0.001484        | (0.001031, 0.001937) | 0.063179                                          | 0.061695                                                |
| Relative Change (%) at 26 Months after Intervention 1 | 2.41            | (1.66, 3.15)         | 0.063179                                          | 0.061695                                                |
| Absolute Change at 27 Months after Intervention 1     | 0.001564        | (0.001097, 0.002030) | 0.063467                                          | 0.061903                                                |
| Absolute Change at 27 Months after Intervention 1     | 0.001564        | (0.001097, 0.002030) | 0.063467                                          | 0.061903                                                |
| Relative Change (%) at 27 Months after Intervention 1 | 2.53            | (1.76, 3.29)         | 0.063467                                          | 0.061903                                                |
| Relative Change (%) at 27 Months after Intervention 1 | 2.53            | (1.76, 3.29)         | 0.063467                                          | 0.061903                                                |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 29. Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Table 59. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup>**

|                                                                         | Estimate  | 95% CI                 | Approximate Pr >  t |
|-------------------------------------------------------------------------|-----------|------------------------|---------------------|
| <b>Initial Model Parameters (df = 62)<sup>2</sup></b>                   |           |                        |                     |
| Intercept                                                               | 0.022996  | (0.022696, 0.023296)   | <.001               |
| Baseline trend                                                          | 0.000125  | (0.000113, 0.000137)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000517 | (-0.000998, -0.000036) | 0.036               |
| Trend Change (After Intervention 1)                                     | -0.000091 | (-0.000117, -0.000065) | <.001               |
| <b>Most Parsimonious Final Model Parameters (df = 62)<sup>2,3</sup></b> |           |                        |                     |
| Intercept                                                               | 0.022996  | (0.022696, 0.023296)   | <.001               |
| Baseline trend                                                          | 0.000125  | (0.000113, 0.000137)   | <.001               |
| Level Change (After Intervention 1)                                     | -0.000517 | (-0.000998, -0.000036) | 0.036               |
| Trend Change (After Intervention 1)                                     | -0.000091 | (-0.000117, -0.000065) | <.001               |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

<sup>2</sup>Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

<sup>3</sup>Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

**Table 60. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                      | Estimate  | 95% CI          | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|------------------------------------------------------|-----------|-----------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 1 Months after Intervention 1     | N/A       | (N/A, N/A)      | N/A                                   | N/A                                         |
| Relative Change (%) at 1 Months after Intervention 1 | N/A       | (N/A, N/A)      | N/A                                   | N/A                                         |
| Absolute Change at 2 Months after Intervention 1     | -0.000699 | (-0.001203, -   | 0.028030                              | 0.028728                                    |
| Relative Change (%) at 2 Months after Intervention 1 | -2.43     | (-4.17, -0.70)  | 0.02803                               | 0.028728                                    |
| Absolute Change at 3 Months after Intervention 1     | -0.000790 | (-0.001288, -   | 0.028063                              | 0.028853                                    |
| Relative Change (%) at 3 Months after Intervention 1 | -2.74     | (-4.44, -1.03)  | 0.028063                              | 0.028853                                    |
| Absolute Change at 4 Months after Intervention 1     | -0.000880 | (-0.001373, -   | 0.028097                              | 0.028977                                    |
| Relative Change (%) at 4 Months after Intervention 1 | -3.04     | (-4.71, -1.37)  | 0.028097                              | 0.028977                                    |
| Absolute Change at 5 Months after Intervention 1     | -0.000971 | (-0.001460, -   | 0.028130                              | 0.029102                                    |
| Relative Change (%) at 5 Months after Intervention 1 | -3.34     | (-4.98, -1.69)  | 0.028130                              | 0.029102                                    |
| Absolute Change at 6 Months after Intervention 1     | -0.001062 | (-0.001549, -   | 0.028164                              | 0.029227                                    |
| Relative Change (%) at 6 Months after Intervention 1 | -3.64     | (-5.26, -2.01)  | 0.028164                              | 0.029227                                    |
| Absolute Change at 7 Months after Intervention 1     | -0.001153 | (-0.001638, -   | 0.028198                              | 0.029351                                    |
| Relative Change (%) at 7 Months after Intervention 1 | -3.93     | (-5.54, -2.32)  | 0.028198                              | 0.029351                                    |
| Absolute Change at 8 Months after Intervention 1     | -0.001244 | (-0.001729, -   | 0.028231                              | 0.029476                                    |
| Relative Change (%) at 8 Months after Intervention 1 | -4.22     | (-5.82, -2.63)  | 0.028231                              | 0.029476                                    |
| Absolute Change at 9 Months after Intervention 1     | -0.001335 | (-0.001822, -   | 0.028265                              | 0.029600                                    |
| Relative Change (%) at 9 Months after Intervention 1 | -4.51     | (-6.10, -2.92)  | 0.028265                              | 0.029600                                    |
| Absolute Change at 10 Months after Intervention 1    | -0.001426 | (-0.001916, -   | 0.028299                              | 0.029725                                    |
| Relative Change (%) at 10 Months after Intervention  | -4.80     | (-6.38, -3.21)  | 0.028299                              | 0.029725                                    |
| Absolute Change at 11 Months after Intervention 1    | -0.001517 | (-0.002011, -   | 0.028332                              | 0.029850                                    |
| Relative Change (%) at 11 Months after Intervention  | -5.08     | (-6.67, -3.50)  | 0.028332                              | 0.029850                                    |
| Absolute Change at 12 Months after Intervention 1    | -0.001608 | (-0.002108, -   | 0.028366                              | 0.029974                                    |
| Relative Change (%) at 12 Months after Intervention  | -5.36     | (-6.96, -3.77)  | 0.028366                              | 0.029974                                    |
| Absolute Change at 13 Months after Intervention 1    | -0.001699 | (-0.002206, -   | 0.028400                              | 0.030099                                    |
| Relative Change (%) at 13 Months after Intervention  | -5.64     | (-7.25, -4.04)  | 0.028400                              | 0.030099                                    |
| Absolute Change at 14 Months after Intervention 1    | -0.001790 | (-0.002305, -   | 0.028433                              | 0.030223                                    |
| Relative Change (%) at 14 Months after Intervention  | -5.92     | (-7.54, -4.31)  | 0.028433                              | 0.030223                                    |
| Absolute Change at 15 Months after Intervention 1    | -0.001881 | (-0.002405, -   | 0.028467                              | 0.030348                                    |
| Relative Change (%) at 15 Months after Intervention  | -6.20     | (-7.83, -4.56)  | 0.028467                              | 0.030348                                    |
| Absolute Change at 16 Months after Intervention 1    | -0.001972 | (-0.002506, -   | 0.028501                              | 0.030473                                    |
| Relative Change (%) at 16 Months after Intervention  | -6.47     | (-8.13, -4.81)  | 0.028501                              | 0.030473                                    |
| Absolute Change at 17 Months after Intervention 1    | -0.002063 | (-0.002609, -   | 0.028534                              | 0.030597                                    |
| Relative Change (%) at 17 Months after Intervention  | -6.74     | (-8.42, -5.06)  | 0.028534                              | 0.030597                                    |
| Absolute Change at 18 Months after Intervention 1    | -0.002154 | (-0.002712, -   | 0.028568                              | 0.030722                                    |
| Relative Change (%) at 18 Months after Intervention  | -7.01     | (-8.72, -5.30)  | 0.028568                              | 0.030722                                    |
| Absolute Change at 19 Months after Intervention 1    | -0.002245 | (-0.002817, -   | 0.028602                              | 0.030846                                    |
| Relative Change (%) at 19 Months after Intervention  | -7.28     | (-9.02, -5.54)  | 0.028602                              | 0.030846                                    |
| Absolute Change at 20 Months after Intervention 1    | -0.002336 | (-0.002922, -   | 0.028635                              | 0.030971                                    |
| Relative Change (%) at 20 Months after Intervention  | -7.54     | (-9.31, -5.77)  | 0.028635                              | 0.030971                                    |
| Absolute Change at 21 Months after Intervention 1    | -0.002427 | (-0.003028, -   | 0.028669                              | 0.031096                                    |
| Relative Change (%) at 21 Months after Intervention  | -7.80     | (-9.61, -6.00)  | 0.028669                              | 0.031096                                    |
| Absolute Change at 22 Months after Intervention 1    | -0.002518 | (-0.003135, -   | 0.028703                              | 0.031220                                    |
| Relative Change (%) at 22 Months after Intervention  | -8.06     | (-9.91, -6.22)  | 0.028703                              | 0.031220                                    |
| Absolute Change at 23 Months after Intervention 1    | -0.002609 | (-0.003242, -   | 0.028736                              | 0.031345                                    |
| Relative Change (%) at 23 Months after Intervention  | -8.32     | (-10.21, -6.44) | 0.028736                              | 0.031345                                    |
| Absolute Change at 24 Months after Intervention 1    | -0.002700 | (-0.003350, -   | 0.028770                              | 0.031470                                    |
| Relative Change (%) at 24 Months after Intervention  | -8.58     | (-10.50, -6.65) | 0.028770                              | 0.031470                                    |
| Absolute Change at 25 Months after Intervention 1    | -0.002790 | (-0.003459, -   | 0.028804                              | 0.031594                                    |
| Relative Change (%) at 25 Months after Intervention  | -8.83     | (-10.80, -6.86) | 0.028804                              | 0.031594                                    |

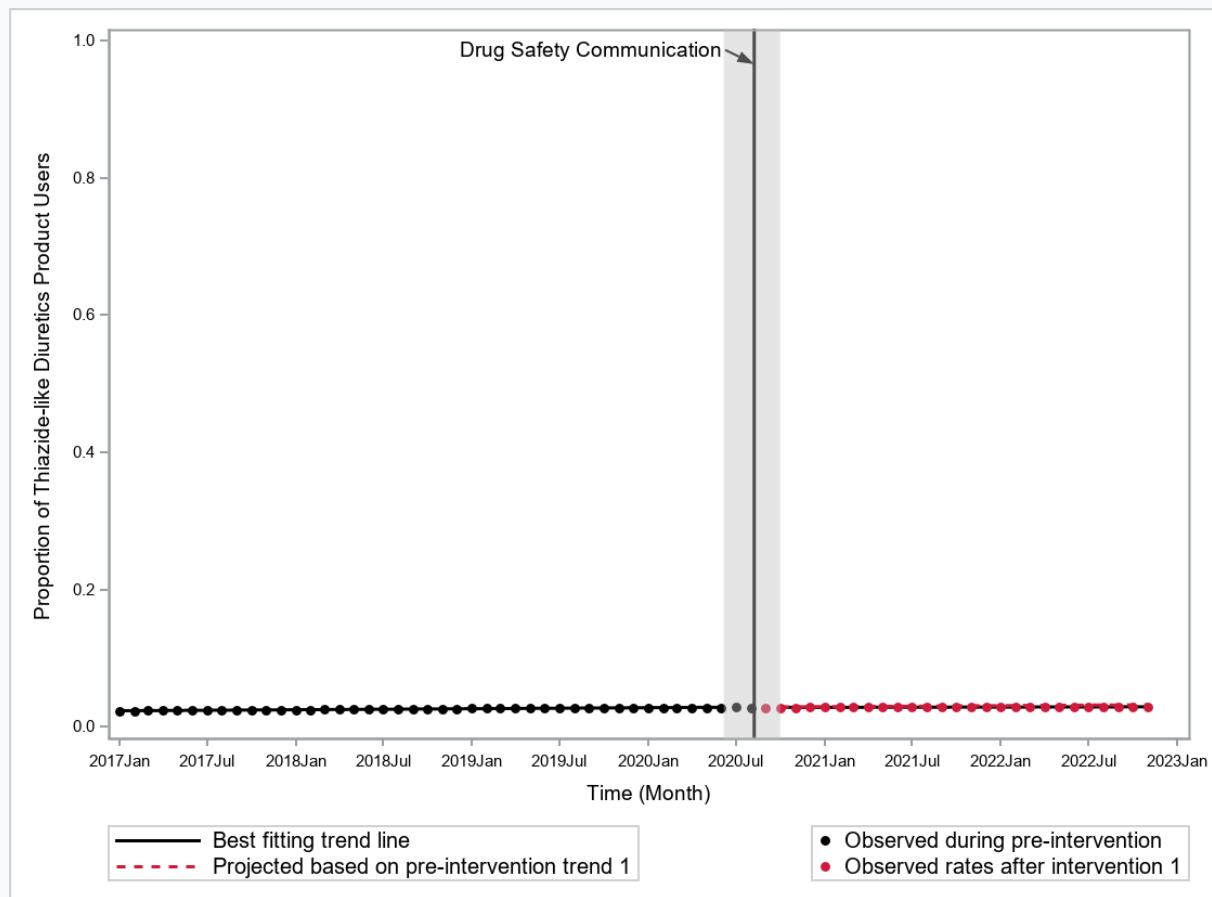
**Table 60. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives After August 8, 2020<sup>1</sup> Compared with Expected Rates Derived from Baseline Trend**

| Outcome Measure                                     | Estimate  | 95% CI          | Predicted Rate<br>(With Intervention) | Extrapolated Rate<br>(Without Intervention) |
|-----------------------------------------------------|-----------|-----------------|---------------------------------------|---------------------------------------------|
| Absolute Change at 26 Months after Intervention 1   | -0.002881 | (-0.003568, -   | 0.028837                              | 0.031719                                    |
| Relative Change (%) at 26 Months after Intervention | -9.08     | (-11.10, -7.07) | 0.028837                              | 0.031719                                    |
| Absolute Change at 27 Months after Intervention 1   | -0.002972 | (-0.003677, -   | 0.028871                              | 0.031843                                    |
| Absolute Change at 27 Months after Intervention 1   | -0.002972 | (-0.003677, -   | 0.028871                              | 0.031843                                    |
| Relative Change (%) at 27 Months after Intervention | -9.33     | (-11.39, -7.28) | 0.028871                              | 0.031843                                    |
| Relative Change (%) at 27 Months after Intervention | -9.33     | (-11.39, -7.28) | 0.028871                              | 0.031843                                    |

<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model. An anticipatory period starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the intervention was implemented.

N/A means Not Applicable.

**Figure 30. Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives Before and After August 8, 2020<sup>1,2</sup>**



<sup>1</sup>The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

<sup>2</sup>The gray box indicates the timing of the anticipatory/lag period, from July 1, 2020 to September 30, 2020, during which observations were not included in the autoregression model.

**Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (August 30, 2023)**

| Masked DP ID | DP Start Date | DP End Date <sup>1</sup> |
|--------------|---------------|--------------------------|
| DP01         | 01/01/2007    | 01/31/2023               |
| DP02         | 01/01/2008    | 12/31/2022               |
| DP03         | 01/01/2006    | 02/28/2023               |
| DP04         | 01/01/2010    | 12/31/2022               |
| DP05         | 01/01/2008    | 04/30/2023               |

<sup>1</sup>End Date represents the earliest of: (1) query end date, or (2) last day of the most recent month for which all of a Data Partner's data tables (enrollment, dispensing, etc.) have at least 80% of the record count relative to the prior month.

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                                   | Brand Name                     |
|---------------------------------------------------|--------------------------------|
| <b>HCTZ single ingredient/monotherapy</b>         |                                |
| hydrochlorothiazide                               | hydrochlorothiazide            |
| hydrochlorothiazide                               | Microzide                      |
| <b>HCTZ combination products</b>                  |                                |
| benazepril HCl/hydrochlorothiazide                | benazepril-hydrochlorothiazide |
| benazepril HCl/hydrochlorothiazide                | Lotensin HCT                   |
| captopril/hydrochlorothiazide                     | captopril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide             | enalapril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide             | Vaseretic                      |
| fosinopril sodium/hydrochlorothiazide             | fosinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                    | lisinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                    | Zestoretic                     |
| moexipril HCl/hydrochlorothiazide                 | moexipril-hydrochlorothiazide  |
| quinapril HCl/hydrochlorothiazide                 | Accuretic                      |
| quinapril HCl/hydrochlorothiazide                 | quinapril-hydrochlorothiazide  |
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| olmesartan medoxomil/amlodipine                   | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide                      |                                |
| olmesartan medoxomil/amlodipine                   | Tribenzor                      |
| besylate/hydrochlorothiazide                      |                                |
| candesartan cilexetil/hydrochlorothiazide         | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide         | candesartan-hydrochlorothiazid |
| irbesartan/hydrochlorothiazide                    | Avalide                        |
| irbesartan/hydrochlorothiazide                    | irbesartan-hydrochlorothiazide |
| losartan potassium/hydrochlorothiazide            | Hyzaar                         |
| losartan potassium/hydrochlorothiazide            | losartan-hydrochlorothiazide   |
| olmesartan medoxomil/hydrochlorothiazide          | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide          | olmesartan-hydrochlorothiazide |
| telmisartan/hydrochlorothiazide                   | Micardis HCT                   |
| telmisartan/hydrochlorothiazide                   | telmisartan-hydrochlorothiazid |
| valsartan/hydrochlorothiazide                     | Diovan HCT                     |
| valsartan/hydrochlorothiazide                     | valsartan-hydrochlorothiazide  |
| bisoprolol fumarate/hydrochlorothiazide           | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide           | Ziac                           |
| metoprolol succinate/hydrochlorothiazide          | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide          | metoprolol su-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide           | metoprolol ta-hydrochlorothiaz |
| propranolol HCl/hydrochlorothiazide               | propranolol-hydrochlorothiazid |
| methyldopa/hydrochlorothiazide                    | methyldopa-hydrochlorothiazide |
| aliskiren hemifumarate/hydrochlorothiazide        | Tekturna HCT                   |
| amiloride HCl/hydrochlorothiazide                 | amiloride-hydrochlorothiazide  |
| spironolactone/hydrochlorothiazide                | Aldactazide                    |
| spironolactone/hydrochlorothiazide                | spironolacton-hydrochlorothiaz |
| triamterene/hydrochlorothiazide                   | Dyazide                        |
| triamterene/hydrochlorothiazide                   | Maxzide                        |
| triamterene/hydrochlorothiazide                   | Maxzide-25mg                   |
| triamterene/hydrochlorothiazide                   | triamterene-hydrochlorothiazid |
| <b>HCTZ ACE inhibitor combination</b>             |                                |
| benazepril HCl/hydrochlorothiazide                | benazepril-hydrochlorothiazide |
| benazepril HCl/hydrochlorothiazide                | Lotensin HCT                   |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                                                        | Brand Name                     |
|------------------------------------------------------------------------|--------------------------------|
| captopril/hydrochlorothiazide                                          | captopril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide                                  | enalapril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide                                  | Vaseretic                      |
| fosinopril sodium/hydrochlorothiazide                                  | fosinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                                         | lisinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                                         | Zestoretic                     |
| moexipril HCl/hydrochlorothiazide                                      | moexipril-hydrochlorothiazide  |
| quinapril HCl/hydrochlorothiazide                                      | Accuretic                      |
| quinapril HCl/hydrochlorothiazide                                      | quinapril-hydrochlorothiazide  |
| <b>HCTZ ARB combination</b>                                            |                                |
| amlodipine besylate/valsartan/hydrochlorothiazide                      | amlodipine-valsartan-hcthiazid |
| candesartan cilexetil/hydrochlorothiazide                              | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide                              | candesartan-hydrochlorothiazid |
| irbesartan/hydrochlorothiazide                                         | Avalide                        |
| irbesartan/hydrochlorothiazide                                         | irbesartan-hydrochlorothiazide |
| losartan potassium/hydrochlorothiazide                                 | Hyzaar                         |
| losartan potassium/hydrochlorothiazide                                 | losartan-hydrochlorothiazide   |
| olmesartan medoxomil/hydrochlorothiazide                               | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide                               | olmesartan-hydrochlorothiazide |
| telmisartan/hydrochlorothiazide                                        | Micardis HCT                   |
| telmisartan/hydrochlorothiazide                                        | telmisartan-hydrochlorothiazid |
| valsartan/hydrochlorothiazide                                          | Diovan HCT                     |
| valsartan/hydrochlorothiazide                                          | valsartan-hydrochlorothiazide  |
| <b>HCTZ potassium sparing diuretics combination</b>                    |                                |
| amiloride HCl/hydrochlorothiazide                                      | amiloride-hydrochlorothiazide  |
| spironolactone/hydrochlorothiazide                                     | Aldactazide                    |
| spironolactone/hydrochlorothiazide                                     | spironolacton-hydrochlorothiaz |
| triamterene/hydrochlorothiazide                                        | Dyazide                        |
| triamterene/hydrochlorothiazide                                        | Maxzide                        |
| triamterene/hydrochlorothiazide                                        | Maxzide-25mg                   |
| triamterene/hydrochlorothiazide                                        | triamterene-hydrochlorothiazid |
| <b>HCTZ beta blocker combination</b>                                   |                                |
| bisoprolol fumarate/hydrochlorothiazide                                | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide                                | Ziac                           |
| metoprolol succinate/hydrochlorothiazide                               | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide                               | metoprolol su-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide                                | metoprolol ta-hydrochlorothiaz |
| propranolol HCl/hydrochlorothiazide                                    | propranolol-hydrochlorothiazid |
| <b>HCTZ ARB calcium channel blocker combination</b>                    |                                |
| amlodipine besylate/valsartan/hydrochlorothiazide                      | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide                      | Exforge HCT                    |
| olmesartan medoxomil/amlodipine                                        | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide                                           |                                |
| olmesartan medoxomil/amlodipine                                        | Tribenzor                      |
| besylate/hydrochlorothiazide                                           |                                |
| <b>Chlorothiazide, Bendroflumethiazide, or Thiazide-like diuretics</b> |                                |
| chlorthalidone                                                         | chlorthalidone                 |
| chlorthalidone                                                         | Thalitone                      |
| indapamide                                                             | indapamide                     |
| metolazone                                                             | metolazone                     |
| chlorothiazide                                                         | chlorothiazide                 |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                          | Brand Name                  |
|------------------------------------------|-----------------------------|
| chlorothiazide                           | Diuril                      |
| nadolol/bendroflumethiazide              | Corzide                     |
| nadolol/bendroflumethiazide              | nadolol-bendroflumethiazide |
| <b>Chlorothiazide</b>                    |                             |
| chlorothiazide                           | chlorothiazide              |
| chlorothiazide                           | Diuril                      |
| <b>Bendroflumethiazide</b>               |                             |
| nadolol/bendroflumethiazide              | Corzide                     |
| nadolol/bendroflumethiazide              | nadolol-bendroflumethiazide |
| <b>Thiazide-like diuretics</b>           |                             |
| chlorthalidone                           | chlorthalidone              |
| chlorthalidone                           | Thalitone                   |
| indapamide                               | indapamide                  |
| metolazone                               | metolazone                  |
| <b>ACE inhibitors</b>                    |                             |
| amlodipine besylate/benazepril HCl       | amlodipine-benazepril       |
| amlodipine besylate/benazepril HCl       | Lotrel                      |
| benazepril HCl                           | benazepril                  |
| benazepril HCl                           | Lotensin                    |
| captopril                                | captopril                   |
| enalapril maleate                        | enalapril maleate           |
| enalapril maleate                        | Epaned                      |
| enalapril maleate                        | Vasotec                     |
| fosinopril sodium                        | fosinopril                  |
| lisinopril                               | lisinopril                  |
| lisinopril                               | Prinivil                    |
| lisinopril                               | Qbrelis                     |
| lisinopril                               | Zestril                     |
| moexipril HCl                            | moexipril                   |
| perindopril arginine/amlodipine besylate | Prestalia                   |
| perindopril erbumine                     | Aceon                       |
| perindopril erbumine                     | perindopril erbumine        |
| quinapril HCl                            | Accupril                    |
| quinapril HCl                            | quinapril                   |
| ramipril                                 | Altace                      |
| ramipril                                 | ramipril                    |
| trandolapril                             | Mavik                       |
| trandolapril                             | trandolapril                |
| trandolapril/verapamil HCl               | Tarka                       |
| trandolapril/verapamil HCl               | trandolapril-verapamil      |
| <b>Calcium channel blockers</b>          |                             |
| amlodipine benzoate                      | Katerzia                    |
| amlodipine besylate                      | amlodipine                  |
| amlodipine besylate                      | Norliqva                    |
| amlodipine besylate                      | Norvasc                     |
| amlodipine besylate/celecoxib            | Consensi                    |
| diltiazem HCl                            | Cardizem                    |
| diltiazem HCl                            | Cardizem CD                 |
| diltiazem HCl                            | Cardizem LA                 |
| diltiazem HCl                            | Cartia XT                   |
| diltiazem HCl                            | diltiazem HCl               |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                                                                                                          | Brand Name                     |
|--------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| diltiazem HCl                                                                                                            | DILT-XR                        |
| diltiazem HCl                                                                                                            | Matzim LA                      |
| diltiazem HCl                                                                                                            | Taztia XT                      |
| diltiazem HCl                                                                                                            | Tiadyt ER                      |
| diltiazem HCl                                                                                                            | Tiazac                         |
| felodipine                                                                                                               | felodipine                     |
| isradipine                                                                                                               | isradipine                     |
| levamlodipine maleate                                                                                                    | Conjupri                       |
| levamlodipine maleate                                                                                                    | levamlodipine                  |
| nicardipine HCl                                                                                                          | nicardipine                    |
| nifedipine                                                                                                               | Adalat CC                      |
| nifedipine                                                                                                               | Afeditab CR                    |
| nifedipine                                                                                                               | Nifedical XL                   |
| nifedipine                                                                                                               | nifedipine                     |
| nifedipine                                                                                                               | Procardia                      |
| nifedipine                                                                                                               | Procardia XL                   |
| nimodipine                                                                                                               | nimodipine                     |
| nimodipine                                                                                                               | Nymalize                       |
| nisoldipine                                                                                                              | nisoldipine                    |
| nisoldipine                                                                                                              | Sular                          |
| verapamil HCl                                                                                                            | Calan                          |
| verapamil HCl                                                                                                            | Calan SR                       |
| verapamil HCl                                                                                                            | verapamil                      |
| verapamil HCl                                                                                                            | Verelan                        |
| verapamil HCl                                                                                                            | Verelan PM                     |
| <b>Potassium-sparing diuretics</b>                                                                                       |                                |
| amiloride HCl                                                                                                            | amiloride                      |
| eplerenone                                                                                                               | eplerenone                     |
| eplerenone                                                                                                               | Inspira                        |
| spironolactone                                                                                                           | Aldactone                      |
| spironolactone                                                                                                           | CaroSpir                       |
| spironolactone                                                                                                           | spironolactone                 |
| triamterene                                                                                                              | Dyrenium                       |
| triamterene                                                                                                              | triamterene                    |
| <b>Loop diuretics</b>                                                                                                    |                                |
| bumetanide                                                                                                               | bumetanide                     |
| ethacrynic acid                                                                                                          | Edecrin                        |
| ethacrynic acid                                                                                                          | ethacrynic acid                |
| furosemide                                                                                                               | furosemide                     |
| furosemide                                                                                                               | Lasix                          |
| torsemide                                                                                                                | Demadex                        |
| torsemide                                                                                                                | Soaanz                         |
| torsemide                                                                                                                | torsemide                      |
| <b>Limited denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide or thiazide-like diuretics)</b> |                                |
| aliskiren hemifumarate/hydrochlorothiazide                                                                               | Tekturna HCT                   |
| amiloride HCl/hydrochlorothiazide                                                                                        | amiloride-hydrochlorothiazide  |
| amlodipine besylate/valsartan/hydrochlorothiazide                                                                        | amlodipine-valsartan-hcthiacid |
| amlodipine besylate/valsartan/hydrochlorothiazide                                                                        | Exforge HCT                    |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                           | Brand Name                     |
|-------------------------------------------|--------------------------------|
| benazepril HCl/hydrochlorothiazide        | benazepril-hydrochlorothiazide |
| benazepril HCl/hydrochlorothiazide        | Lotensin HCT                   |
| bisoprolol fumarate/hydrochlorothiazide   | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide   | Ziac                           |
| candesartan cilexetil/hydrochlorothiazide | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide | candesartan-hydrochlorothiazid |
| captopril/hydrochlorothiazide             | captopril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide     | enalapril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide     | Vaseretic                      |
| fosinopril sodium/hydrochlorothiazide     | fosinopril-hydrochlorothiazide |
| hydrochlorothiazide                       | hydrochlorothiazide            |
| hydrochlorothiazide                       | Microzide                      |
| irbesartan/hydrochlorothiazide            | Avalide                        |
| irbesartan/hydrochlorothiazide            | irbesartan-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide            | lisinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide            | Zestoretic                     |
| losartan potassium/hydrochlorothiazide    | Hyzaar                         |
| losartan potassium/hydrochlorothiazide    | losartan-hydrochlorothiazide   |
| methyldopa/hydrochlorothiazide            | methyldopa-hydrochlorothiazide |
| metoprolol succinate/hydrochlorothiazide  | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide  | metoprolol su-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide   | metoprolol ta-hydrochlorothiaz |
| moexipril HCl/hydrochlorothiazide         | moexipril-hydrochlorothiazide  |
| olmesartan medoxomil/amlodipine           | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide              |                                |
| olmesartan medoxomil/amlodipine           | Tribenzor                      |
| besylate/hydrochlorothiazide              |                                |
| olmesartan medoxomil/hydrochlorothiazide  | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide  | olmesartan-hydrochlorothiazide |
| propranolol HCl/hydrochlorothiazide       | propranolol-hydrochlorothiazid |
| quinapril HCl/hydrochlorothiazide         | Accuretic                      |
| quinapril HCl/hydrochlorothiazide         | quinapril-hydrochlorothiazide  |
| spironolactone/hydrochlorothiazide        | Aldactazide                    |
| spironolactone/hydrochlorothiazide        | spironolacton-hydrochlorothiaz |
| telmisartan/hydrochlorothiazide           | Micardis HCT                   |
| telmisartan/hydrochlorothiazide           | telmisartan-hydrochlorothiazid |
| triamterene/hydrochlorothiazide           | Dyazide                        |
| triamterene/hydrochlorothiazide           | Maxzide                        |
| triamterene/hydrochlorothiazide           | Maxzide-25mg                   |
| triamterene/hydrochlorothiazide           | triamterene-hydrochlorothiazid |
| valsartan/hydrochlorothiazide             | Diovan HCT                     |
| valsartan/hydrochlorothiazide             | valsartan-hydrochlorothiazide  |
| chlorothiazide                            | chlorothiazide                 |
| chlorothiazide                            | Diuril                         |
| nadolol/bendroflumethiazide               | Corzide                        |
| nadolol/bendroflumethiazide               | nadolol-bendroflumethiazide    |
| chlorthalidone                            | chlorthalidone                 |
| chlorthalidone                            | Thalitone                      |
| indapamide                                | indapamide                     |
| metolazone                                | metolazone                     |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                                                                                                 | Brand Name                     |
|-----------------------------------------------------------------------------------------------------------------|--------------------------------|
| Full denominator (any HCTZ-containing products, any thiazide diuretics, any diuretics or any antihypertensives) |                                |
| aliskiren hemifumarate/hydrochlorothiazide                                                                      | Tekturna HCT                   |
| amiloride HCl/hydrochlorothiazide                                                                               | amiloride-hydrochlorothiazide  |
| amlodipine besylate/valsartan/hydrochlorothiazide                                                               | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide                                                               | Exforge HCT                    |
| benazepril HCl/hydrochlorothiazide                                                                              | benazepril-hydrochlorothiazide |
| benazepril HCl/hydrochlorothiazide                                                                              | Lotensin HCT                   |
| bisoprolol fumarate/hydrochlorothiazide                                                                         | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide                                                                         | Ziac                           |
| candesartan cilexetil/hydrochlorothiazide                                                                       | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide                                                                       | candesartan-hydrochlorothiazid |
| captopril/hydrochlorothiazide                                                                                   | captopril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide                                                                           | enalapril-hydrochlorothiazide  |
| enalapril maleate/hydrochlorothiazide                                                                           | Vaseretic                      |
| fosinopril sodium/hydrochlorothiazide                                                                           | fosinopril-hydrochlorothiazide |
| hydrochlorothiazide                                                                                             | hydrochlorothiazide            |
| hydrochlorothiazide                                                                                             | Microzide                      |
| irbesartan/hydrochlorothiazide                                                                                  | Avalide                        |
| irbesartan/hydrochlorothiazide                                                                                  | irbesartan-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                                                                                  | lisinopril-hydrochlorothiazide |
| lisinopril/hydrochlorothiazide                                                                                  | Zestoretic                     |
| losartan potassium/hydrochlorothiazide                                                                          | Hyzaar                         |
| losartan potassium/hydrochlorothiazide                                                                          | losartan-hydrochlorothiazide   |
| methyldopa/hydrochlorothiazide                                                                                  | methyldopa-hydrochlorothiazide |
| metoprolol succinate/hydrochlorothiazide                                                                        | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide                                                                        | metoprolol su-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide                                                                         | metoprolol ta-hydrochlorothiaz |
| moexipril HCl/hydrochlorothiazide                                                                               | moexipril-hydrochlorothiazide  |
| olmesartan medoxomil/amlodipine                                                                                 | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide                                                                                    |                                |
| olmesartan medoxomil/amlodipine                                                                                 | Tribenzor                      |
| besylate/hydrochlorothiazide                                                                                    |                                |
| olmesartan medoxomil/hydrochlorothiazide                                                                        | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide                                                                        | olmesartan-hydrochlorothiazide |
| propranolol HCl/hydrochlorothiazide                                                                             | propranolol-hydrochlorothiazid |
| quinapril HCl/hydrochlorothiazide                                                                               | Accuretic                      |
| quinapril HCl/hydrochlorothiazide                                                                               | quinapril-hydrochlorothiazide  |
| spironolactone/hydrochlorothiazide                                                                              | Aldactazide                    |
| spironolactone/hydrochlorothiazide                                                                              | spironolacton-hydrochlorothiaz |
| telmisartan/hydrochlorothiazide                                                                                 | Micardis HCT                   |
| telmisartan/hydrochlorothiazide                                                                                 | telmisartan-hydrochlorothiazid |
| triamterene/hydrochlorothiazide                                                                                 | Dyazide                        |
| triamterene/hydrochlorothiazide                                                                                 | Maxzide                        |
| triamterene/hydrochlorothiazide                                                                                 | Maxzide-25mg                   |
| triamterene/hydrochlorothiazide                                                                                 | triamterene-hydrochlorothiazid |
| valsartan/hydrochlorothiazide                                                                                   | Diovan HCT                     |
| valsartan/hydrochlorothiazide                                                                                   | valsartan-hydrochlorothiazide  |
| chlorothiazide                                                                                                  | chlorothiazide                 |
| chlorothiazide                                                                                                  | Diuril                         |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                          | Brand Name                  |
|------------------------------------------|-----------------------------|
| nadolol/bendroflumethiazide              | Corzide                     |
| nadolol/bendroflumethiazide              | nadolol-bendroflumethiazide |
| chlorthalidone                           | chlorthalidone              |
| chlorthalidone                           | Thalitone                   |
| indapamide                               | indapamide                  |
| metolazone                               | metolazone                  |
| amlodipine besylate/benazepril HCl       | amlodipine-benazepril       |
| amlodipine besylate/benazepril HCl       | Lotrel                      |
| benazepril HCl                           | benazepril                  |
| benazepril HCl                           | Lotensin                    |
| captopril                                | captopril                   |
| enalapril maleate                        | enalapril maleate           |
| enalapril maleate                        | Epaned                      |
| enalapril maleate                        | Vasotec                     |
| fosinopril sodium                        | fosinopril                  |
| lisinopril                               | lisinopril                  |
| lisinopril                               | Prinivil                    |
| lisinopril                               | Qbrelis                     |
| lisinopril                               | Zestril                     |
| moexipril HCl                            | moexipril                   |
| perindopril arginine/amlodipine besylate | Prestalia                   |
| perindopril erbumine                     | Aceon                       |
| perindopril erbumine                     | perindopril erbumine        |
| quinapril HCl                            | Accupril                    |
| quinapril HCl                            | quinapril                   |
| ramipril                                 | Altace                      |
| ramipril                                 | ramipril                    |
| trandolapril                             | Mavik                       |
| trandolapril                             | trandolapril                |
| trandolapril/verapamil HCl               | Tarka                       |
| trandolapril/verapamil HCl               | trandolapril-verapamil      |
| amlodipine benzoate                      | Katerzia                    |
| amlodipine besylate                      | amlodipine                  |
| amlodipine besylate                      | Norliqva                    |
| amlodipine besylate                      | Norvasc                     |
| amlodipine besylate/celecoxib            | Consensi                    |
| diltiazem HCl                            | Cardizem                    |
| diltiazem HCl                            | Cardizem CD                 |
| diltiazem HCl                            | Cardizem LA                 |
| diltiazem HCl                            | Cartia XT                   |
| diltiazem HCl                            | diltiazem HCl               |
| diltiazem HCl                            | DILT-XR                     |
| diltiazem HCl                            | Matzim LA                   |
| diltiazem HCl                            | Taztia XT                   |
| diltiazem HCl                            | Tiadyt ER                   |
| diltiazem HCl                            | Tiazac                      |
| felodipine                               | felodipine                  |
| isradipine                               | isradipine                  |
| levamlodipine maleate                    | Conjupri                    |
| levamlodipine maleate                    | levamlodipine               |
| nicardipine HCl                          | nicardipine                 |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                                   | Brand Name                     |
|---------------------------------------------------|--------------------------------|
| nifedipine                                        | Adalat CC                      |
| nifedipine                                        | Afeditab CR                    |
| nifedipine                                        | Nifedical XL                   |
| nifedipine                                        | nifedipine                     |
| nifedipine                                        | Procardia                      |
| nifedipine                                        | Procardia XL                   |
| nimodipine                                        | nimodipine                     |
| nimodipine                                        | Nymalize                       |
| nisoldipine                                       | nisoldipine                    |
| nisoldipine                                       | Sular                          |
| verapamil HCl                                     | Calan                          |
| verapamil HCl                                     | Calan SR                       |
| verapamil HCl                                     | verapamil                      |
| verapamil HCl                                     | Verelan                        |
| verapamil HCl                                     | Verelan PM                     |
| amiloride HCl                                     | amiloride                      |
| eplerenone                                        | eplerenone                     |
| eplerenone                                        | Inspira                        |
| spironolactone                                    | Aldactone                      |
| spironolactone                                    | CaroSpir                       |
| spironolactone                                    | spironolactone                 |
| triamterene                                       | Dyrenium                       |
| triamterene                                       | triamterene                    |
| bumetanide                                        | bumetanide                     |
| ethacrynic acid                                   | Edecrin                        |
| ethacrynic acid                                   | ethacrynic acid                |
| furosemide                                        | furosemide                     |
| furosemide                                        | Lasix                          |
| torsemide                                         | Demadex                        |
| torsemide                                         | Soaanz                         |
| torsemide                                         | torsemide                      |
| <b>ARB Generics</b>                               |                                |
| amlodipine besylate/olmesartan medoxomil          | amlodipine-olmesartan          |
| amlodipine besylate/olmesartan medoxomil          | amlodipine-olmesartan          |
| amlodipine besylate/olmesartan medoxomil          | amlodipine-olmesartan          |
| amlodipine besylate/olmesartan medoxomil          | amlodipine-olmesartan          |
| amlodipine besylate/olmesartan medoxomil          | Azor                           |
| amlodipine besylate/olmesartan medoxomil          | Azor                           |
| amlodipine besylate/olmesartan medoxomil          | Azor                           |
| amlodipine besylate/olmesartan medoxomil          | Azor                           |
| amlodipine besylate/valsartan                     | amlodipine-valsartan           |
| amlodipine besylate/valsartan                     | amlodipine-valsartan           |
| amlodipine besylate/valsartan                     | amlodipine-valsartan           |
| amlodipine besylate/valsartan                     | amlodipine-valsartan           |
| amlodipine besylate/valsartan                     | Exforge                        |
| amlodipine besylate/valsartan                     | Exforge                        |
| amlodipine besylate/valsartan                     | Exforge                        |
| amlodipine besylate/valsartan                     | Exforge                        |
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                                   | Brand Name                     |
|---------------------------------------------------|--------------------------------|
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide | amlodipine-valsartan-hcthiazid |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| amlodipine besylate/valsartan/hydrochlorothiazide | Exforge HCT                    |
| azilsartan medoxomil                              | Edarbi                         |
| azilsartan medoxomil                              | Edarbi                         |
| azilsartan medoxomil/chlorthalidone               | Edarbyclor                     |
| azilsartan medoxomil/chlorthalidone               | Edarbyclor                     |
| candesartan cilexetil                             | Atacand                        |
| candesartan cilexetil                             | Atacand                        |
| candesartan cilexetil                             | Atacand                        |
| candesartan cilexetil                             | Atacand                        |
| candesartan cilexetil                             | candesartan                    |
| candesartan cilexetil                             | candesartan                    |
| candesartan cilexetil                             | candesartan                    |
| candesartan cilexetil                             | candesartan                    |
| candesartan cilexetil/hydrochlorothiazide         | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide         | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide         | Atacand HCT                    |
| candesartan cilexetil/hydrochlorothiazide         | candesartan-hydrochlorothiazid |
| candesartan cilexetil/hydrochlorothiazide         | candesartan-hydrochlorothiazid |
| candesartan cilexetil/hydrochlorothiazide         | candesartan-hydrochlorothiazid |
| eprosartan mesylate                               | eprosartan                     |
| irbesartan                                        | Avapro                         |
| irbesartan                                        | Avapro                         |
| irbesartan                                        | Avapro                         |
| irbesartan                                        | irbesartan                     |
| irbesartan                                        | irbesartan                     |
| irbesartan                                        | irbesartan                     |
| irbesartan/hydrochlorothiazide                    | Avalide                        |
| irbesartan/hydrochlorothiazide                    | Avalide                        |
| irbesartan/hydrochlorothiazide                    | irbesartan-hydrochlorothiazide |
| irbesartan/hydrochlorothiazide                    | irbesartan-hydrochlorothiazide |
| losartan potassium                                | Cozaar                         |
| losartan potassium                                | Cozaar                         |
| losartan potassium                                | Cozaar                         |
| losartan potassium                                | losartan                       |
| losartan potassium                                | losartan                       |
| losartan potassium                                | losartan                       |
| losartan potassium/hydrochlorothiazide            | Hyzaar                         |
| losartan potassium/hydrochlorothiazide            | Hyzaar                         |
| losartan potassium/hydrochlorothiazide            | Hyzaar                         |
| losartan potassium/hydrochlorothiazide            | losartan-hydrochlorothiazide   |
| losartan potassium/hydrochlorothiazide            | losartan-hydrochlorothiazide   |
| losartan potassium/hydrochlorothiazide            | losartan-hydrochlorothiazide   |
| nebivolol HCl/valsartan                           | Byvalson                       |
| olmesartan medoxomil                              | Benicar                        |
| olmesartan medoxomil                              | Benicar                        |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                          | Brand Name                     |
|------------------------------------------|--------------------------------|
| olmesartan medoxomil                     | Benicar                        |
| olmesartan medoxomil                     | olmesartan                     |
| olmesartan medoxomil                     | olmesartan                     |
| olmesartan medoxomil                     | olmesartan                     |
| olmesartan medoxomil/amlodipine          | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | olmesartan-amlodipin-hcthiazid |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | Tribenzor                      |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | Tribenzor                      |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | Tribenzor                      |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | Tribenzor                      |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/amlodipine          | Tribenzor                      |
| besylate/hydrochlorothiazide             |                                |
| olmesartan medoxomil/hydrochlorothiazide | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide | Benicar HCT                    |
| olmesartan medoxomil/hydrochlorothiazide | olmesartan-hydrochlorothiazide |
| olmesartan medoxomil/hydrochlorothiazide | olmesartan-hydrochlorothiazide |
| olmesartan medoxomil/hydrochlorothiazide | olmesartan-hydrochlorothiazide |
| sacubitril/valsartan                     | Entresto                       |
| sacubitril/valsartan                     | Entresto                       |
| sacubitril/valsartan                     | Entresto                       |
| telmisartan                              | Micardis                       |
| telmisartan                              | Micardis                       |
| telmisartan                              | Micardis                       |
| telmisartan                              | telmisartan                    |
| telmisartan                              | telmisartan                    |
| telmisartan                              | telmisartan                    |
| telmisartan/amlodipine besylate          | telmisartan-amlodipine         |
| telmisartan/amlodipine besylate          | telmisartan-amlodipine         |
| telmisartan/amlodipine besylate          | telmisartan-amlodipine         |
| telmisartan/amlodipine besylate          | telmisartan-amlodipine         |
| telmisartan/amlodipine besylate          | Twynsta                        |
| telmisartan/amlodipine besylate          | Twynsta                        |
| telmisartan/amlodipine besylate          | Twynsta                        |
| telmisartan/amlodipine besylate          | Twynsta                        |
| telmisartan/hydrochlorothiazide          | Micardis HCT                   |
| telmisartan/hydrochlorothiazide          | Micardis HCT                   |
| telmisartan/hydrochlorothiazide          | Micardis HCT                   |
| telmisartan/hydrochlorothiazide          | telmisartan-hydrochlorothiazid |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                         | Brand Name                     |
|-----------------------------------------|--------------------------------|
| telmisartan/hydrochlorothiazide         | telmisartan-hydrochlorothiazid |
| telmisartan/hydrochlorothiazide         | telmisartan-hydrochlorothiazid |
| valsartan                               | Diovan                         |
| valsartan                               | Diovan                         |
| valsartan                               | Diovan                         |
| valsartan                               | Diovan                         |
| valsartan                               | valsartan                      |
| valsartan                               | valsartan                      |
| valsartan                               | valsartan                      |
| valsartan                               | valsartan                      |
| valsartan                               | valsartan                      |
| valsartan/hydrochlorothiazide           | Diovan HCT                     |
| valsartan/hydrochlorothiazide           | Diovan HCT                     |
| valsartan/hydrochlorothiazide           | Diovan HCT                     |
| valsartan/hydrochlorothiazide           | Diovan HCT                     |
| valsartan/hydrochlorothiazide           | Diovan HCT                     |
| valsartan/hydrochlorothiazide           | valsartan-hydrochlorothiazide  |
| valsartan/hydrochlorothiazide           | valsartan-hydrochlorothiazide  |
| valsartan/hydrochlorothiazide           | valsartan-hydrochlorothiazide  |
| valsartan/hydrochlorothiazide           | valsartan-hydrochlorothiazide  |
| valsartan/hydrochlorothiazide           | valsartan-hydrochlorothiazide  |
| <b>Beta Blockers Generic</b>            |                                |
| acebutolol HCl                          | acebutolol                     |
| acebutolol HCl                          | acebutolol                     |
| acebutolol HCl                          | Sectral                        |
| acebutolol HCl                          | Sectral                        |
| atenolol                                | atenolol                       |
| atenolol                                | atenolol                       |
| atenolol                                | atenolol                       |
| atenolol                                | Tenormin                       |
| atenolol                                | Tenormin                       |
| atenolol                                | Tenormin                       |
| atenolol/chlorthalidone                 | atenolol-chlorthalidone        |
| atenolol/chlorthalidone                 | atenolol-chlorthalidone        |
| atenolol/chlorthalidone                 | Tenoretic 100                  |
| atenolol/chlorthalidone                 | Tenoretic 50                   |
| betaxolol HCl                           | betaxolol                      |
| betaxolol HCl                           | betaxolol                      |
| bisoprolol fumarate                     | bisoprolol fumarate            |
| bisoprolol fumarate                     | bisoprolol fumarate            |
| bisoprolol fumarate                     | Zebeta                         |
| bisoprolol fumarate                     | Zebeta                         |
| bisoprolol fumarate/hydrochlorothiazide | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide | bisoprolol-hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide | Ziac                           |
| bisoprolol fumarate/hydrochlorothiazide | Ziac                           |
| bisoprolol fumarate/hydrochlorothiazide | Ziac                           |
| carvedilol                              | carvedilol                     |
| carvedilol                              | carvedilol                     |
| carvedilol                              | carvedilol                     |

## Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request

| Non-Proprietary                               | Brand Name                     |
|-----------------------------------------------|--------------------------------|
| carvedilol                                    | carvedilol                     |
| carvedilol                                    | Coreg                          |
| carvedilol                                    | Coreg                          |
| carvedilol                                    | Coreg                          |
| carvedilol                                    | Coreg                          |
| carvedilol phosphate                          | carvedilol phosphate           |
| carvedilol phosphate                          | carvedilol phosphate           |
| carvedilol phosphate                          | carvedilol phosphate           |
| carvedilol phosphate                          | carvedilol phosphate           |
| carvedilol phosphate                          | Coreg CR                       |
| carvedilol phosphate                          | Coreg CR                       |
| carvedilol phosphate                          | Coreg CR                       |
| carvedilol phosphate                          | Coreg CR                       |
| esmolol HCl                                   | Brevibloc                      |
| esmolol HCl                                   | esmolol                        |
| esmolol HCl                                   | esmolol                        |
| esmolol HCl in sodium chloride, iso-osmotic   | Brevibloc in NaCl (iso-osm)    |
| esmolol HCl in sodium chloride, iso-osmotic   | Brevibloc in NaCl (iso-osm)    |
| esmolol HCl in sodium chloride, iso-osmotic   | esmolol in NaCl (iso-osm)      |
| esmolol HCl in sodium chloride, iso-osmotic   | esmolol in NaCl (iso-osm)      |
| esmolol HCl in sterile water                  | esmolol in sterile water       |
| esmolol HCl in sterile water                  | esmolol in sterile water       |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl                                 | labetalol                      |
| labetalol HCl in dextrose, iso-osmotic        | labetalol in dextrose,iso-osm  |
| labetalol HCl in sodium chloride, iso-osmotic | labetalol in NaCl (iso-osmot)  |
| labetalol in dextrose 5 % in water            | labetalol in dextrose 5 %      |
| metoprolol succinate                          | Kaspargo Sprinkle              |
| metoprolol succinate                          | Kaspargo Sprinkle              |
| metoprolol succinate                          | Kaspargo Sprinkle              |
| metoprolol succinate                          | Kaspargo Sprinkle              |
| metoprolol succinate                          | metoprolol succinate           |
| metoprolol succinate                          | metoprolol succinate           |
| metoprolol succinate                          | metoprolol succinate           |
| metoprolol succinate                          | metoprolol succinate           |
| metoprolol succinate                          | Toprol XL                      |
| metoprolol succinate                          | Toprol XL                      |
| metoprolol succinate                          | Toprol XL                      |
| metoprolol succinate                          | Toprol XL                      |
| metoprolol succinate/hydrochlorothiazide      | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide      | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide      | Dutoprol                       |
| metoprolol succinate/hydrochlorothiazide      | metoprolol su-hydrochlorothiaz |
| metoprolol succinate/hydrochlorothiazide      | metoprolol su-hydrochlorothiaz |
| metoprolol succinate/hydrochlorothiazide      | metoprolol su-hydrochlorothiaz |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                         | Brand Name                     |
|-----------------------------------------|--------------------------------|
| metoprolol tartrate                     | Lopressor                      |
| metoprolol tartrate                     | Lopressor                      |
| metoprolol tartrate                     | Lopressor                      |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate                     | metoprolol tartrate            |
| metoprolol tartrate/hydrochlorothiazide | metoprolol ta-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide | metoprolol ta-hydrochlorothiaz |
| metoprolol tartrate/hydrochlorothiazide | metoprolol ta-hydrochlorothiaz |
| nadolol                                 | Corgard                        |
| nadolol                                 | Corgard                        |
| nadolol                                 | Corgard                        |
| nadolol                                 | nadolol                        |
| nadolol                                 | nadolol                        |
| nadolol                                 | nadolol                        |
| nadolol/bendroflumethiazide             | Corzide                        |
| nadolol/bendroflumethiazide             | Corzide                        |
| nadolol/bendroflumethiazide             | nadolol-bendroflumethiazide    |
| nadolol/bendroflumethiazide             | nadolol-bendroflumethiazide    |
| nebivolol HCl                           | Bystolic                       |
| nebivolol HCl                           | Bystolic                       |
| nebivolol HCl                           | Bystolic                       |
| nebivolol HCl                           | Bystolic                       |
| nebivolol HCl                           | nebivolol                      |
| nebivolol HCl                           | nebivolol                      |
| nebivolol HCl                           | nebivolol                      |
| nebivolol HCl                           | nebivolol                      |
| nebivolol HCl                           | nebivolol                      |
| pindolol                                | pindolol                       |
| pindolol                                | pindolol                       |
| propranolol HCl                         | Hemangeol                      |
| propranolol HCl                         | Inderal LA                     |
| propranolol HCl                         | Inderal LA                     |
| propranolol HCl                         | Inderal LA                     |
| propranolol HCl                         | Inderal LA                     |
| propranolol HCl                         | Inderal XL                     |
| propranolol HCl                         | Inderal XL                     |
| propranolol HCl                         | InnoPran XL                    |
| propranolol HCl                         | InnoPran XL                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |
| propranolol HCl                         | propranolol                    |

**Appendix B. Non-Proprietary and Brand Names of Medical Products Used to Define Exposures in this Request**

| Non-Proprietary                     | Brand Name                     |
|-------------------------------------|--------------------------------|
| propranolol HCl                     | propranolol                    |
| propranolol HCl                     | propranolol                    |
| propranolol HCl                     | propranolol                    |
| propranolol HCl/hydrochlorothiazide | propranolol-hydrochlorothiazid |
| propranolol HCl/hydrochlorothiazide | propranolol-hydrochlorothiazid |
| sotalol HCl                         | Betapace                       |
| sotalol HCl                         | Betapace                       |
| sotalol HCl                         | Betapace                       |
| sotalol HCl                         | Betapace                       |
| sotalol HCl                         | Betapace AF                    |
| sotalol HCl                         | Betapace AF                    |
| sotalol HCl                         | Betapace AF                    |
| sotalol HCl                         | Sorine                         |
| sotalol HCl                         | Sorine                         |
| sotalol HCl                         | Sorine                         |
| sotalol HCl                         | Sorine                         |
| sotalol HCl                         | sotalol                        |
| sotalol HCl                         | sotalol                        |
| sotalol HCl                         | sotalol                        |
| sotalol HCl                         | sotalol                        |
| sotalol HCl                         | sotalol                        |
| sotalol HCl                         | Sotalol AF                     |
| sotalol HCl                         | Sotalol AF                     |
| sotalol HCl                         | Sotalol AF                     |
| sotalol HCl                         | Sotylyze                       |
| timolol maleate                     | timolol maleate                |
| timolol maleate                     | timolol maleate                |
| timolol maleate                     | timolol maleate                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 1                                                                                                  | Multiple Events Group 2                                                                                                  |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: HCTZ-containing products                                                                                      | Numerator: HCTZ single ingredient/monotherapy                                                                            |
| Multiple Events | Multiple Events Composition (Primary)                | denom_limited                                                                                                            | denom_limited                                                                                                            |
|                 | Multiple Events Composition (Secondary)              | hctz_containing_all                                                                                                      | hctz_mono_all                                                                                                            |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics |
|                 | ITS Numerator                                        | Number of patients with use of any HCTZ-containing product                                                               | Number of patients with use of HCTZ single ingredient                                                                    |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 1A                                                                                                          | ITS Analysis 2A                                                                                                          |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date2 | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 1                                           | Multiple Events Group 2                                           |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 1B                                                   | ITS Analysis 2B                                                   |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 3                                                                                                  | Multiple Events Group 4                                                                                                  |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: ACEI + HCTZ                                                                                                   | Numerator: ARB + HCTZ                                                                                                    |
| Multiple Events | Multiple Events Composition (Primary)                | denom_limited                                                                                                            | denom_limited                                                                                                            |
|                 | Multiple Events Composition (Secondary)              | hctz_acei_combo                                                                                                          | hctz_arb_combo                                                                                                           |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics |
|                 | ITS Numerator                                        | Number of patients with use of ACEI + HCTZ combo product                                                                 | Number of patients with use of ARB + HCTZ combo product                                                                  |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 3A                                                                                                          | ITS Analysis 4A                                                                                                          |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 3                                           | Multiple Events Group 4                                           |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 3B                                                   | ITS Analysis 4B                                                   |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 5                                                                                                  | Multiple Events Group 6                                                                                                  |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: Potassium-sparing diuretic + HCTZ                                                                             | Numerator: Beta blocker + HCTZ                                                                                           |
| Multiple Events | Multiple Events Composition (Primary)                | denom_limited                                                                                                            | denom_limited                                                                                                            |
|                 | Multiple Events Composition (Secondary)              | hctz_potass_combo                                                                                                        | hctz_beta_combo                                                                                                          |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics |
|                 | ITS Numerator                                        | Number of patients with use of potassium-sparing diuretic + HCTZ combo product                                           | Number of patients with use of beta blocker + HCTZ combo product                                                         |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 5A                                                                                                          | ITS Analysis 6A                                                                                                          |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 5                                           | Multiple Events Group 6                                           |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 5B                                                   | ITS Analysis 6B                                                   |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 7                                                                                                  | Multiple Events Group 8                                                                                                  |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: ARB + CCB + HCTZ                                                                                              | Numerator: Direct renin inhibitor + HCTZ                                                                                 |
| Multiple Events | Multiple Events Composition (Primary)                | denom_limited                                                                                                            | denom_limited                                                                                                            |
|                 | Multiple Events Composition (Secondary)              | hctz_arb_ccb_combo                                                                                                       | hctz_direct                                                                                                              |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics |
|                 | ITS Numerator                                        | Number of patients with use of ARB + CCB + HCTZ combo product                                                            | Number of patients with use of direct renin inhibitor + HCTZ combo product                                               |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 7A                                                                                                          | ITS Analysis 8A                                                                                                          |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 7                                           | Multiple Events Group 8                                           |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
|              |                                                      | ITS Analysis 7B                                                   | ITS Analysis 8B                                                   |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
| ITS Analysis | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 9                                                                                                  | Multiple Events Group 10                                                                                                 |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: Central alpha 2 agonist + HCTZ                                                                                | Numerator: HCTZ-containing products                                                                                      |
| Multiple Events | Multiple Events Composition (Primary)                | denom_limited                                                                                                            | denom_all                                                                                                                |
|                 | Multiple Events Composition (Secondary)              | hctz_central                                                                                                             | hctz_containing_all                                                                                                      |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives |
|                 | ITS Numerator                                        | Number of patients with use of central alpha 2 agonist + HCTZ combo product                                              | Number of patients with use of HCTZ-containing products                                                                  |
|                 | Observation Window around Primary Episode            | All enrollment history before and after index date                                                                       | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 9A                                                                                                          | ITS Analysis 10A                                                                                                         |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 9                                           | Multiple Events Group 10                                          |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 9B                                                   | ITS Analysis 10B                                                  |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 11                                                                                                 | Multiple Events Group 12                                                                                                 |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: Chlorothiazide, bendroflumethiazide, or thiazide-like diuretics                                               | Numerator: ACEIs (non-HCTZ combination)                                                                                  |
| Multiple Events | Multiple Events Composition (Primary)                | denom_all                                                                                                                | denom_all                                                                                                                |
|                 | Multiple Events Composition (Secondary)              | other_thiazide_plus                                                                                                      | other_acei                                                                                                               |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives |
|                 | ITS Numerator                                        | Number of patients with use of chlorothiazide, bendroflumethiazide, or thiazide-like diuretics                           | Number of patients with use of ACEIs (non-HCTZ combination)                                                              |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 11A                                                                                                         | ITS Analysis 12A                                                                                                         |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 11                                          | Multiple Events Group 12                                          |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 11B                                                  | ITS Analysis 12B                                                  |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 13                                                                                                 | Multiple Events Group 14                                                                                                 |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: CCBs (non-HCTZ combination)                                                                                   | Numerator: Potassium-sparing diuretics (non-HCTZ combination)                                                            |
| Multiple Events | Multiple Events Composition (Primary)                | denom_all                                                                                                                | denom_all                                                                                                                |
|                 | Multiple Events Composition (Secondary)              | other_ccb                                                                                                                | other_potass                                                                                                             |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives |
|                 | ITS Numerator                                        | Number of patients with use of CCBs (non-HCTZ combination)                                                               | Number of patients with use of potassium-sparing diuretics (non-HCTZ combination)                                        |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 13A                                                                                                         | ITS Analysis 14A                                                                                                         |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 13                                          | Multiple Events Group 14                                          |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 13B                                                  | ITS Analysis 14B                                                  |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 15                                                                                                 | Multiple Events Group 16                                                                                                 |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: Loop diuretics                                                                                                | Numerator: ARBs (non-HCTZ combination)                                                                                   |
| Multiple Events | Multiple Events Composition (Primary)                | denom_all                                                                                                                | denom_all                                                                                                                |
|                 | Multiple Events Composition (Secondary)              | other_loop                                                                                                               | other_arbs                                                                                                               |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives |
|                 | ITS Numerator                                        | Number of patients with use of loop diuretics                                                                            | Number of patients with use of ARBs (non-HCTZ combination)                                                               |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 15A                                                                                                         | ITS Analysis 14A                                                                                                         |
|                 |                                                      | Intervention date 8/8/2020                                                                                               | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

|              |                                                      | Multiple Events Group 15                                          | Multiple Events Group 16                                          |
|--------------|------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis |                                                      | ITS Analysis 15B                                                  | ITS Analysis 14B                                                  |
|              |                                                      | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 | Anticipatory/lag period from 6/1/2020 - 10/1/2020                 |
|              | Data Range Start, End                                | 1/1/2017 - most recent available data                             | 1/1/2017 - most recent available data                             |
|              | Anticipatory/Lag Period                              | 6/1/2020 - 10/1/2020                                              | 6/1/2020 - 10/1/2020                                              |
|              | Intervention Date                                    | 8/8/2020                                                          | 8/8/2020                                                          |
|              | Truncation of Exposure Episode at Intervention Date? | Yes                                                               | Yes                                                               |
|              | Interval Length                                      | Monthly                                                           | Monthly                                                           |
|              | p-value                                              | 0.05                                                              | 0.05                                                              |
|              | Autoregression Lag                                   | 12 (12 months)                                                    | 12 (12 months)                                                    |
|              | Autoregression Model Parameter Cutoff                | 0.2                                                               | 0.2                                                               |
|              | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end | All available months between intervention date and data range end |
|              | Continuous Enrollment Required?                      | No                                                                | No                                                                |

# Appendix C. Specifications Defining Parameters for this Request

|                 |                                                      | Multiple Events Group 17                                                                                                 |
|-----------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                 |                                                      | Numerator: Beta blockers (non-HCTZ combination)                                                                          |
| Multiple Events | Multiple Events Composition (Primary)                | denom_all                                                                                                                |
|                 | Multiple Events Composition (Secondary)              | other_bb                                                                                                                 |
|                 | ITS Denominator                                      | Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives |
|                 | ITS Numerator                                        | Number of patients with use of beta blockers (non-HCTZ combination)                                                      |
|                 | Observation Window around Primary Episode            | Start of primary episode (index date) to end of primary episode                                                          |
|                 | Secondary Episode to Use for Time Metrics            | First occurrence of secondary index                                                                                      |
|                 | Minimum Cutoff to be Considered Adherent             | 1 adherent episode                                                                                                       |
|                 | Categories for Length of Primary Episode             | N/A                                                                                                                      |
|                 |                                                      | ITS Analysis 15A                                                                                                         |
|                 |                                                      | Intervention date 8/8/2020                                                                                               |
| ITS Analysis    | Data Range Start, End                                | 1/1/2017 - most recent available data                                                                                    |
|                 | Anticipatory Date Period                             | N/A                                                                                                                      |
|                 | Intervention Date                                    | 8/8/2020                                                                                                                 |
|                 | Truncation of Exposure Episode at Intervention Date? | Yes                                                                                                                      |
|                 | Interval Length                                      | Monthly                                                                                                                  |
|                 | p-value                                              | 0.05                                                                                                                     |
|                 | Autoregression Lag                                   | 12 (12 months)                                                                                                           |
|                 | Autoregression Model Parameter Cutoff                | 0.2                                                                                                                      |
|                 | Time Points at which to Report Difference Metrics    | All available months between intervention date and data range end                                                        |
|                 | Continuous Enrollment Required?                      | No                                                                                                                       |

# Appendix C. Specifications Defining Parameters for this Request

| Multiple Events Group 17                          |                                                                   |
|---------------------------------------------------|-------------------------------------------------------------------|
| ITS Analysis 15B                                  |                                                                   |
| Anticipatory/lag period from 6/1/2020 - 10/1/2020 |                                                                   |
| ITS Analysis                                      | Data Range Start, End                                             |
|                                                   | 1/1/2017 - most recent available data                             |
|                                                   | Anticipatory/Lag Period                                           |
|                                                   | 6/1/2020 - 10/1/2020                                              |
|                                                   | Intervention Date                                                 |
|                                                   | 8/8/2020                                                          |
|                                                   | Truncation of Exposure Episode at Intervention Date?              |
|                                                   | Yes                                                               |
|                                                   | Interval Length                                                   |
|                                                   | Monthly                                                           |
|                                                   | p-value                                                           |
|                                                   | 0.05                                                              |
|                                                   | Autoregression Lag                                                |
|                                                   | 12 (12 months)                                                    |
|                                                   | Autoregression Model Parameter Cutoff                             |
|                                                   | 0.2                                                               |
|                                                   | Time Points at which to Report Difference Metrics                 |
|                                                   | All available months between intervention date and data range end |
|                                                   | Continuous Enrollment Required?                                   |
|                                                   | No                                                                |

N/A: Not applicable