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The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

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_nsd2_v01 (Report 2, ITS)

Request ID: cder_mpl2p_wp046_nsd2_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 with and without history of skin cancer 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 two of a two-part analysis and 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 2. Please refer to Report 2 for the Appendices.

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

Exposures 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 single ingredient HCTZ product with strength < 25 mg, any single ingredient HCTZ product with 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.

Inclusion Criteria: We required patients with history of skin cancer to have evidence of skin cancer diagnosis in all enrollment history.

Exclusion Criteria: We required patients without history of skin cancer to have no evidence of skin cancer diagnosis in all enrollment history. We defined skin cancer using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes. See Appendix C for diagnosis codes used to define the outcome.

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).

Overview for Request: cder_mpl2p_wp046_nsd2_v01 (Report 2, ITS)

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)¹ 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:

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 Appendices C.1-C.2 for the specifications of parameters used in the analyses for this request.

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

Notes: Please contact the Sentinel Operations Center (info@sentinelssystem.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.sentinelssystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse>).

¹Food and Drug Administration (FDA). 2020 Drug Safety Communications. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer>. Last updated August 20, 2020. Accessed January 22, 2021.

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No Skin Cancer Analysis Results, with Anticipatory Period

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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.1 Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

Appendix C.2 Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsd1_v01)

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 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.

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

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.

Glossary of Terms for Analyses Using

Cohort Identification and Descriptive Analysis (CIDA) Module*

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 Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.155399	(0.154485, 0.156312)	<.001
Baseline trend	-0.000272	(-0.000306, -0.000239)	<.001
Level Change (After Intervention 1)	-0.000481	(-0.001113, 0.000151)	0.134
Trend Change (After Intervention 1)	-0.000102	(-0.000187, -0.000018)	0.018
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.155399	(0.154485, 0.156312)	<.001
Baseline trend	-0.000272	(-0.000306, -0.000239)	<.001
Level Change (After Intervention 1)	-0.000481	(-0.001113, 0.000151)	0.134
Trend Change (After Intervention 1)	-0.000102	(-0.000187, -0.000018)	0.018

¹The 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.

²Maximum 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.

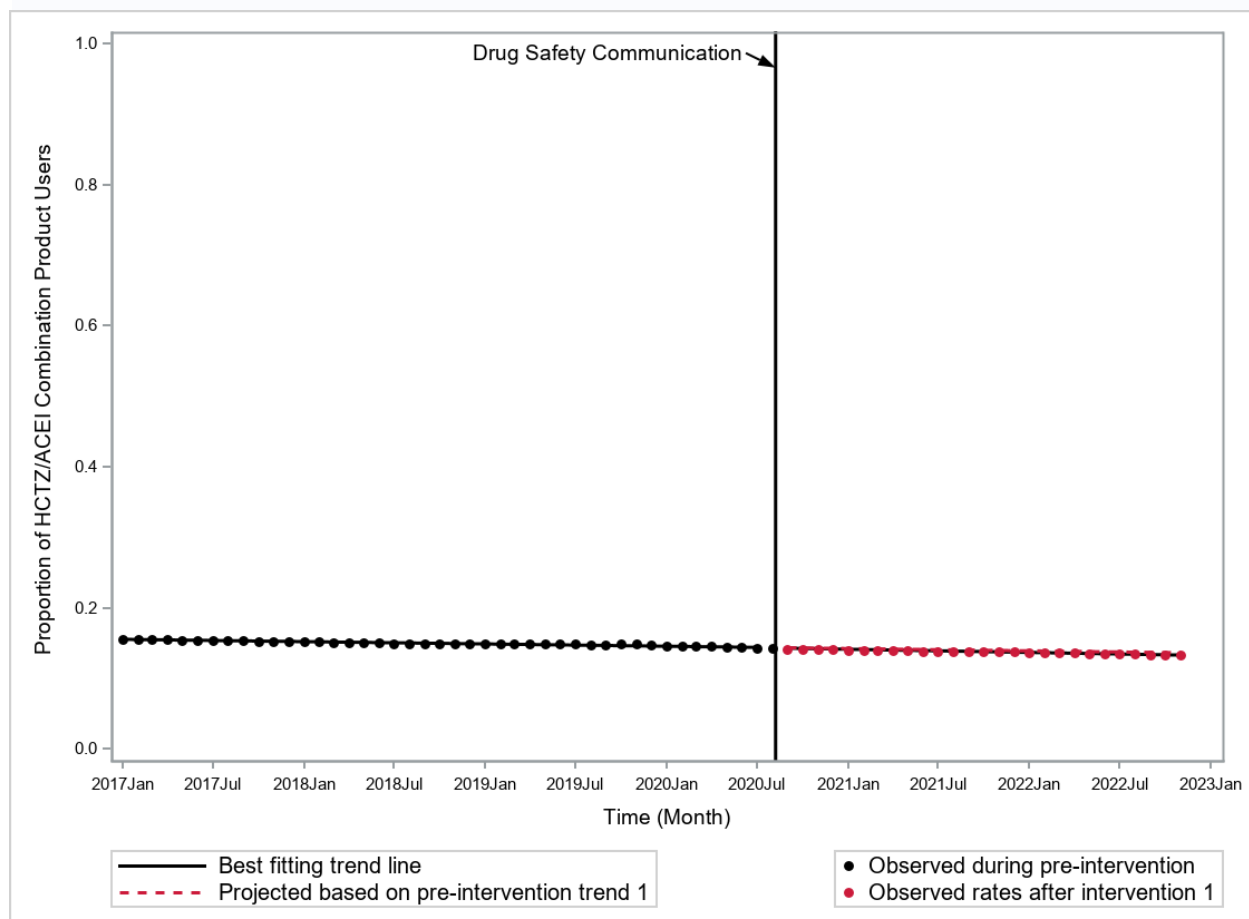
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 2. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEI) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer after August 8, 2020¹ 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	-0.000583	(-0.001230, 0.000064)	0.142555	0.143138
Relative Change (%) at 1 Months after Intervention 1	-0.41	(-0.86, 0.04)	0.142555	0.143138
Absolute Change at 2 Months after Intervention 1	-0.000686	(-0.001334, -0.000037)	0.142180	0.142866
Relative Change (%) at 2 Months after Intervention 1	-0.48	(-0.93, -0.03)	0.142180	0.142866
Absolute Change at 3 Months after Intervention 1	-0.000788	(-0.001450, -0.000126)	0.141805	0.142593
Relative Change (%) at 3 Months after Intervention 1	-0.55	(-1.02, -0.09)	0.141805	0.142593
Absolute Change at 4 Months after Intervention 1	-0.000890	(-0.001577, -0.000204)	0.141430	0.142321
Relative Change (%) at 4 Months after Intervention 1	-0.63	(-1.11, -0.15)	0.141430	0.142321
Absolute Change at 5 Months after Intervention 1	-0.000993	(-0.001714, -0.000272)	0.141055	0.142048
Relative Change (%) at 5 Months after Intervention 1	-0.70	(-1.20, -0.19)	0.141055	0.142048
Absolute Change at 6 Months after Intervention 1	-0.001095	(-0.001859, -0.000331)	0.140681	0.141776
Relative Change (%) at 6 Months after Intervention 1	-0.77	(-1.31, -0.24)	0.140681	0.141776
Absolute Change at 7 Months after Intervention 1	-0.001198	(-0.002012, -0.000383)	0.140306	0.141503
Relative Change (%) at 7 Months after Intervention 1	-0.85	(-1.42, -0.28)	0.140306	0.141503
Absolute Change at 8 Months after Intervention 1	-0.001300	(-0.002170, -0.000430)	0.139931	0.141231
Relative Change (%) at 8 Months after Intervention 1	-0.92	(-1.53, -0.31)	0.139931	0.141231
Absolute Change at 9 Months after Intervention 1	-0.001402	(-0.002333, -0.000471)	0.139556	0.140958
Relative Change (%) at 9 Months after Intervention 1	-0.99	(-1.65, -0.34)	0.139556	0.140958
Absolute Change at 10 Months after Intervention 1	-0.001505	(-0.002501, -0.000509)	0.139181	0.140686
Relative Change (%) at 10 Months after Intervention 1	-1.07	(-1.77, -0.37)	0.139181	0.140686
Absolute Change at 11 Months after Intervention 1	-0.001607	(-0.002671, -0.000543)	0.138806	0.140413
Relative Change (%) at 11 Months after Intervention 1	-1.14	(-1.89, -0.40)	0.138806	0.140413
Absolute Change at 12 Months after Intervention 1	-0.001709	(-0.002844, -0.000575)	0.138431	0.140141
Relative Change (%) at 12 Months after Intervention 1	-1.22	(-2.02, -0.42)	0.138431	0.140141
Absolute Change at 13 Months after Intervention 1	-0.001812	(-0.003020, -0.000604)	0.138057	0.139868
Relative Change (%) at 13 Months after Intervention 1	-1.30	(-2.15, -0.44)	0.138057	0.139868
Absolute Change at 14 Months after Intervention 1	-0.001914	(-0.003197, -0.000631)	0.137682	0.139596
Relative Change (%) at 14 Months after Intervention 1	-1.37	(-2.28, -0.46)	0.137682	0.139596
Absolute Change at 15 Months after Intervention 1	-0.002017	(-0.003376, -0.000657)	0.137307	0.139324
Relative Change (%) at 15 Months after Intervention 1	-1.45	(-2.41, -0.48)	0.137307	0.139324
Absolute Change at 16 Months after Intervention 1	-0.002119	(-0.003556, -0.000682)	0.136932	0.139051
Relative Change (%) at 16 Months after Intervention 1	-1.52	(-2.54, -0.50)	0.136932	0.139051
Absolute Change at 17 Months after Intervention 1	-0.002221	(-0.003737, -0.000706)	0.136557	0.138779
Relative Change (%) at 17 Months after Intervention 1	-1.60	(-2.68, -0.52)	0.136557	0.138779
Absolute Change at 18 Months after Intervention 1	-0.002324	(-0.003919, -0.000729)	0.136182	0.138506
Relative Change (%) at 18 Months after Intervention 1	-1.68	(-2.81, -0.54)	0.136182	0.138506
Absolute Change at 19 Months after Intervention 1	-0.002426	(-0.004102, -0.000751)	0.135808	0.138234
Relative Change (%) at 19 Months after Intervention 1	-1.76	(-2.95, -0.56)	0.135808	0.138234
Absolute Change at 20 Months after Intervention 1	-0.002529	(-0.004285, -0.000772)	0.135433	0.137961
Relative Change (%) at 20 Months after Intervention 1	-1.83	(-3.09, -0.58)	0.135433	0.137961
Absolute Change at 21 Months after Intervention 1	-0.002631	(-0.004469, -0.000793)	0.135058	0.137689
Relative Change (%) at 21 Months after Intervention 1	-1.91	(-3.23, -0.59)	0.135058	0.137689
Absolute Change at 22 Months after Intervention 1	-0.002733	(-0.004654, -0.000813)	0.134683	0.137416
Relative Change (%) at 22 Months after Intervention 1	-1.99	(-3.37, -0.61)	0.134683	0.137416
Absolute Change at 23 Months after Intervention 1	-0.002836	(-0.004839, -0.000832)	0.134308	0.137144
Relative Change (%) at 23 Months after Intervention 1	-2.07	(-3.51, -0.63)	0.134308	0.137144
Absolute Change at 24 Months after Intervention 1	-0.002938	(-0.005025, -0.000852)	0.133933	0.136871
Relative Change (%) at 24 Months after Intervention 1	-2.15	(-3.65, -0.64)	0.133933	0.136871
Absolute Change at 25 Months after Intervention 1	-0.003040	(-0.005210, -0.000871)	0.133558	0.136599
Relative Change (%) at 25 Months after Intervention 1	-2.23	(-3.79, -0.66)	0.133558	0.136599
Absolute Change at 26 Months after Intervention 1	-0.003143	(-0.005396, -0.000889)	0.133184	0.136326
Relative Change (%) at 26 Months after Intervention 1	-2.31	(-3.93, -0.68)	0.133184	0.136326
Absolute Change at 27 Months after Intervention 1	-0.003245	(-0.005583, -0.000908)	0.132809	0.136054
Relative Change (%) at 27 Months after Intervention 1	-2.39	(-4.08, -0.69)	0.132809	0.136054

¹The 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 Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.004389	(0.004149, 0.004629)	<.001
Baseline trend	-0.000030	(-0.000039, -0.000021)	<.001
Level Change (After Intervention 1)	-0.000001	(-0.000084, 0.000081)	0.975
Trend Change (After Intervention 1)	-0.000004	(-0.000025, 0.000017)	0.704
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.004416	(0.004210, 0.004623)	<.001
Baseline trend	-0.000031	(-0.000036, -0.000026)	<.001

¹The 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.

²Maximum 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.

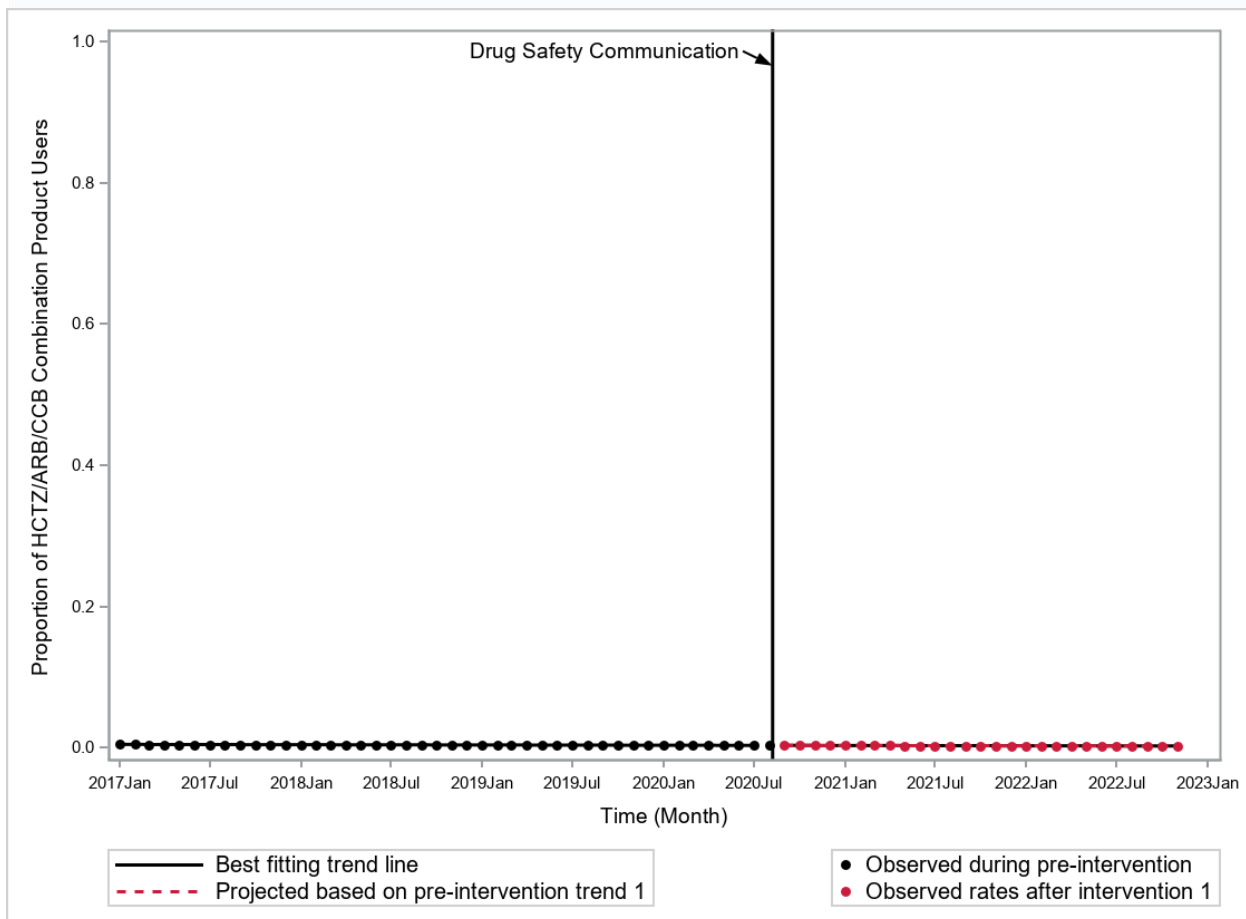
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000000	(0.000000, 0.000000)	0.003007	0.003007
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.003007	0.003007
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002976	0.002976
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.002976	0.002976
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002944	0.002944
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.002944	0.002944
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002913	0.002913
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.002913	0.002913
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002882	0.002882
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.002882	0.002882
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002850	0.002850
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.002850	0.002850
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002819	0.002819
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.002819	0.002819
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002788	0.002788
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.002788	0.002788
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002756	0.002756
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.002756	0.002756
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002725	0.002725
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.002725	0.002725
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002694	0.002694
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.002694	0.002694
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002662	0.002662
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.002662	0.002662
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002631	0.002631
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.002631	0.002631
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002600	0.002600
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.002600	0.002600
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002568	0.002568
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.002568	0.002568
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002537	0.002537
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.002537	0.002537
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002506	0.002506
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.002506	0.002506
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002474	0.002474
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.002474	0.002474
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002443	0.002443
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.002443	0.002443
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002412	0.002412
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.002412	0.002412
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002380	0.002380
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.002380	0.002380
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002349	0.002349
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.002349	0.002349
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002318	0.002318
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.002318	0.002318
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002287	0.002287
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.002287	0.002287
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002255	0.002255
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.002255	0.002255
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002224	0.002224
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.002224	0.002224
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002193	0.002193
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.002193	0.002193
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.002193	0.002193

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.257409	(0.242020, 0.272799)	<.001
Baseline trend	-0.001482	(-0.002031, -0.000934)	<.001
Level Change (After Intervention 1)	-0.000259	(-0.002786, 0.002269)	0.839
Trend Change (After Intervention 1)	0.001267	(-0.000077, 0.002611)	0.064
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.257192	(0.241931, 0.272454)	<.001
Baseline trend	-0.001472	(-0.002012, -0.000932)	<.001
Trend Change (After Intervention 1)	0.001226	(-0.000056, 0.002507)	0.061

¹The 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.

²Maximum 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.

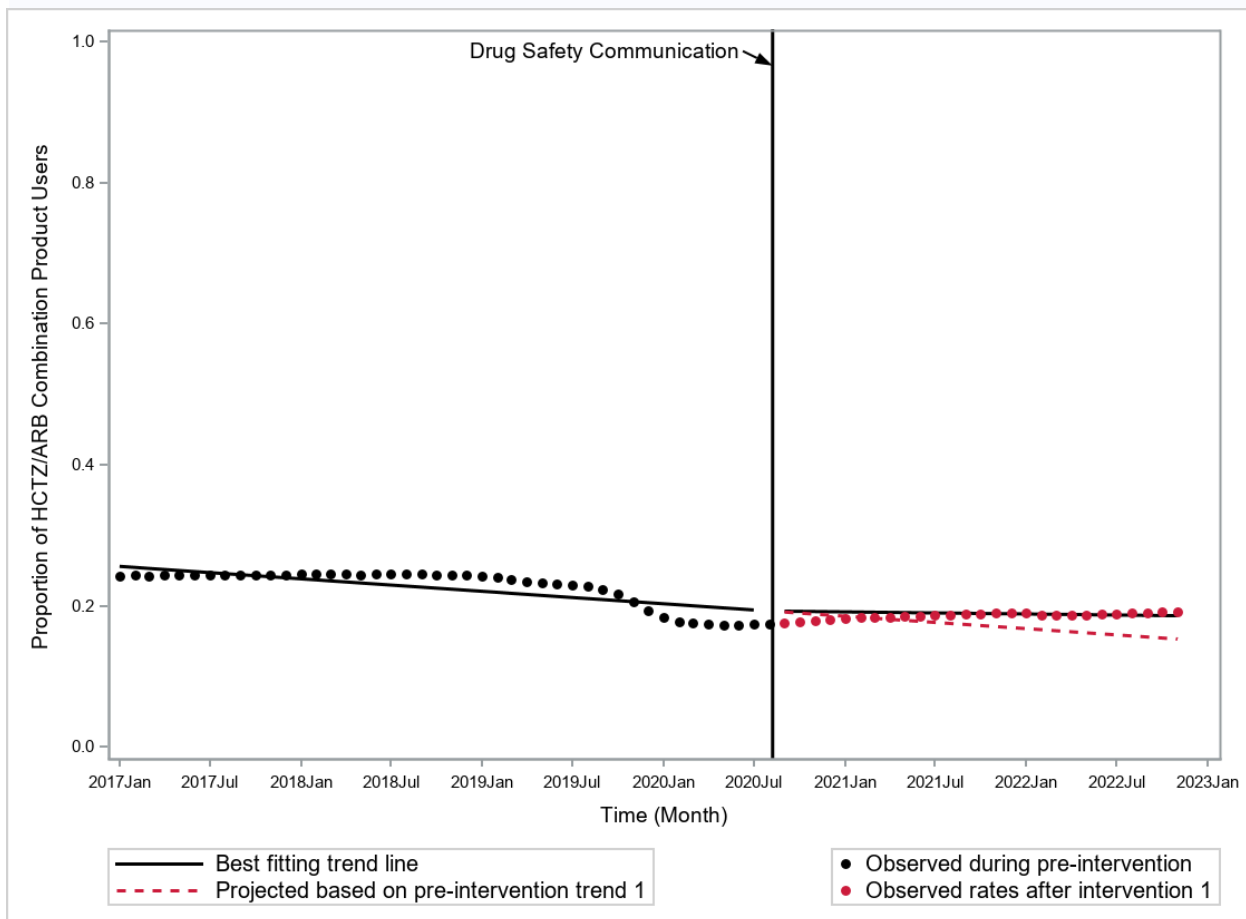
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.001226	(-0.000087, 0.002538)	0.192178	0.190953
Relative Change (%) at 1 Months after Intervention 1	0.64	(-0.09, 1.37)	0.192178	0.190953
Absolute Change at 2 Months after Intervention 1	0.002451	(-0.000174, 0.005076)	0.191932	0.189481
Relative Change (%) at 2 Months after Intervention 1	1.29	(-0.18, 2.76)	0.191932	0.189481
Absolute Change at 3 Months after Intervention 1	0.003677	(-0.000261, 0.007614)	0.191686	0.188009
Relative Change (%) at 3 Months after Intervention 1	1.96	(-0.27, 4.18)	0.191686	0.188009
Absolute Change at 4 Months after Intervention 1	0.004902	(-0.000348, 0.010152)	0.191439	0.186537
Relative Change (%) at 4 Months after Intervention 1	2.63	(-0.38, 5.63)	0.191439	0.186537
Absolute Change at 5 Months after Intervention 1	0.006128	(-0.000435, 0.012690)	0.191193	0.185065
Relative Change (%) at 5 Months after Intervention 1	3.31	(-0.48, 7.11)	0.191193	0.185065
Absolute Change at 6 Months after Intervention 1	0.007353	(-0.000522, 0.015228)	0.190946	0.183593
Relative Change (%) at 6 Months after Intervention 1	4.01	(-0.60, 8.61)	0.190946	0.183593
Absolute Change at 7 Months after Intervention 1	0.008579	(-0.000609, 0.017766)	0.190700	0.182121
Relative Change (%) at 7 Months after Intervention 1	4.71	(-0.72, 10.14)	0.190700	0.182121
Absolute Change at 8 Months after Intervention 1	0.009804	(-0.000696, 0.020304)	0.190453	0.180649
Relative Change (%) at 8 Months after Intervention 1	5.43	(-0.84, 11.70)	0.190453	0.180649
Absolute Change at 9 Months after Intervention 1	0.011030	(-0.000782, 0.022842)	0.190207	0.179177
Relative Change (%) at 9 Months after Intervention 1	6.16	(-0.98, 13.29)	0.190207	0.179177
Absolute Change at 10 Months after Intervention 1	0.012255	(-0.000869, 0.025380)	0.189960	0.177705
Relative Change (%) at 10 Months after Intervention 1	6.90	(-1.12, 14.91)	0.189960	0.177705
Absolute Change at 11 Months after Intervention 1	0.013481	(-0.000956, 0.027918)	0.189714	0.176233
Relative Change (%) at 11 Months after Intervention 1	7.65	(-1.26, 16.56)	0.189714	0.176233
Absolute Change at 12 Months after Intervention 1	0.014706	(-0.001043, 0.030456)	0.189467	0.174761
Relative Change (%) at 12 Months after Intervention 1	8.42	(-1.42, 18.25)	0.189467	0.174761
Absolute Change at 13 Months after Intervention 1	0.015932	(-0.001130, 0.032994)	0.189221	0.173289
Relative Change (%) at 13 Months after Intervention 1	9.19	(-1.58, 19.97)	0.189221	0.173289
Absolute Change at 14 Months after Intervention 1	0.017158	(-0.001217, 0.035532)	0.188975	0.171817
Relative Change (%) at 14 Months after Intervention 1	9.99	(-1.76, 21.73)	0.188975	0.171817
Absolute Change at 15 Months after Intervention 1	0.018383	(-0.001304, 0.038070)	0.188728	0.170345
Relative Change (%) at 15 Months after Intervention 1	10.79	(-1.94, 23.52)	0.188728	0.170345
Absolute Change at 16 Months after Intervention 1	0.019609	(-0.001391, 0.040608)	0.188482	0.168873
Relative Change (%) at 16 Months after Intervention 1	11.61	(-2.13, 25.35)	0.188482	0.168873
Absolute Change at 17 Months after Intervention 1	0.020834	(-0.001478, 0.043146)	0.188235	0.167401
Relative Change (%) at 17 Months after Intervention 1	12.45	(-2.33, 27.22)	0.188235	0.167401
Absolute Change at 18 Months after Intervention 1	0.022060	(-0.001565, 0.045684)	0.187989	0.165929
Relative Change (%) at 18 Months after Intervention 1	13.29	(-2.54, 29.12)	0.187989	0.165929
Absolute Change at 19 Months after Intervention 1	0.023285	(-0.001652, 0.048222)	0.187742	0.164457
Relative Change (%) at 19 Months after Intervention 1	14.16	(-2.76, 31.07)	0.187742	0.164457
Absolute Change at 20 Months after Intervention 1	0.024511	(-0.001739, 0.050760)	0.187496	0.162985
Relative Change (%) at 20 Months after Intervention 1	15.04	(-2.99, 33.06)	0.187496	0.162985
Absolute Change at 21 Months after Intervention 1	0.025736	(-0.001826, 0.053298)	0.187249	0.161513
Relative Change (%) at 21 Months after Intervention 1	15.93	(-3.23, 35.10)	0.187249	0.161513
Absolute Change at 22 Months after Intervention 1	0.026962	(-0.001913, 0.055836)	0.187003	0.160041
Relative Change (%) at 22 Months after Intervention 1	16.85	(-3.48, 37.18)	0.187003	0.160041
Absolute Change at 23 Months after Intervention 1	0.028187	(-0.002000, 0.058374)	0.186756	0.158569
Relative Change (%) at 23 Months after Intervention 1	17.78	(-3.75, 39.30)	0.186756	0.158569
Absolute Change at 24 Months after Intervention 1	0.029413	(-0.002087, 0.060912)	0.186510	0.157097
Relative Change (%) at 24 Months after Intervention 1	18.72	(-4.03, 41.48)	0.186510	0.157097
Absolute Change at 25 Months after Intervention 1	0.030638	(-0.002174, 0.063450)	0.186264	0.155625
Relative Change (%) at 25 Months after Intervention 1	19.69	(-4.32, 43.70)	0.186264	0.155625
Absolute Change at 26 Months after Intervention 1	0.031864	(-0.002261, 0.065988)	0.186017	0.154153
Relative Change (%) at 26 Months after Intervention 1	20.67	(-4.63, 45.97)	0.186017	0.154153
Absolute Change at 27 Months after Intervention 1	0.033089	(-0.002347, 0.068526)	0.185771	0.152681
Relative Change (%) at 27 Months after Intervention 1	21.67	(-4.96, 48.30)	0.185771	0.152681
Absolute Change at 27 Months after Intervention 1	0.033089	(-0.002347, 0.068526)	0.185771	0.152681
Relative Change (%) at 27 Months after Intervention 1	21.67	(-4.96, 48.30)	0.185771	0.152681

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.020350	(0.020268, 0.020432)	<.001
Baseline trend	-0.000068	(-0.000071, -0.000065)	<.001
Level Change (After Intervention 1)	0.000011	(-0.000090, 0.000112)	0.830
Trend Change (After Intervention 1)	0.000008	(0.000000, 0.000015)	0.040
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.020348	(0.020269, 0.020427)	<.001
Baseline trend	-0.000068	(-0.000071, -0.000065)	<.001
Trend Change (After Intervention 1)	0.000008	(0.000001, 0.000015)	0.023

¹The 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.

²Maximum 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.

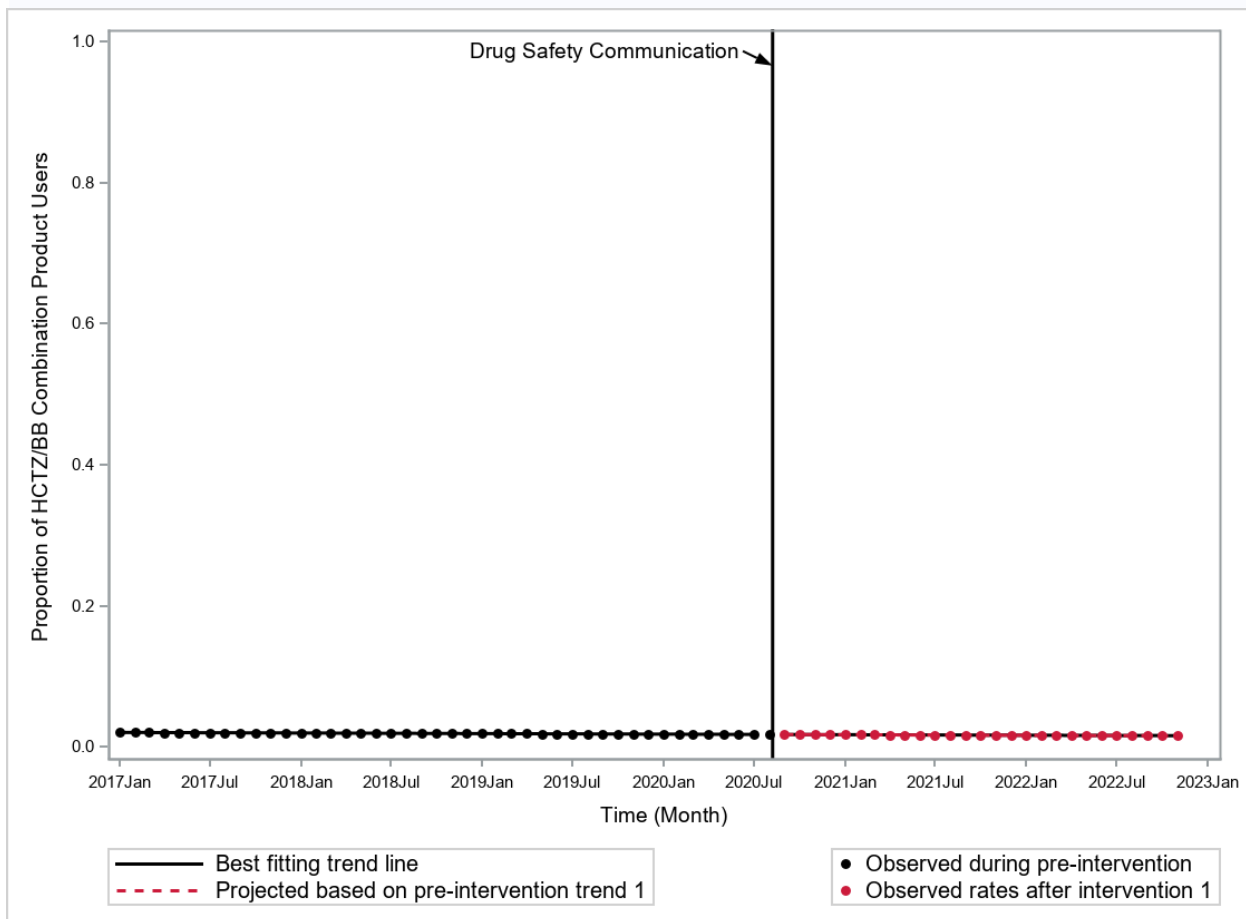
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000008	(0.000001, 0.000015)	0.017290	0.017282
Relative Change (%) at 1 Months after Intervention 1	0.05	(0.01, 0.09)	0.017290	0.017282
Absolute Change at 2 Months after Intervention 1	0.000016	(0.000002, 0.000030)	0.017230	0.017214
Relative Change (%) at 2 Months after Intervention 1	0.09	(0.01, 0.17)	0.017230	0.017214
Absolute Change at 3 Months after Intervention 1	0.000024	(0.000004, 0.000044)	0.017170	0.017146
Relative Change (%) at 3 Months after Intervention 1	0.14	(0.02, 0.26)	0.017170	0.017146
Absolute Change at 4 Months after Intervention 1	0.000032	(0.000005, 0.000059)	0.017110	0.017078
Relative Change (%) at 4 Months after Intervention 1	0.19	(0.03, 0.35)	0.017110	0.017078
Absolute Change at 5 Months after Intervention 1	0.000040	(0.000006, 0.000074)	0.017050	0.017010
Relative Change (%) at 5 Months after Intervention 1	0.24	(0.04, 0.44)	0.017050	0.017010
Absolute Change at 6 Months after Intervention 1	0.000048	(0.000007, 0.000089)	0.016990	0.016942
Relative Change (%) at 6 Months after Intervention 1	0.28	(0.04, 0.53)	0.016990	0.016942
Absolute Change at 7 Months after Intervention 1	0.000056	(0.000009, 0.000104)	0.016930	0.016873
Relative Change (%) at 7 Months after Intervention 1	0.33	(0.05, 0.62)	0.016930	0.016873
Absolute Change at 8 Months after Intervention 1	0.000064	(0.000010, 0.000118)	0.016869	0.016805
Relative Change (%) at 8 Months after Intervention 1	0.38	(0.06, 0.71)	0.016869	0.016805
Absolute Change at 9 Months after Intervention 1	0.000072	(0.000011, 0.000133)	0.016809	0.016737
Relative Change (%) at 9 Months after Intervention 1	0.43	(0.06, 0.80)	0.016809	0.016737
Absolute Change at 10 Months after Intervention 1	0.000080	(0.000012, 0.000148)	0.016749	0.016669
Relative Change (%) at 10 Months after Intervention 1	0.48	(0.07, 0.89)	0.016749	0.016669
Absolute Change at 11 Months after Intervention 1	0.000088	(0.000014, 0.000163)	0.016689	0.016601
Relative Change (%) at 11 Months after Intervention 1	0.53	(0.08, 0.98)	0.016689	0.016601
Absolute Change at 12 Months after Intervention 1	0.000096	(0.000015, 0.000178)	0.016629	0.016533
Relative Change (%) at 12 Months after Intervention 1	0.58	(0.09, 1.08)	0.016629	0.016533
Absolute Change at 13 Months after Intervention 1	0.000104	(0.000016, 0.000192)	0.016569	0.016465
Relative Change (%) at 13 Months after Intervention 1	0.63	(0.09, 1.17)	0.016569	0.016465
Absolute Change at 14 Months after Intervention 1	0.000112	(0.000017, 0.000207)	0.016509	0.016397
Relative Change (%) at 14 Months after Intervention 1	0.68	(0.10, 1.27)	0.016509	0.016397
Absolute Change at 15 Months after Intervention 1	0.000120	(0.000018, 0.000222)	0.016449	0.016328
Relative Change (%) at 15 Months after Intervention 1	0.74	(0.11, 1.36)	0.016449	0.016328
Absolute Change at 16 Months after Intervention 1	0.000128	(0.000020, 0.000237)	0.016389	0.016260
Relative Change (%) at 16 Months after Intervention 1	0.79	(0.12, 1.46)	0.016389	0.016260
Absolute Change at 17 Months after Intervention 1	0.000136	(0.000025, 0.000252)	0.016328	0.016192
Relative Change (%) at 17 Months after Intervention 1	0.84	(0.12, 1.56)	0.016328	0.016192
Absolute Change at 18 Months after Intervention 1	0.000144	(0.000022, 0.000266)	0.016268	0.016124
Relative Change (%) at 18 Months after Intervention 1	0.90	(0.13, 1.66)	0.016268	0.016124
Absolute Change at 19 Months after Intervention 1	0.000152	(0.000023, 0.000281)	0.016208	0.016056
Relative Change (%) at 19 Months after Intervention 1	0.95	(0.14, 1.76)	0.016208	0.016056
Absolute Change at 20 Months after Intervention 1	0.000160	(0.000025, 0.000296)	0.016148	0.015988
Relative Change (%) at 20 Months after Intervention 1	1.00	(0.15, 1.86)	0.016148	0.015988
Absolute Change at 21 Months after Intervention 1	0.000168	(0.000026, 0.000311)	0.016088	0.015920
Relative Change (%) at 21 Months after Intervention 1	1.06	(0.16, 1.96)	0.016088	0.015920
Absolute Change at 22 Months after Intervention 1	0.000176	(0.000027, 0.000326)	0.016028	0.015851
Relative Change (%) at 22 Months after Intervention 1	1.11	(0.16, 2.06)	0.016028	0.015851
Absolute Change at 23 Months after Intervention 1	0.000184	(0.000028, 0.000341)	0.015968	0.015783
Relative Change (%) at 23 Months after Intervention 1	1.17	(0.17, 2.17)	0.015968	0.015783
Absolute Change at 24 Months after Intervention 1	0.000192	(0.000030, 0.000355)	0.015908	0.015715
Relative Change (%) at 24 Months after Intervention 1	1.22	(0.18, 2.27)	0.015908	0.015715
Absolute Change at 25 Months after Intervention 1	0.000200	(0.000031, 0.000370)	0.015848	0.015647
Relative Change (%) at 25 Months after Intervention 1	1.28	(0.19, 2.37)	0.015848	0.015647
Absolute Change at 26 Months after Intervention 1	0.000208	(0.000032, 0.000385)	0.015787	0.015579
Relative Change (%) at 26 Months after Intervention 1	1.34	(0.20, 2.48)	0.015787	0.015579
Absolute Change at 27 Months after Intervention 1	0.000216	(0.000033, 0.000400)	0.015727	0.015511
Relative Change (%) at 27 Months after Intervention 1	1.40	(0.20, 2.59)	0.015727	0.015511
Absolute Change at 27 Months after Intervention 1	0.000216	(0.000033, 0.000400)	0.015727	0.015511
Relative Change (%) at 27 Months after Intervention 1	1.40	(0.20, 2.59)	0.015727	0.015511

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.000049	(0.000033, 0.000065)	<.001
Baseline trend	-0.000001	(-0.000001, -0.000001)	<.001
Level Change (After Intervention 1)	0.000000	(-0.000004, 0.000004)	0.994
Trend Change (After Intervention 1)	0.000001	(-0.000000, 0.000002)	0.134
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.000047	(0.000039, 0.000056)	<.001
<u>Baseline trend</u>	<u>-0.000001</u>	<u>(-0.000001, -0.000001)</u>	<u><.001</u>

¹The 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.

²Maximum 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.

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

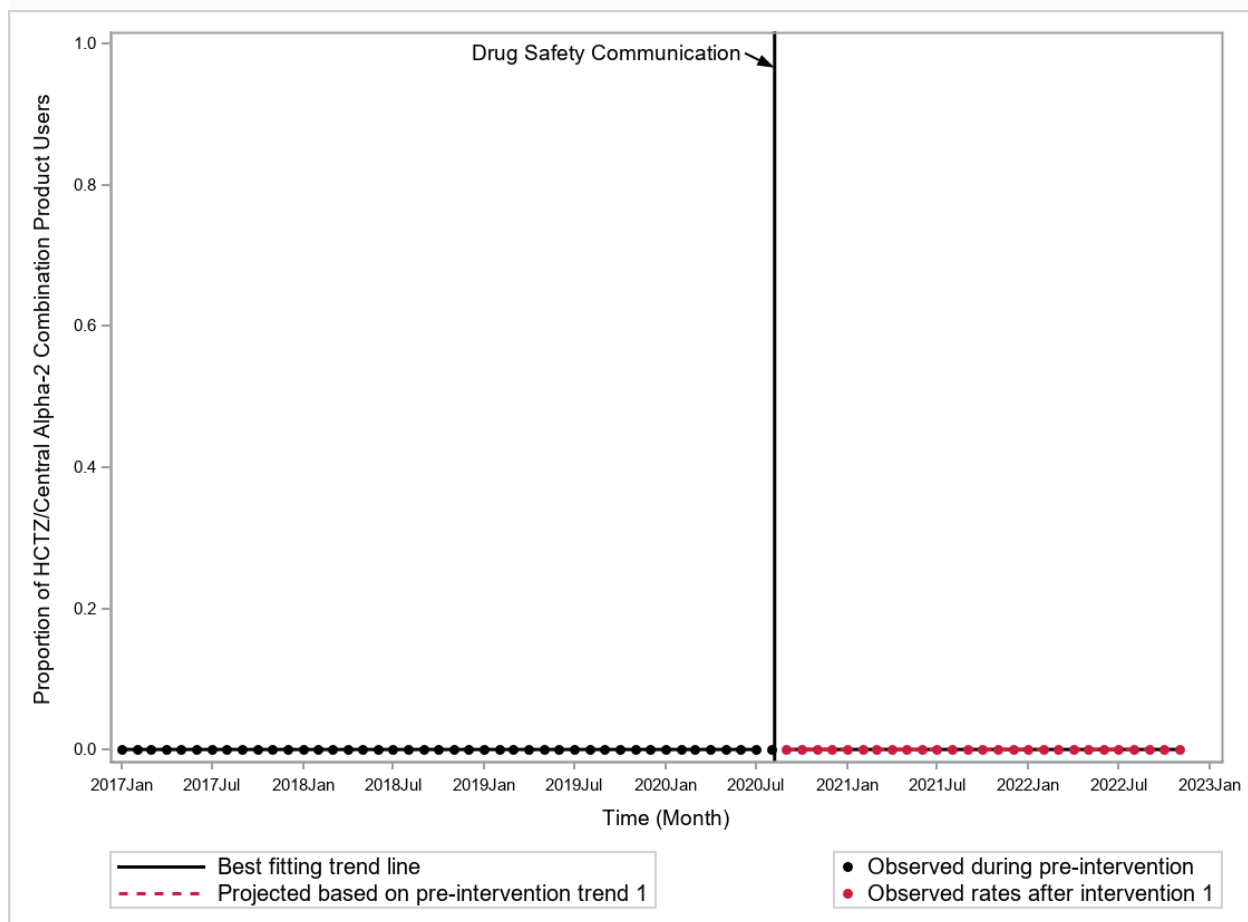
Table 10. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer after August 8, 2020¹ Compared with Expected Rates 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	0.000000	(0.000000, 0.000000)	0.000014	0.000014
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.000014	0.000014
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000013	0.000013
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.000013	0.000013
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000013	0.000013
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.000013	0.000013
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000012	0.000012
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.000012	0.000012
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000011	0.000011
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.000011	0.000011
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000010	0.000010
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.000010	0.000010
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000010	0.000010
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.000010	0.000010
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000009	0.000009
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.000009	0.000009
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000008	0.000008
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.000008	0.000008
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000007	0.000007
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.000007	0.000007
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000007	0.000007
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.000007	0.000007
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000006	0.000006
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.000006	0.000006
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000005	0.000005
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.000005	0.000005
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000004	0.000004
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.000004	0.000004
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000004	0.000004
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.000004	0.000004
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000003	0.000003
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.000003	0.000003
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000002	0.000002
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.000002	0.000002
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000001	0.000001
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.000001	0.000001
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000001	0.000001
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.000001	0.000001
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
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
Relative 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

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 64)²			
Intercept	0.329594	(0.328148, 0.331040)	<.001
Baseline trend	-0.000821	(-0.000872, -0.000771)	<.001
Level Change (After Intervention 1)	0.000259	(-0.000421, 0.000938)	0.449
Trend Change (After Intervention 1)	0.000062	(-0.000057, 0.000181)	0.300
Most Parsimonious Final Model Parameters (df = 64)^{2,3}			
Intercept	0.329785	(0.328664, 0.330906)	<.001
Baseline trend	-0.000830	(-0.000871, -0.000790)	<.001
Trend Change (After Intervention 1)	0.000115	(0.000013, 0.000218)	0.028

¹The 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.

²Maximum 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.

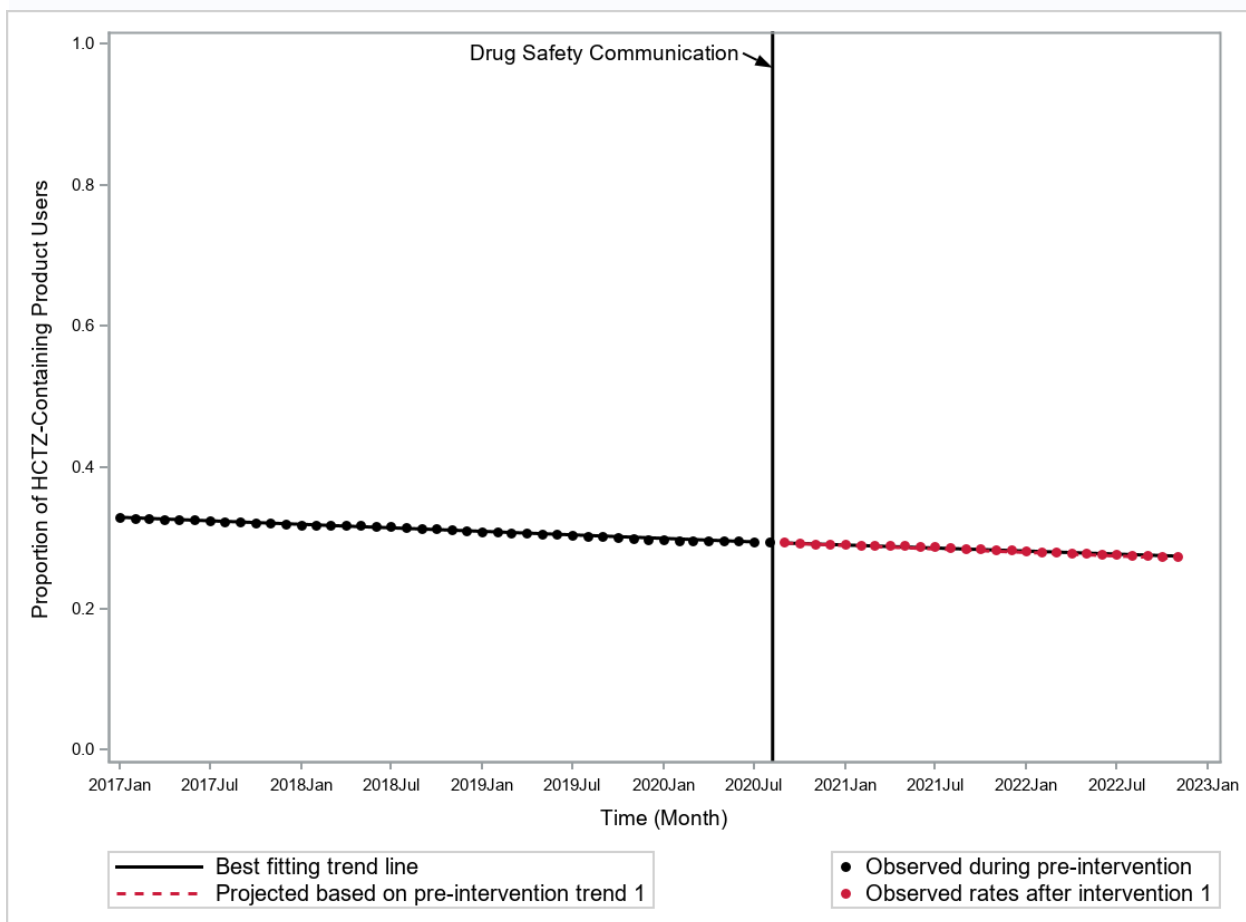
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000115	(0.000001, 0.000229)	0.292535	0.292419
Relative Change (%) at 1 Months after Intervention 1	0.04	(0.00, 0.08)	0.292535	0.292419
Absolute Change at 2 Months after Intervention 1	0.000231	(0.000003, 0.000458)	0.291819	0.291589
Relative Change (%) at 2 Months after Intervention 1	0.08	(0.00, 0.16)	0.291819	0.291589
Absolute Change at 3 Months after Intervention 1	0.000346	(0.000004, 0.000687)	0.291104	0.290759
Relative Change (%) at 3 Months after Intervention 1	0.12	(0.00, 0.24)	0.291104	0.290759
Absolute Change at 4 Months after Intervention 1	0.000461	(0.000006, 0.000916)	0.290389	0.289928
Relative Change (%) at 4 Months after Intervention 1	0.16	(0.00, 0.32)	0.290389	0.289928
Absolute Change at 5 Months after Intervention 1	0.000576	(0.000007, 0.001145)	0.289674	0.289098
Relative Change (%) at 5 Months after Intervention 1	0.20	(0.00, 0.40)	0.289674	0.289098
Absolute Change at 6 Months after Intervention 1	0.000692	(0.000009, 0.001375)	0.288959	0.288268
Relative Change (%) at 6 Months after Intervention 1	0.24	(0.00, 0.48)	0.288959	0.288268
Absolute Change at 7 Months after Intervention 1	0.000807	(0.000010, 0.001604)	0.288244	0.287437
Relative Change (%) at 7 Months after Intervention 1	0.28	(0.00, 0.56)	0.288244	0.287437
Absolute Change at 8 Months after Intervention 1	0.000922	(0.000012, 0.001833)	0.287529	0.286607
Relative Change (%) at 8 Months after Intervention 1	0.32	(0.00, 0.64)	0.287529	0.286607
Absolute Change at 9 Months after Intervention 1	0.001037	(0.000013, 0.002062)	0.286814	0.285776
Relative Change (%) at 9 Months after Intervention 1	0.36	(0.00, 0.72)	0.286814	0.285776
Absolute Change at 10 Months after Intervention 1	0.001153	(0.000014, 0.002291)	0.286099	0.284946
Relative Change (%) at 10 Months after Intervention 1	0.40	(0.00, 0.81)	0.286099	0.284946
Absolute Change at 11 Months after Intervention 1	0.001268	(0.000016, 0.002520)	0.285384	0.284116
Relative Change (%) at 11 Months after Intervention 1	0.45	(0.00, 0.89)	0.285384	0.284116
Absolute Change at 12 Months after Intervention 1	0.001383	(0.000017, 0.002749)	0.284669	0.283285
Relative Change (%) at 12 Months after Intervention 1	0.49	(0.00, 0.97)	0.284669	0.283285
Absolute Change at 13 Months after Intervention 1	0.001498	(0.000019, 0.002978)	0.283954	0.282455
Relative Change (%) at 13 Months after Intervention 1	0.53	(0.00, 1.06)	0.283954	0.282455
Absolute Change at 14 Months after Intervention 1	0.001614	(0.000020, 0.003207)	0.283238	0.281625
Relative Change (%) at 14 Months after Intervention 1	0.57	(0.00, 1.14)	0.283238	0.281625
Absolute Change at 15 Months after Intervention 1	0.001729	(0.000022, 0.003436)	0.282523	0.280794
Relative Change (%) at 15 Months after Intervention 1	0.62	(0.00, 1.23)	0.282523	0.280794
Absolute Change at 16 Months after Intervention 1	0.001844	(0.000023, 0.003665)	0.281808	0.279964
Relative Change (%) at 16 Months after Intervention 1	0.66	(0.00, 1.31)	0.281808	0.279964
Absolute Change at 17 Months after Intervention 1	0.001960	(0.000025, 0.003895)	0.281093	0.279134
Relative Change (%) at 17 Months after Intervention 1	0.70	(0.01, 1.40)	0.281093	0.279134
Absolute Change at 18 Months after Intervention 1	0.002075	(0.000026, 0.004124)	0.280378	0.278303
Relative Change (%) at 18 Months after Intervention 1	0.75	(0.01, 1.49)	0.280378	0.278303
Absolute Change at 19 Months after Intervention 1	0.002190	(0.000028, 0.004353)	0.279663	0.277473
Relative Change (%) at 19 Months after Intervention 1	0.79	(0.01, 1.57)	0.279663	0.277473
Absolute Change at 20 Months after Intervention 1	0.002305	(0.000029, 0.004582)	0.278948	0.276643
Relative Change (%) at 20 Months after Intervention 1	0.83	(0.01, 1.66)	0.278948	0.276643
Absolute Change at 21 Months after Intervention 1	0.002421	(0.000030, 0.004811)	0.278233	0.275812
Relative Change (%) at 21 Months after Intervention 1	0.88	(0.01, 1.75)	0.278233	0.275812
Absolute Change at 22 Months after Intervention 1	0.002536	(0.000032, 0.005040)	0.277518	0.274982
Relative Change (%) at 22 Months after Intervention 1	0.92	(0.01, 1.84)	0.277518	0.274982
Absolute Change at 23 Months after Intervention 1	0.002651	(0.000033, 0.005269)	0.276803	0.274152
Relative Change (%) at 23 Months after Intervention 1	0.97	(0.01, 1.93)	0.276803	0.274152
Absolute Change at 24 Months after Intervention 1	0.002766	(0.000035, 0.005498)	0.276088	0.273321
Relative Change (%) at 24 Months after Intervention 1	1.01	(0.01, 2.02)	0.276088	0.273321
Absolute Change at 25 Months after Intervention 1	0.002882	(0.000036, 0.005727)	0.275373	0.272491
Relative Change (%) at 25 Months after Intervention 1	1.06	(0.01, 2.11)	0.275373	0.272491
Absolute Change at 26 Months after Intervention 1	0.002997	(0.000038, 0.005956)	0.274658	0.271661
Relative Change (%) at 26 Months after Intervention 1	1.10	(0.01, 2.20)	0.274658	0.271661
Absolute Change at 27 Months after Intervention 1	0.003112	(0.000039, 0.006185)	0.273942	0.270830
Relative Change (%) at 27 Months after Intervention 1	1.15	(0.01, 2.29)	0.273942	0.270830
Absolute Change at 27 Months after Intervention 1	0.003112	(0.000039, 0.006185)	0.273942	0.270830
Relative Change (%) at 27 Months after Intervention 1	1.15	(0.01, 2.29)	0.273942	0.270830

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.931819	(0.930933, 0.932704)	<.001
Baseline trend	-0.000414	(-0.000445, -0.000382)	<.001
Level Change (After Intervention 1)	0.000562	(-0.000124, 0.001247)	0.107
Trend Change (After Intervention 1)	0.000218	(0.000140, 0.000297)	<.001
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.931819	(0.930933, 0.932704)	<.001
Baseline trend	-0.000414	(-0.000445, -0.000382)	<.001
Level Change (After Intervention 1)	0.000562	(-0.000124, 0.001247)	0.107
Trend Change (After Intervention 1)	0.000218	(0.000140, 0.000297)	<.001

¹The 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.

²Maximum 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.

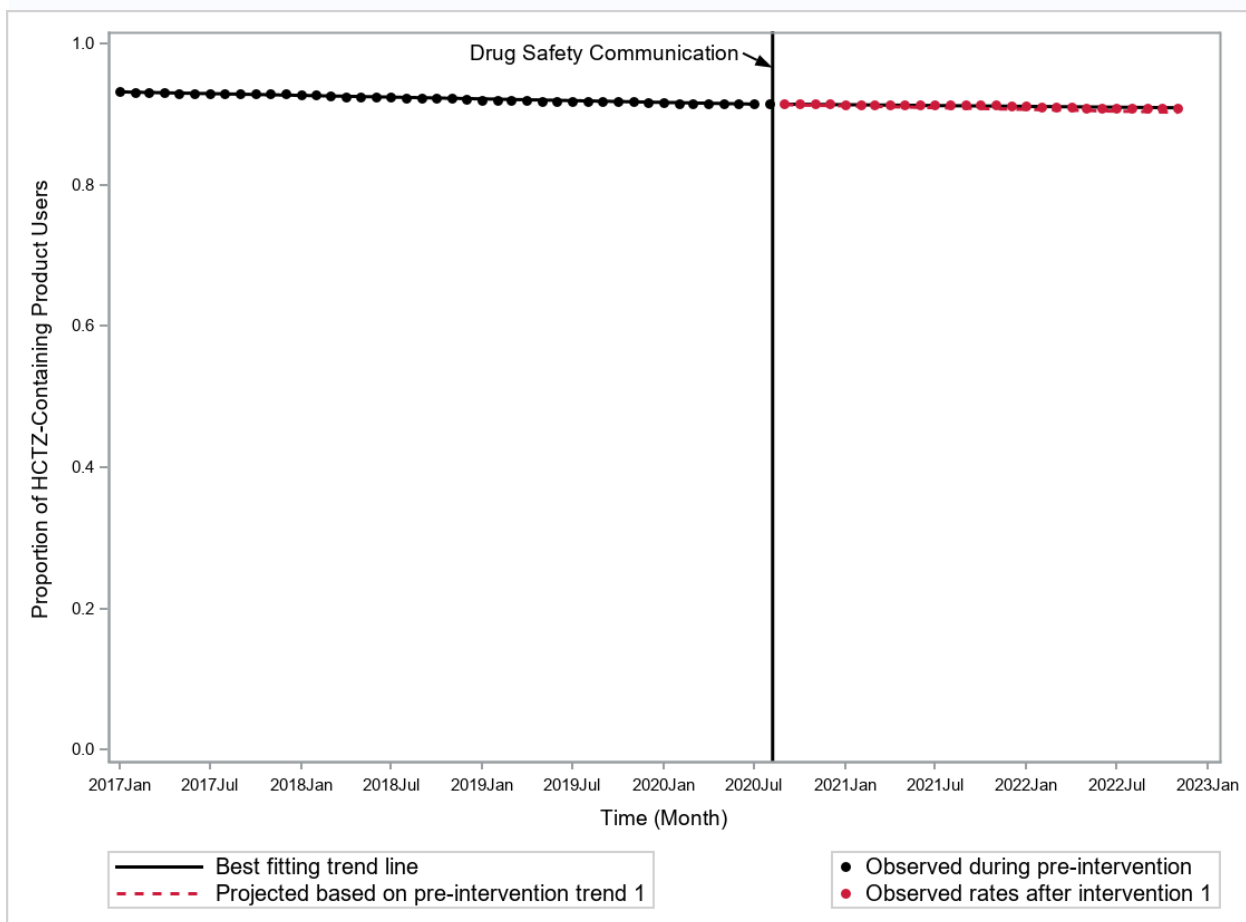
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000780	(0.000093, 0.001467)	0.913989	0.913209
Relative Change (%) at 1 Months after Intervention 1	0.09	(0.01, 0.16)	0.913989	0.913209
Absolute Change at 2 Months after Intervention 1	0.000999	(0.000315, 0.001682)	0.913793	0.912795
Relative Change (%) at 2 Months after Intervention 1	0.11	(0.03, 0.18)	0.913793	0.912795
Absolute Change at 3 Months after Intervention 1	0.001217	(0.000529, 0.001905)	0.913598	0.912381
Relative Change (%) at 3 Months after Intervention 1	0.13	(0.06, 0.21)	0.913598	0.912381
Absolute Change at 4 Months after Intervention 1	0.001435	(0.000734, 0.002137)	0.913403	0.911968
Relative Change (%) at 4 Months after Intervention 1	0.16	(0.08, 0.23)	0.913403	0.911968
Absolute Change at 5 Months after Intervention 1	0.001654	(0.000931, 0.002377)	0.913208	0.911554
Relative Change (%) at 5 Months after Intervention 1	0.18	(0.10, 0.26)	0.913208	0.911554
Absolute Change at 6 Months after Intervention 1	0.001872	(0.001120, 0.002624)	0.913013	0.911141
Relative Change (%) at 6 Months after Intervention 1	0.21	(0.12, 0.29)	0.913013	0.911141
Absolute Change at 7 Months after Intervention 1	0.002091	(0.001303, 0.002879)	0.912818	0.910727
Relative Change (%) at 7 Months after Intervention 1	0.23	(0.14, 0.32)	0.912818	0.910727
Absolute Change at 8 Months after Intervention 1	0.002309	(0.001480, 0.003138)	0.912623	0.910314
Relative Change (%) at 8 Months after Intervention 1	0.25	(0.16, 0.34)	0.912623	0.910314
Absolute Change at 9 Months after Intervention 1	0.002528	(0.001653, 0.003403)	0.912428	0.909900
Relative Change (%) at 9 Months after Intervention 1	0.28	(0.18, 0.37)	0.912428	0.909900
Absolute Change at 10 Months after Intervention 1	0.002746	(0.001821, 0.003672)	0.912233	0.909486
Relative Change (%) at 10 Months after Intervention 1	0.30	(0.20, 0.40)	0.912233	0.909486
Absolute Change at 11 Months after Intervention 1	0.002965	(0.001985, 0.003945)	0.912038	0.909073
Relative Change (%) at 11 Months after Intervention 1	0.33	(0.22, 0.43)	0.912038	0.909073
Absolute Change at 12 Months after Intervention 1	0.003183	(0.002146, 0.004220)	0.911843	0.908659
Relative Change (%) at 12 Months after Intervention 1	0.35	(0.24, 0.46)	0.911843	0.908659
Absolute Change at 13 Months after Intervention 1	0.003402	(0.002305, 0.004498)	0.911648	0.908246
Relative Change (%) at 13 Months after Intervention 1	0.37	(0.25, 0.50)	0.911648	0.908246
Absolute Change at 14 Months after Intervention 1	0.003620	(0.002462, 0.004779)	0.911453	0.907832
Relative Change (%) at 14 Months after Intervention 1	0.40	(0.27, 0.53)	0.911453	0.907832
Absolute Change at 15 Months after Intervention 1	0.003839	(0.002617, 0.005061)	0.911257	0.907419
Relative Change (%) at 15 Months after Intervention 1	0.42	(0.29, 0.56)	0.911257	0.907419
Absolute Change at 16 Months after Intervention 1	0.004057	(0.002770, 0.005344)	0.911062	0.907005
Relative Change (%) at 16 Months after Intervention 1	0.45	(0.30, 0.59)	0.911062	0.907005
Absolute Change at 17 Months after Intervention 1	0.004276	(0.002922, 0.005629)	0.910867	0.906592
Relative Change (%) at 17 Months after Intervention 1	0.47	(0.32, 0.62)	0.910867	0.906592
Absolute Change at 18 Months after Intervention 1	0.004494	(0.003073, 0.005915)	0.910672	0.906178
Relative Change (%) at 18 Months after Intervention 1	0.50	(0.34, 0.65)	0.910672	0.906178
Absolute Change at 19 Months after Intervention 1	0.004713	(0.003223, 0.006202)	0.910477	0.905764
Relative Change (%) at 19 Months after Intervention 1	0.52	(0.36, 0.69)	0.910477	0.905764
Absolute Change at 20 Months after Intervention 1	0.004931	(0.003372, 0.006490)	0.910282	0.905351
Relative Change (%) at 20 Months after Intervention 1	0.54	(0.37, 0.72)	0.910282	0.905351
Absolute Change at 21 Months after Intervention 1	0.005150	(0.003521, 0.006779)	0.910087	0.904937
Relative Change (%) at 21 Months after Intervention 1	0.57	(0.39, 0.75)	0.910087	0.904937
Absolute Change at 22 Months after Intervention 1	0.005368	(0.003668, 0.007068)	0.909892	0.904524
Relative Change (%) at 22 Months after Intervention 1	0.59	(0.40, 0.78)	0.909892	0.904524
Absolute Change at 23 Months after Intervention 1	0.005587	(0.003815, 0.007358)	0.909697	0.904110
Relative Change (%) at 23 Months after Intervention 1	0.62	(0.42, 0.81)	0.909697	0.904110
Absolute Change at 24 Months after Intervention 1	0.005805	(0.003962, 0.007648)	0.909502	0.903697
Relative Change (%) at 24 Months after Intervention 1	0.64	(0.44, 0.85)	0.909502	0.903697
Absolute Change at 25 Months after Intervention 1	0.006024	(0.004108, 0.007939)	0.909307	0.903283
Relative Change (%) at 25 Months after Intervention 1	0.67	(0.45, 0.88)	0.909307	0.903283
Absolute Change at 26 Months after Intervention 1	0.006242	(0.004254, 0.008230)	0.909112	0.902870
Relative Change (%) at 26 Months after Intervention 1	0.69	(0.47, 0.91)	0.909112	0.902870
Absolute Change at 27 Months after Intervention 1	0.006461	(0.004399, 0.008522)	0.908917	0.902456
Relative Change (%) at 27 Months after Intervention 1	0.72	(0.49, 0.95)	0.908917	0.902456
Absolute Change at 27 Months after Intervention 1	0.006461	(0.004399, 0.008522)	0.908917	0.902456
Relative Change (%) at 27 Months after Intervention 1	0.72	(0.49, 0.95)	0.908917	0.902456

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.000521	(0.000495, 0.000546)	<.001
Baseline trend	-0.000006	(-0.000007, -0.000005)	<.001
Level Change (After Intervention 1)	-0.000001	(-0.000016, 0.000015)	0.910
Trend Change (After Intervention 1)	0.000001	(-0.000001, 0.000004)	0.214
Most Parsimonious Final Model Parameters (df = 68)^{2,3}			
Intercept	0.000527	(0.000490, 0.000565)	<.001
Baseline trend	-0.000006	(-0.000007, -0.000005)	<.001

¹The 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.

²Maximum 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.

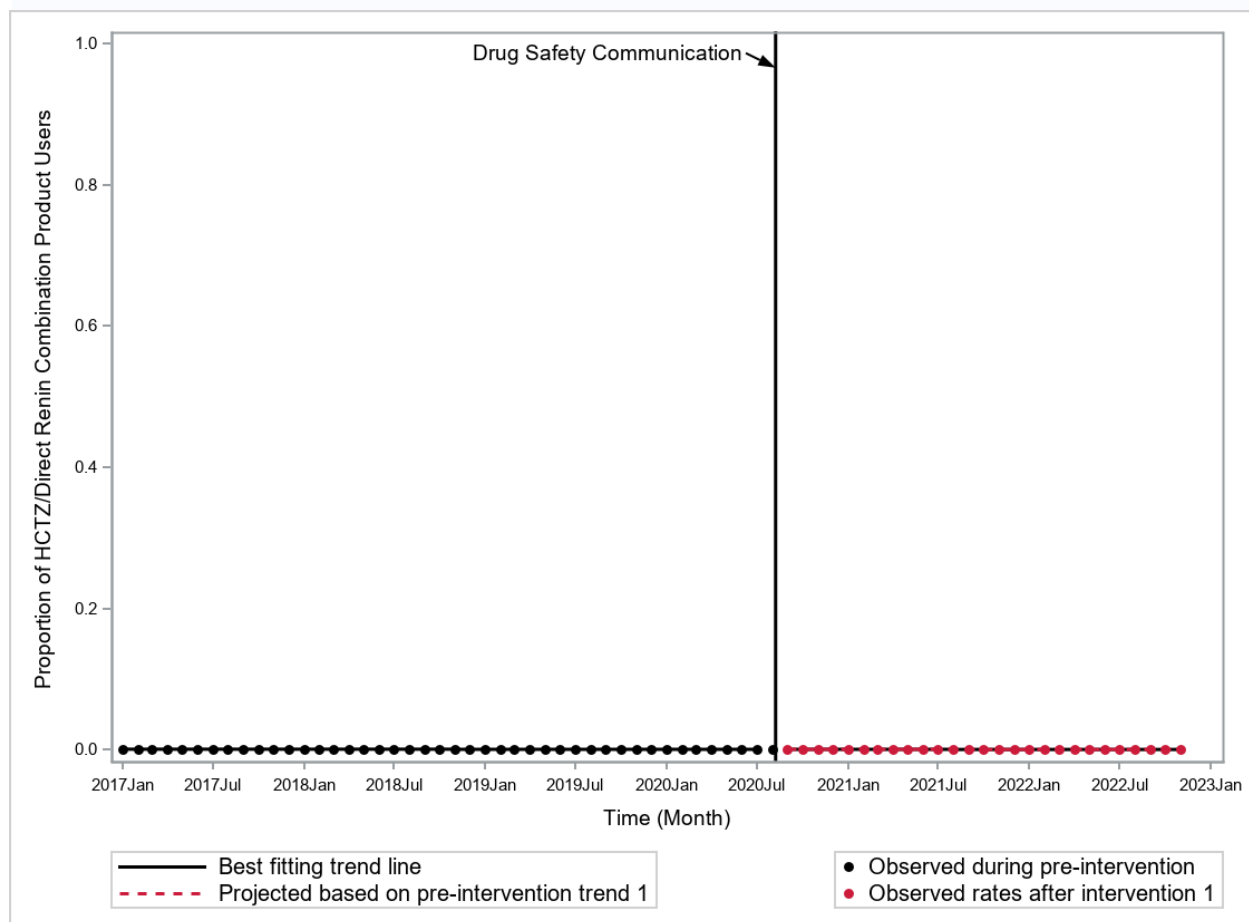
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000000	(0.000000, 0.000000)	0.000254	0.000254
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.000254	0.000254
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000248	0.000248
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.000248	0.000248
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000242	0.000242
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.000242	0.000242
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000236	0.000236
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.000236	0.000236
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000229	0.000229
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.000229	0.000229
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000223	0.000223
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.000223	0.000223
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000217	0.000217
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.000217	0.000217
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000211	0.000211
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.000211	0.000211
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000205	0.000205
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.000205	0.000205
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000199	0.000199
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.000199	0.000199
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000193	0.000193
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.000193	0.000193
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000187	0.000187
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.000187	0.000187
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000181	0.000181
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.000181	0.000181
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000175	0.000175
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.000175	0.000175
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000169	0.000169
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.000169	0.000169
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000163	0.000163
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.000163	0.000163
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000156	0.000156
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.000156	0.000156
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000150	0.000150
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.000150	0.000150
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000144	0.000144
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.000144	0.000144
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000138	0.000138
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.000138	0.000138
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000132	0.000132
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.000132	0.000132
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000126	0.000126
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.000126	0.000126
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000120	0.000120
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.000120	0.000120
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000114	0.000114
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.000114	0.000114
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000108	0.000108
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.000108	0.000108
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000102	0.000102
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.000102	0.000102
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.000096	0.000096
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.000096	0.000096

¹The 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 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.366448	(0.351386, 0.381511)	<.001
Baseline trend	0.002048	(0.001512, 0.002585)	<.001
Level Change (After Intervention 1)	0.000793	(-0.002255, 0.003841)	0.605
Trend Change (After Intervention 1)	-0.001715	(-0.003044, -0.000386)	0.012
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.366951	(0.351839, 0.382063)	<.001
Baseline trend	0.002027	(0.001490, 0.002565)	<.001
Trend Change (After Intervention 1)	-0.001618	(-0.002910, -0.000327)	0.015

¹The 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.

²Maximum 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.

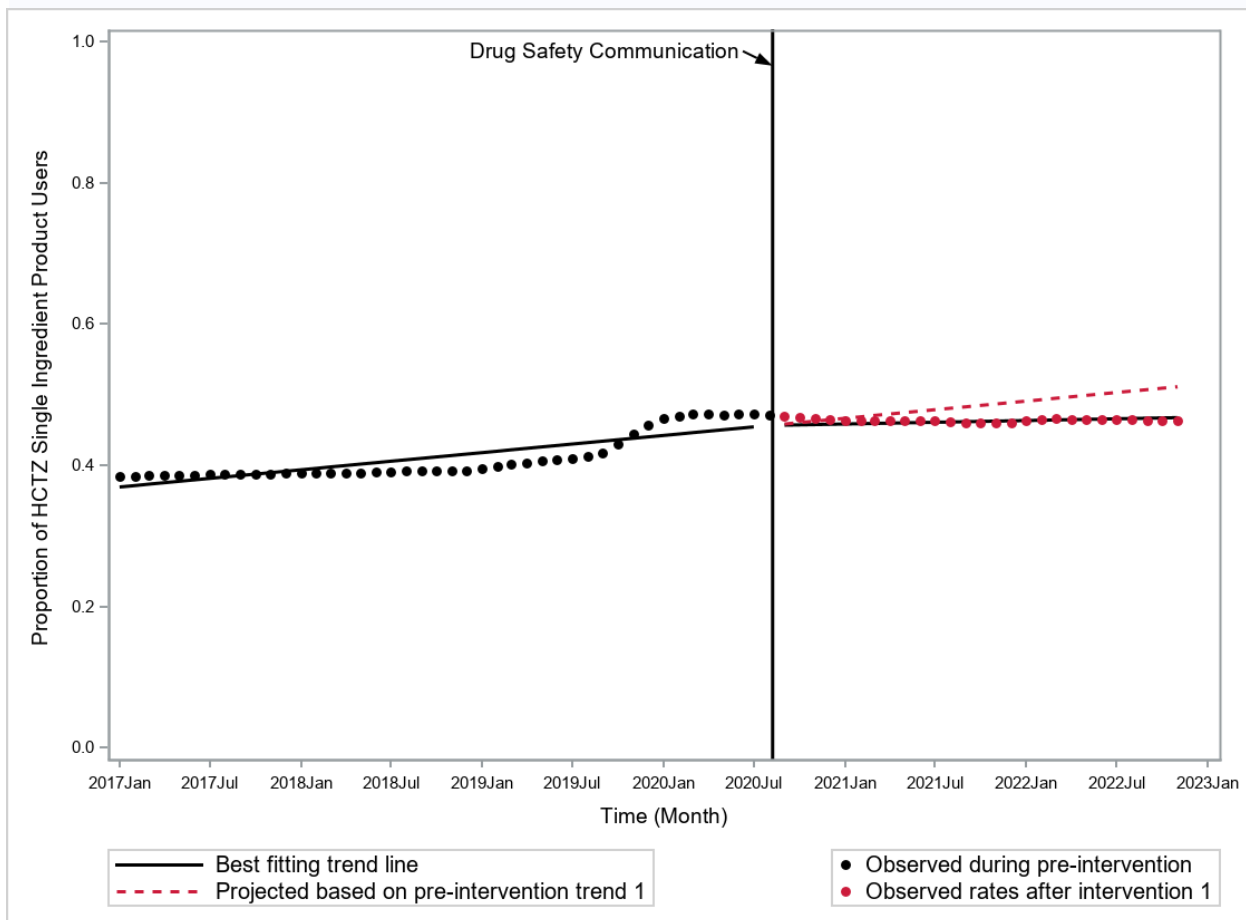
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	-0.001618	(-0.002910, -0.000327)	0.456567	0.458186
Relative Change (%) at 1 Months after Intervention 1	-0.35	(-0.63, -0.08)	0.456567	0.458186
Absolute Change at 2 Months after Intervention 1	-0.003236	(-0.005820, -0.000653)	0.456977	0.460213
Relative Change (%) at 2 Months after Intervention 1	-0.70	(-1.25, -0.16)	0.456977	0.460213
Absolute Change at 3 Months after Intervention 1	-0.004855	(-0.008729, -0.000980)	0.457386	0.462241
Relative Change (%) at 3 Months after Intervention 1	-1.05	(-1.86, -0.24)	0.457386	0.462241
Absolute Change at 4 Months after Intervention 1	-0.006473	(-0.011639, -0.001307)	0.457795	0.464268
Relative Change (%) at 4 Months after Intervention 1	-1.39	(-2.47, -0.32)	0.457795	0.464268
Absolute Change at 5 Months after Intervention 1	-0.008091	(-0.014549, -0.001634)	0.458204	0.466295
Relative Change (%) at 5 Months after Intervention 1	-1.74	(-3.07, -0.40)	0.458204	0.466295
Absolute Change at 6 Months after Intervention 1	-0.009709	(-0.017459, -0.001960)	0.458613	0.468323
Relative Change (%) at 6 Months after Intervention 1	-2.07	(-3.67, -0.48)	0.458613	0.468323
Absolute Change at 7 Months after Intervention 1	-0.011328	(-0.020368, -0.002287)	0.459023	0.470350
Relative Change (%) at 7 Months after Intervention 1	-2.41	(-4.26, -0.56)	0.459023	0.470350
Absolute Change at 8 Months after Intervention 1	-0.012946	(-0.023278, -0.002614)	0.459432	0.472378
Relative Change (%) at 8 Months after Intervention 1	-2.74	(-4.84, -0.64)	0.459432	0.472378
Absolute Change at 9 Months after Intervention 1	-0.014564	(-0.026188, -0.002940)	0.459841	0.474405
Relative Change (%) at 9 Months after Intervention 1	-3.07	(-5.42, -0.72)	0.459841	0.474405
Absolute Change at 10 Months after Intervention 1	-0.016182	(-0.029098, -0.003267)	0.460250	0.476433
Relative Change (%) at 10 Months after Intervention 1	-3.40	(-6.00, -0.80)	0.460250	0.476433
Absolute Change at 11 Months after Intervention 1	-0.017801	(-0.032007, -0.003594)	0.460660	0.478460
Relative Change (%) at 11 Months after Intervention 1	-3.72	(-6.57, -0.88)	0.460660	0.478460
Absolute Change at 12 Months after Intervention 1	-0.019419	(-0.034917, -0.003921)	0.461069	0.480488
Relative Change (%) at 12 Months after Intervention 1	-4.04	(-7.13, -0.95)	0.461069	0.480488
Absolute Change at 13 Months after Intervention 1	-0.021037	(-0.037827, -0.004247)	0.461478	0.482515
Relative Change (%) at 13 Months after Intervention 1	-4.36	(-7.69, -1.03)	0.461478	0.482515
Absolute Change at 14 Months after Intervention 1	-0.022655	(-0.040737, -0.004574)	0.461887	0.484542
Relative Change (%) at 14 Months after Intervention 1	-4.68	(-8.24, -1.11)	0.461887	0.484542
Absolute Change at 15 Months after Intervention 1	-0.024274	(-0.043646, -0.004901)	0.462296	0.486570
Relative Change (%) at 15 Months after Intervention 1	-4.99	(-8.79, -1.19)	0.462296	0.486570
Absolute Change at 16 Months after Intervention 1	-0.025892	(-0.046556, -0.005228)	0.462706	0.488597
Relative Change (%) at 16 Months after Intervention 1	-5.30	(-9.33, -1.27)	0.462706	0.488597
Absolute Change at 17 Months after Intervention 1	-0.027510	(-0.049466, -0.005554)	0.463115	0.490625
Relative Change (%) at 17 Months after Intervention 1	-5.61	(-9.87, -1.34)	0.463115	0.490625
Absolute Change at 18 Months after Intervention 1	-0.029128	(-0.052376, -0.005881)	0.463524	0.492652
Relative Change (%) at 18 Months after Intervention 1	-5.91	(-10.40, -1.42)	0.463524	0.492652
Absolute Change at 19 Months after Intervention 1	-0.030746	(-0.055285, -0.006208)	0.463933	0.494680
Relative Change (%) at 19 Months after Intervention 1	-6.22	(-10.93, -1.50)	0.463933	0.494680
Absolute Change at 20 Months after Intervention 1	-0.032365	(-0.058195, -0.006534)	0.464342	0.496707
Relative Change (%) at 20 Months after Intervention 1	-6.52	(-11.46, -1.58)	0.464342	0.496707
Absolute Change at 21 Months after Intervention 1	-0.033983	(-0.061105, -0.006861)	0.464752	0.498734
Relative Change (%) at 21 Months after Intervention 1	-6.81	(-11.97, -1.65)	0.464752	0.498734
Absolute Change at 22 Months after Intervention 1	-0.035601	(-0.064015, -0.007188)	0.465161	0.500762
Relative Change (%) at 22 Months after Intervention 1	-7.11	(-12.49, -1.73)	0.465161	0.500762
Absolute Change at 23 Months after Intervention 1	-0.037219	(-0.066924, -0.007515)	0.465570	0.502789
Relative Change (%) at 23 Months after Intervention 1	-7.40	(-13.00, -1.81)	0.465570	0.502789
Absolute Change at 24 Months after Intervention 1	-0.038838	(-0.069834, -0.007841)	0.465979	0.504817
Relative Change (%) at 24 Months after Intervention 1	-7.69	(-13.50, -1.88)	0.465979	0.504817
Absolute Change at 25 Months after Intervention 1	-0.040456	(-0.072744, -0.008168)	0.466388	0.506844
Relative Change (%) at 25 Months after Intervention 1	-7.98	(-14.00, -1.96)	0.466388	0.506844
Absolute Change at 26 Months after Intervention 1	-0.042074	(-0.075654, -0.008495)	0.466798	0.508872
Relative Change (%) at 26 Months after Intervention 1	-8.27	(-14.50, -2.04)	0.466798	0.508872
Absolute Change at 27 Months after Intervention 1	-0.043692	(-0.078563, -0.008821)	0.467207	0.510899
Relative Change (%) at 27 Months after Intervention 1	-8.55	(-14.99, -2.11)	0.467207	0.510899
Absolute Change at 27 Months after Intervention 1	-0.043692	(-0.078563, -0.008821)	0.467207	0.510899
Relative Change (%) at 27 Months after Intervention 1	-8.55	(-14.99, -2.11)	0.467207	0.510899

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	c	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.134527	(0.133292, 0.135761)	<.001
Baseline trend	-0.000407	(-0.000445, -0.000369)	<.001
Level Change (After Intervention 1)	0.000164	(-0.000222, 0.000550)	0.399
Trend Change (After Intervention 1)	0.000070	(-0.000009, 0.000149)	0.080
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.134542	(0.133285, 0.135799)	<.001
Baseline trend	-0.000407	(-0.000445, -0.000369)	<.001
Trend Change (After Intervention 1)	0.000075	(-0.000004, 0.000153)	0.061

¹The 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.

²Maximum 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.

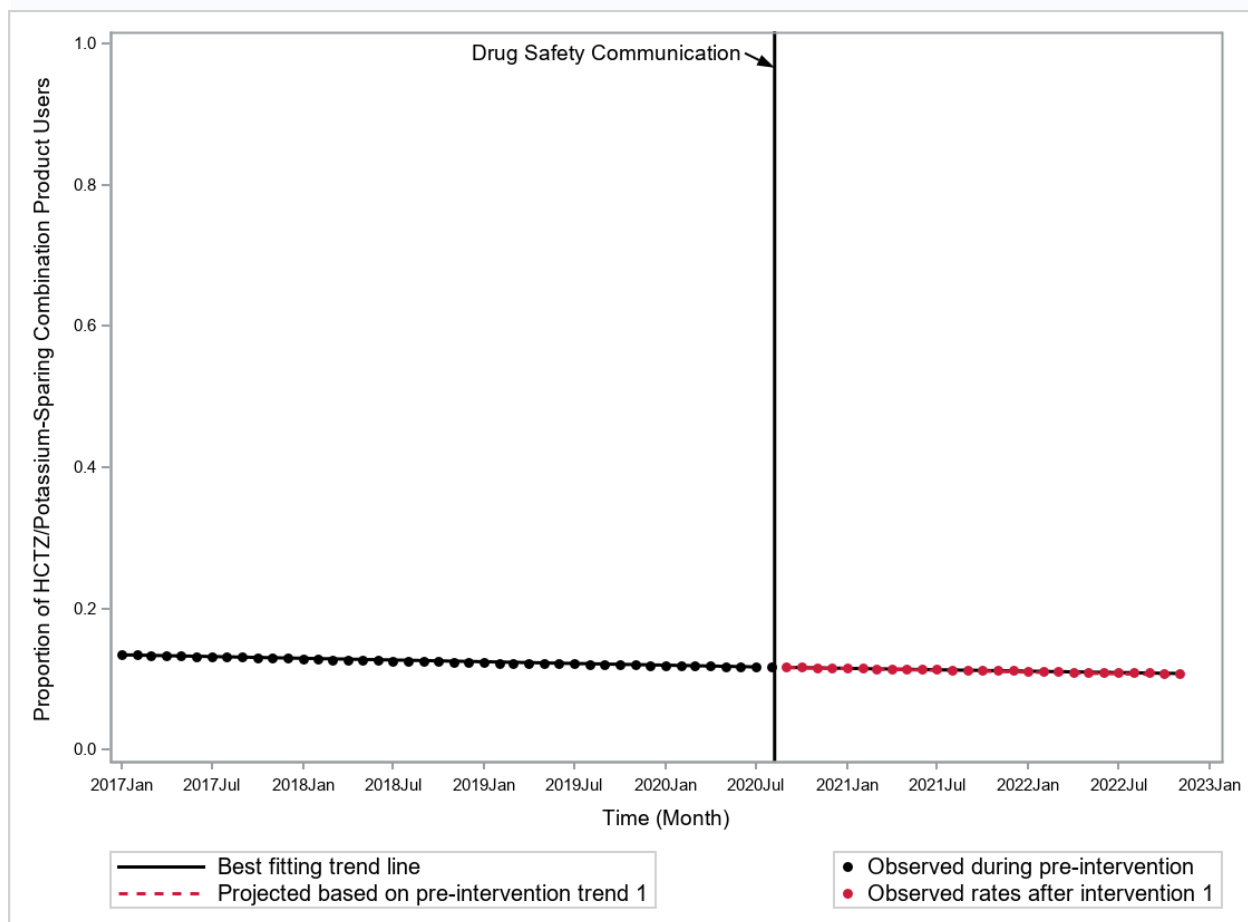
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000075	(-0.000039, 0.000189)	0.116312	0.116237
Relative Change (%) at 1 Months after Intervention 1	0.06	(-0.03, 0.16)	0.116312	0.116237
Absolute Change at 2 Months after Intervention 1	0.000150	(-0.000077, 0.000377)	0.115980	0.115830
Relative Change (%) at 2 Months after Intervention 1	0.13	(-0.07, 0.33)	0.115980	0.115830
Absolute Change at 3 Months after Intervention 1	0.000225	(-0.000116, 0.000566)	0.115648	0.115423
Relative Change (%) at 3 Months after Intervention 1	0.19	(-0.10, 0.49)	0.115648	0.115423
Absolute Change at 4 Months after Intervention 1	0.000300	(-0.000155, 0.000754)	0.115316	0.115016
Relative Change (%) at 4 Months after Intervention 1	0.26	(-0.14, 0.66)	0.115316	0.115016
Absolute Change at 5 Months after Intervention 1	0.000375	(-0.000193, 0.000943)	0.114984	0.114610
Relative Change (%) at 5 Months after Intervention 1	0.33	(-0.17, 0.83)	0.114984	0.114610
Absolute Change at 6 Months after Intervention 1	0.000450	(-0.000232, 0.001131)	0.114652	0.114203
Relative Change (%) at 6 Months after Intervention 1	0.39	(-0.21, 1.00)	0.114652	0.114203
Absolute Change at 7 Months after Intervention 1	0.000525	(-0.000271, 0.001320)	0.114321	0.113796
Relative Change (%) at 7 Months after Intervention 1	0.46	(-0.24, 1.17)	0.114321	0.113796
Absolute Change at 8 Months after Intervention 1	0.000599	(-0.000310, 0.001508)	0.113989	0.113389
Relative Change (%) at 8 Months after Intervention 1	0.53	(-0.28, 1.34)	0.113989	0.113389
Absolute Change at 9 Months after Intervention 1	0.000674	(-0.000348, 0.001697)	0.113657	0.112983
Relative Change (%) at 9 Months after Intervention 1	0.60	(-0.32, 1.51)	0.113657	0.112983
Absolute Change at 10 Months after Intervention 1	0.000749	(-0.000387, 0.001886)	0.113325	0.112576
Relative Change (%) at 10 Months after Intervention 1	0.67	(-0.35, 1.69)	0.113325	0.112576
Absolute Change at 11 Months after Intervention 1	0.000824	(-0.000426, 0.002074)	0.112993	0.112169
Relative Change (%) at 11 Months after Intervention 1	0.73	(-0.39, 1.86)	0.112993	0.112169
Absolute Change at 12 Months after Intervention 1	0.000899	(-0.000464, 0.002263)	0.112661	0.111762
Relative Change (%) at 12 Months after Intervention 1	0.80	(-0.43, 2.04)	0.112661	0.111762
Absolute Change at 13 Months after Intervention 1	0.000974	(-0.000503, 0.002451)	0.112330	0.111355
Relative Change (%) at 13 Months after Intervention 1	0.87	(-0.47, 2.22)	0.112330	0.111355
Absolute Change at 14 Months after Intervention 1	0.001049	(-0.000542, 0.002640)	0.111998	0.110949
Relative Change (%) at 14 Months after Intervention 1	0.95	(-0.51, 2.40)	0.111998	0.110949
Absolute Change at 15 Months after Intervention 1	0.001124	(-0.000580, 0.002828)	0.111666	0.110542
Relative Change (%) at 15 Months after Intervention 1	1.02	(-0.54, 2.58)	0.111666	0.110542
Absolute Change at 16 Months after Intervention 1	0.001199	(-0.000619, 0.003017)	0.111334	0.110135
Relative Change (%) at 16 Months after Intervention 1	1.09	(-0.58, 2.76)	0.111334	0.110135
Absolute Change at 17 Months after Intervention 1	0.001274	(-0.000658, 0.003206)	0.111002	0.109728
Relative Change (%) at 17 Months after Intervention 1	1.16	(-0.62, 2.94)	0.111002	0.109728
Absolute Change at 18 Months after Intervention 1	0.001349	(-0.000696, 0.003394)	0.110670	0.109321
Relative Change (%) at 18 Months after Intervention 1	1.23	(-0.66, 3.13)	0.110670	0.109321
Absolute Change at 19 Months after Intervention 1	0.001424	(-0.000735, 0.003583)	0.110338	0.108915
Relative Change (%) at 19 Months after Intervention 1	1.31	(-0.70, 3.32)	0.110338	0.108915
Absolute Change at 20 Months after Intervention 1	0.001499	(-0.000774, 0.003771)	0.110007	0.108508
Relative Change (%) at 20 Months after Intervention 1	1.38	(-0.74, 3.50)	0.110007	0.108508
Absolute Change at 21 Months after Intervention 1	0.001574	(-0.000813, 0.003960)	0.109675	0.108101
Relative Change (%) at 21 Months after Intervention 1	1.46	(-0.78, 3.69)	0.109675	0.108101
Absolute Change at 22 Months after Intervention 1	0.001649	(-0.000851, 0.004148)	0.109343	0.107694
Relative Change (%) at 22 Months after Intervention 1	1.53	(-0.82, 3.89)	0.109343	0.107694
Absolute Change at 23 Months after Intervention 1	0.001724	(-0.000890, 0.004337)	0.109011	0.107288
Relative Change (%) at 23 Months after Intervention 1	1.61	(-0.87, 4.08)	0.109011	0.107288
Absolute Change at 24 Months after Intervention 1	0.001798	(-0.000929, 0.004525)	0.108679	0.106881
Relative Change (%) at 24 Months after Intervention 1	1.68	(-0.91, 4.27)	0.108679	0.106881
Absolute Change at 25 Months after Intervention 1	0.001873	(-0.000967, 0.004714)	0.108347	0.106474
Relative Change (%) at 25 Months after Intervention 1	1.76	(-0.95, 4.47)	0.108347	0.106474
Absolute Change at 26 Months after Intervention 1	0.001948	(-0.001006, 0.004903)	0.108015	0.106067
Relative Change (%) at 26 Months after Intervention 1	1.84	(-0.99, 4.67)	0.108015	0.106067
Absolute Change at 27 Months after Intervention 1	0.002023	(-0.001045, 0.005091)	0.107684	0.105660
Relative Change (%) at 27 Months after Intervention 1	1.91	(-1.04, 4.87)	0.107684	0.105660
Absolute Change at 27 Months after Intervention 1	0.002023	(-0.001045, 0.005091)	0.107684	0.105660
Relative Change (%) at 27 Months after Intervention 1	1.91	(-1.04, 4.87)	0.107684	0.105660

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.382170	(0.379492, 0.384847)	<.001
Baseline trend	-0.001000	(-0.001084, -0.000916)	<.001
Level Change (After Intervention 1)	0.000576	(-0.000308, 0.001461)	0.198
Trend Change (After Intervention 1)	0.000053	(-0.000123, 0.000229)	0.551
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.382003	(0.379358, 0.384647)	<.001
Baseline trend	-0.000982	(-0.001039, -0.000926)	<.001
Level Change (After Intervention 1)	0.000609	(-0.000260, 0.001477)	0.167

¹The 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.

²Maximum 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.

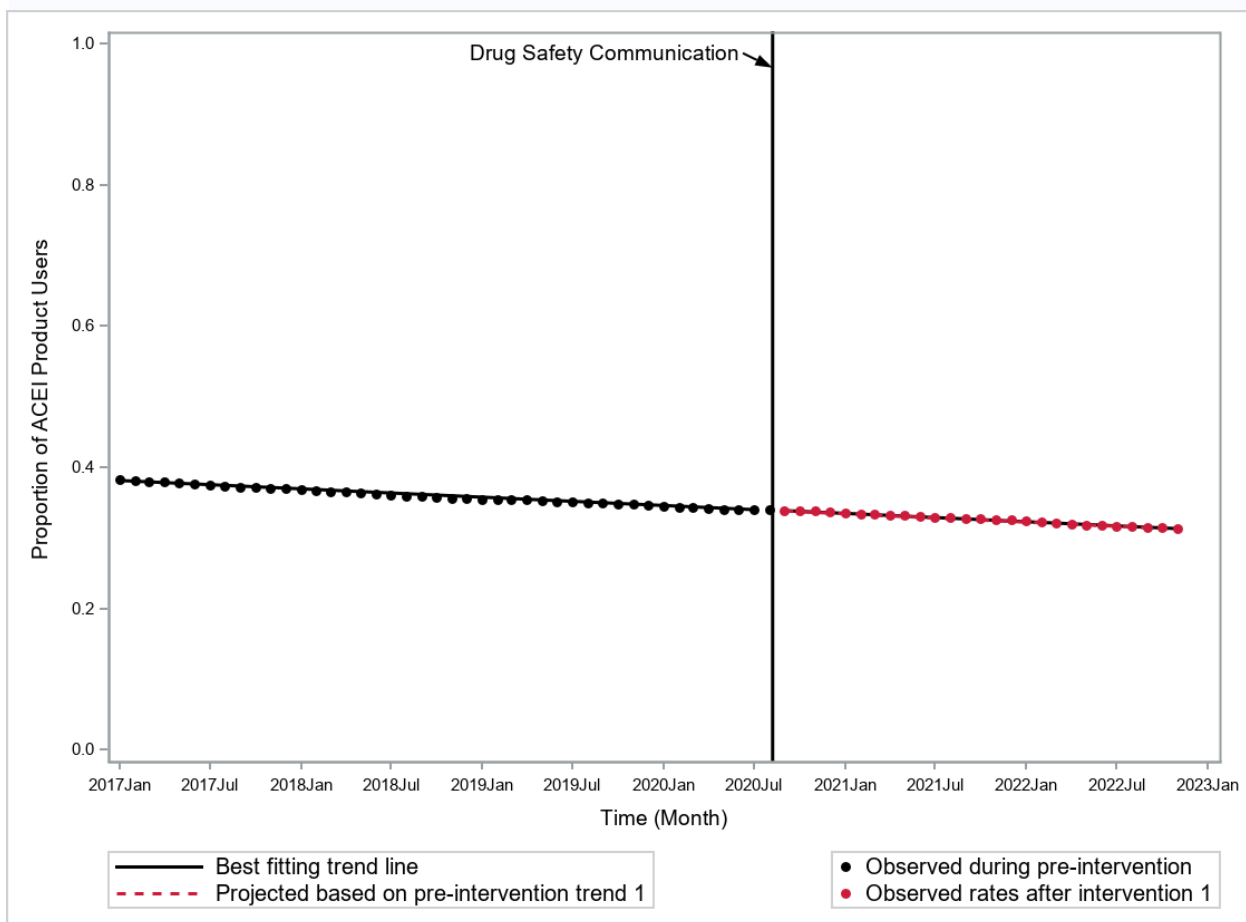
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000609	(-0.000255, 0.001472)	0.338400	0.337792
Relative Change (%) at 1 Months after Intervention 1	0.18	(-0.08, 0.44)	0.338400	0.337792
Absolute Change at 2 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.337418	0.336809
Relative Change (%) at 2 Months after Intervention 1	0.18	(-0.08, 0.44)	0.337418	0.336809
Absolute Change at 3 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.336435	0.335827
Relative Change (%) at 3 Months after Intervention 1	0.18	(-0.08, 0.44)	0.336435	0.335827
Absolute Change at 4 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.335453	0.334844
Relative Change (%) at 4 Months after Intervention 1	0.18	(-0.08, 0.44)	0.335453	0.334844
Absolute Change at 5 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.334470	0.333862
Relative Change (%) at 5 Months after Intervention 1	0.18	(-0.08, 0.44)	0.334470	0.333862
Absolute Change at 6 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.333488	0.332879
Relative Change (%) at 6 Months after Intervention 1	0.18	(-0.08, 0.44)	0.333488	0.332879
Absolute Change at 7 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.332505	0.331897
Relative Change (%) at 7 Months after Intervention 1	0.18	(-0.08, 0.44)	0.332505	0.331897
Absolute Change at 8 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.331523	0.330914
Relative Change (%) at 8 Months after Intervention 1	0.18	(-0.08, 0.45)	0.331523	0.330914
Absolute Change at 9 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.330541	0.329932
Relative Change (%) at 9 Months after Intervention 1	0.18	(-0.08, 0.45)	0.330541	0.329932
Absolute Change at 10 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.329558	0.328949
Relative Change (%) at 10 Months after Intervention 1	0.19	(-0.08, 0.45)	0.329558	0.328949
Absolute Change at 11 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.328576	0.327967
Relative Change (%) at 11 Months after Intervention 1	0.19	(-0.08, 0.45)	0.328576	0.327967
Absolute Change at 12 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.327593	0.326984
Relative Change (%) at 12 Months after Intervention 1	0.19	(-0.08, 0.45)	0.327593	0.326984
Absolute Change at 13 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.326611	0.326002
Relative Change (%) at 13 Months after Intervention 1	0.19	(-0.08, 0.45)	0.326611	0.326002
Absolute Change at 14 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.325628	0.325020
Relative Change (%) at 14 Months after Intervention 1	0.19	(-0.08, 0.45)	0.325628	0.325020
Absolute Change at 15 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.324646	0.324037
Relative Change (%) at 15 Months after Intervention 1	0.19	(-0.08, 0.45)	0.324646	0.324037
Absolute Change at 16 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.323663	0.323055
Relative Change (%) at 16 Months after Intervention 1	0.19	(-0.08, 0.46)	0.323663	0.323055
Absolute Change at 17 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.322681	0.322072
Relative Change (%) at 17 Months after Intervention 1	0.19	(-0.08, 0.46)	0.322681	0.322072
Absolute Change at 18 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.321698	0.321090
Relative Change (%) at 18 Months after Intervention 1	0.19	(-0.08, 0.46)	0.321698	0.321090
Absolute Change at 19 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.320716	0.320107
Relative Change (%) at 19 Months after Intervention 1	0.19	(-0.08, 0.46)	0.320716	0.320107
Absolute Change at 20 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.319733	0.319125
Relative Change (%) at 20 Months after Intervention 1	0.19	(-0.08, 0.46)	0.319733	0.319125
Absolute Change at 21 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.318751	0.318142
Relative Change (%) at 21 Months after Intervention 1	0.19	(-0.08, 0.46)	0.318751	0.318142
Absolute Change at 22 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.317768	0.317160
Relative Change (%) at 22 Months after Intervention 1	0.19	(-0.08, 0.46)	0.317768	0.317160
Absolute Change at 23 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.316786	0.316177
Relative Change (%) at 23 Months after Intervention 1	0.19	(-0.08, 0.47)	0.316786	0.316177
Absolute Change at 24 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.315803	0.315195
Relative Change (%) at 24 Months after Intervention 1	0.19	(-0.08, 0.47)	0.315803	0.315195
Absolute Change at 25 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.314821	0.314212
Relative Change (%) at 25 Months after Intervention 1	0.19	(-0.08, 0.47)	0.314821	0.314212
Absolute Change at 26 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.313839	0.313230
Relative Change (%) at 26 Months after Intervention 1	0.19	(-0.08, 0.47)	0.313839	0.313230
Absolute Change at 27 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.312856	0.312247
Relative Change (%) at 27 Months after Intervention 1	0.19	(-0.08, 0.47)	0.312856	0.312247
Absolute Change at 27 Months after Intervention 1	0.000609	(-0.000255, 0.001472)	0.312856	0.312247
Relative Change (%) at 27 Months after Intervention 1	0.19	(-0.08, 0.47)	0.312856	0.312247

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 64)²			
Intercept	0.396493	(0.394225, 0.398761)	<.001
Baseline trend	0.000115	(0.000048, 0.000183)	0.001
Level Change (After Intervention 1)	0.000620	(-0.000332, 0.001572)	0.198
Trend Change (After Intervention 1)	0.000205	(0.000065, 0.000345)	0.005
Most Parsimonious Final Model Parameters (df = 64)^{2,3}			
Intercept	0.396493	(0.394225, 0.398761)	<.001
Baseline trend	0.000115	(0.000048, 0.000183)	0.001
Level Change (After Intervention 1)	0.000620	(-0.000332, 0.001572)	0.198
Trend Change (After Intervention 1)	0.000205	(0.000065, 0.000345)	0.005

¹The 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.

²Maximum 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.

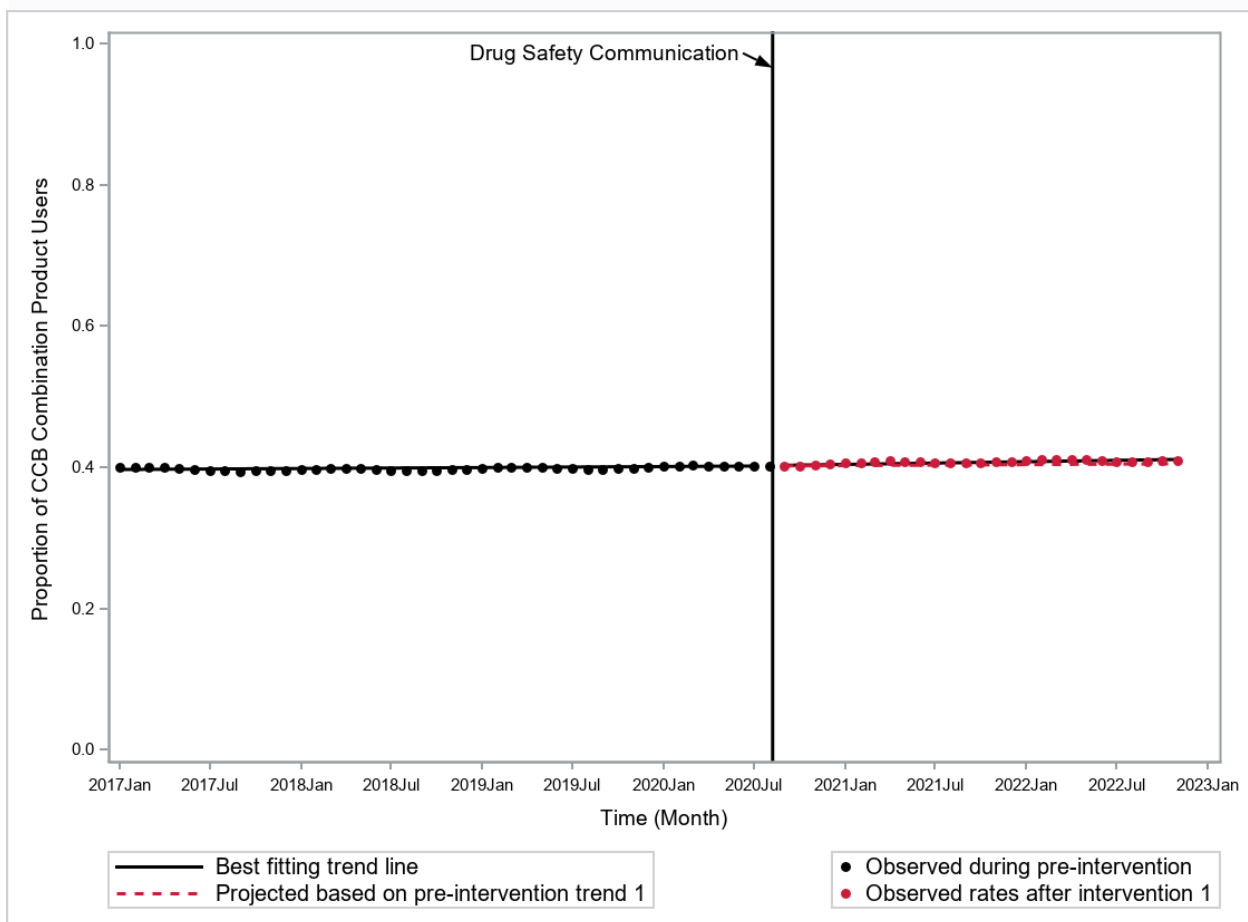
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000825	(-0.000137, 0.001788)	0.402514	0.401689
Relative Change (%) at 1 Months after Intervention 1	0.21	(-0.03, 0.45)	0.402514	0.401689
Absolute Change at 2 Months after Intervention 1	0.001030	(-0.000007, 0.002067)	0.402835	0.401804
Relative Change (%) at 2 Months after Intervention 1	0.26	(0.00, 0.52)	0.402835	0.401804
Absolute Change at 3 Months after Intervention 1	0.001235	(0.000076, 0.002395)	0.403155	0.401920
Relative Change (%) at 3 Months after Intervention 1	0.31	(0.02, 0.60)	0.403155	0.401920
Absolute Change at 4 Months after Intervention 1	0.001440	(0.000123, 0.002758)	0.403476	0.402035
Relative Change (%) at 4 Months after Intervention 1	0.36	(0.03, 0.69)	0.403476	0.402035
Absolute Change at 5 Months after Intervention 1	0.001646	(0.000147, 0.003144)	0.403796	0.402151
Relative Change (%) at 5 Months after Intervention 1	0.41	(0.03, 0.78)	0.403796	0.402151
Absolute Change at 6 Months after Intervention 1	0.001851	(0.000154, 0.003547)	0.404117	0.402266
Relative Change (%) at 6 Months after Intervention 1	0.46	(0.04, 0.89)	0.404117	0.402266
Absolute Change at 7 Months after Intervention 1	0.002056	(0.000150, 0.003961)	0.404437	0.402382
Relative Change (%) at 7 Months after Intervention 1	0.51	(0.03, 0.99)	0.404437	0.402382
Absolute Change at 8 Months after Intervention 1	0.002261	(0.000139, 0.004383)	0.404758	0.402497
Relative Change (%) at 8 Months after Intervention 1	0.56	(0.03, 1.09)	0.404758	0.402497
Absolute Change at 9 Months after Intervention 1	0.002466	(0.000121, 0.004811)	0.405079	0.402613
Relative Change (%) at 9 Months after Intervention 1	0.61	(0.03, 1.20)	0.405079	0.402613
Absolute Change at 10 Months after Intervention 1	0.002671	(0.000100, 0.005243)	0.405399	0.402728
Relative Change (%) at 10 Months after Intervention 1	0.66	(0.02, 1.31)	0.405399	0.402728
Absolute Change at 11 Months after Intervention 1	0.002876	(0.000075, 0.005678)	0.405720	0.402844
Relative Change (%) at 11 Months after Intervention 1	0.71	(0.01, 1.42)	0.405720	0.402844
Absolute Change at 12 Months after Intervention 1	0.003081	(0.000048, 0.006115)	0.406040	0.402959
Relative Change (%) at 12 Months after Intervention 1	0.76	(0.00, 1.52)	0.406040	0.402959
Absolute Change at 13 Months after Intervention 1	0.003287	(0.000019, 0.006555)	0.406361	0.403074
Relative Change (%) at 13 Months after Intervention 1	0.82	(0.00, 1.63)	0.406361	0.403074
Absolute Change at 14 Months after Intervention 1	0.003492	(-0.000012, 0.006995)	0.406682	0.403190
Relative Change (%) at 14 Months after Intervention 1	0.87	(-0.01, 1.74)	0.406682	0.403190
Absolute Change at 15 Months after Intervention 1	0.003697	(-0.000044, 0.007438)	0.407002	0.403305
Relative Change (%) at 15 Months after Intervention 1	0.92	(-0.02, 1.85)	0.407002	0.403305
Absolute Change at 16 Months after Intervention 1	0.003902	(-0.000077, 0.007881)	0.407323	0.403421
Relative Change (%) at 16 Months after Intervention 1	0.97	(-0.03, 1.96)	0.407323	0.403421
Absolute Change at 17 Months after Intervention 1	0.004107	(-0.000111, 0.008325)	0.407643	0.403536
Relative Change (%) at 17 Months after Intervention 1	1.02	(-0.04, 2.07)	0.407643	0.403536
Absolute Change at 18 Months after Intervention 1	0.004312	(-0.000145, 0.008770)	0.407964	0.403652
Relative Change (%) at 18 Months after Intervention 1	1.07	(-0.05, 2.18)	0.407964	0.403652
Absolute Change at 19 Months after Intervention 1	0.004517	(-0.000181, 0.009215)	0.408285	0.403767
Relative Change (%) at 19 Months after Intervention 1	1.12	(-0.06, 2.29)	0.408285	0.403767
Absolute Change at 20 Months after Intervention 1	0.004723	(-0.000216, 0.009661)	0.408605	0.403883
Relative Change (%) at 20 Months after Intervention 1	1.17	(-0.07, 2.41)	0.408605	0.403883
Absolute Change at 21 Months after Intervention 1	0.004928	(-0.000253, 0.010108)	0.408926	0.403998
Relative Change (%) at 21 Months after Intervention 1	1.22	(-0.08, 2.52)	0.408926	0.403998
Absolute Change at 22 Months after Intervention 1	0.005133	(-0.000289, 0.010555)	0.409246	0.404114
Relative Change (%) at 22 Months after Intervention 1	1.27	(-0.09, 2.63)	0.409246	0.404114
Absolute Change at 23 Months after Intervention 1	0.005338	(-0.000326, 0.011002)	0.409567	0.404229
Relative Change (%) at 23 Months after Intervention 1	1.32	(-0.10, 2.74)	0.409567	0.404229
Absolute Change at 24 Months after Intervention 1	0.005543	(-0.000363, 0.011449)	0.409888	0.404345
Relative Change (%) at 24 Months after Intervention 1	1.37	(-0.11, 2.85)	0.409888	0.404345
Absolute Change at 25 Months after Intervention 1	0.005748	(-0.000401, 0.011897)	0.410208	0.404460
Relative Change (%) at 25 Months after Intervention 1	1.42	(-0.12, 2.96)	0.410208	0.404460
Absolute Change at 26 Months after Intervention 1	0.005953	(-0.000438, 0.012345)	0.410529	0.404576
Relative Change (%) at 26 Months after Intervention 1	1.47	(-0.13, 3.07)	0.410529	0.404576
Absolute Change at 27 Months after Intervention 1	0.006158	(-0.000476, 0.012793)	0.410849	0.404691
Relative Change (%) at 27 Months after Intervention 1	1.52	(-0.14, 3.18)	0.410849	0.404691
Absolute Change at 27 Months after Intervention 1	0.006158	(-0.000476, 0.012793)	0.410849	0.404691
Relative Change (%) at 27 Months after Intervention 1	1.52	(-0.14, 3.18)	0.410849	0.404691

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 64)²			
Intercept	0.207751	(0.207082, 0.208419)	<.001
Baseline trend	-0.000277	(-0.000300, -0.000254)	<.001
Level Change (After Intervention 1)	-0.000746	(-0.001476, -0.000016)	0.045
Trend Change (After Intervention 1)	-0.000040	(-0.000089, 0.000009)	0.110
Most Parsimonious Final Model Parameters (df = 64)^{2,3}			
Intercept	0.207751	(0.207082, 0.208419)	<.001
Baseline trend	-0.000277	(-0.000300, -0.000254)	<.001
Level Change (After Intervention 1)	-0.000746	(-0.001476, -0.000016)	0.045
Trend Change (After Intervention 1)	-0.000040	(-0.000089, 0.000009)	0.110

¹The 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.

²Maximum 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.

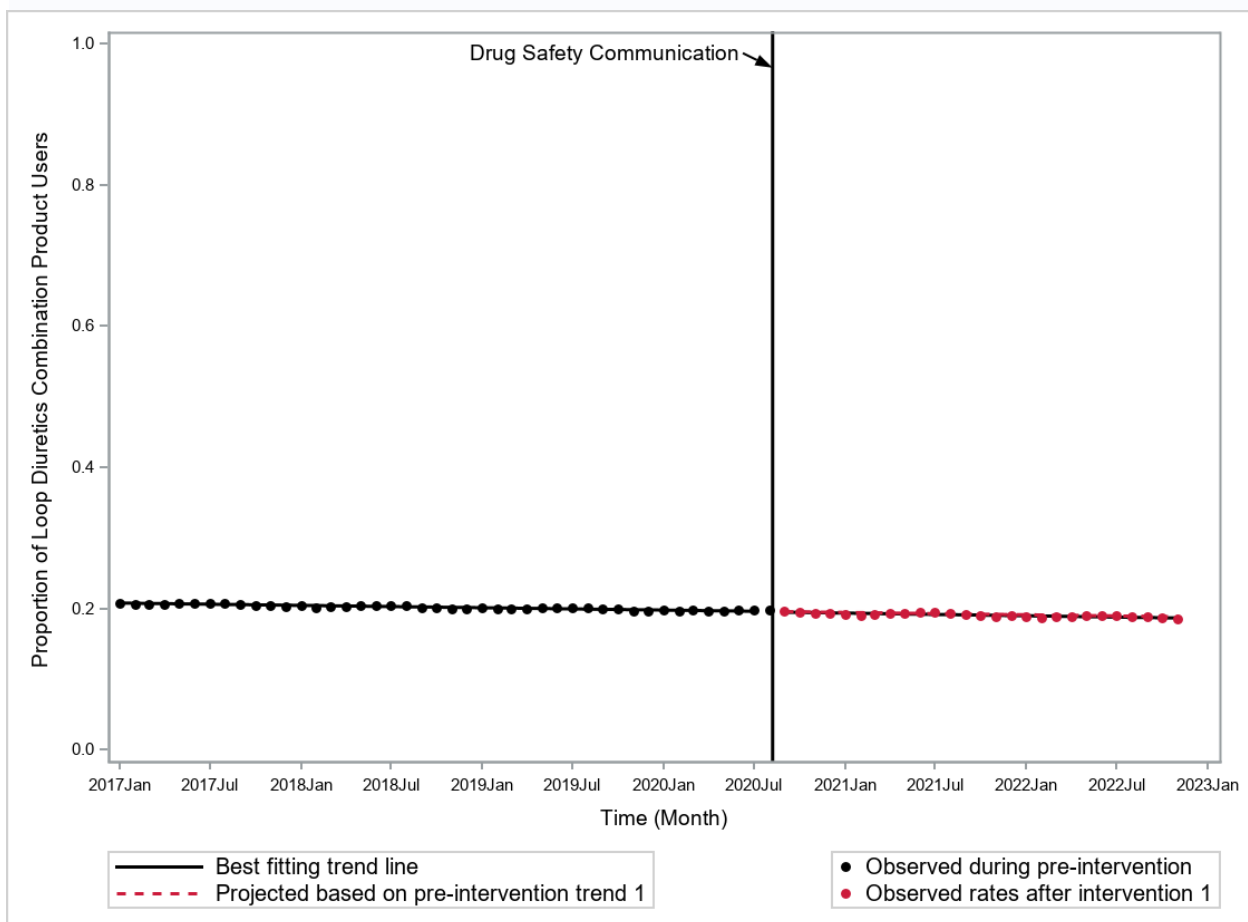
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	-0.000786	(-0.001493, -0.000078)	0.194510	0.195296
Relative Change (%) at 1 Months after Intervention 1	-0.40	(-0.76, -0.04)	0.194510	0.195296
Absolute Change at 2 Months after Intervention 1	-0.000825	(-0.001524, -0.000126)	0.194194	0.195019
Relative Change (%) at 2 Months after Intervention 1	-0.42	(-0.78, -0.07)	0.194194	0.195019
Absolute Change at 3 Months after Intervention 1	-0.000865	(-0.001559, -0.000171)	0.193878	0.194743
Relative Change (%) at 3 Months after Intervention 1	-0.44	(-0.80, -0.09)	0.193878	0.194743
Absolute Change at 4 Months after Intervention 1	-0.000905	(-0.001597, -0.000213)	0.193561	0.194466
Relative Change (%) at 4 Months after Intervention 1	-0.47	(-0.82, -0.11)	0.193561	0.194466
Absolute Change at 5 Months after Intervention 1	-0.000944	(-0.001638, -0.000251)	0.193245	0.194189
Relative Change (%) at 5 Months after Intervention 1	-0.49	(-0.84, -0.13)	0.193245	0.194189
Absolute Change at 6 Months after Intervention 1	-0.000984	(-0.001682, -0.000286)	0.192928	0.193912
Relative Change (%) at 6 Months after Intervention 1	-0.51	(-0.87, -0.15)	0.192928	0.193912
Absolute Change at 7 Months after Intervention 1	-0.001024	(-0.001730, -0.000317)	0.192612	0.193636
Relative Change (%) at 7 Months after Intervention 1	-0.53	(-0.89, -0.17)	0.192612	0.193636
Absolute Change at 8 Months after Intervention 1	-0.001063	(-0.001781, -0.000345)	0.192296	0.193359
Relative Change (%) at 8 Months after Intervention 1	-0.55	(-0.92, -0.18)	0.192296	0.193359
Absolute Change at 9 Months after Intervention 1	-0.001103	(-0.001835, -0.000371)	0.191979	0.193082
Relative Change (%) at 9 Months after Intervention 1	-0.57	(-0.95, -0.19)	0.191979	0.193082
Absolute Change at 10 Months after Intervention 1	-0.001142	(-0.001892, -0.000393)	0.191663	0.192805
Relative Change (%) at 10 Months after Intervention 1	-0.59	(-0.98, -0.21)	0.191663	0.192805
Absolute Change at 11 Months after Intervention 1	-0.001182	(-0.001951, -0.000413)	0.191347	0.192529
Relative Change (%) at 11 Months after Intervention 1	-0.61	(-1.01, -0.22)	0.191347	0.192529
Absolute Change at 12 Months after Intervention 1	-0.001222	(-0.002013, -0.000430)	0.191030	0.192252
Relative Change (%) at 12 Months after Intervention 1	-0.64	(-1.04, -0.23)	0.191030	0.192252
Absolute Change at 13 Months after Intervention 1	-0.001261	(-0.002078, -0.000445)	0.190714	0.191975
Relative Change (%) at 13 Months after Intervention 1	-0.66	(-1.08, -0.23)	0.190714	0.191975
Absolute Change at 14 Months after Intervention 1	-0.001301	(-0.002144, -0.000458)	0.190397	0.191698
Relative Change (%) at 14 Months after Intervention 1	-0.68	(-1.12, -0.24)	0.190397	0.191698
Absolute Change at 15 Months after Intervention 1	-0.001340	(-0.002212, -0.000469)	0.190081	0.191422
Relative Change (%) at 15 Months after Intervention 1	-0.70	(-1.15, -0.25)	0.190081	0.191422
Absolute Change at 16 Months after Intervention 1	-0.001380	(-0.002282, -0.000478)	0.189765	0.191145
Relative Change (%) at 16 Months after Intervention 1	-0.72	(-1.19, -0.25)	0.189765	0.191145
Absolute Change at 17 Months after Intervention 1	-0.001420	(-0.002354, -0.000486)	0.189448	0.190868
Relative Change (%) at 17 Months after Intervention 1	-0.74	(-1.23, -0.26)	0.189448	0.190868
Absolute Change at 18 Months after Intervention 1	-0.001459	(-0.002426, -0.000492)	0.189132	0.190591
Relative Change (%) at 18 Months after Intervention 1	-0.77	(-1.27, -0.26)	0.189132	0.190591
Absolute Change at 19 Months after Intervention 1	-0.001499	(-0.002501, -0.000497)	0.188816	0.190314
Relative Change (%) at 19 Months after Intervention 1	-0.79	(-1.31, -0.26)	0.188816	0.190314
Absolute Change at 20 Months after Intervention 1	-0.001538	(-0.002576, -0.000501)	0.188499	0.190038
Relative Change (%) at 20 Months after Intervention 1	-0.81	(-1.35, -0.27)	0.188499	0.190038
Absolute Change at 21 Months after Intervention 1	-0.001578	(-0.002652, -0.000504)	0.188183	0.189761
Relative Change (%) at 21 Months after Intervention 1	-0.83	(-1.39, -0.27)	0.188183	0.189761
Absolute Change at 22 Months after Intervention 1	-0.001618	(-0.002729, -0.000506)	0.187867	0.189484
Relative Change (%) at 22 Months after Intervention 1	-0.85	(-1.44, -0.27)	0.187867	0.189484
Absolute Change at 23 Months after Intervention 1	-0.001657	(-0.002807, -0.000508)	0.187550	0.189207
Relative Change (%) at 23 Months after Intervention 1	-0.88	(-1.48, -0.27)	0.187550	0.189207
Absolute Change at 24 Months after Intervention 1	-0.001697	(-0.002886, -0.000508)	0.187234	0.188931
Relative Change (%) at 24 Months after Intervention 1	-0.90	(-1.52, -0.27)	0.187234	0.188931
Absolute Change at 25 Months after Intervention 1	-0.001737	(-0.002965, -0.000508)	0.186917	0.188654
Relative Change (%) at 25 Months after Intervention 1	-0.92	(-1.57, -0.27)	0.186917	0.188654
Absolute Change at 26 Months after Intervention 1	-0.001776	(-0.003045, -0.000507)	0.186601	0.188377
Relative Change (%) at 26 Months after Intervention 1	-0.94	(-1.61, -0.27)	0.186601	0.188377
Absolute Change at 27 Months after Intervention 1	-0.001816	(-0.003126, -0.000506)	0.186285	0.188100
Relative Change (%) at 27 Months after Intervention 1	-0.97	(-1.66, -0.27)	0.186285	0.188100
Absolute Change at 27 Months after Intervention 1	-0.001816	(-0.003126, -0.000506)	0.186285	0.188100
Relative Change (%) at 27 Months after Intervention 1	-0.97	(-1.66, -0.27)	0.186285	0.188100

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.047142	(0.046601, 0.047684)	<.001
Baseline trend	0.000057	(0.000038, 0.000076)	<.001
Level Change (After Intervention 1)	-0.000126	(-0.000481, 0.000230)	0.483
Trend Change (After Intervention 1)	0.000113	(0.000069, 0.000157)	<.001
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.047162	(0.046581, 0.047742)	<.001
Baseline trend	0.000055	(0.000035, 0.000075)	<.001
Trend Change (After Intervention 1)	0.000111	(0.000066, 0.000157)	<.001

¹The 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.

²Maximum 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.

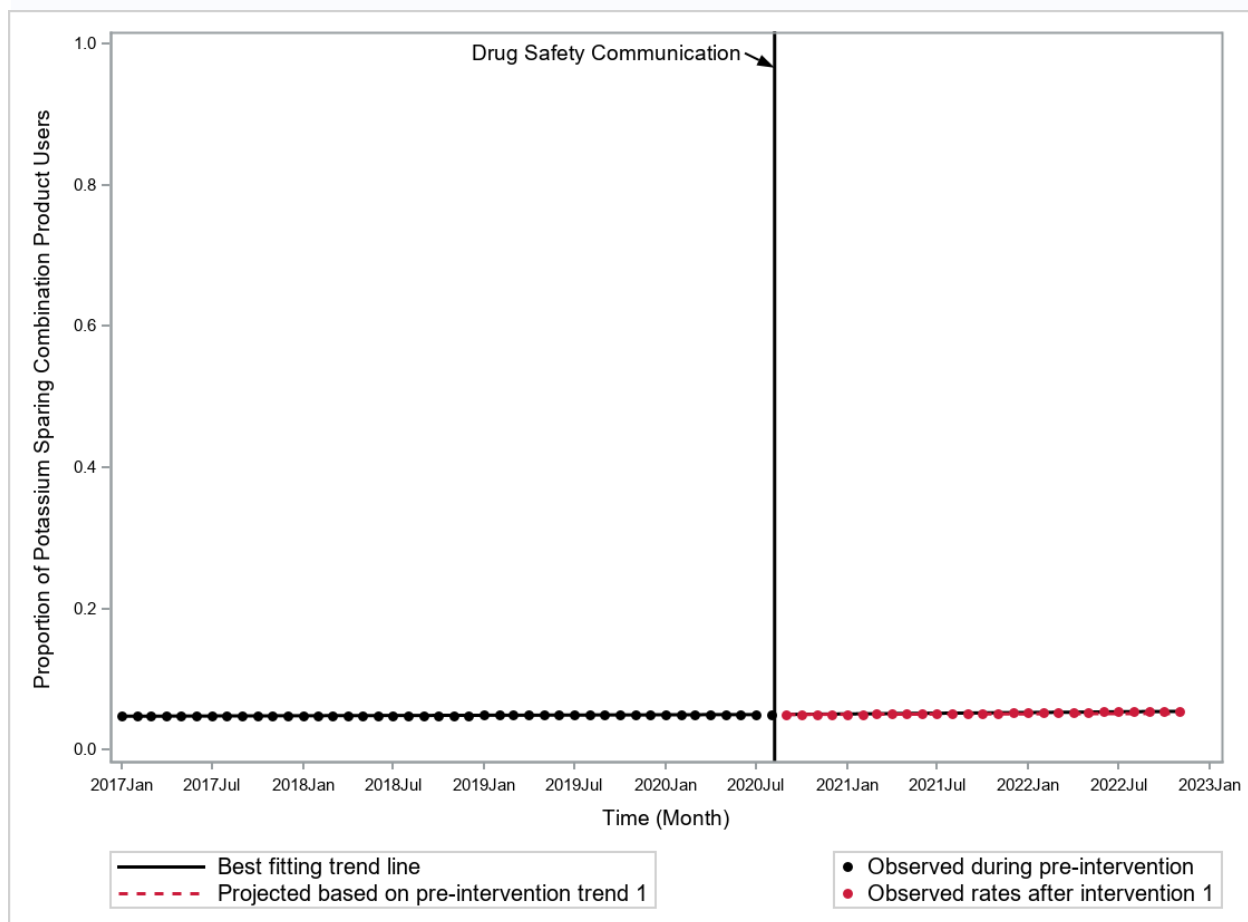
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	0.000111	(0.000062, 0.000161)	0.049762	0.049650
Relative Change (%) at 1 Months after Intervention 1	0.22	(0.12, 0.33)	0.049762	0.049650
Absolute Change at 2 Months after Intervention 1	0.000223	(0.000124, 0.000322)	0.049929	0.049706
Relative Change (%) at 2 Months after Intervention 1	0.45	(0.25, 0.65)	0.049929	0.049706
Absolute Change at 3 Months after Intervention 1	0.000334	(0.000186, 0.000483)	0.050095	0.049761
Relative Change (%) at 3 Months after Intervention 1	0.67	(0.37, 0.98)	0.050095	0.049761
Absolute Change at 4 Months after Intervention 1	0.000446	(0.000248, 0.000644)	0.050262	0.049816
Relative Change (%) at 4 Months after Intervention 1	0.90	(0.49, 1.30)	0.050262	0.049816
Absolute Change at 5 Months after Intervention 1	0.000557	(0.000310, 0.000804)	0.050429	0.049872
Relative Change (%) at 5 Months after Intervention 1	1.12	(0.61, 1.62)	0.050429	0.049872
Absolute Change at 6 Months after Intervention 1	0.000669	(0.000372, 0.000965)	0.050596	0.049927
Relative Change (%) at 6 Months after Intervention 1	1.34	(0.73, 1.95)	0.050596	0.049927
Absolute Change at 7 Months after Intervention 1	0.000780	(0.000435, 0.001126)	0.050763	0.049982
Relative Change (%) at 7 Months after Intervention 1	1.56	(0.85, 2.27)	0.050763	0.049982
Absolute Change at 8 Months after Intervention 1	0.000892	(0.000497, 0.001287)	0.050929	0.050038
Relative Change (%) at 8 Months after Intervention 1	1.78	(0.97, 2.59)	0.050929	0.050038
Absolute Change at 9 Months after Intervention 1	0.001003	(0.000559, 0.001448)	0.051096	0.050093
Relative Change (%) at 9 Months after Intervention 1	2.00	(1.09, 2.91)	0.051096	0.050093
Absolute Change at 10 Months after Intervention 1	0.001115	(0.000621, 0.001609)	0.051263	0.050148
Relative Change (%) at 10 Months after Intervention 1	2.22	(1.21, 3.24)	0.051263	0.050148
Absolute Change at 11 Months after Intervention 1	0.001226	(0.000683, 0.001770)	0.051430	0.050203
Relative Change (%) at 11 Months after Intervention 1	2.44	(1.33, 3.56)	0.051430	0.050203
Absolute Change at 12 Months after Intervention 1	0.001338	(0.000745, 0.001931)	0.051597	0.050259
Relative Change (%) at 12 Months after Intervention 1	2.66	(1.45, 3.88)	0.051597	0.050259
Absolute Change at 13 Months after Intervention 1	0.001449	(0.000807, 0.002092)	0.051763	0.050314
Relative Change (%) at 13 Months after Intervention 1	2.88	(1.57, 4.20)	0.051763	0.050314
Absolute Change at 14 Months after Intervention 1	0.001561	(0.000869, 0.002252)	0.051930	0.050369
Relative Change (%) at 14 Months after Intervention 1	3.10	(1.68, 4.51)	0.051930	0.050369
Absolute Change at 15 Months after Intervention 1	0.001672	(0.000931, 0.002413)	0.052097	0.050425
Relative Change (%) at 15 Months after Intervention 1	3.32	(1.80, 4.83)	0.052097	0.050425
Absolute Change at 16 Months after Intervention 1	0.001784	(0.000993, 0.002574)	0.052264	0.050480
Relative Change (%) at 16 Months after Intervention 1	3.53	(1.92, 5.15)	0.052264	0.050480
Absolute Change at 17 Months after Intervention 1	0.001895	(0.001055, 0.002735)	0.052430	0.050535
Relative Change (%) at 17 Months after Intervention 1	3.75	(2.03, 5.47)	0.052430	0.050535
Absolute Change at 18 Months after Intervention 1	0.002007	(0.001117, 0.002896)	0.052597	0.050591
Relative Change (%) at 18 Months after Intervention 1	3.97	(2.15, 5.78)	0.052597	0.050591
Absolute Change at 19 Months after Intervention 1	0.002118	(0.001179, 0.003057)	0.052764	0.050646
Relative Change (%) at 19 Months after Intervention 1	4.18	(2.27, 6.10)	0.052764	0.050646
Absolute Change at 20 Months after Intervention 1	0.002230	(0.001242, 0.003218)	0.052931	0.050701
Relative Change (%) at 20 Months after Intervention 1	4.40	(2.38, 6.41)	0.052931	0.050701
Absolute Change at 21 Months after Intervention 1	0.002341	(0.001304, 0.003379)	0.053098	0.050756
Relative Change (%) at 21 Months after Intervention 1	4.61	(2.50, 6.73)	0.053098	0.050756
Absolute Change at 22 Months after Intervention 1	0.002453	(0.001366, 0.003540)	0.053264	0.050812
Relative Change (%) at 22 Months after Intervention 1	4.83	(2.61, 7.04)	0.053264	0.050812
Absolute Change at 23 Months after Intervention 1	0.002564	(0.001428, 0.003700)	0.053431	0.050867
Relative Change (%) at 23 Months after Intervention 1	5.04	(2.72, 7.36)	0.053431	0.050867
Absolute Change at 24 Months after Intervention 1	0.002676	(0.001490, 0.003861)	0.053598	0.050922
Relative Change (%) at 24 Months after Intervention 1	5.25	(2.84, 7.67)	0.053598	0.050922
Absolute Change at 25 Months after Intervention 1	0.002787	(0.001552, 0.004022)	0.053765	0.050978
Relative Change (%) at 25 Months after Intervention 1	5.47	(2.95, 7.98)	0.053765	0.050978
Absolute Change at 26 Months after Intervention 1	0.002899	(0.001614, 0.004183)	0.053932	0.051033
Relative Change (%) at 26 Months after Intervention 1	5.68	(3.06, 8.29)	0.053932	0.051033
Absolute Change at 27 Months after Intervention 1	0.003010	(0.001676, 0.004344)	0.054098	0.051088
Relative Change (%) at 27 Months after Intervention 1	5.89	(3.18, 8.61)	0.054098	0.051088
Absolute Change at 27 Months after Intervention 1	0.003010	(0.001676, 0.004344)	0.054098	0.051088
Relative Change (%) at 27 Months after Intervention 1	5.89	(3.18, 8.61)	0.054098	0.051088

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.024325	(0.024023, 0.024627)	<.001
Baseline trend	0.000037	(0.000026, 0.000048)	<.001
Level Change (After Intervention 1)	-0.000142	(-0.000358, 0.000073)	0.192
Trend Change (After Intervention 1)	-0.000071	(-0.000099, -0.000042)	<.001
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.024325	(0.024023, 0.024627)	<.001
Baseline trend	0.000037	(0.000026, 0.000048)	<.001
Level Change (After Intervention 1)	-0.000142	(-0.000358, 0.000073)	0.192
Trend Change (After Intervention 1)	-0.000071	(-0.000099, -0.000042)	<.001

¹The 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.

²Maximum 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.

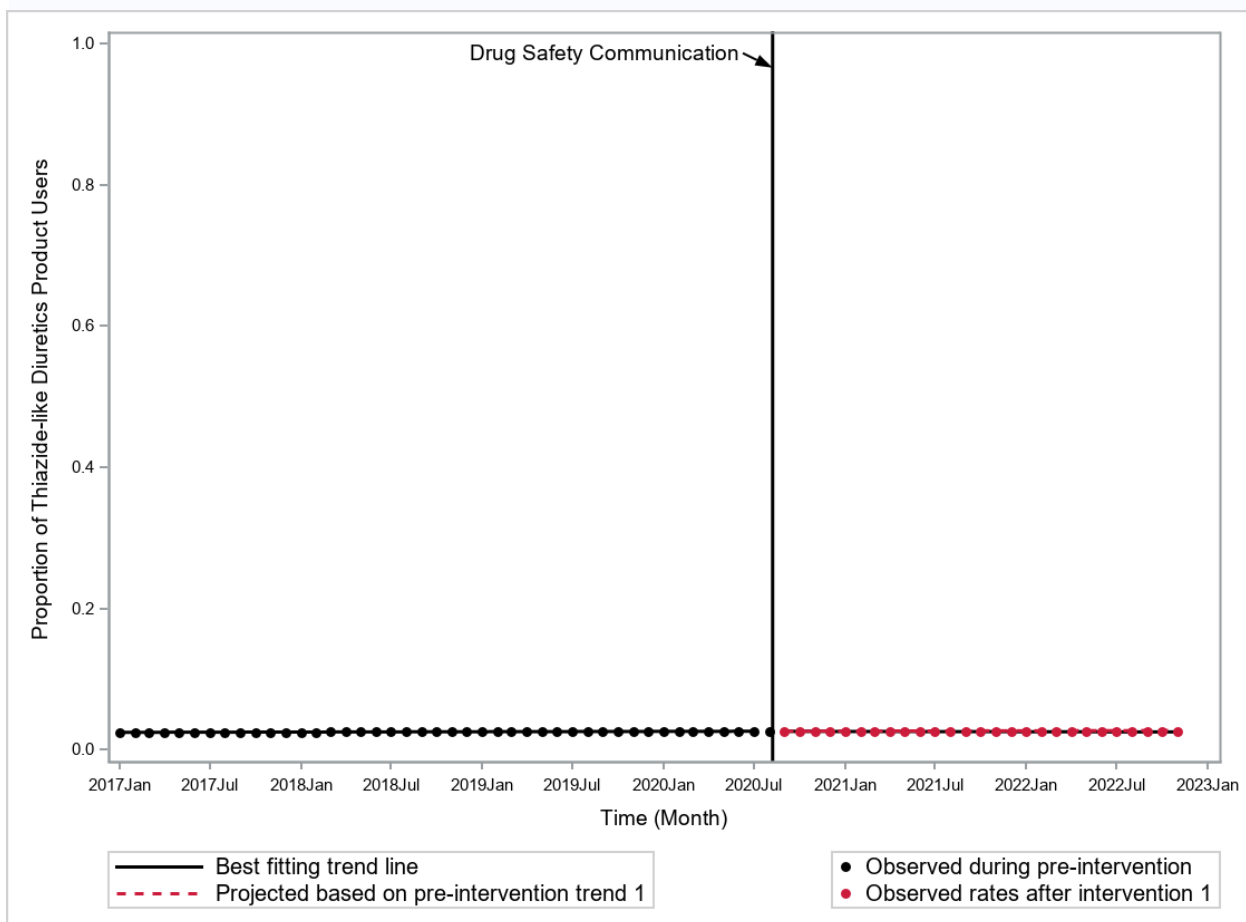
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with History of Skin Cancer after August 8, 2020¹ 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	-0.000213	(-0.000427, 0.000001)	0.025766	0.025979
Relative Change (%) at 1 Months after Intervention 1	-0.82	(-1.64, 0.00)	0.025766	0.025979
Absolute Change at 2 Months after Intervention 1	-0.000284	(-0.000498, -0.000069)	0.025732	0.026015
Relative Change (%) at 2 Months after Intervention 1	-1.09	(-1.91, -0.27)	0.025732	0.026015
Absolute Change at 3 Months after Intervention 1	-0.000354	(-0.000573, -0.000135)	0.025698	0.026052
Relative Change (%) at 3 Months after Intervention 1	-1.36	(-2.19, -0.53)	0.025698	0.026052
Absolute Change at 4 Months after Intervention 1	-0.000425	(-0.000652, -0.000198)	0.025664	0.026089
Relative Change (%) at 4 Months after Intervention 1	-1.63	(-2.49, -0.77)	0.025664	0.026089
Absolute Change at 5 Months after Intervention 1	-0.000496	(-0.000734, -0.000257)	0.025630	0.026126
Relative Change (%) at 5 Months after Intervention 1	-1.90	(-2.79, -1.00)	0.025630	0.026126
Absolute Change at 6 Months after Intervention 1	-0.000566	(-0.000819, -0.000313)	0.025596	0.026162
Relative Change (%) at 6 Months after Intervention 1	-2.16	(-3.11, -1.22)	0.025596	0.026162
Absolute Change at 7 Months after Intervention 1	-0.000637	(-0.000906, -0.000367)	0.025562	0.026199
Relative Change (%) at 7 Months after Intervention 1	-2.43	(-3.43, -1.43)	0.025562	0.026199
Absolute Change at 8 Months after Intervention 1	-0.000707	(-0.000995, -0.000420)	0.025528	0.026236
Relative Change (%) at 8 Months after Intervention 1	-2.70	(-3.76, -1.63)	0.025528	0.026236
Absolute Change at 9 Months after Intervention 1	-0.000778	(-0.001086, -0.000470)	0.025494	0.026273
Relative Change (%) at 9 Months after Intervention 1	-2.96	(-4.10, -1.82)	0.025494	0.026273
Absolute Change at 10 Months after Intervention 1	-0.000849	(-0.001178, -0.000519)	0.025461	0.026309
Relative Change (%) at 10 Months after Intervention 1	-3.23	(-4.44, -2.01)	0.025461	0.026309
Absolute Change at 11 Months after Intervention 1	-0.000919	(-0.001272, -0.000567)	0.025427	0.026346
Relative Change (%) at 11 Months after Intervention 1	-3.49	(-4.78, -2.20)	0.025427	0.026346
Absolute Change at 12 Months after Intervention 1	-0.000990	(-0.001366, -0.000614)	0.025393	0.026383
Relative Change (%) at 12 Months after Intervention 1	-3.75	(-5.13, -2.38)	0.025393	0.026383
Absolute Change at 13 Months after Intervention 1	-0.001061	(-0.001461, -0.000661)	0.025359	0.026420
Relative Change (%) at 13 Months after Intervention 1	-4.01	(-5.48, -2.55)	0.025359	0.026420
Absolute Change at 14 Months after Intervention 1	-0.001131	(-0.001556, -0.000706)	0.025325	0.026456
Relative Change (%) at 14 Months after Intervention 1	-4.28	(-5.82, -2.73)	0.025325	0.026456
Absolute Change at 15 Months after Intervention 1	-0.001202	(-0.001652, -0.000752)	0.025291	0.026493
Relative Change (%) at 15 Months after Intervention 1	-4.54	(-6.17, -2.90)	0.025291	0.026493
Absolute Change at 16 Months after Intervention 1	-0.001273	(-0.001749, -0.000796)	0.025257	0.026530
Relative Change (%) at 16 Months after Intervention 1	-4.80	(-6.52, -3.07)	0.025257	0.026530
Absolute Change at 17 Months after Intervention 1	-0.001343	(-0.001845, -0.000841)	0.025223	0.026567
Relative Change (%) at 17 Months after Intervention 1	-5.06	(-6.87, -3.24)	0.025223	0.026567
Absolute Change at 18 Months after Intervention 1	-0.001414	(-0.001942, -0.000885)	0.025190	0.026603
Relative Change (%) at 18 Months after Intervention 1	-5.31	(-7.22, -3.41)	0.025190	0.026603
Absolute Change at 19 Months after Intervention 1	-0.001484	(-0.002040, -0.000929)	0.025156	0.026640
Relative Change (%) at 19 Months after Intervention 1	-5.57	(-7.57, -3.57)	0.025156	0.026640
Absolute Change at 20 Months after Intervention 1	-0.001555	(-0.002137, -0.000973)	0.025122	0.026677
Relative Change (%) at 20 Months after Intervention 1	-5.83	(-7.92, -3.74)	0.025122	0.026677
Absolute Change at 21 Months after Intervention 1	-0.001626	(-0.002235, -0.001016)	0.025088	0.026714
Relative Change (%) at 21 Months after Intervention 1	-6.09	(-8.27, -3.90)	0.025088	0.026714
Absolute Change at 22 Months after Intervention 1	-0.001696	(-0.002333, -0.001060)	0.025054	0.026750
Relative Change (%) at 22 Months after Intervention 1	-6.34	(-8.62, -4.06)	0.025054	0.026750
Absolute Change at 23 Months after Intervention 1	-0.001767	(-0.002431, -0.001103)	0.025020	0.026787
Relative Change (%) at 23 Months after Intervention 1	-6.60	(-8.97, -4.23)	0.025020	0.026787
Absolute Change at 24 Months after Intervention 1	-0.001838	(-0.002529, -0.001146)	0.024986	0.026824
Relative Change (%) at 24 Months after Intervention 1	-6.85	(-9.31, -4.39)	0.024986	0.026824
Absolute Change at 25 Months after Intervention 1	-0.001908	(-0.002628, -0.001189)	0.024952	0.026861
Relative Change (%) at 25 Months after Intervention 1	-7.10	(-9.66, -4.55)	0.024952	0.026861
Absolute Change at 26 Months after Intervention 1	-0.001979	(-0.002726, -0.001232)	0.024918	0.026897
Relative Change (%) at 26 Months after Intervention 1	-7.36	(-10.01, -4.71)	0.024918	0.026897
Absolute Change at 27 Months after Intervention 1	-0.002049	(-0.002825, -0.001274)	0.024885	0.026934
Relative Change (%) at 27 Months after Intervention 1	-7.61	(-10.35, -4.87)	0.024885	0.026934
Absolute Change at 27 Months after Intervention 1	-0.002049	(-0.002825, -0.001274)	0.024885	0.026934
Relative Change (%) at 27 Months after Intervention 1	-7.61	(-10.35, -4.87)	0.024885	0.026934

¹The 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 with History of Skin Cancer Before and After August 8, 2020¹



¹The 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 Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.199202	(0.197776, 0.200628)	<.001
Baseline trend	-0.000322	(-0.000374, -0.000270)	<.001
Level Change (After Intervention 1)	-0.000792	(-0.001765, 0.000181)	0.109
Trend Change (After Intervention 1)	-0.000221	(-0.000350, -0.000091)	0.001
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.199202	(0.197776, 0.200628)	<.001
Baseline trend	-0.000322	(-0.000374, -0.000270)	<.001
Level Change (After Intervention 1)	-0.000792	(-0.001765, 0.000181)	0.109
Trend Change (After Intervention 1)	-0.000221	(-0.000350, -0.000091)	0.001

¹The 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.

²Maximum 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.

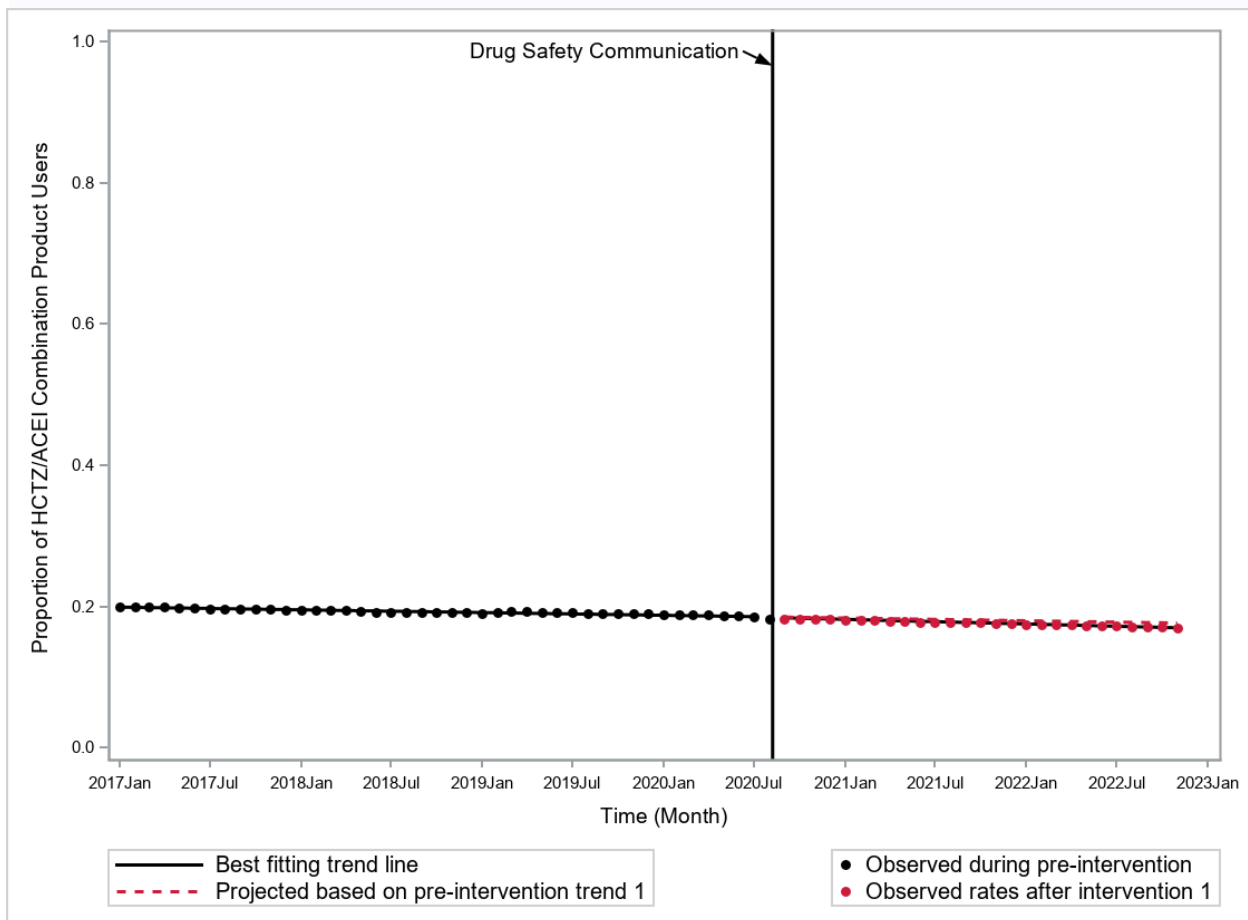
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 32. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Converting Enzyme Inhibitor (ACEi) Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer after August 8, 2020¹ 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	-0.001013	(-0.002015, -0.000010)	0.183704	0.184717
Relative Change (%) at 1 Months after Intervention 1	-0.55	(-1.09, -0.01)	0.183704	0.184717
Absolute Change at 2 Months after Intervention 1	-0.001233	(-0.002242, -0.000225)	0.183161	0.184395
Relative Change (%) at 2 Months after Intervention 1	-0.67	(-1.21, -0.12)	0.183161	0.184395
Absolute Change at 3 Months after Intervention 1	-0.001454	(-0.002487, -0.000422)	0.182619	0.184073
Relative Change (%) at 3 Months after Intervention 1	-0.79	(-1.35, -0.23)	0.182619	0.184073
Absolute Change at 4 Months after Intervention 1	-0.001675	(-0.002748, -0.000602)	0.182076	0.183751
Relative Change (%) at 4 Months after Intervention 1	-0.91	(-1.49, -0.33)	0.182076	0.183751
Absolute Change at 5 Months after Intervention 1	-0.001896	(-0.003024, -0.000767)	0.181533	0.183429
Relative Change (%) at 5 Months after Intervention 1	-1.03	(-1.64, -0.42)	0.181533	0.183429
Absolute Change at 6 Months after Intervention 1	-0.002117	(-0.003313, -0.000920)	0.180991	0.183107
Relative Change (%) at 6 Months after Intervention 1	-1.16	(-1.80, -0.51)	0.180991	0.183107
Absolute Change at 7 Months after Intervention 1	-0.002337	(-0.003614, -0.001061)	0.180448	0.182785
Relative Change (%) at 7 Months after Intervention 1	-1.28	(-1.97, -0.59)	0.180448	0.182785
Absolute Change at 8 Months after Intervention 1	-0.002558	(-0.003923, -0.001194)	0.179905	0.182463
Relative Change (%) at 8 Months after Intervention 1	-1.40	(-2.14, -0.67)	0.179905	0.182463
Absolute Change at 9 Months after Intervention 1	-0.002779	(-0.004239, -0.001319)	0.179363	0.182142
Relative Change (%) at 9 Months after Intervention 1	-1.53	(-2.31, -0.74)	0.179363	0.182142
Absolute Change at 10 Months after Intervention 1	-0.003000	(-0.004562, -0.001438)	0.178820	0.181820
Relative Change (%) at 10 Months after Intervention 1	-1.65	(-2.49, -0.81)	0.178820	0.181820
Absolute Change at 11 Months after Intervention 1	-0.003221	(-0.004889, -0.001552)	0.178277	0.181498
Relative Change (%) at 11 Months after Intervention 1	-1.77	(-2.68, -0.87)	0.178277	0.181498
Absolute Change at 12 Months after Intervention 1	-0.003441	(-0.005220, -0.001663)	0.177735	0.181176
Relative Change (%) at 12 Months after Intervention 1	-1.90	(-2.86, -0.94)	0.177735	0.181176
Absolute Change at 13 Months after Intervention 1	-0.003662	(-0.005555, -0.001769)	0.177192	0.180854
Relative Change (%) at 13 Months after Intervention 1	-2.02	(-3.05, -1.00)	0.177192	0.180854
Absolute Change at 14 Months after Intervention 1	-0.003883	(-0.005892, -0.001874)	0.176649	0.180532
Relative Change (%) at 14 Months after Intervention 1	-2.15	(-3.24, -1.06)	0.176649	0.180532
Absolute Change at 15 Months after Intervention 1	-0.004104	(-0.006232, -0.001976)	0.176107	0.180210
Relative Change (%) at 15 Months after Intervention 1	-2.28	(-3.43, -1.12)	0.176107	0.180210
Absolute Change at 16 Months after Intervention 1	-0.004324	(-0.006573, -0.002076)	0.175564	0.179888
Relative Change (%) at 16 Months after Intervention 1	-2.40	(-3.63, -1.18)	0.175564	0.179888
Absolute Change at 17 Months after Intervention 1	-0.004545	(-0.006916, -0.002174)	0.175021	0.179566
Relative Change (%) at 17 Months after Intervention 1	-2.53	(-3.82, -1.24)	0.175021	0.179566
Absolute Change at 18 Months after Intervention 1	-0.004766	(-0.007261, -0.002271)	0.174479	0.179244
Relative Change (%) at 18 Months after Intervention 1	-2.66	(-4.02, -1.30)	0.174479	0.179244
Absolute Change at 19 Months after Intervention 1	-0.004987	(-0.007607, -0.002367)	0.173936	0.178923
Relative Change (%) at 19 Months after Intervention 1	-2.79	(-4.22, -1.35)	0.173936	0.178923
Absolute Change at 20 Months after Intervention 1	-0.005208	(-0.007954, -0.002461)	0.173393	0.178601
Relative Change (%) at 20 Months after Intervention 1	-2.92	(-4.42, -1.41)	0.173393	0.178601
Absolute Change at 21 Months after Intervention 1	-0.005428	(-0.008301, -0.002555)	0.172850	0.178279
Relative Change (%) at 21 Months after Intervention 1	-3.04	(-4.62, -1.47)	0.172850	0.178279
Absolute Change at 22 Months after Intervention 1	-0.005649	(-0.008650, -0.002648)	0.172308	0.177957
Relative Change (%) at 22 Months after Intervention 1	-3.17	(-4.82, -1.53)	0.172308	0.177957
Absolute Change at 23 Months after Intervention 1	-0.005870	(-0.008999, -0.002741)	0.171765	0.177635
Relative Change (%) at 23 Months after Intervention 1	-3.30	(-5.03, -1.58)	0.171765	0.177635
Absolute Change at 24 Months after Intervention 1	-0.006091	(-0.009349, -0.002832)	0.171222	0.177313
Relative Change (%) at 24 Months after Intervention 1	-3.43	(-5.23, -1.64)	0.171222	0.177313
Absolute Change at 25 Months after Intervention 1	-0.006311	(-0.009699, -0.002923)	0.170680	0.176991
Relative Change (%) at 25 Months after Intervention 1	-3.57	(-5.43, -1.70)	0.170680	0.176991
Absolute Change at 26 Months after Intervention 1	-0.006532	(-0.010050, -0.003014)	0.170137	0.176669
Relative Change (%) at 26 Months after Intervention 1	-3.70	(-5.64, -1.75)	0.170137	0.176669
Absolute Change at 27 Months after Intervention 1	-0.006753	(-0.010402, -0.003104)	0.169594	0.176347
Relative Change (%) at 27 Months after Intervention 1	-3.83	(-5.85, -1.81)	0.169594	0.176347
Absolute Change at 27 Months after Intervention 1	-0.006753	(-0.010402, -0.003104)	0.169594	0.176347
Relative Change (%) at 27 Months after Intervention 1	-3.83	(-5.85, -1.81)	0.169594	0.176347

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.006034	(0.005717, 0.006351)	<.001
Baseline trend	-0.000033	(-0.000045, -0.000022)	<.001
Level Change (After Intervention 1)	-0.000011	(-0.000105, 0.000084)	0.824
Trend Change (After Intervention 1)	-0.000015	(-0.000044, 0.000013)	0.283
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.005970	(0.005596, 0.006345)	<.001
Baseline trend	-0.000031	(-0.000044, -0.000018)	<.001
Trend Change (After Intervention 1)	-0.000021	(-0.000052, 0.000011)	0.193

¹The 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.

²Maximum 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.

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

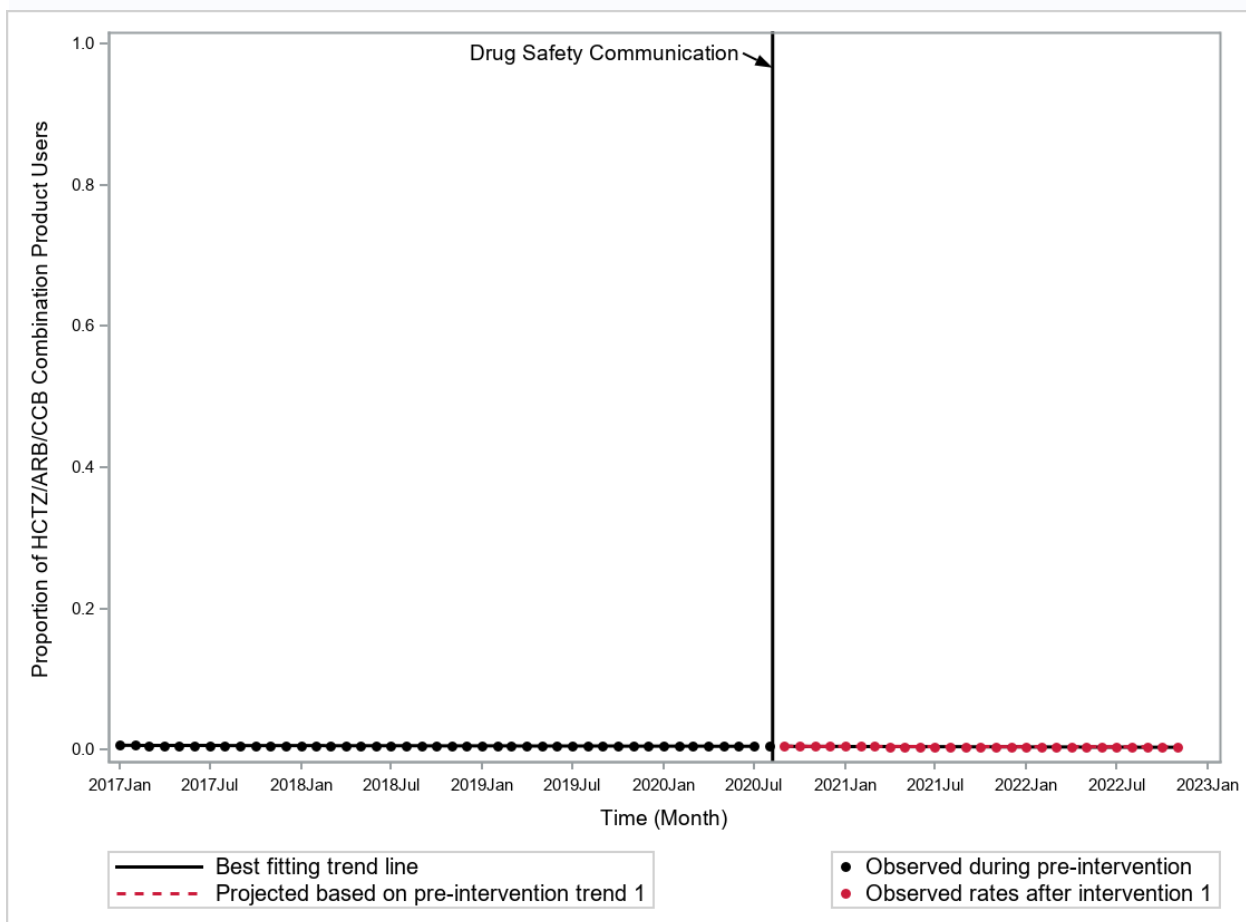
Table 34. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Angiotensin Receptor Blocker (ARB)-Calcium Channel Blocker (CCB) Combination

Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer after August 8, 2020¹ 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	-0.000021	(-0.000057, 0.000016)	0.004557	0.004578
Relative Change (%) at 1 Months after Intervention 1	-0.45	(-1.22, 0.31)	0.004557	0.004578
Absolute Change at 2 Months after Intervention 1	-0.000042	(-0.000114, 0.000031)	0.004505	0.004547
Relative Change (%) at 2 Months after Intervention 1	-0.91	(-2.46, 0.63)	0.004505	0.004547
Absolute Change at 3 Months after Intervention 1	-0.000062	(-0.000172, 0.000047)	0.004453	0.004516
Relative Change (%) at 3 Months after Intervention 1	-1.38	(-3.70, 0.94)	0.004453	0.004516
Absolute Change at 4 Months after Intervention 1	-0.000083	(-0.000229, 0.000063)	0.004402	0.004485
Relative Change (%) at 4 Months after Intervention 1	-1.85	(-4.97, 1.26)	0.004402	0.004485
Absolute Change at 5 Months after Intervention 1	-0.000104	(-0.000286, 0.000078)	0.004350	0.004454
Relative Change (%) at 5 Months after Intervention 1	-2.33	(-6.25, 1.58)	0.004350	0.004454
Absolute Change at 6 Months after Intervention 1	-0.000125	(-0.000343, 0.000094)	0.004298	0.004423
Relative Change (%) at 6 Months after Intervention 1	-2.82	(-7.54, 1.90)	0.004298	0.004423
Absolute Change at 7 Months after Intervention 1	-0.000145	(-0.000401, 0.000110)	0.004246	0.004392
Relative Change (%) at 7 Months after Intervention 1	-3.31	(-8.85, 2.22)	0.004246	0.004392
Absolute Change at 8 Months after Intervention 1	-0.000166	(-0.000458, 0.000125)	0.004195	0.004361
Relative Change (%) at 8 Months after Intervention 1	-3.81	(-10.17, 2.54)	0.004195	0.004361
Absolute Change at 9 Months after Intervention 1	-0.000187	(-0.000515, 0.000141)	0.004143	0.004330
Relative Change (%) at 9 Months after Intervention 1	-4.32	(-11.51, 2.87)	0.004143	0.004330
Absolute Change at 10 Months after Intervention 1	-0.000208	(-0.000572, 0.000157)	0.004091	0.004299
Relative Change (%) at 10 Months after Intervention 1	-4.83	(-12.86, 3.19)	0.004091	0.004299
Absolute Change at 11 Months after Intervention 1	-0.000229	(-0.000630, 0.000172)	0.004040	0.004268
Relative Change (%) at 11 Months after Intervention 1	-5.36	(-14.23, 3.52)	0.004040	0.004268
Absolute Change at 12 Months after Intervention 1	-0.000249	(-0.000687, 0.000188)	0.003988	0.004237
Relative Change (%) at 12 Months after Intervention 1	-5.89	(-15.62, 3.85)	0.003988	0.004237
Absolute Change at 13 Months after Intervention 1	-0.000270	(-0.000744, 0.000204)	0.003936	0.004206
Relative Change (%) at 13 Months after Intervention 1	-6.42	(-17.02, 4.18)	0.003936	0.004206
Absolute Change at 14 Months after Intervention 1	-0.000291	(-0.000801, 0.000219)	0.003884	0.004175
Relative Change (%) at 14 Months after Intervention 1	-6.97	(-18.45, 4.51)	0.003884	0.004175
Absolute Change at 15 Months after Intervention 1	-0.000312	(-0.000859, 0.000235)	0.003833	0.004144
Relative Change (%) at 15 Months after Intervention 1	-7.52	(-19.88, 4.84)	0.003833	0.004144
Absolute Change at 16 Months after Intervention 1	-0.000333	(-0.000916, 0.000251)	0.003781	0.004113
Relative Change (%) at 16 Months after Intervention 1	-8.08	(-21.34, 5.17)	0.003781	0.004113
Absolute Change at 17 Months after Intervention 1	-0.000353	(-0.000973, 0.000266)	0.003729	0.004082
Relative Change (%) at 17 Months after Intervention 1	-8.66	(-22.81, 5.50)	0.003729	0.004082
Absolute Change at 18 Months after Intervention 1	-0.000374	(-0.001030, 0.000282)	0.003677	0.004052
Relative Change (%) at 18 Months after Intervention 1	-9.23	(-24.31, 5.84)	0.003677	0.004052
Absolute Change at 19 Months after Intervention 1	-0.000395	(-0.001088, 0.000298)	0.003626	0.004021
Relative Change (%) at 19 Months after Intervention 1	-9.82	(-25.82, 6.17)	0.003626	0.004021
Absolute Change at 20 Months after Intervention 1	-0.000416	(-0.001145, 0.000313)	0.003574	0.003990
Relative Change (%) at 20 Months after Intervention 1	-10.42	(-27.35, 6.51)	0.003574	0.003990
Absolute Change at 21 Months after Intervention 1	-0.000436	(-0.001202, 0.000329)	0.003522	0.003959
Relative Change (%) at 21 Months after Intervention 1	-11.03	(-28.89, 6.84)	0.003522	0.003959
Absolute Change at 22 Months after Intervention 1	-0.000457	(-0.001259, 0.000345)	0.003471	0.003928
Relative Change (%) at 22 Months after Intervention 1	-11.64	(-30.46, 7.18)	0.003471	0.003928
Absolute Change at 23 Months after Intervention 1	-0.000478	(-0.001317, 0.000360)	0.003419	0.003897
Relative Change (%) at 23 Months after Intervention 1	-12.27	(-32.05, 7.52)	0.003419	0.003897
Absolute Change at 24 Months after Intervention 1	-0.000499	(-0.001374, 0.000376)	0.003367	0.003866
Relative Change (%) at 24 Months after Intervention 1	-12.90	(-33.66, 7.85)	0.003367	0.003866
Absolute Change at 25 Months after Intervention 1	-0.000520	(-0.001431, 0.000392)	0.003315	0.003835
Relative Change (%) at 25 Months after Intervention 1	-13.55	(-35.29, 8.19)	0.003315	0.003835
Absolute Change at 26 Months after Intervention 1	-0.000540	(-0.001488, 0.000407)	0.003264	0.003804
Relative Change (%) at 26 Months after Intervention 1	-14.21	(-36.94, 8.53)	0.003264	0.003804
Absolute Change at 27 Months after Intervention 1	-0.000561	(-0.001546, 0.000423)	0.003212	0.003773
Relative Change (%) at 27 Months after Intervention 1	-14.87	(-38.61, 8.87)	0.003212	0.003773
Absolute Change at 27 Months after Intervention 1	-0.000561	(-0.001546, 0.000423)	0.003212	0.003773
Relative Change (%) at 27 Months after Intervention 1	-14.87	(-38.61, 8.87)	0.003212	0.003773

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.268059	(0.251115, 0.285003)	<.001
Baseline trend	-0.001479	(-0.002083, -0.000875)	<.001
Level Change (After Intervention 1)	-0.000799	(-0.003585, 0.001987)	0.569
Trend Change (After Intervention 1)	0.001559	(0.000077, 0.003041)	0.040
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.267208	(0.250115, 0.284301)	<.001
Baseline trend	-0.001440	(-0.002045, -0.000835)	<.001
Trend Change (After Intervention 1)	0.001415	(-0.000020, 0.002849)	0.053

¹The 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.

²Maximum 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.

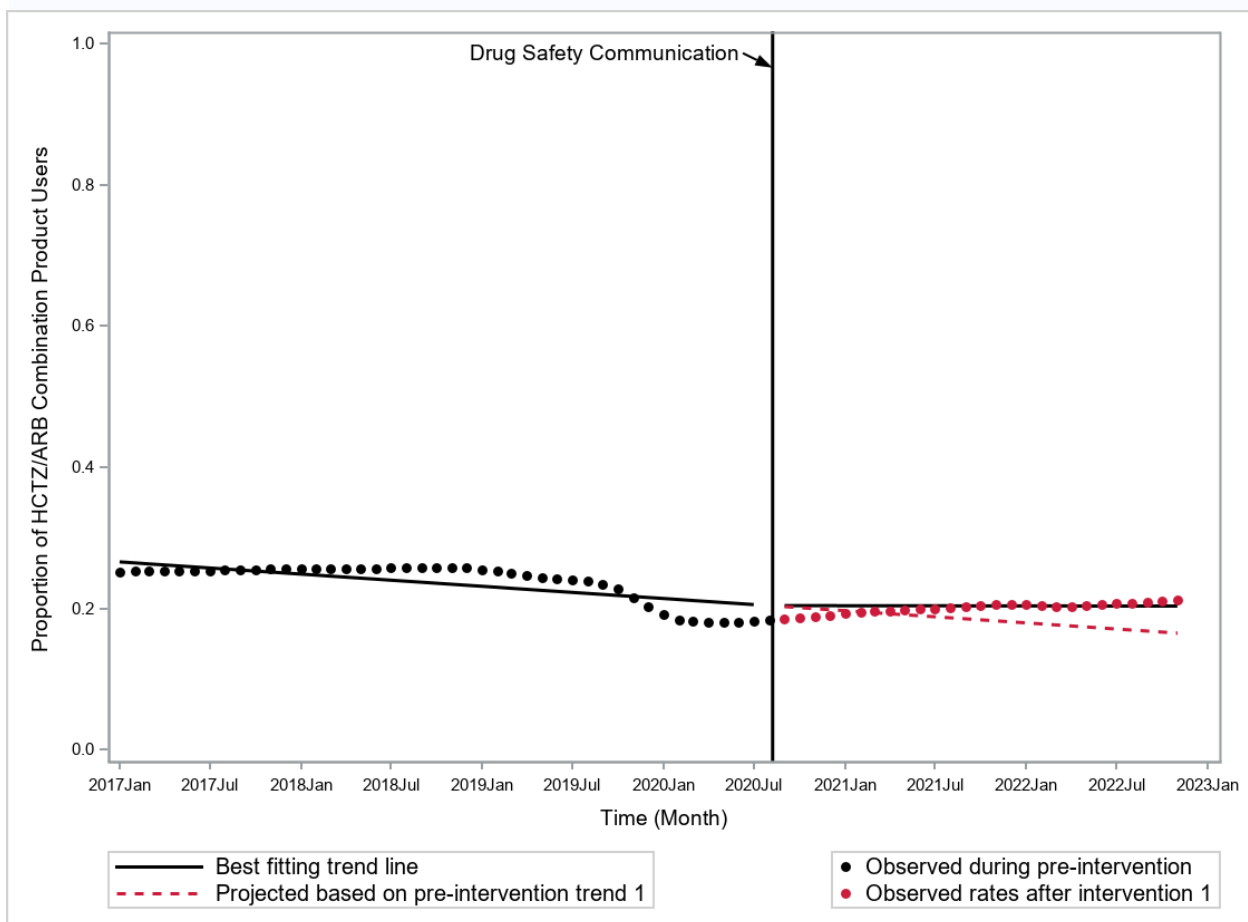
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 3b. 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 with no History of Skin Cancer after August 8, 2020¹ 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	0.001415	(-0.000061, 0.002890)	0.203808	0.202394
Relative Change (%) at 1 Months after Intervention 1	0.70	(-0.08, 1.47)	0.203808	0.202394
Absolute Change at 2 Months after Intervention 1	0.002829	(-0.000123, 0.005781)	0.203782	0.200953
Relative Change (%) at 2 Months after Intervention 1	1.41	(-0.16, 2.98)	0.203782	0.200953
Absolute Change at 3 Months after Intervention 1	0.004244	(-0.000184, 0.008671)	0.203757	0.199513
Relative Change (%) at 3 Months after Intervention 1	2.13	(-0.25, 4.50)	0.203757	0.199513
Absolute Change at 4 Months after Intervention 1	0.005658	(-0.000245, 0.011562)	0.203731	0.198073
Relative Change (%) at 4 Months after Intervention 1	2.86	(-0.34, 6.05)	0.203731	0.198073
Absolute Change at 5 Months after Intervention 1	0.007073	(-0.000307, 0.014452)	0.203705	0.196632
Relative Change (%) at 5 Months after Intervention 1	3.60	(-0.44, 7.64)	0.203705	0.196632
Absolute Change at 6 Months after Intervention 1	0.008487	(-0.000368, 0.017342)	0.203679	0.195192
Relative Change (%) at 6 Months after Intervention 1	4.35	(-0.55, 9.24)	0.203679	0.195192
Absolute Change at 7 Months after Intervention 1	0.009902	(-0.000429, 0.020233)	0.203654	0.193752
Relative Change (%) at 7 Months after Intervention 1	5.11	(-0.66, 10.88)	0.203654	0.193752
Absolute Change at 8 Months after Intervention 1	0.011316	(-0.000491, 0.023123)	0.203628	0.192312
Relative Change (%) at 8 Months after Intervention 1	5.88	(-0.78, 12.55)	0.203628	0.192312
Absolute Change at 9 Months after Intervention 1	0.012731	(-0.000552, 0.026014)	0.203602	0.190871
Relative Change (%) at 9 Months after Intervention 1	6.67	(-0.91, 14.25)	0.203602	0.190871
Absolute Change at 10 Months after Intervention 1	0.014145	(-0.000614, 0.028904)	0.203576	0.189431
Relative Change (%) at 10 Months after Intervention 1	7.47	(-1.04, 15.98)	0.203576	0.189431
Absolute Change at 11 Months after Intervention 1	0.015560	(-0.000675, 0.031795)	0.203550	0.187991
Relative Change (%) at 11 Months after Intervention 1	8.28	(-1.18, 17.74)	0.203550	0.187991
Absolute Change at 12 Months after Intervention 1	0.016974	(-0.000736, 0.034685)	0.203525	0.186550
Relative Change (%) at 12 Months after Intervention 1	9.10	(-1.33, 19.53)	0.203525	0.186550
Absolute Change at 13 Months after Intervention 1	0.018389	(-0.000798, 0.037575)	0.203499	0.185110
Relative Change (%) at 13 Months after Intervention 1	9.93	(-1.49, 21.36)	0.203499	0.185110
Absolute Change at 14 Months after Intervention 1	0.019803	(-0.000859, 0.040466)	0.203473	0.183670
Relative Change (%) at 14 Months after Intervention 1	10.78	(-1.66, 23.22)	0.203473	0.183670
Absolute Change at 15 Months after Intervention 1	0.021218	(-0.000920, 0.043356)	0.203447	0.182229
Relative Change (%) at 15 Months after Intervention 1	11.64	(-1.84, 25.12)	0.203447	0.182229
Absolute Change at 16 Months after Intervention 1	0.022632	(-0.000982, 0.046247)	0.203422	0.180789
Relative Change (%) at 16 Months after Intervention 1	12.52	(-2.02, 27.06)	0.203422	0.180789
Absolute Change at 17 Months after Intervention 1	0.024047	(-0.001043, 0.049137)	0.203396	0.179349
Relative Change (%) at 17 Months after Intervention 1	13.41	(-2.22, 29.03)	0.203396	0.179349
Absolute Change at 18 Months after Intervention 1	0.025462	(-0.001104, 0.052027)	0.203370	0.177908
Relative Change (%) at 18 Months after Intervention 1	14.31	(-2.42, 31.04)	0.203370	0.177908
Absolute Change at 19 Months after Intervention 1	0.026876	(-0.001166, 0.054918)	0.203344	0.176468
Relative Change (%) at 19 Months after Intervention 1	15.23	(-2.64, 33.10)	0.203344	0.176468
Absolute Change at 20 Months after Intervention 1	0.028291	(-0.001227, 0.057808)	0.203318	0.175028
Relative Change (%) at 20 Months after Intervention 1	16.16	(-2.87, 35.19)	0.203318	0.175028
Absolute Change at 21 Months after Intervention 1	0.029705	(-0.001288, 0.060699)	0.203293	0.173587
Relative Change (%) at 21 Months after Intervention 1	17.11	(-3.10, 37.33)	0.203293	0.173587
Absolute Change at 22 Months after Intervention 1	0.031120	(-0.001350, 0.063589)	0.203267	0.172147
Relative Change (%) at 22 Months after Intervention 1	18.08	(-3.36, 39.51)	0.203267	0.172147
Absolute Change at 23 Months after Intervention 1	0.032534	(-0.001411, 0.066479)	0.203241	0.170707
Relative Change (%) at 23 Months after Intervention 1	19.06	(-3.62, 41.74)	0.203241	0.170707
Absolute Change at 24 Months after Intervention 1	0.033949	(-0.001472, 0.069370)	0.203215	0.169267
Relative Change (%) at 24 Months after Intervention 1	20.06	(-3.90, 44.01)	0.203215	0.169267
Absolute Change at 25 Months after Intervention 1	0.035363	(-0.001534, 0.072260)	0.203189	0.167826
Relative Change (%) at 25 Months after Intervention 1	21.07	(-4.19, 46.33)	0.203189	0.167826
Absolute Change at 26 Months after Intervention 1	0.036778	(-0.001595, 0.075151)	0.203164	0.166386
Relative Change (%) at 26 Months after Intervention 1	22.10	(-4.49, 48.70)	0.203164	0.166386
Absolute Change at 27 Months after Intervention 1	0.038192	(-0.001656, 0.078041)	0.203138	0.164946
Relative Change (%) at 27 Months after Intervention 1	23.15	(-4.81, 51.12)	0.203138	0.164946
Absolute Change at 27 Months after Intervention 1	0.038192	(-0.001656, 0.078041)	0.203138	0.164946
Relative Change (%) at 27 Months after Intervention 1	23.15	(-4.81, 51.12)	0.203138	0.164946

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.021667	(0.021564, 0.021769)	<.001
Baseline trend	-0.000072	(-0.000076, -0.000069)	<.001
Level Change (After Intervention 1)	0.000021	(-0.000055, 0.000097)	0.581
Trend Change (After Intervention 1)	0.000014	(0.000005, 0.000023)	0.003
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.021663	(0.021540, 0.021786)	<.001
Baseline trend	-0.000072	(-0.000076, -0.000068)	<.001
Trend Change (After Intervention 1)	0.000014	(0.000003, 0.000024)	0.010

¹The 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.

²Maximum 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.

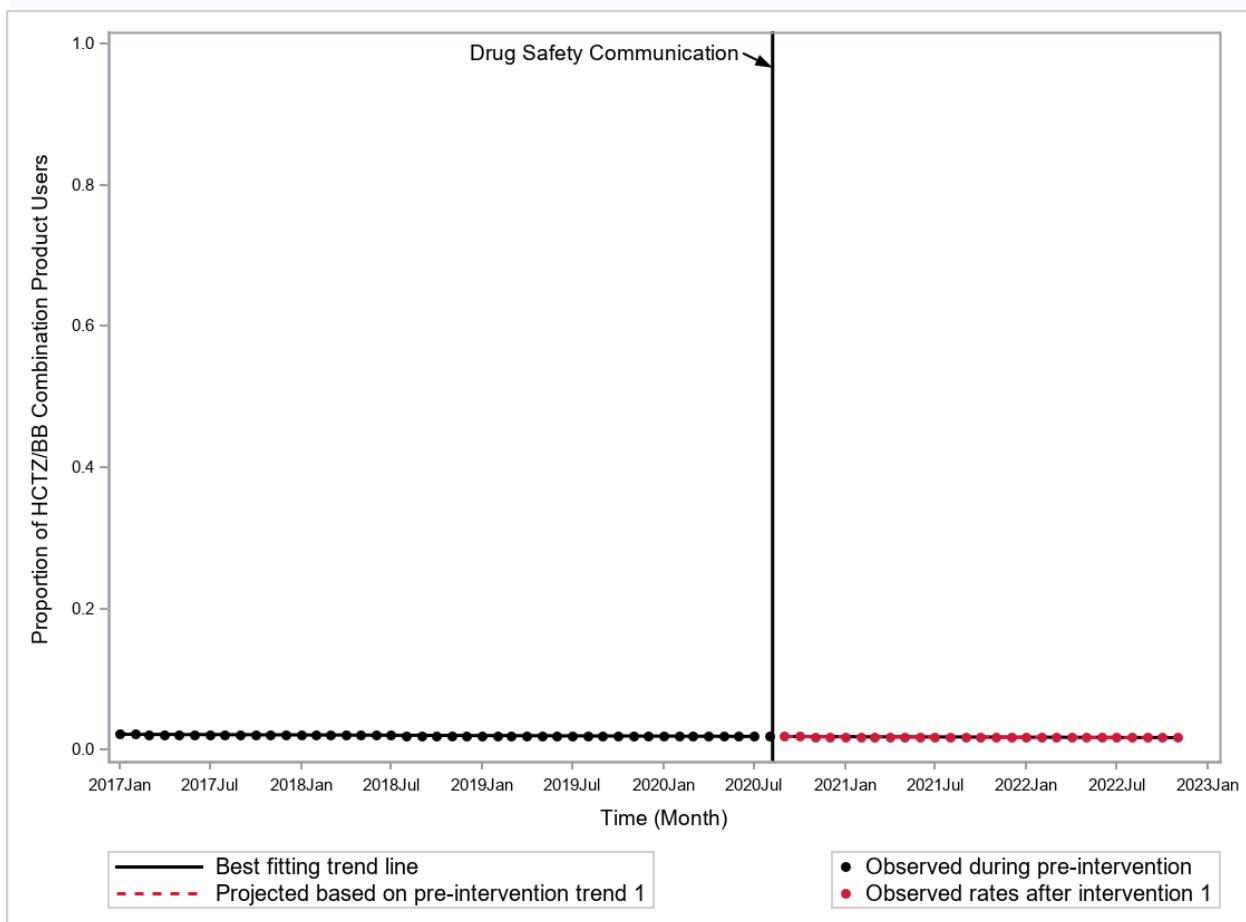
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.000014	(0.000003, 0.000024)	0.018444	0.018430
Relative Change (%) at 1 Months after Intervention 1	0.07	(0.02, 0.13)	0.018444	0.018430
Absolute Change at 2 Months after Intervention 1	0.000027	(0.000007, 0.000048)	0.018386	0.018358
Relative Change (%) at 2 Months after Intervention 1	0.15	(0.04, 0.26)	0.018386	0.018358
Absolute Change at 3 Months after Intervention 1	0.000041	(0.000010, 0.000072)	0.018328	0.018286
Relative Change (%) at 3 Months after Intervention 1	0.23	(0.05, 0.40)	0.018328	0.018286
Absolute Change at 4 Months after Intervention 1	0.000055	(0.000013, 0.000097)	0.018270	0.018215
Relative Change (%) at 4 Months after Intervention 1	0.30	(0.07, 0.53)	0.018270	0.018215
Absolute Change at 5 Months after Intervention 1	0.000069	(0.000017, 0.000121)	0.018212	0.018143
Relative Change (%) at 5 Months after Intervention 1	0.38	(0.09, 0.67)	0.018212	0.018143
Absolute Change at 6 Months after Intervention 1	0.000082	(0.000020, 0.000145)	0.018153	0.018071
Relative Change (%) at 6 Months after Intervention 1	0.46	(0.11, 0.81)	0.018153	0.018071
Absolute Change at 7 Months after Intervention 1	0.000096	(0.000023, 0.000169)	0.018095	0.017999
Relative Change (%) at 7 Months after Intervention 1	0.53	(0.13, 0.94)	0.018095	0.017999
Absolute Change at 8 Months after Intervention 1	0.000110	(0.000027, 0.000193)	0.018037	0.017927
Relative Change (%) at 8 Months after Intervention 1	0.61	(0.14, 1.08)	0.018037	0.017927
Absolute Change at 9 Months after Intervention 1	0.000124	(0.000030, 0.000217)	0.017979	0.017855
Relative Change (%) at 9 Months after Intervention 1	0.69	(0.16, 1.22)	0.017979	0.017855
Absolute Change at 10 Months after Intervention 1	0.000137	(0.000033, 0.000242)	0.017921	0.017784
Relative Change (%) at 10 Months after Intervention 1	0.77	(0.18, 1.36)	0.017921	0.017784
Absolute Change at 11 Months after Intervention 1	0.000151	(0.000037, 0.000266)	0.017863	0.017712
Relative Change (%) at 11 Months after Intervention 1	0.85	(0.20, 1.51)	0.017863	0.017712
Absolute Change at 12 Months after Intervention 1	0.000165	(0.000040, 0.000290)	0.017805	0.017640
Relative Change (%) at 12 Months after Intervention 1	0.94	(0.22, 1.65)	0.017805	0.017640
Absolute Change at 13 Months after Intervention 1	0.000179	(0.000043, 0.000314)	0.017747	0.017568
Relative Change (%) at 13 Months after Intervention 1	1.02	(0.24, 1.80)	0.017747	0.017568
Absolute Change at 14 Months after Intervention 1	0.000192	(0.000047, 0.000338)	0.017689	0.017496
Relative Change (%) at 14 Months after Intervention 1	1.10	(0.26, 1.94)	0.017689	0.017496
Absolute Change at 15 Months after Intervention 1	0.000206	(0.000050, 0.000362)	0.017631	0.017425
Relative Change (%) at 15 Months after Intervention 1	1.18	(0.28, 2.09)	0.017631	0.017425
Absolute Change at 16 Months after Intervention 1	0.000220	(0.000053, 0.000387)	0.017573	0.017353
Relative Change (%) at 16 Months after Intervention 1	1.27	(0.30, 2.24)	0.017573	0.017353
Absolute Change at 17 Months after Intervention 1	0.000234	(0.000057, 0.000411)	0.017515	0.017281
Relative Change (%) at 17 Months after Intervention 1	1.35	(0.32, 2.39)	0.017515	0.017281
Absolute Change at 18 Months after Intervention 1	0.000247	(0.000060, 0.000435)	0.017456	0.017209
Relative Change (%) at 18 Months after Intervention 1	1.44	(0.34, 2.54)	0.017456	0.017209
Absolute Change at 19 Months after Intervention 1	0.000261	(0.000063, 0.000459)	0.017398	0.017137
Relative Change (%) at 19 Months after Intervention 1	1.52	(0.36, 2.69)	0.017398	0.017137
Absolute Change at 20 Months after Intervention 1	0.000275	(0.000067, 0.000483)	0.017340	0.017065
Relative Change (%) at 20 Months after Intervention 1	1.61	(0.38, 2.85)	0.017340	0.017065
Absolute Change at 21 Months after Intervention 1	0.000289	(0.000070, 0.000507)	0.017282	0.016994
Relative Change (%) at 21 Months after Intervention 1	1.70	(0.40, 3.00)	0.017282	0.016994
Absolute Change at 22 Months after Intervention 1	0.000302	(0.000073, 0.000532)	0.017224	0.016922
Relative Change (%) at 22 Months after Intervention 1	1.79	(0.42, 3.16)	0.017224	0.016922
Absolute Change at 23 Months after Intervention 1	0.000316	(0.000077, 0.000556)	0.017166	0.016850
Relative Change (%) at 23 Months after Intervention 1	1.88	(0.44, 3.32)	0.017166	0.016850
Absolute Change at 24 Months after Intervention 1	0.000330	(0.000080, 0.000580)	0.017108	0.016778
Relative Change (%) at 24 Months after Intervention 1	1.97	(0.46, 3.48)	0.017108	0.016778
Absolute Change at 25 Months after Intervention 1	0.000344	(0.000083, 0.000604)	0.017050	0.016706
Relative Change (%) at 25 Months after Intervention 1	2.06	(0.48, 3.64)	0.017050	0.016706
Absolute Change at 26 Months after Intervention 1	0.000357	(0.000087, 0.000628)	0.016992	0.016634
Relative Change (%) at 26 Months after Intervention 1	2.15	(0.50, 3.80)	0.016992	0.016634
Absolute Change at 27 Months after Intervention 1	0.000371	(0.000090, 0.000652)	0.016934	0.016563
Relative Change (%) at 27 Months after Intervention 1	2.24	(0.52, 3.96)	0.016934	0.016563
Absolute Change at 27 Months after Intervention 1	0.000371	(0.000090, 0.000652)	0.016934	0.016563
Relative Change (%) at 27 Months after Intervention 1	2.24	(0.52, 3.96)	0.016934	0.016563

¹The 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 19. Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.000031	(0.000025, 0.000036)	<.001
Baseline trend	-0.000001	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000002	(-0.000004, -0.000001)	0.003
Trend Change (After Intervention 1)	0.000000	(0.000000, 0.000001)	0.004
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.000031	(0.000025, 0.000036)	<.001
Baseline trend	-0.000001	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000002	(-0.000004, -0.000001)	0.003
Trend Change (After Intervention 1)	0.000000	(0.000000, 0.000001)	0.004

¹The 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.

²Maximum 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.

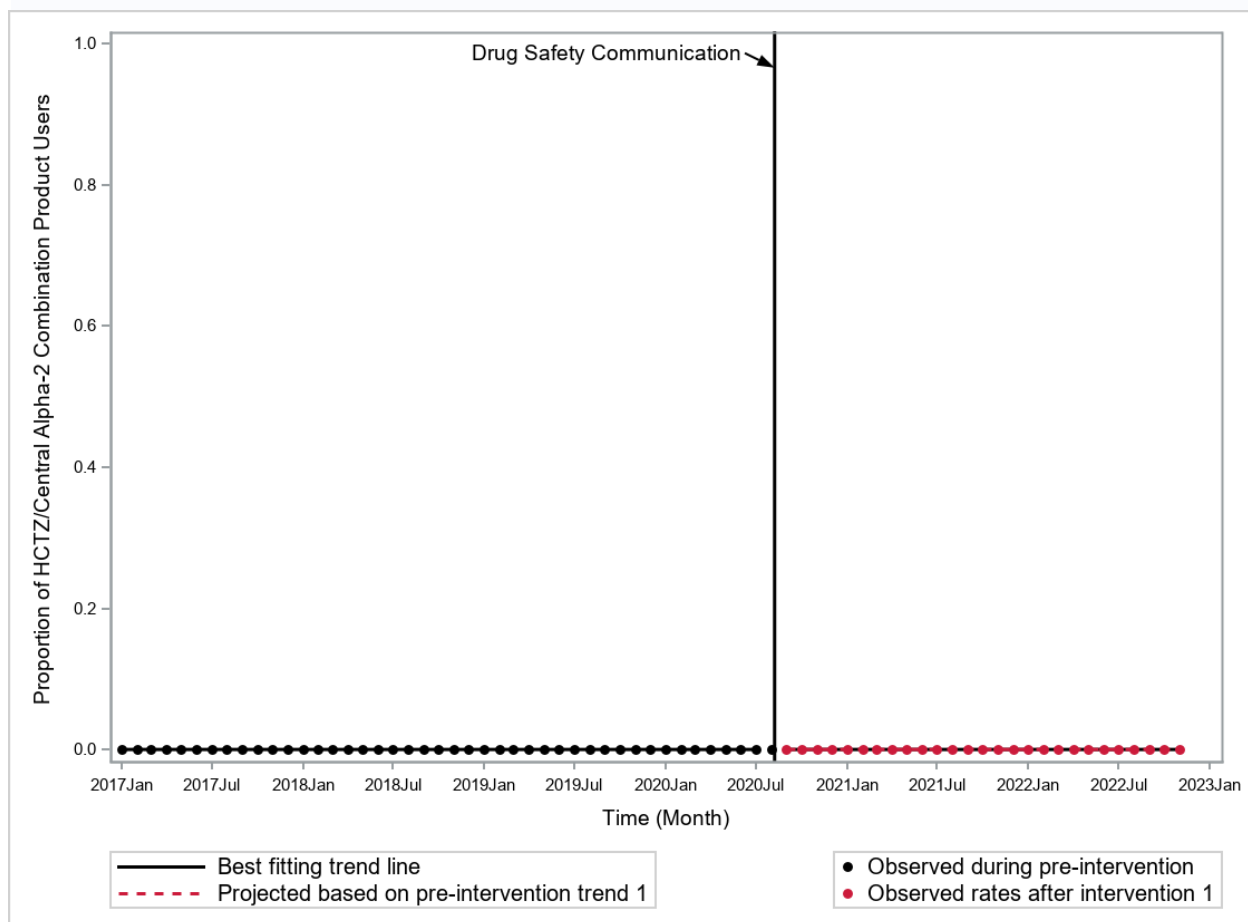
Table 40. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Central Alpha-2 Agonist Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer after August 8, 2020¹ Compared with Expected Rates 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	-0.000002	(-0.000003, 0.000000)	0.000003	0.000005
Relative Change (%) at 1 Months after Intervention 1	-38.91	(-94.71, 16.89)	0.000003	0.000005
Absolute Change at 2 Months after Intervention 1	-0.000001	(-0.000003, 0.000000)	0.000003	0.000004
Relative Change (%) at 2 Months after Intervention 1	-32.38	(-82.52, 17.75)	0.000003	0.000004
Absolute Change at 3 Months after Intervention 1	-0.000001	(-0.000003, 0.000001)	0.000003	0.000003
Relative Change (%) at 3 Months after Intervention 1	-23.69	(-68.85, 21.48)	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	-11.53	(-68.26, 45.20)	0.000003	0.000003
Absolute Change at 5 Months after Intervention 1	0.000000	(-0.000002, 0.000003)	0.000002	0.000002
Relative Change (%) at 5 Months after Intervention 1	6.68	(-112.23, 125.59)	0.000002	0.000002
Absolute Change at 6 Months after Intervention 1	0.000001	(-0.000002, 0.000003)	0.000002	0.000002
Relative Change (%) at 6 Months after Intervention 1	36.95	(-256.82, 330.72)	0.000002	0.000002
Absolute Change at 7 Months after Intervention 1	0.000001	(-0.000002, 0.000004)	0.000002	0.000001
Relative Change (%) at 7 Months after Intervention 1	97.21	(-755.82, 950.24)	0.000002	0.000001
Absolute Change at 8 Months after Intervention 1	0.000002	(-0.000002, 0.000005)	0.000002	0.000001
Relative Change (%) at 8 Months after Intervention 1	275.71	(-3823.52, 4374.95)	0.000002	0.000001
Absolute Change at 9 Months after Intervention 1	0.000002	(-0.000002, 0.000006)	0.000002	0.000000
Relative Change (%) at 9 Months after Intervention 1	19098.46	(-1.362E7, 13653840)	0.000002	0.000000
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
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
Relative 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

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 64)²			
Intercept	0.365418	(0.363335, 0.367501)	<.001
Baseline trend	-0.000641	(-0.000715, -0.000567)	<.001
Level Change (After Intervention 1)	0.001301	(-0.000140, 0.002742)	0.076
Trend Change (After Intervention 1)	-0.000046	(-0.000222, 0.000130)	0.605
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.365391	(0.363484, 0.367297)	<.001
Baseline trend	-0.000634	(-0.000679, -0.000589)	<.001

¹The 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.

²Maximum 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.

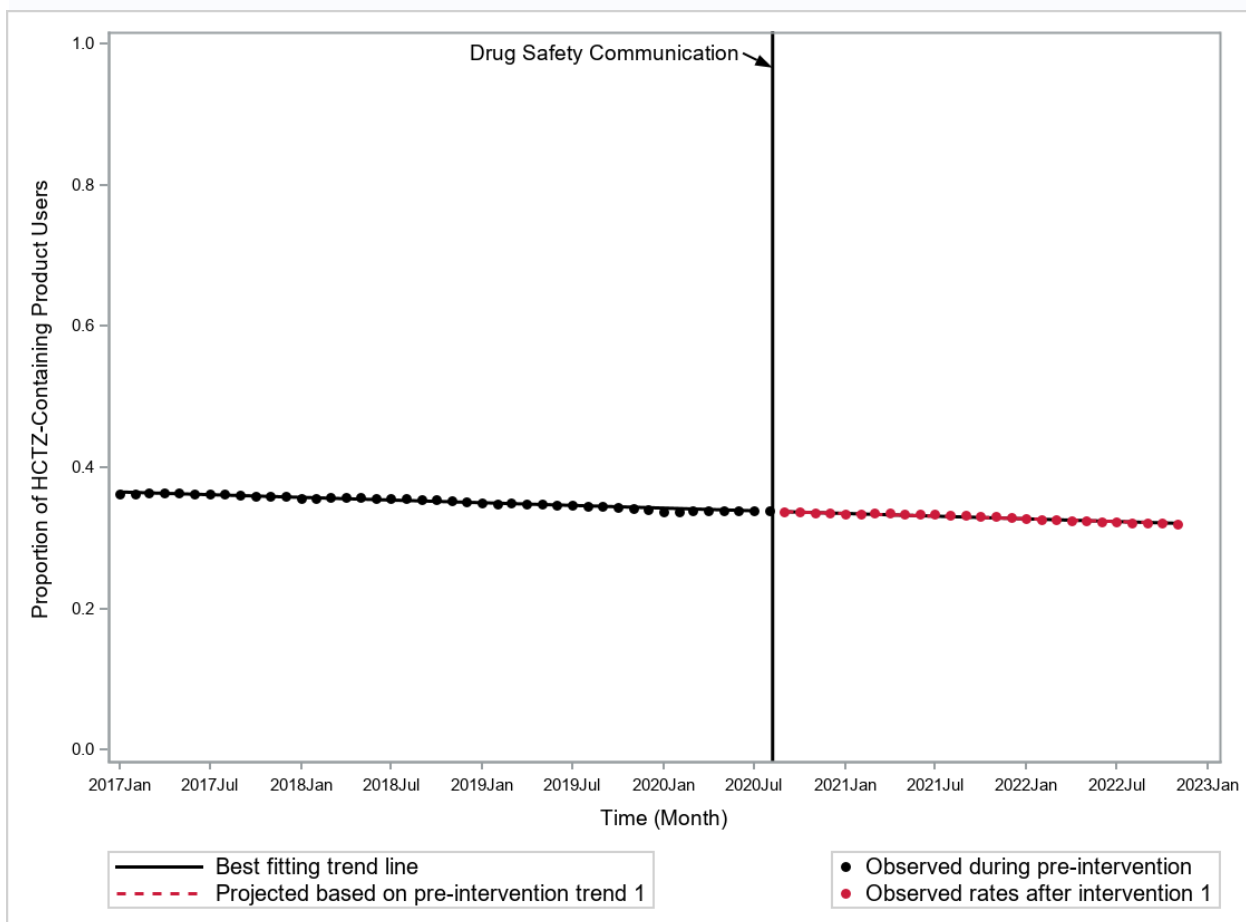
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.000000	(0.000000, 0.000000)	0.336868	0.336868
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.336868	0.336868
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.336234	0.336234
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.336234	0.336234
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.335600	0.335600
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.335600	0.335600
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.334966	0.334966
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.334966	0.334966
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.334332	0.334332
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.334332	0.334332
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.333698	0.333698
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.333698	0.333698
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.333065	0.333065
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.333065	0.333065
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.332431	0.332431
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.332431	0.332431
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.331797	0.331797
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.331797	0.331797
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.331163	0.331163
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.331163	0.331163
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.330529	0.330529
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.330529	0.330529
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.329895	0.329895
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.329895	0.329895
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.329262	0.329262
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.329262	0.329262
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.328628	0.328628
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.328628	0.328628
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.327994	0.327994
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.327994	0.327994
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.327360	0.327360
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.327360	0.327360
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.326726	0.326726
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.326726	0.326726
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.326092	0.326092
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.326092	0.326092
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.325458	0.325458
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.325458	0.325458
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.324825	0.324825
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.324825	0.324825
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.324191	0.324191
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.324191	0.324191
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.323557	0.323557
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.323557	0.323557
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.322923	0.322923
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.322923	0.322923
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.322289	0.322289
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.322289	0.322289
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.321655	0.321655
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.321655	0.321655
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.321022	0.321022
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.321022	0.321022
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.320388	0.320388
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.320388	0.320388
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.320388	0.320388
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.320388	0.320388

¹The 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 21. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.943374	(0.942696, 0.944053)	<.001
Baseline trend	-0.000412	(-0.000437, -0.000388)	<.001
Level Change (After Intervention 1)	0.000302	(-0.000200, 0.000805)	0.234
Trend Change (After Intervention 1)	0.000178	(0.000118, 0.000237)	<.001
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.943273	(0.942496, 0.944049)	<.001
Baseline trend	-0.000407	(-0.000434, -0.000380)	<.001
Trend Change (After Intervention 1)	0.000179	(0.000113, 0.000245)	<.001

¹The 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.

²Maximum 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.

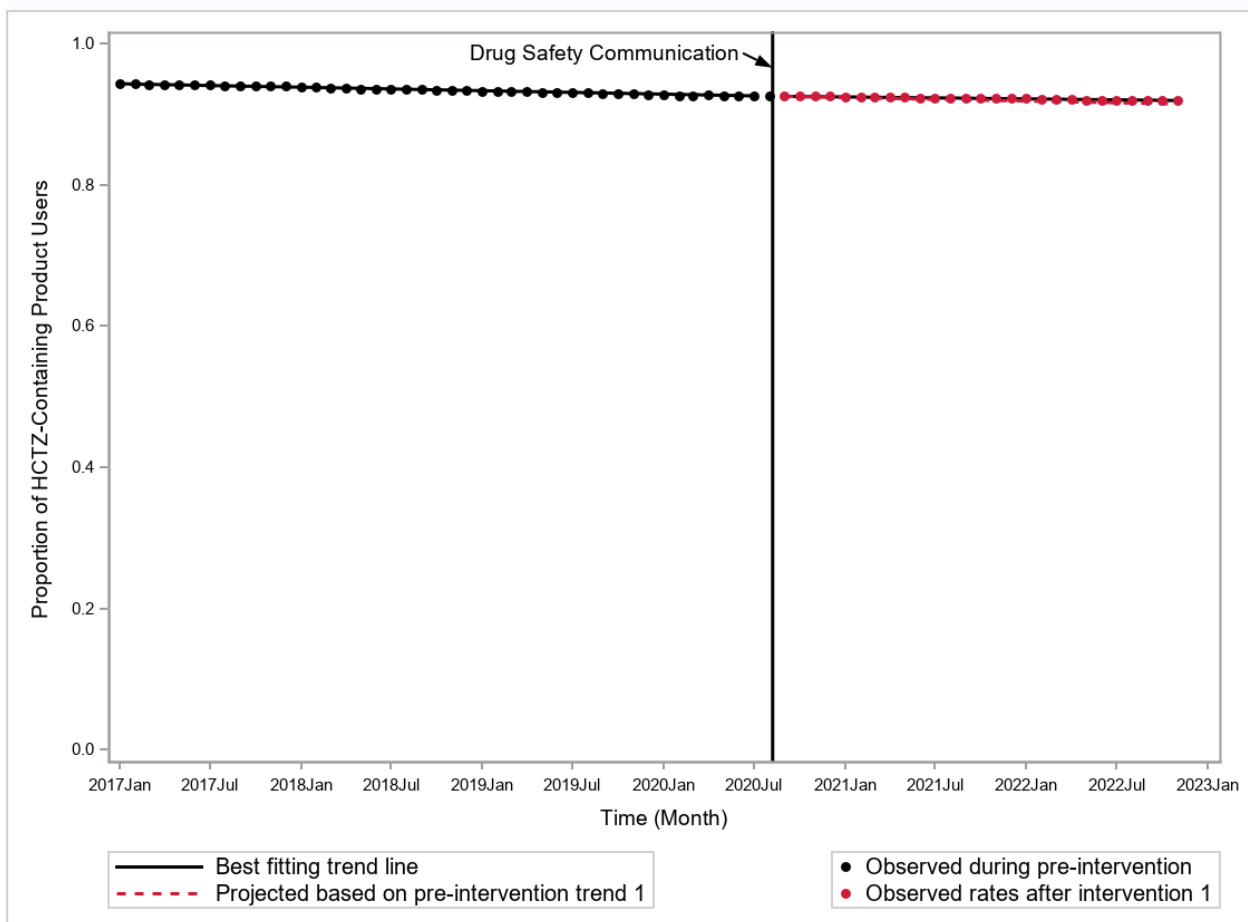
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.000179	(0.000111, 0.000247)	0.925142	0.924963
Relative Change (%) at 1 Months after Intervention 1	0.02	(0.01, 0.03)	0.925142	0.924963
Absolute Change at 2 Months after Intervention 1	0.000357	(0.000221, 0.000494)	0.924914	0.924556
Relative Change (%) at 2 Months after Intervention 1	0.04	(0.02, 0.05)	0.924914	0.924556
Absolute Change at 3 Months after Intervention 1	0.000536	(0.000332, 0.000741)	0.924685	0.924149
Relative Change (%) at 3 Months after Intervention 1	0.06	(0.04, 0.08)	0.924685	0.924149
Absolute Change at 4 Months after Intervention 1	0.000715	(0.000442, 0.000987)	0.924457	0.923742
Relative Change (%) at 4 Months after Intervention 1	0.08	(0.05, 0.11)	0.924457	0.923742
Absolute Change at 5 Months after Intervention 1	0.000894	(0.000553, 0.001234)	0.924229	0.923335
Relative Change (%) at 5 Months after Intervention 1	0.10	(0.06, 0.13)	0.924229	0.923335
Absolute Change at 6 Months after Intervention 1	0.001072	(0.000664, 0.001481)	0.924001	0.922929
Relative Change (%) at 6 Months after Intervention 1	0.12	(0.07, 0.16)	0.924001	0.922929
Absolute Change at 7 Months after Intervention 1	0.001251	(0.000774, 0.001728)	0.923773	0.922522
Relative Change (%) at 7 Months after Intervention 1	0.14	(0.08, 0.19)	0.923773	0.922522
Absolute Change at 8 Months after Intervention 1	0.001430	(0.000885, 0.001975)	0.923545	0.922115
Relative Change (%) at 8 Months after Intervention 1	0.16	(0.10, 0.21)	0.923545	0.922115
Absolute Change at 9 Months after Intervention 1	0.001609	(0.000995, 0.002222)	0.923316	0.921708
Relative Change (%) at 9 Months after Intervention 1	0.17	(0.11, 0.24)	0.923316	0.921708
Absolute Change at 10 Months after Intervention 1	0.001787	(0.001106, 0.002469)	0.923088	0.921301
Relative Change (%) at 10 Months after Intervention 1	0.19	(0.12, 0.27)	0.923088	0.921301
Absolute Change at 11 Months after Intervention 1	0.001966	(0.001217, 0.002715)	0.922860	0.920894
Relative Change (%) at 11 Months after Intervention 1	0.21	(0.13, 0.30)	0.922860	0.920894
Absolute Change at 12 Months after Intervention 1	0.002145	(0.001327, 0.002962)	0.922632	0.920487
Relative Change (%) at 12 Months after Intervention 1	0.23	(0.14, 0.32)	0.922632	0.920487
Absolute Change at 13 Months after Intervention 1	0.002323	(0.001438, 0.003209)	0.922404	0.920080
Relative Change (%) at 13 Months after Intervention 1	0.25	(0.16, 0.35)	0.922404	0.920080
Absolute Change at 14 Months after Intervention 1	0.002502	(0.001548, 0.003456)	0.922176	0.919674
Relative Change (%) at 14 Months after Intervention 1	0.27	(0.17, 0.38)	0.922176	0.919674
Absolute Change at 15 Months after Intervention 1	0.002681	(0.001659, 0.003703)	0.921948	0.919267
Relative Change (%) at 15 Months after Intervention 1	0.29	(0.18, 0.40)	0.921948	0.919267
Absolute Change at 16 Months after Intervention 1	0.002860	(0.001770, 0.003950)	0.921719	0.918860
Relative Change (%) at 16 Months after Intervention 1	0.31	(0.19, 0.43)	0.921719	0.918860
Absolute Change at 17 Months after Intervention 1	0.003038	(0.001880, 0.004196)	0.921491	0.918453
Relative Change (%) at 17 Months after Intervention 1	0.33	(0.20, 0.46)	0.921491	0.918453
Absolute Change at 18 Months after Intervention 1	0.003217	(0.001991, 0.004443)	0.921263	0.918046
Relative Change (%) at 18 Months after Intervention 1	0.35	(0.22, 0.48)	0.921263	0.918046
Absolute Change at 19 Months after Intervention 1	0.003396	(0.002101, 0.004690)	0.921035	0.917639
Relative Change (%) at 19 Months after Intervention 1	0.37	(0.23, 0.51)	0.921035	0.917639
Absolute Change at 20 Months after Intervention 1	0.003574	(0.002212, 0.004937)	0.920807	0.917232
Relative Change (%) at 20 Months after Intervention 1	0.39	(0.24, 0.54)	0.920807	0.917232
Absolute Change at 21 Months after Intervention 1	0.003753	(0.002323, 0.005184)	0.920579	0.916825
Relative Change (%) at 21 Months after Intervention 1	0.41	(0.25, 0.57)	0.920579	0.916825
Absolute Change at 22 Months after Intervention 1	0.003932	(0.002433, 0.005431)	0.920350	0.916418
Relative Change (%) at 22 Months after Intervention 1	0.43	(0.26, 0.59)	0.920350	0.916418
Absolute Change at 23 Months after Intervention 1	0.004111	(0.002544, 0.005678)	0.920122	0.916012
Relative Change (%) at 23 Months after Intervention 1	0.45	(0.28, 0.62)	0.920122	0.916012
Absolute Change at 24 Months after Intervention 1	0.004289	(0.002654, 0.005924)	0.919894	0.915605
Relative Change (%) at 24 Months after Intervention 1	0.47	(0.29, 0.65)	0.919894	0.915605
Absolute Change at 25 Months after Intervention 1	0.004468	(0.002765, 0.006171)	0.919666	0.915198
Relative Change (%) at 25 Months after Intervention 1	0.49	(0.30, 0.67)	0.919666	0.915198
Absolute Change at 26 Months after Intervention 1	0.004647	(0.002876, 0.006418)	0.919438	0.914791
Relative Change (%) at 26 Months after Intervention 1	0.51	(0.31, 0.70)	0.919438	0.914791
Absolute Change at 27 Months after Intervention 1	0.004826	(0.002986, 0.006665)	0.919210	0.914384
Relative Change (%) at 27 Months after Intervention 1	0.53	(0.33, 0.73)	0.919210	0.914384
Relative Change (%) at 27 Months after Intervention 1	0.53	(0.33, 0.73)	0.919210	0.914384

¹The 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 22. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.000493	(0.000440, 0.000547)	<.001
Baseline trend	-0.000007	(-0.000009, -0.000006)	<.001
Level Change (After Intervention 1)	0.000002	(-0.000011, 0.000014)	0.811
Trend Change (After Intervention 1)	0.000004	(0.000001, 0.000006)	0.016
Most Parsimonious Final Model Parameters (df = 67)^{2,3}			
Intercept	0.000494	(0.000440, 0.000548)	<.001
Baseline trend	-0.000007	(-0.000009, -0.000006)	<.001
Trend Change (After Intervention 1)	0.000004	(0.000001, 0.000006)	0.012

¹The 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.

²Maximum 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.

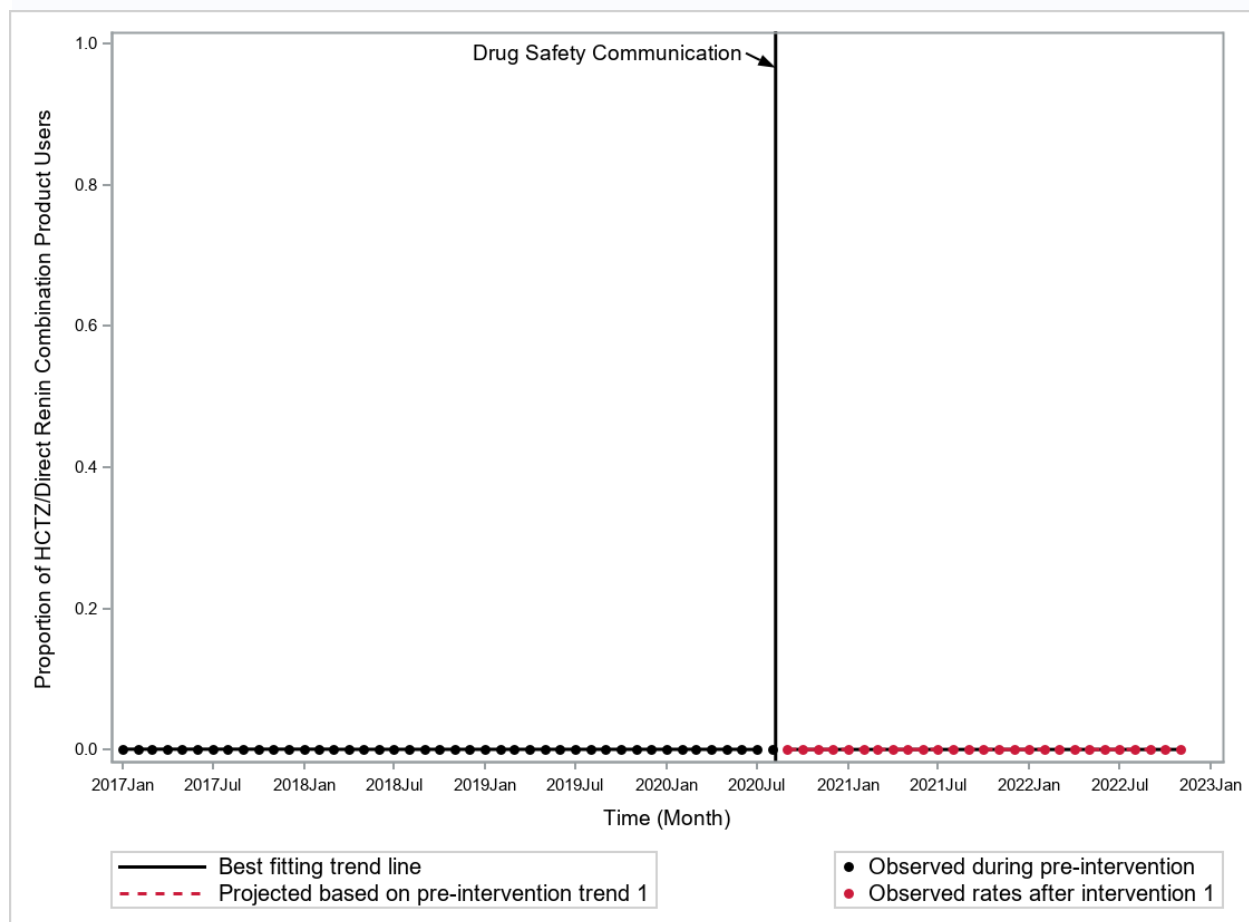
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.000004	(0.000000, 0.000007)	0.000171	0.000167
Relative Change (%) at 1 Months after Intervention 1	2.14	(-0.87, 5.14)	0.000171	0.000167
Absolute Change at 2 Months after Intervention 1	0.000007	(-0.000001, 0.000015)	0.000167	0.000160
Relative Change (%) at 2 Months after Intervention 1	4.47	(-1.92, 10.86)	0.000167	0.000160
Absolute Change at 3 Months after Intervention 1	0.000011	(-0.000001, 0.000022)	0.000164	0.000153
Relative Change (%) at 3 Months after Intervention 1	7.02	(-3.22, 17.25)	0.000164	0.000153
Absolute Change at 4 Months after Intervention 1	0.000014	(-0.000001, 0.000030)	0.000160	0.000146
Relative Change (%) at 4 Months after Intervention 1	9.82	(-4.82, 24.46)	0.000160	0.000146
Absolute Change at 5 Months after Intervention 1	0.000018	(-0.000001, 0.000037)	0.000156	0.000138
Relative Change (%) at 5 Months after Intervention 1	12.92	(-6.78, 32.62)	0.000156	0.000138
Absolute Change at 6 Months after Intervention 1	0.000021	(-0.000002, 0.000044)	0.000153	0.000131
Relative Change (%) at 6 Months after Intervention 1	16.36	(-9.22, 41.94)	0.000153	0.000131
Absolute Change at 7 Months after Intervention 1	0.000025	(-0.000002, 0.000052)	0.000149	0.000124
Relative Change (%) at 7 Months after Intervention 1	20.20	(-12.25, 52.66)	0.000149	0.000124
Absolute Change at 8 Months after Intervention 1	0.000029	(-0.000002, 0.000059)	0.000145	0.000117
Relative Change (%) at 8 Months after Intervention 1	24.52	(-16.06, 65.11)	0.000145	0.000117
Absolute Change at 9 Months after Intervention 1	0.000032	(-0.000002, 0.000067)	0.000142	0.000109
Relative Change (%) at 9 Months after Intervention 1	29.42	(-20.89, 79.73)	0.000142	0.000109
Absolute Change at 10 Months after Intervention 1	0.000036	(-0.000003, 0.000074)	0.000138	0.000102
Relative Change (%) at 10 Months after Intervention 1	35.01	(-27.07, 97.08)	0.000138	0.000102
Absolute Change at 11 Months after Intervention 1	0.000039	(-0.000003, 0.000082)	0.000134	0.000095
Relative Change (%) at 11 Months after Intervention 1	41.45	(-35.08, 117.98)	0.000134	0.000095
Absolute Change at 12 Months after Intervention 1	0.000043	(-0.000003, 0.000089)	0.000131	0.000088
Relative Change (%) at 12 Months after Intervention 1	48.96	(-45.62, 143.54)	0.000131	0.000088
Absolute Change at 13 Months after Intervention 1	0.000047	(-0.000003, 0.000096)	0.000127	0.000080
Relative Change (%) at 13 Months after Intervention 1	57.82	(-59.73, 175.38)	0.000127	0.000080
Absolute Change at 14 Months after Intervention 1	0.000050	(-0.000004, 0.000104)	0.000123	0.000073
Relative Change (%) at 14 Months after Intervention 1	68.44	(-79.03, 215.92)	0.000123	0.000073
Absolute Change at 15 Months after Intervention 1	0.000054	(-0.000004, 0.000111)	0.000120	0.000066
Relative Change (%) at 15 Months after Intervention 1	81.40	(-106.13, 268.93)	0.000120	0.000066
Absolute Change at 16 Months after Intervention 1	0.000057	(-0.000004, 0.000119)	0.000116	0.000059
Relative Change (%) at 16 Months after Intervention 1	97.56	(-145.40, 340.52)	0.000116	0.000059
Absolute Change at 17 Months after Intervention 1	0.000061	(-0.000004, 0.000126)	0.000112	0.000051
Relative Change (%) at 17 Months after Intervention 1	118.28	(-204.67, 441.24)	0.000112	0.000051
Absolute Change at 18 Months after Intervention 1	0.000064	(-0.000005, 0.000133)	0.000109	0.000044
Relative Change (%) at 18 Months after Intervention 1	145.81	(-298.97, 590.59)	0.000109	0.000044
Absolute Change at 19 Months after Intervention 1	0.000068	(-0.000005, 0.000141)	0.000105	0.000037
Relative Change (%) at 19 Months after Intervention 1	184.16	(-459.97, 828.28)	0.000105	0.000037
Absolute Change at 20 Months after Intervention 1	0.000072	(-0.000005, 0.000148)	0.000101	0.000030
Relative Change (%) at 20 Months after Intervention 1	241.26	(-763.83, 1246.35)	0.000101	0.000030
Absolute Change at 21 Months after Intervention 1	0.000075	(-0.000005, 0.000156)	0.000098	0.000022
Relative Change (%) at 21 Months after Intervention 1	335.34	(-1432.01, 2102.69)	0.000098	0.000022
Absolute Change at 22 Months after Intervention 1	0.000079	(-0.000006, 0.000163)	0.000094	0.000015
Relative Change (%) at 22 Months after Intervention 1	519.51	(-3344.37, 4383.40)	0.000094	0.000015
Absolute Change at 23 Months after Intervention 1	0.000082	(-0.000006, 0.000171)	0.000090	0.000008
Relative Change (%) at 23 Months after Intervention 1	1042.04	(-13128.2, 15212.29)	0.000090	0.000008
Absolute Change at 24 Months after Intervention 1	0.000086	(-0.000006, 0.000178)	0.000086	0.000001
Relative Change (%) at 24 Months after Intervention 1	13358.36	(-2110477, 2137193)	0.000086	0.000001
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
Relative 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

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.350476	(0.334247, 0.366705)	<.001
Baseline trend	0.002141	(0.001562, 0.002719)	<.001
Level Change (After Intervention 1)	0.000958	(-0.002330, 0.004246)	0.563
Trend Change (After Intervention 1)	-0.002103	(-0.003535, -0.000671)	0.005
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.351236	(0.334944, 0.367529)	<.001
Baseline trend	0.002110	(0.001531, 0.002689)	<.001
Trend Change (After Intervention 1)	-0.001975	(-0.003368, -0.000582)	0.006

¹The 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.

²Maximum 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.

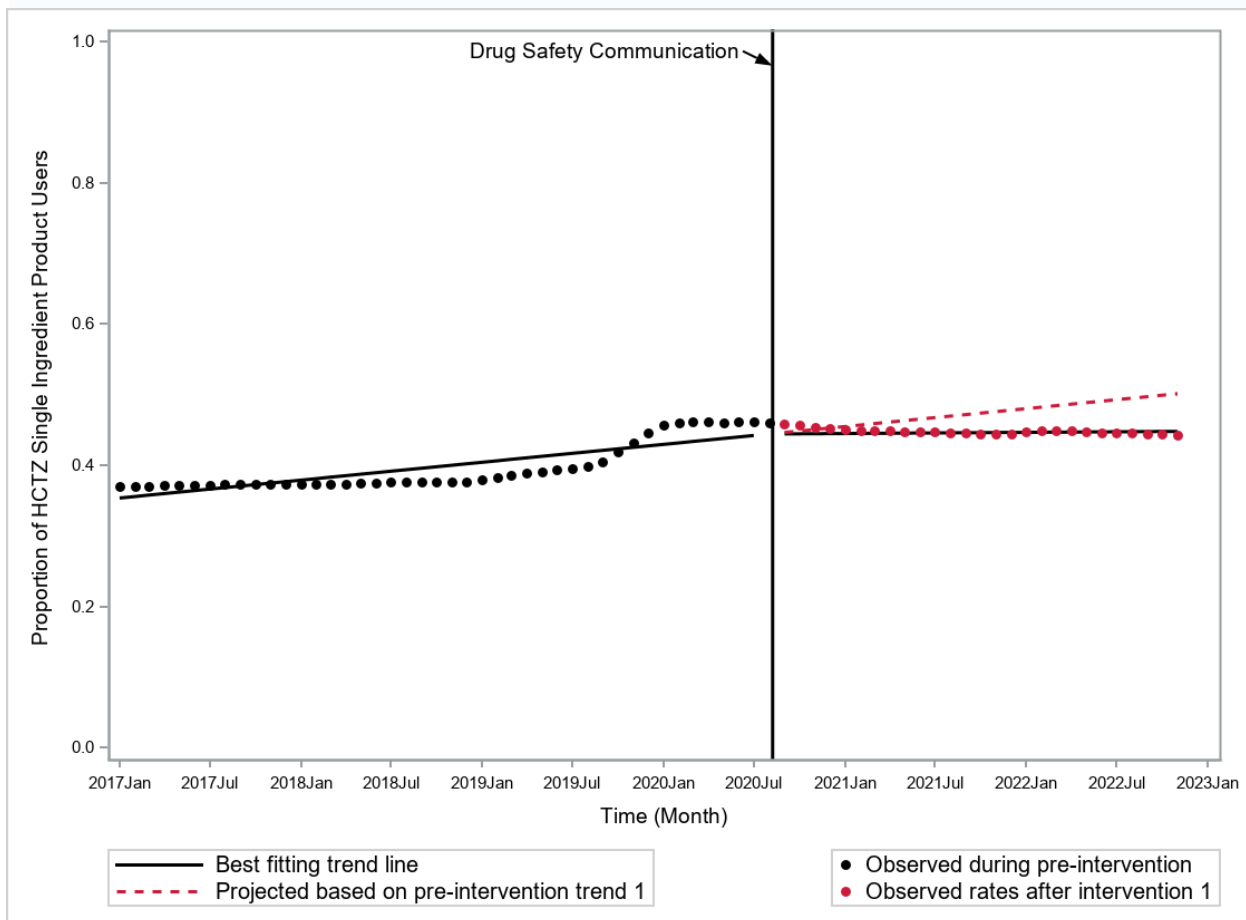
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	-0.001975	(-0.003366, -0.000584)	0.444213	0.446188
Relative Change (%) at 1 Months after Intervention 1	-0.44	(-0.74, -0.14)	0.444213	0.446188
Absolute Change at 2 Months after Intervention 1	-0.003950	(-0.006733, -0.001168)	0.444348	0.448299
Relative Change (%) at 2 Months after Intervention 1	-0.88	(-1.48, -0.29)	0.444348	0.448299
Absolute Change at 3 Months after Intervention 1	-0.005925	(-0.010099, -0.001752)	0.444483	0.450409
Relative Change (%) at 3 Months after Intervention 1	-1.32	(-2.20, -0.43)	0.444483	0.450409
Absolute Change at 4 Months after Intervention 1	-0.007901	(-0.013465, -0.002336)	0.444618	0.452519
Relative Change (%) at 4 Months after Intervention 1	-1.75	(-2.92, -0.57)	0.444618	0.452519
Absolute Change at 5 Months after Intervention 1	-0.009876	(-0.016832, -0.002920)	0.444753	0.454629
Relative Change (%) at 5 Months after Intervention 1	-2.17	(-3.63, -0.71)	0.444753	0.454629
Absolute Change at 6 Months after Intervention 1	-0.011851	(-0.020198, -0.003504)	0.444888	0.456739
Relative Change (%) at 6 Months after Intervention 1	-2.59	(-4.34, -0.85)	0.444888	0.456739
Absolute Change at 7 Months after Intervention 1	-0.013826	(-0.023564, -0.004088)	0.445023	0.458849
Relative Change (%) at 7 Months after Intervention 1	-3.01	(-5.04, -0.99)	0.445023	0.458849
Absolute Change at 8 Months after Intervention 1	-0.015801	(-0.026930, -0.004672)	0.445158	0.460959
Relative Change (%) at 8 Months after Intervention 1	-3.43	(-5.73, -1.13)	0.445158	0.460959
Absolute Change at 9 Months after Intervention 1	-0.017776	(-0.030297, -0.005256)	0.445293	0.463069
Relative Change (%) at 9 Months after Intervention 1	-3.84	(-6.41, -1.27)	0.445293	0.463069
Absolute Change at 10 Months after Intervention 1	-0.019751	(-0.033663, -0.005839)	0.445428	0.465179
Relative Change (%) at 10 Months after Intervention 1	-4.25	(-7.08, -1.41)	0.445428	0.465179
Absolute Change at 11 Months after Intervention 1	-0.021726	(-0.037029, -0.006423)	0.445563	0.467289
Relative Change (%) at 11 Months after Intervention 1	-4.65	(-7.75, -1.55)	0.445563	0.467289
Absolute Change at 12 Months after Intervention 1	-0.023702	(-0.040396, -0.007007)	0.445698	0.469399
Relative Change (%) at 12 Months after Intervention 1	-5.05	(-8.42, -1.68)	0.445698	0.469399
Absolute Change at 13 Months after Intervention 1	-0.025677	(-0.043762, -0.007591)	0.445832	0.471509
Relative Change (%) at 13 Months after Intervention 1	-5.45	(-9.07, -1.82)	0.445832	0.471509
Absolute Change at 14 Months after Intervention 1	-0.027652	(-0.047128, -0.008175)	0.445967	0.473619
Relative Change (%) at 14 Months after Intervention 1	-5.84	(-9.72, -1.95)	0.445967	0.473619
Absolute Change at 15 Months after Intervention 1	-0.029627	(-0.050495, -0.008759)	0.446102	0.475729
Relative Change (%) at 15 Months after Intervention 1	-6.23	(-10.37, -2.09)	0.446102	0.475729
Absolute Change at 16 Months after Intervention 1	-0.031602	(-0.053861, -0.009343)	0.446237	0.477839
Relative Change (%) at 16 Months after Intervention 1	-6.61	(-11.00, -2.23)	0.446237	0.477839
Absolute Change at 17 Months after Intervention 1	-0.033577	(-0.057227, -0.009927)	0.446372	0.479949
Relative Change (%) at 17 Months after Intervention 1	-7.00	(-11.63, -2.36)	0.446372	0.479949
Absolute Change at 18 Months after Intervention 1	-0.035552	(-0.060594, -0.010511)	0.446507	0.482059
Relative Change (%) at 18 Months after Intervention 1	-7.38	(-12.26, -2.49)	0.446507	0.482059
Absolute Change at 19 Months after Intervention 1	-0.037527	(-0.063960, -0.011095)	0.446642	0.484169
Relative Change (%) at 19 Months after Intervention 1	-7.75	(-12.88, -2.63)	0.446642	0.484169
Absolute Change at 20 Months after Intervention 1	-0.039503	(-0.067326, -0.011679)	0.446777	0.486280
Relative Change (%) at 20 Months after Intervention 1	-8.12	(-13.49, -2.76)	0.446777	0.486280
Absolute Change at 21 Months after Intervention 1	-0.041478	(-0.070693, -0.012263)	0.446912	0.488390
Relative Change (%) at 21 Months after Intervention 1	-8.49	(-14.09, -2.89)	0.446912	0.488390
Absolute Change at 22 Months after Intervention 1	-0.043453	(-0.074059, -0.012847)	0.447047	0.490500
Relative Change (%) at 22 Months after Intervention 1	-8.86	(-14.70, -3.02)	0.447047	0.490500
Absolute Change at 23 Months after Intervention 1	-0.045428	(-0.077425, -0.013431)	0.447182	0.492610
Relative Change (%) at 23 Months after Intervention 1	-9.22	(-15.29, -3.15)	0.447182	0.492610
Absolute Change at 24 Months after Intervention 1	-0.047403	(-0.080791, -0.014015)	0.447317	0.494720
Relative Change (%) at 24 Months after Intervention 1	-9.58	(-15.88, -3.28)	0.447317	0.494720
Absolute Change at 25 Months after Intervention 1	-0.049378	(-0.084158, -0.014599)	0.447452	0.496830
Relative Change (%) at 25 Months after Intervention 1	-9.94	(-16.46, -3.41)	0.447452	0.496830
Absolute Change at 26 Months after Intervention 1	-0.051353	(-0.087524, -0.015183)	0.447586	0.498940
Relative Change (%) at 26 Months after Intervention 1	-10.29	(-17.04, -3.54)	0.447586	0.498940
Absolute Change at 27 Months after Intervention 1	-0.053328	(-0.090890, -0.015767)	0.447721	0.501050
Relative Change (%) at 27 Months after Intervention 1	-10.64	(-17.62, -3.67)	0.447721	0.501050
Absolute Change at 27 Months after Intervention 1	-0.053328	(-0.090890, -0.015767)	0.447721	0.501050
Relative Change (%) at 27 Months after Intervention 1	-10.64	(-17.62, -3.67)	0.447721	0.501050

¹The 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 24. Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 66)²			
Intercept	0.104645	(0.103338, 0.105953)	<.001
Baseline trend	-0.000338	(-0.000374, -0.000302)	<.001
Level Change (After Intervention 1)	0.000056	(-0.000260, 0.000371)	0.726
Trend Change (After Intervention 1)	0.000008	(-0.000062, 0.000079)	0.814
Most Parsimonious Final Model Parameters (df = 68)^{2,3}			
Intercept	0.104638	(0.103328, 0.105949)	<.001
Baseline trend	-0.000334	(-0.000359, -0.000310)	<.001

¹The 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.

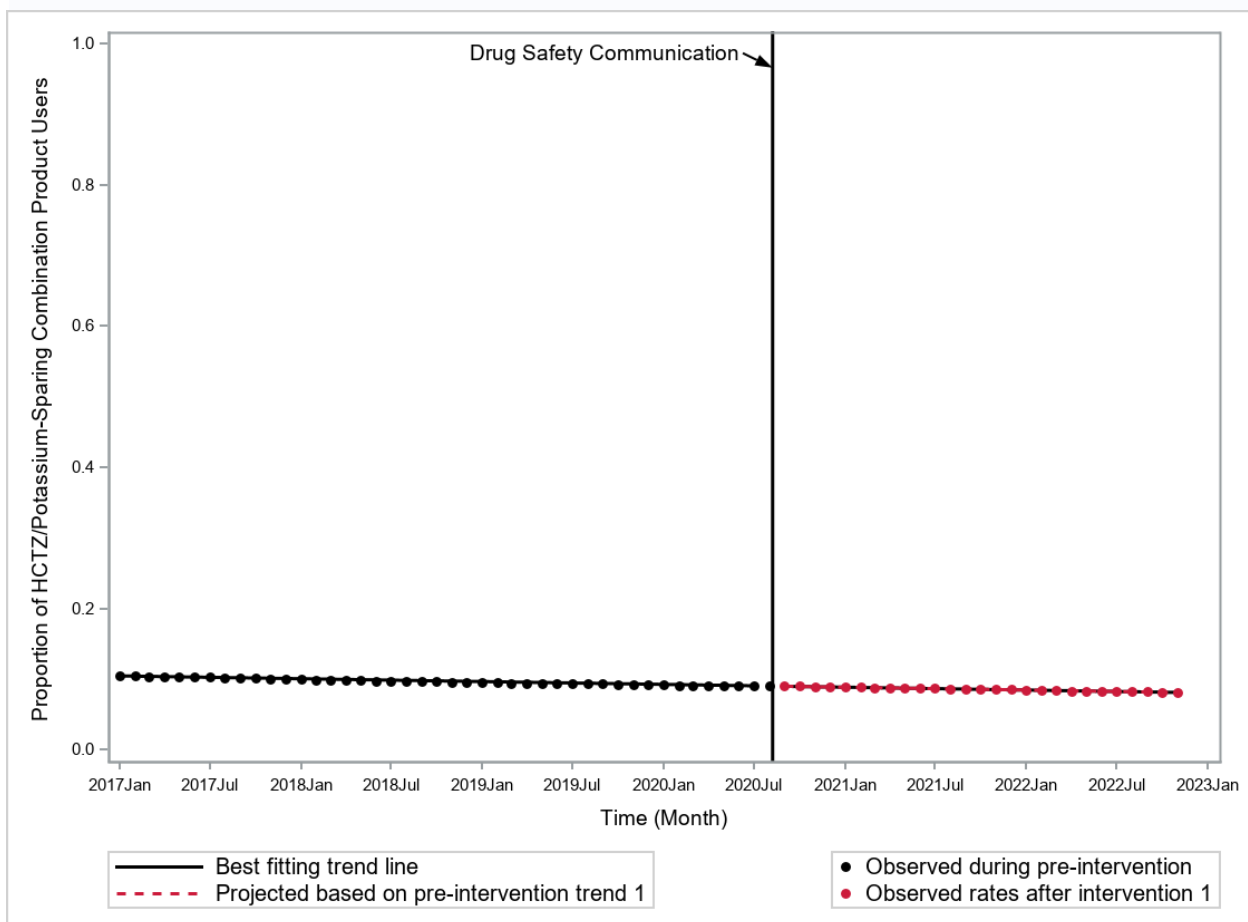
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.000000	(0.000000, 0.000000)	0.089592	0.089592
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.089592	0.089592
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.089257	0.089257
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.089257	0.089257
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088923	0.088923
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.088923	0.088923
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088588	0.088588
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.088588	0.088588
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088254	0.088254
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.088254	0.088254
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087920	0.087920
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.087920	0.087920
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087585	0.087585
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.087585	0.087585
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087251	0.087251
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.087251	0.087251
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086917	0.086917
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.086917	0.086917
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086582	0.086582
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.086582	0.086582
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086248	0.086248
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.086248	0.086248
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085914	0.085914
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.085914	0.085914
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085579	0.085579
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.085579	0.085579
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085245	0.085245
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.085245	0.085245
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084910	0.084910
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.084910	0.084910
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084576	0.084576
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.084576	0.084576
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084242	0.084242
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.084242	0.084242
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083907	0.083907
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.083907	0.083907
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083573	0.083573
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.083573	0.083573
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083239	0.083239
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.083239	0.083239
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082904	0.082904
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.082904	0.082904
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082570	0.082570
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.082570	0.082570
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082235	0.082235
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.082235	0.082235
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081901	0.081901
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.081901	0.081901
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081567	0.081567
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.081567	0.081567
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081232	0.081232
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.081232	0.081232
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.080898	0.080898
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.080898	0.080898
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.080898	0.080898
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.080898	0.080898

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 61)²			
Intercept	0.401526	(0.400586, 0.402466)	<.001
Baseline trend	-0.000612	(-0.000647, -0.000577)	<.001
Level Change (After Intervention 1)	0.002059	(0.000959, 0.003159)	<.001
Trend Change (After Intervention 1)	-0.000290	(-0.000378, -0.000202)	<.001
Most Parsimonious Final Model Parameters (df = 61)^{2,3}			
Intercept	0.401526	(0.400586, 0.402466)	<.001
Baseline trend	-0.000612	(-0.000647, -0.000577)	<.001
Level Change (After Intervention 1)	0.002059	(0.000959, 0.003159)	<.001
Trend Change (After Intervention 1)	-0.000290	(-0.000378, -0.000202)	<.001

¹The 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.

²Maximum 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.

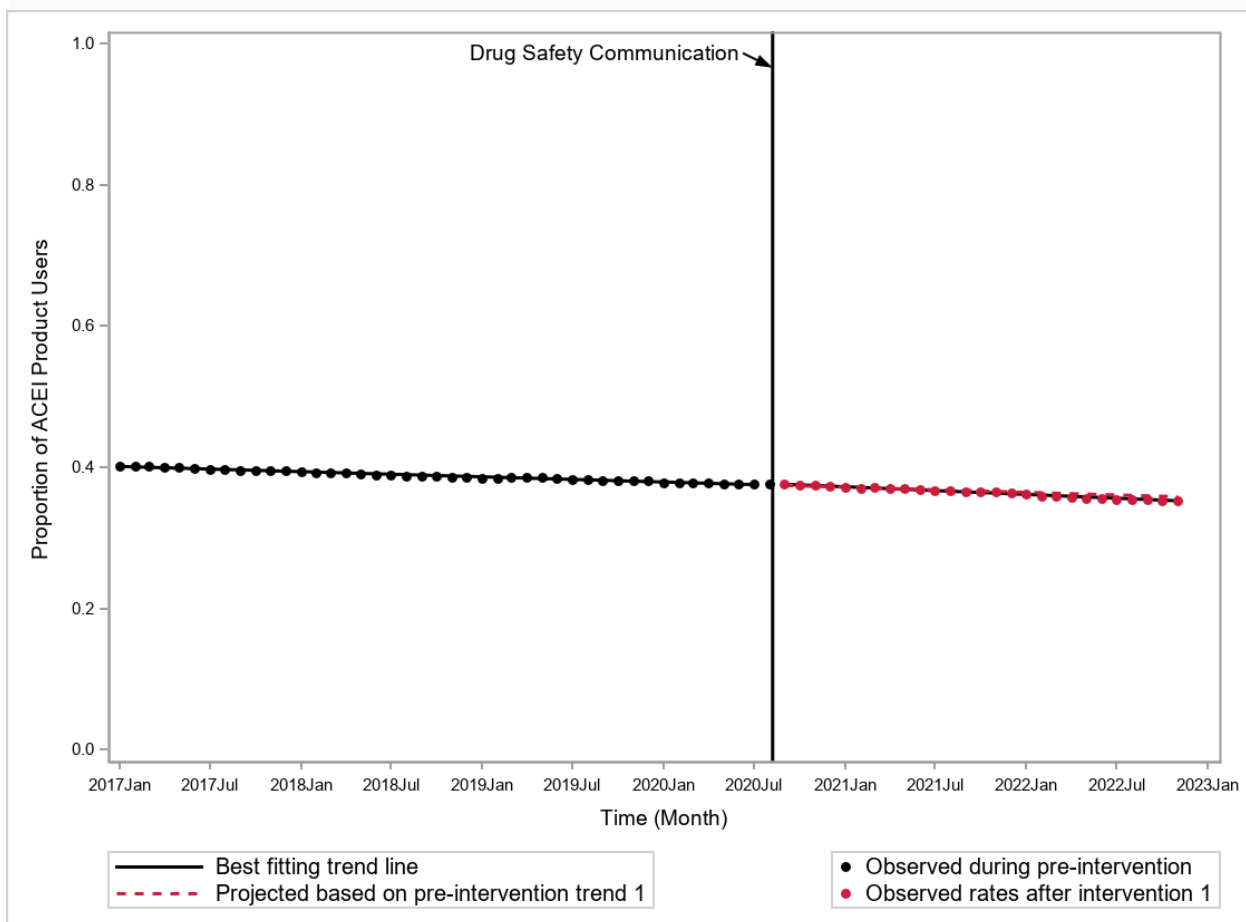
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.001769	(0.000631, 0.002906)	0.375766	0.373997
Relative Change (%) at 1 Months after Intervention 1	0.47	(0.17, 0.78)	0.375766	0.373997
Absolute Change at 2 Months after Intervention 1	0.001478	(0.000364, 0.002593)	0.374864	0.373386
Relative Change (%) at 2 Months after Intervention 1	0.40	(0.10, 0.69)	0.374864	0.373386
Absolute Change at 3 Months after Intervention 1	0.001188	(0.000089, 0.002287)	0.373962	0.372774
Relative Change (%) at 3 Months after Intervention 1	0.32	(0.02, 0.61)	0.373962	0.372774
Absolute Change at 4 Months after Intervention 1	0.000898	(-0.000193, 0.001988)	0.373060	0.372162
Relative Change (%) at 4 Months after Intervention 1	0.24	(-0.05, 0.53)	0.373060	0.372162
Absolute Change at 5 Months after Intervention 1	0.000607	(-0.000482, 0.001697)	0.372158	0.371550
Relative Change (%) at 5 Months after Intervention 1	0.16	(-0.13, 0.46)	0.372158	0.371550
Absolute Change at 6 Months after Intervention 1	0.000317	(-0.000779, 0.001413)	0.371256	0.370939
Relative Change (%) at 6 Months after Intervention 1	0.09	(-0.21, 0.38)	0.371256	0.370939
Absolute Change at 7 Months after Intervention 1	0.000027	(-0.001083, 0.001137)	0.370354	0.370327
Relative Change (%) at 7 Months after Intervention 1	0.01	(-0.29, 0.31)	0.370354	0.370327
Absolute Change at 8 Months after Intervention 1	-0.000263	(-0.001394, 0.000868)	0.369452	0.369715
Relative Change (%) at 8 Months after Intervention 1	-0.07	(-0.38, 0.23)	0.369452	0.369715
Absolute Change at 9 Months after Intervention 1	-0.000554	(-0.001712, 0.000605)	0.368550	0.369103
Relative Change (%) at 9 Months after Intervention 1	-0.15	(-0.46, 0.16)	0.368550	0.369103
Absolute Change at 10 Months after Intervention 1	-0.000844	(-0.002037, 0.000349)	0.367648	0.368492
Relative Change (%) at 10 Months after Intervention 1	-0.23	(-0.55, 0.09)	0.367648	0.368492
Absolute Change at 11 Months after Intervention 1	-0.001134	(-0.002367, 0.000098)	0.366746	0.367880
Relative Change (%) at 11 Months after Intervention 1	-0.31	(-0.64, 0.03)	0.366746	0.367880
Absolute Change at 12 Months after Intervention 1	-0.001425	(-0.002702, -0.000148)	0.365844	0.367268
Relative Change (%) at 12 Months after Intervention 1	-0.39	(-0.73, -0.04)	0.365844	0.367268
Absolute Change at 13 Months after Intervention 1	-0.001715	(-0.003041, -0.000388)	0.364942	0.366656
Relative Change (%) at 13 Months after Intervention 1	-0.47	(-0.83, -0.11)	0.364942	0.366656
Absolute Change at 14 Months after Intervention 1	-0.002005	(-0.003385, -0.000625)	0.364040	0.366045
Relative Change (%) at 14 Months after Intervention 1	-0.55	(-0.92, -0.17)	0.364040	0.366045
Absolute Change at 15 Months after Intervention 1	-0.002295	(-0.003733, -0.000858)	0.363138	0.365433
Relative Change (%) at 15 Months after Intervention 1	-0.63	(-1.02, -0.24)	0.363138	0.365433
Absolute Change at 16 Months after Intervention 1	-0.002586	(-0.004084, -0.001088)	0.362236	0.364821
Relative Change (%) at 16 Months after Intervention 1	-0.71	(-1.12, -0.30)	0.362236	0.364821
Absolute Change at 17 Months after Intervention 1	-0.002876	(-0.004438, -0.001314)	0.361333	0.364210
Relative Change (%) at 17 Months after Intervention 1	-0.79	(-1.22, -0.36)	0.361333	0.364210
Absolute Change at 18 Months after Intervention 1	-0.003166	(-0.004794, -0.001539)	0.360431	0.363598
Relative Change (%) at 18 Months after Intervention 1	-0.87	(-1.32, -0.43)	0.360431	0.363598
Absolute Change at 19 Months after Intervention 1	-0.003457	(-0.005152, -0.001761)	0.359529	0.362986
Relative Change (%) at 19 Months after Intervention 1	-0.95	(-1.42, -0.49)	0.359529	0.362986
Absolute Change at 20 Months after Intervention 1	-0.003747	(-0.005513, -0.001981)	0.358627	0.362374
Relative Change (%) at 20 Months after Intervention 1	-1.03	(-1.52, -0.55)	0.358627	0.362374
Absolute Change at 21 Months after Intervention 1	-0.004037	(-0.005875, -0.002199)	0.357725	0.361763
Relative Change (%) at 21 Months after Intervention 1	-1.12	(-1.62, -0.61)	0.357725	0.361763
Absolute Change at 22 Months after Intervention 1	-0.004327	(-0.006239, -0.002416)	0.356823	0.361151
Relative Change (%) at 22 Months after Intervention 1	-1.20	(-1.72, -0.67)	0.356823	0.361151
Absolute Change at 23 Months after Intervention 1	-0.004618	(-0.006604, -0.002631)	0.355921	0.360539
Relative Change (%) at 23 Months after Intervention 1	-1.28	(-1.83, -0.73)	0.355921	0.360539
Absolute Change at 24 Months after Intervention 1	-0.004908	(-0.006971, -0.002845)	0.355019	0.359927
Relative Change (%) at 24 Months after Intervention 1	-1.36	(-1.93, -0.80)	0.355019	0.359927
Absolute Change at 25 Months after Intervention 1	-0.005198	(-0.007339, -0.003058)	0.354117	0.359316
Relative Change (%) at 25 Months after Intervention 1	-1.45	(-2.04, -0.86)	0.354117	0.359316
Absolute Change at 26 Months after Intervention 1	-0.005489	(-0.007707, -0.003270)	0.353215	0.358704
Relative Change (%) at 26 Months after Intervention 1	-1.53	(-2.14, -0.92)	0.353215	0.358704
Absolute Change at 27 Months after Intervention 1	-0.005779	(-0.008077, -0.003481)	0.352313	0.358092
Relative Change (%) at 27 Months after Intervention 1	-1.61	(-2.25, -0.98)	0.352313	0.358092
Absolute Change at 27 Months after Intervention 1	-0.005779	(-0.008077, -0.003481)	0.352313	0.358092
Relative Change (%) at 27 Months after Intervention 1	-1.61	(-2.25, -0.98)	0.352313	0.358092

¹The 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 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 with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.369462	(0.368340, 0.370583)	<.001
Baseline trend	0.000687	(0.000646, 0.000727)	<.001
Level Change (After Intervention 1)	0.001418	(0.000413, 0.002423)	0.006
Trend Change (After Intervention 1)	-0.000256	(-0.000353, -0.000159)	<.001
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.369462	(0.368340, 0.370583)	<.001
Baseline trend	0.000687	(0.000646, 0.000727)	<.001
Level Change (After Intervention 1)	0.001418	(0.000413, 0.002423)	0.006
Trend Change (After Intervention 1)	-0.000256	(-0.000353, -0.000159)	<.001

¹The 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.

²Maximum 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.

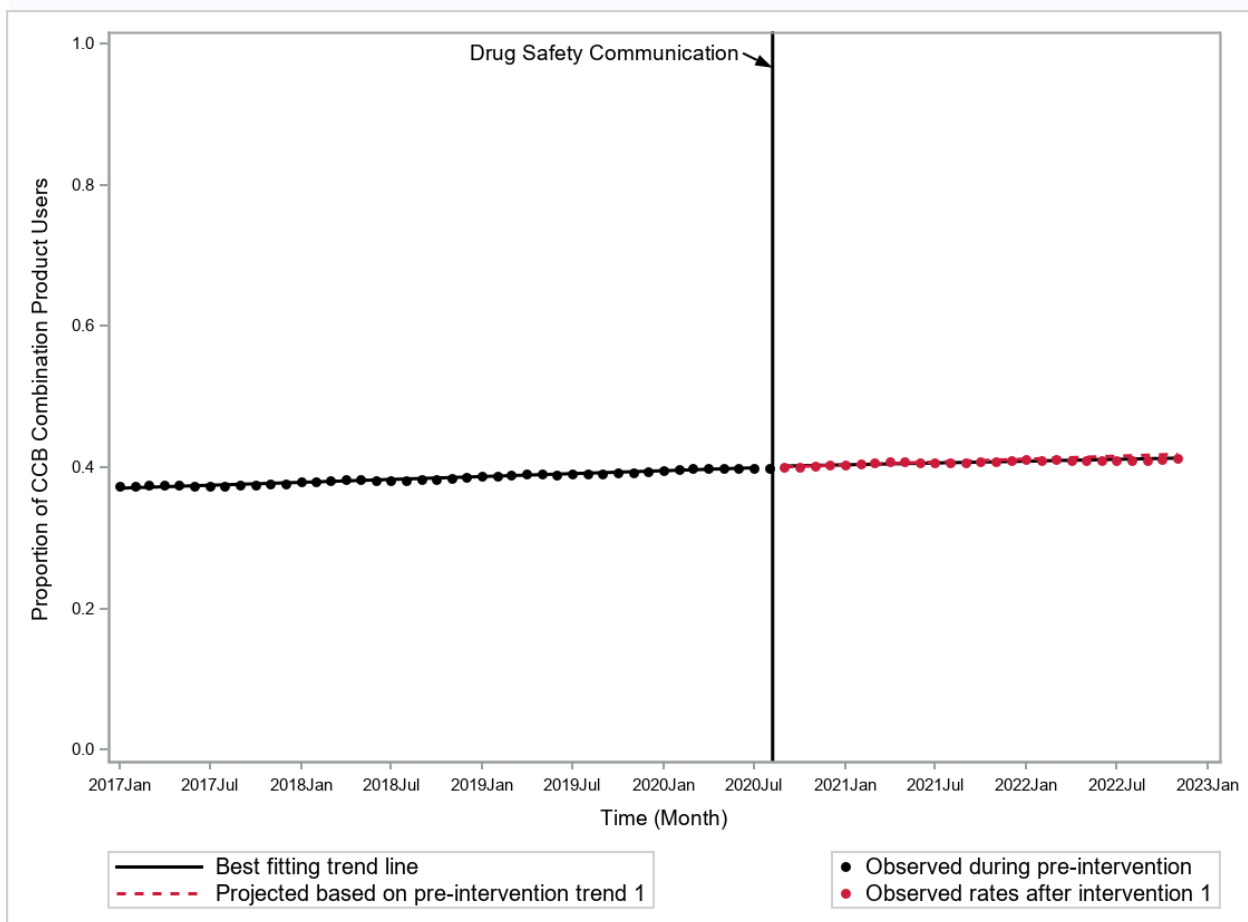
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	0.001162	(0.000145, 0.002180)	0.401519	0.400356
Relative Change (%) at 1 Months after Intervention 1	0.29	(0.04, 0.54)	0.401519	0.400356
Absolute Change at 2 Months after Intervention 1	0.000907	(-0.000109, 0.001923)	0.401950	0.401043
Relative Change (%) at 2 Months after Intervention 1	0.23	(-0.03, 0.48)	0.401950	0.401043
Absolute Change at 3 Months after Intervention 1	0.000651	(-0.000373, 0.001675)	0.402381	0.401729
Relative Change (%) at 3 Months after Intervention 1	0.16	(-0.09, 0.42)	0.402381	0.401729
Absolute Change at 4 Months after Intervention 1	0.000395	(-0.000648, 0.001439)	0.402811	0.402416
Relative Change (%) at 4 Months after Intervention 1	0.10	(-0.16, 0.36)	0.402811	0.402416
Absolute Change at 5 Months after Intervention 1	0.000140	(-0.000932, 0.001212)	0.403242	0.403103
Relative Change (%) at 5 Months after Intervention 1	0.03	(-0.23, 0.30)	0.403242	0.403103
Absolute Change at 6 Months after Intervention 1	-0.000116	(-0.001226, 0.000994)	0.403673	0.403789
Relative Change (%) at 6 Months after Intervention 1	-0.03	(-0.30, 0.25)	0.403673	0.403789
Absolute Change at 7 Months after Intervention 1	-0.000372	(-0.001528, 0.000784)	0.404104	0.404476
Relative Change (%) at 7 Months after Intervention 1	-0.09	(-0.38, 0.19)	0.404104	0.404476
Absolute Change at 8 Months after Intervention 1	-0.000627	(-0.001837, 0.000582)	0.404535	0.405162
Relative Change (%) at 8 Months after Intervention 1	-0.15	(-0.45, 0.14)	0.404535	0.405162
Absolute Change at 9 Months after Intervention 1	-0.000883	(-0.002152, 0.000386)	0.404966	0.405849
Relative Change (%) at 9 Months after Intervention 1	-0.22	(-0.53, 0.09)	0.404966	0.405849
Absolute Change at 10 Months after Intervention 1	-0.001139	(-0.002473, 0.000196)	0.405397	0.406535
Relative Change (%) at 10 Months after Intervention 1	-0.28	(-0.61, 0.05)	0.405397	0.406535
Absolute Change at 11 Months after Intervention 1	-0.001394	(-0.002799, 0.000010)	0.405827	0.407222
Relative Change (%) at 11 Months after Intervention 1	-0.34	(-0.69, 0.00)	0.405827	0.407222
Absolute Change at 12 Months after Intervention 1	-0.001650	(-0.003128, -0.000172)	0.406258	0.407908
Relative Change (%) at 12 Months after Intervention 1	-0.40	(-0.77, -0.04)	0.406258	0.407908
Absolute Change at 13 Months after Intervention 1	-0.001906	(-0.003462, -0.000350)	0.406689	0.408595
Relative Change (%) at 13 Months after Intervention 1	-0.47	(-0.85, -0.09)	0.406689	0.408595
Absolute Change at 14 Months after Intervention 1	-0.002161	(-0.003798, -0.000525)	0.407120	0.409281
Relative Change (%) at 14 Months after Intervention 1	-0.53	(-0.93, -0.13)	0.407120	0.409281
Absolute Change at 15 Months after Intervention 1	-0.002417	(-0.004137, -0.000698)	0.407551	0.409968
Relative Change (%) at 15 Months after Intervention 1	-0.59	(-1.01, -0.17)	0.407551	0.409968
Absolute Change at 16 Months after Intervention 1	-0.002673	(-0.004478, -0.000868)	0.407982	0.410655
Relative Change (%) at 16 Months after Intervention 1	-0.65	(-1.09, -0.21)	0.407982	0.410655
Absolute Change at 17 Months after Intervention 1	-0.002928	(-0.004820, -0.001036)	0.408413	0.411341
Relative Change (%) at 17 Months after Intervention 1	-0.71	(-1.17, -0.25)	0.408413	0.411341
Absolute Change at 18 Months after Intervention 1	-0.003184	(-0.005165, -0.001203)	0.408844	0.412028
Relative Change (%) at 18 Months after Intervention 1	-0.77	(-1.25, -0.29)	0.408844	0.412028
Absolute Change at 19 Months after Intervention 1	-0.003440	(-0.005511, -0.001369)	0.409274	0.412714
Relative Change (%) at 19 Months after Intervention 1	-0.83	(-1.33, -0.33)	0.409274	0.412714
Absolute Change at 20 Months after Intervention 1	-0.003695	(-0.005858, -0.001533)	0.409705	0.413401
Relative Change (%) at 20 Months after Intervention 1	-0.89	(-1.41, -0.37)	0.409705	0.413401
Absolute Change at 21 Months after Intervention 1	-0.003951	(-0.006206, -0.001696)	0.410136	0.414087
Relative Change (%) at 21 Months after Intervention 1	-0.95	(-1.50, -0.41)	0.410136	0.414087
Absolute Change at 22 Months after Intervention 1	-0.004207	(-0.006556, -0.001858)	0.410567	0.414774
Relative Change (%) at 22 Months after Intervention 1	-1.01	(-1.58, -0.45)	0.410567	0.414774
Absolute Change at 23 Months after Intervention 1	-0.004463	(-0.006906, -0.002019)	0.410998	0.415460
Relative Change (%) at 23 Months after Intervention 1	-1.07	(-1.66, -0.49)	0.410998	0.415460
Absolute Change at 24 Months after Intervention 1	-0.004718	(-0.007257, -0.002179)	0.411429	0.416147
Relative Change (%) at 24 Months after Intervention 1	-1.13	(-1.74, -0.53)	0.411429	0.416147
Absolute Change at 25 Months after Intervention 1	-0.004974	(-0.007609, -0.002339)	0.411860	0.416833
Relative Change (%) at 25 Months after Intervention 1	-1.19	(-1.82, -0.57)	0.411860	0.416833
Absolute Change at 26 Months after Intervention 1	-0.005230	(-0.007961, -0.002498)	0.412290	0.417520
Relative Change (%) at 26 Months after Intervention 1	-1.25	(-1.90, -0.60)	0.412290	0.417520
Absolute Change at 27 Months after Intervention 1	-0.005485	(-0.008314, -0.002657)	0.412721	0.418207
Relative Change (%) at 27 Months after Intervention 1	-1.31	(-1.98, -0.64)	0.412721	0.418207
Absolute Change at 27 Months after Intervention 1	-0.005485	(-0.008314, -0.002657)	0.412721	0.418207
Relative Change (%) at 27 Months after Intervention 1	-1.31	(-1.98, -0.64)	0.412721	0.418207

¹The 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 27. Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 64)²			
Intercept	0.164125	(0.163477, 0.164773)	<.001
Baseline trend	-0.000179	(-0.000200, -0.000158)	<.001
Level Change (After Intervention 1)	0.000381	(-0.000238, 0.001001)	0.223
Trend Change (After Intervention 1)	-0.000181	(-0.000224, -0.000137)	<.001
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.164073	(0.163430, 0.164716)	<.001
Baseline trend	-0.000174	(-0.000194, -0.000154)	<.001
Trend Change (After Intervention 1)	-0.000174	(-0.000217, -0.000131)	<.001

¹The 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.

²Maximum 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.

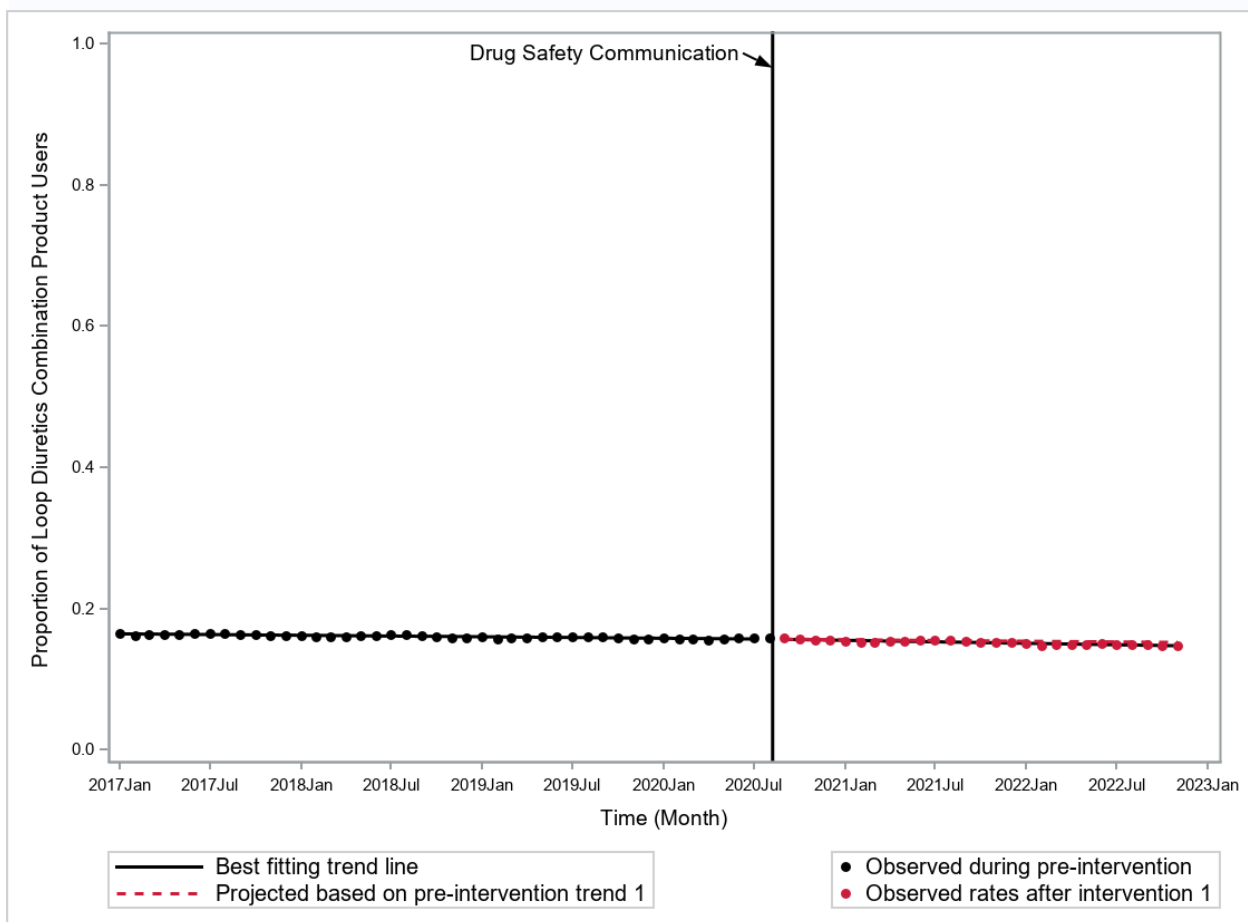
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table S6. 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 with no History of Skin Cancer after August 8, 2020¹ 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	-0.000174	(-0.000219, -0.000129)	0.156056	0.156230
Relative Change (%) at 1 Months after Intervention 1	-0.11	(-0.14, -0.08)	0.156056	0.156230
Absolute Change at 2 Months after Intervention 1	-0.000348	(-0.000438, -0.000259)	0.155707	0.156056
Relative Change (%) at 2 Months after Intervention 1	-0.22	(-0.28, -0.17)	0.155707	0.156056
Absolute Change at 3 Months after Intervention 1	-0.000522	(-0.000657, -0.000388)	0.155359	0.155881
Relative Change (%) at 3 Months after Intervention 1	-0.34	(-0.42, -0.25)	0.155359	0.155881
Absolute Change at 4 Months after Intervention 1	-0.000696	(-0.000876, -0.000517)	0.155011	0.155707
Relative Change (%) at 4 Months after Intervention 1	-0.45	(-0.56, -0.33)	0.155011	0.155707
Absolute Change at 5 Months after Intervention 1	-0.000871	(-0.001095, -0.000646)	0.154662	0.155533
Relative Change (%) at 5 Months after Intervention 1	-0.56	(-0.70, -0.42)	0.154662	0.155533
Absolute Change at 6 Months after Intervention 1	-0.001045	(-0.001313, -0.000776)	0.154314	0.155359
Relative Change (%) at 6 Months after Intervention 1	-0.67	(-0.84, -0.50)	0.154314	0.155359
Absolute Change at 7 Months after Intervention 1	-0.001219	(-0.001532, -0.000905)	0.153966	0.155184
Relative Change (%) at 7 Months after Intervention 1	-0.79	(-0.98, -0.59)	0.153966	0.155184
Absolute Change at 8 Months after Intervention 1	-0.001393	(-0.001751, -0.001034)	0.153617	0.155010
Relative Change (%) at 8 Months after Intervention 1	-0.90	(-1.13, -0.67)	0.153617	0.155010
Absolute Change at 9 Months after Intervention 1	-0.001567	(-0.001970, -0.001164)	0.153269	0.154836
Relative Change (%) at 9 Months after Intervention 1	-1.01	(-1.27, -0.76)	0.153269	0.154836
Absolute Change at 10 Months after Intervention 1	-0.001741	(-0.002189, -0.001293)	0.152920	0.154661
Relative Change (%) at 10 Months after Intervention 1	-1.13	(-1.41, -0.84)	0.152920	0.154661
Absolute Change at 11 Months after Intervention 1	-0.001915	(-0.002408, -0.001422)	0.152572	0.154487
Relative Change (%) at 11 Months after Intervention 1	-1.24	(-1.55, -0.93)	0.152572	0.154487
Absolute Change at 12 Months after Intervention 1	-0.002089	(-0.002627, -0.001552)	0.152224	0.154313
Relative Change (%) at 12 Months after Intervention 1	-1.35	(-1.70, -1.01)	0.152224	0.154313
Absolute Change at 13 Months after Intervention 1	-0.002263	(-0.002846, -0.001681)	0.151875	0.154138
Relative Change (%) at 13 Months after Intervention 1	-1.47	(-1.84, -1.10)	0.151875	0.154138
Absolute Change at 14 Months after Intervention 1	-0.002437	(-0.003065, -0.001810)	0.151527	0.153964
Relative Change (%) at 14 Months after Intervention 1	-1.58	(-1.98, -1.18)	0.151527	0.153964
Absolute Change at 15 Months after Intervention 1	-0.002612	(-0.003284, -0.001939)	0.151178	0.153790
Relative Change (%) at 15 Months after Intervention 1	-1.70	(-2.13, -1.27)	0.151178	0.153790
Absolute Change at 16 Months after Intervention 1	-0.002786	(-0.003503, -0.002069)	0.150830	0.153616
Relative Change (%) at 16 Months after Intervention 1	-1.81	(-2.27, -1.35)	0.150830	0.153616
Absolute Change at 17 Months after Intervention 1	-0.002960	(-0.003721, -0.002198)	0.150482	0.153441
Relative Change (%) at 17 Months after Intervention 1	-1.93	(-2.42, -1.44)	0.150482	0.153441
Absolute Change at 18 Months after Intervention 1	-0.003134	(-0.003940, -0.002327)	0.150133	0.153267
Relative Change (%) at 18 Months after Intervention 1	-2.04	(-2.56, -1.53)	0.150133	0.153267
Absolute Change at 19 Months after Intervention 1	-0.003308	(-0.004159, -0.002457)	0.149785	0.153093
Relative Change (%) at 19 Months after Intervention 1	-2.16	(-2.71, -1.61)	0.149785	0.153093
Absolute Change at 20 Months after Intervention 1	-0.003482	(-0.004378, -0.002586)	0.149436	0.152918
Relative Change (%) at 20 Months after Intervention 1	-2.28	(-2.85, -1.70)	0.149436	0.152918
Absolute Change at 21 Months after Intervention 1	-0.003656	(-0.004597, -0.002715)	0.149088	0.152744
Relative Change (%) at 21 Months after Intervention 1	-2.39	(-3.00, -1.79)	0.149088	0.152744
Absolute Change at 22 Months after Intervention 1	-0.003830	(-0.004816, -0.002845)	0.148740	0.152570
Relative Change (%) at 22 Months after Intervention 1	-2.51	(-3.14, -1.88)	0.148740	0.152570
Absolute Change at 23 Months after Intervention 1	-0.004004	(-0.005035, -0.002974)	0.148391	0.152396
Relative Change (%) at 23 Months after Intervention 1	-2.63	(-3.29, -1.96)	0.148391	0.152396
Absolute Change at 24 Months after Intervention 1	-0.004178	(-0.005254, -0.003103)	0.148043	0.152221
Relative Change (%) at 24 Months after Intervention 1	-2.75	(-3.44, -2.05)	0.148043	0.152221
Absolute Change at 25 Months after Intervention 1	-0.004353	(-0.005473, -0.003232)	0.147694	0.152047
Relative Change (%) at 25 Months after Intervention 1	-2.86	(-3.58, -2.14)	0.147694	0.152047
Absolute Change at 26 Months after Intervention 1	-0.004527	(-0.005692, -0.003362)	0.147346	0.151873
Relative Change (%) at 26 Months after Intervention 1	-2.98	(-3.73, -2.23)	0.147346	0.151873
Absolute Change at 27 Months after Intervention 1	-0.004701	(-0.005911, -0.003491)	0.146998	0.151698
Relative Change (%) at 27 Months after Intervention 1	-3.10	(-3.88, -2.32)	0.146998	0.151698
Absolute Change at 27 Months after Intervention 1	-0.004701	(-0.005911, -0.003491)	0.146998	0.151698
Relative Change (%) at 27 Months after Intervention 1	-3.10	(-3.88, -2.32)	0.146998	0.151698

¹The 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 28. Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.046951	(0.046728, 0.047175)	<.001
Baseline trend	0.000211	(0.000203, 0.000219)	<.001
Level Change (After Intervention 1)	-0.000390	(-0.000692, -0.000088)	0.012
Trend Change (After Intervention 1)	0.000087	(0.000067, 0.000107)	<.001
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.046951	(0.046728, 0.047175)	<.001
Baseline trend	0.000211	(0.000203, 0.000219)	<.001
Level Change (After Intervention 1)	-0.000390	(-0.000692, -0.000088)	0.012
Trend Change (After Intervention 1)	0.000087	(0.000067, 0.000107)	<.001

¹The 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.

²Maximum 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.

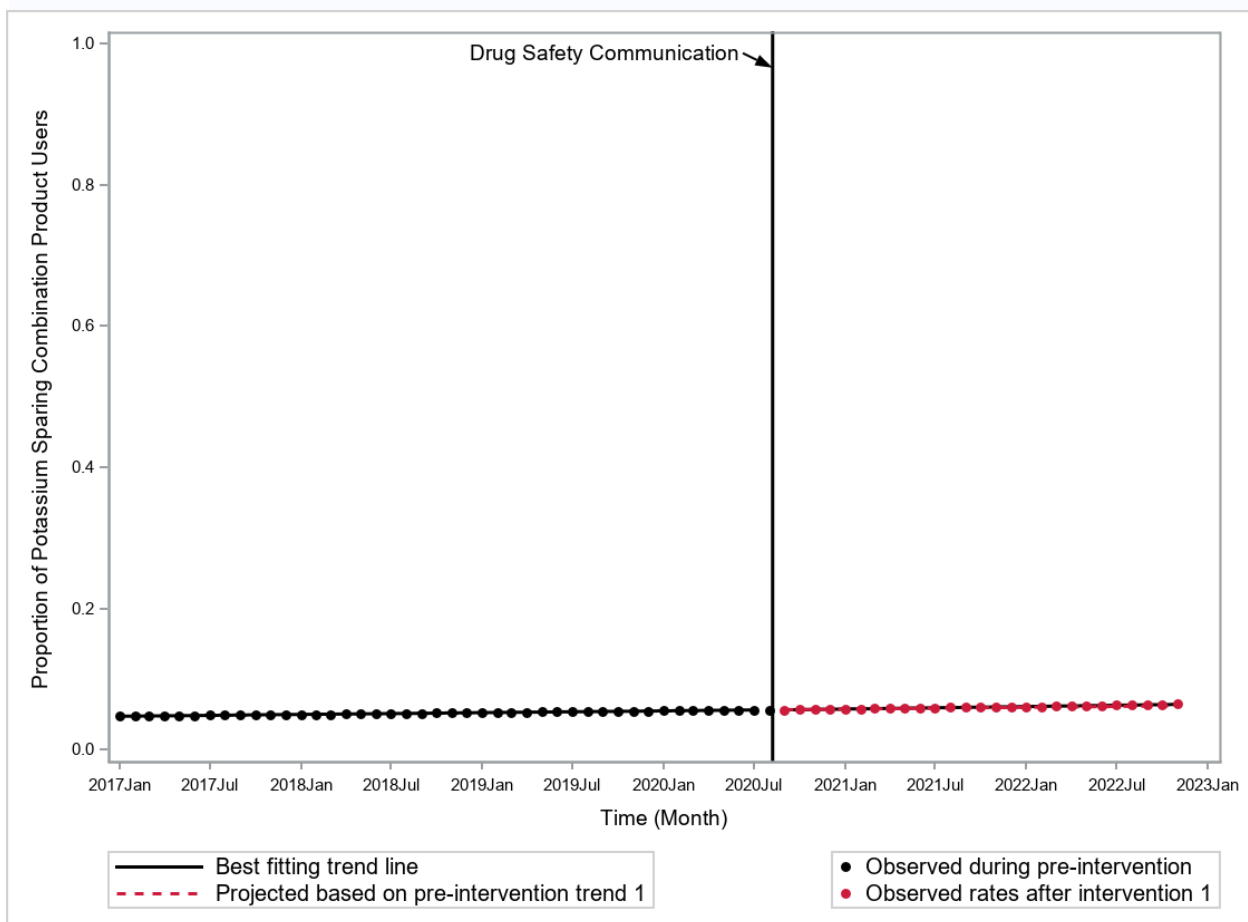
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	-0.000303	(-0.000603, -0.000003)	0.056142	0.056445
Relative Change (%) at 1 Months after Intervention 1	-0.54	(-1.07, -0.01)	0.056142	0.056445
Absolute Change at 2 Months after Intervention 1	-0.000216	(-0.000512, 0.000079)	0.056439	0.056656
Relative Change (%) at 2 Months after Intervention 1	-0.38	(-0.90, 0.14)	0.056439	0.056656
Absolute Change at 3 Months after Intervention 1	-0.000130	(-0.000422, 0.000163)	0.056737	0.056867
Relative Change (%) at 3 Months after Intervention 1	-0.23	(-0.74, 0.29)	0.056737	0.056867
Absolute Change at 4 Months after Intervention 1	-0.000043	(-0.000334, 0.000248)	0.057034	0.057078
Relative Change (%) at 4 Months after Intervention 1	-0.08	(-0.58, 0.43)	0.057034	0.057078
Absolute Change at 5 Months after Intervention 1	0.000044	(-0.000247, 0.000334)	0.057332	0.057288
Relative Change (%) at 5 Months after Intervention 1	0.08	(-0.43, 0.58)	0.057332	0.057288
Absolute Change at 6 Months after Intervention 1	0.000130	(-0.000161, 0.000422)	0.057630	0.057499
Relative Change (%) at 6 Months after Intervention 1	0.23	(-0.28, 0.73)	0.057630	0.057499
Absolute Change at 7 Months after Intervention 1	0.000217	(-0.000077, 0.000511)	0.057927	0.057710
Relative Change (%) at 7 Months after Intervention 1	0.38	(-0.13, 0.89)	0.057927	0.057710
Absolute Change at 8 Months after Intervention 1	0.000304	(0.000006, 0.000601)	0.058225	0.057921
Relative Change (%) at 8 Months after Intervention 1	0.52	(0.01, 1.04)	0.058225	0.057921
Absolute Change at 9 Months after Intervention 1	0.000390	(0.000088, 0.000693)	0.058523	0.058132
Relative Change (%) at 9 Months after Intervention 1	0.67	(0.15, 1.19)	0.058523	0.058132
Absolute Change at 10 Months after Intervention 1	0.000477	(0.000169, 0.000785)	0.058820	0.058343
Relative Change (%) at 10 Months after Intervention 1	0.82	(0.29, 1.35)	0.058820	0.058343
Absolute Change at 11 Months after Intervention 1	0.000564	(0.000248, 0.000879)	0.059118	0.058554
Relative Change (%) at 11 Months after Intervention 1	0.96	(0.42, 1.51)	0.059118	0.058554
Absolute Change at 12 Months after Intervention 1	0.000651	(0.000327, 0.000974)	0.059416	0.058765
Relative Change (%) at 12 Months after Intervention 1	1.11	(0.55, 1.66)	0.059416	0.058765
Absolute Change at 13 Months after Intervention 1	0.000737	(0.000404, 0.001070)	0.059713	0.058976
Relative Change (%) at 13 Months after Intervention 1	1.25	(0.68, 1.82)	0.059713	0.058976
Absolute Change at 14 Months after Intervention 1	0.000824	(0.000481, 0.001167)	0.060011	0.059187
Relative Change (%) at 14 Months after Intervention 1	1.39	(0.81, 1.98)	0.060011	0.059187
Absolute Change at 15 Months after Intervention 1	0.000911	(0.000556, 0.001265)	0.060309	0.059398
Relative Change (%) at 15 Months after Intervention 1	1.53	(0.93, 2.14)	0.060309	0.059398
Absolute Change at 16 Months after Intervention 1	0.000997	(0.000631, 0.001363)	0.060606	0.059609
Relative Change (%) at 16 Months after Intervention 1	1.67	(1.05, 2.30)	0.060606	0.059609
Absolute Change at 17 Months after Intervention 1	0.001084	(0.000705, 0.001463)	0.060904	0.059820
Relative Change (%) at 17 Months after Intervention 1	1.81	(1.17, 2.45)	0.060904	0.059820
Absolute Change at 18 Months after Intervention 1	0.001171	(0.000779, 0.001562)	0.061202	0.060031
Relative Change (%) at 18 Months after Intervention 1	1.95	(1.29, 2.61)	0.061202	0.060031
Absolute Change at 19 Months after Intervention 1	0.001257	(0.000852, 0.001663)	0.061499	0.060242
Relative Change (%) at 19 Months after Intervention 1	2.09	(1.40, 2.77)	0.061499	0.060242
Absolute Change at 20 Months after Intervention 1	0.001344	(0.000925, 0.001763)	0.061797	0.060453
Relative Change (%) at 20 Months after Intervention 1	2.22	(1.52, 2.93)	0.061797	0.060453
Absolute Change at 21 Months after Intervention 1	0.001431	(0.000997, 0.001865)	0.062095	0.060664
Relative Change (%) at 21 Months after Intervention 1	2.36	(1.63, 3.09)	0.062095	0.060664
Absolute Change at 22 Months after Intervention 1	0.001517	(0.001068, 0.001966)	0.062392	0.060875
Relative Change (%) at 22 Months after Intervention 1	2.49	(1.74, 3.24)	0.062392	0.060875
Absolute Change at 23 Months after Intervention 1	0.001604	(0.001140, 0.002068)	0.062690	0.061086
Relative Change (%) at 23 Months after Intervention 1	2.63	(1.85, 3.40)	0.062690	0.061086
Absolute Change at 24 Months after Intervention 1	0.001691	(0.001211, 0.002171)	0.062988	0.061297
Relative Change (%) at 24 Months after Intervention 1	2.76	(1.96, 3.56)	0.062988	0.061297
Absolute Change at 25 Months after Intervention 1	0.001777	(0.001281, 0.002274)	0.063285	0.061508
Relative Change (%) at 25 Months after Intervention 1	2.89	(2.07, 3.71)	0.063285	0.061508
Absolute Change at 26 Months after Intervention 1	0.001864	(0.001352, 0.002376)	0.063583	0.061719
Relative Change (%) at 26 Months after Intervention 1	3.02	(2.17, 3.87)	0.063583	0.061719
Absolute Change at 27 Months after Intervention 1	0.001951	(0.001422, 0.002480)	0.063880	0.061930
Relative Change (%) at 27 Months after Intervention 1	3.15	(2.28, 4.02)	0.063880	0.061930
Absolute Change at 27 Months after Intervention 1	0.001951	(0.001422, 0.002480)	0.063880	0.061930
Relative Change (%) at 27 Months after Intervention 1	3.15	(2.28, 4.02)	0.063880	0.061930

¹The 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 29. Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 65)²			
Intercept	0.022845	(0.022521, 0.023168)	<.001
Baseline trend	0.000121	(0.000110, 0.000133)	<.001
Level Change (After Intervention 1)	-0.000111	(-0.000354, 0.000133)	0.368
Trend Change (After Intervention 1)	-0.000094	(-0.000122, -0.000066)	<.001
Most Parsimonious Final Model Parameters (df = 66)^{2,3}			
Intercept	0.022862	(0.022517, 0.023207)	<.001
Baseline trend	0.000120	(0.000108, 0.000132)	<.001
Trend Change (After Intervention 1)	-0.000097	(-0.000126, -0.000067)	<.001

¹The 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.

²Maximum 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.

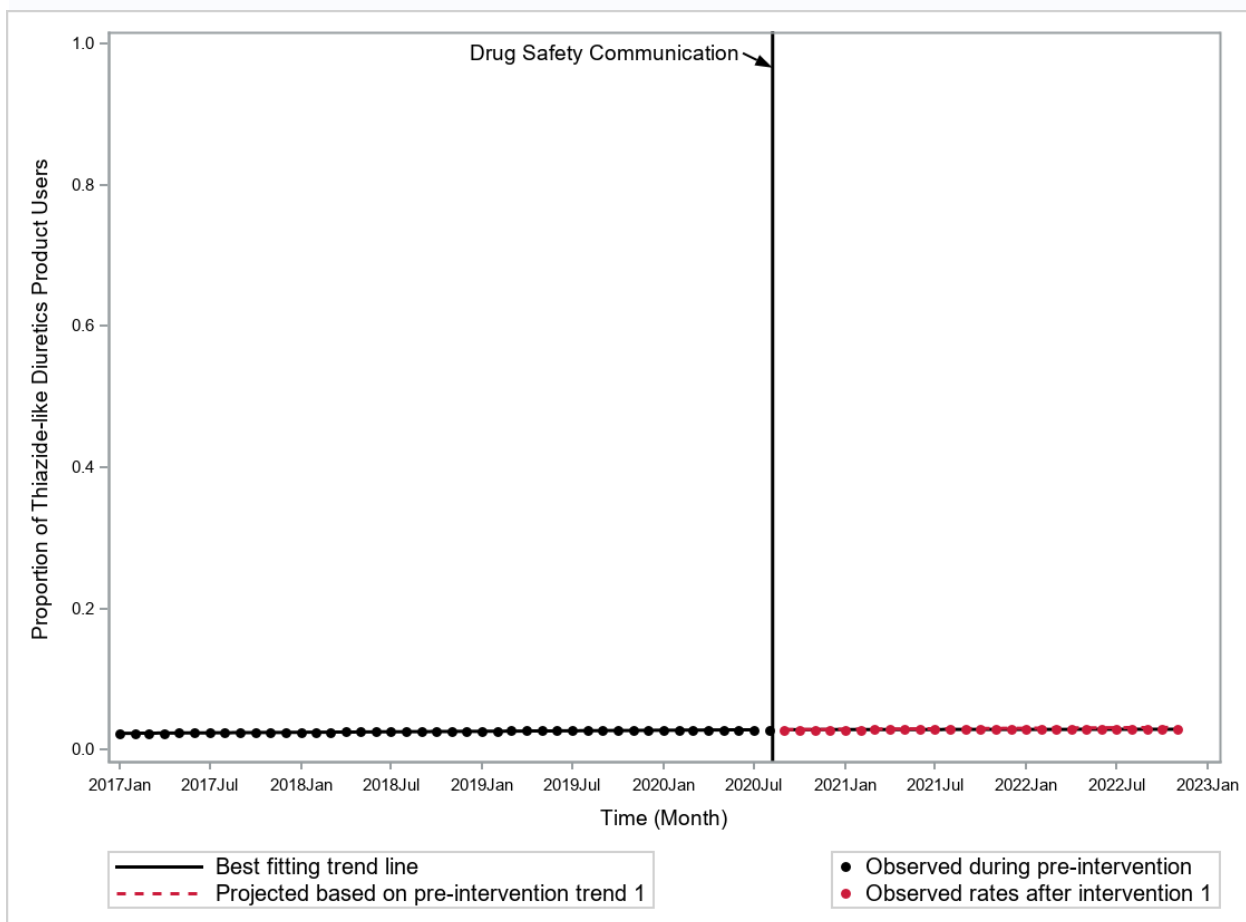
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

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 with no History of Skin Cancer after August 8, 2020¹ 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	-0.000097	(-0.000126, -0.000067)	0.028170	0.028267
Relative Change (%) at 1 Months after Intervention 1	-0.34	(-0.44, -0.24)	0.028170	0.028267
Absolute Change at 2 Months after Intervention 1	-0.000193	(-0.000253, -0.000134)	0.028194	0.028387
Relative Change (%) at 2 Months after Intervention 1	-0.68	(-0.88, -0.48)	0.028194	0.028387
Absolute Change at 3 Months after Intervention 1	-0.000290	(-0.000379, -0.000200)	0.028217	0.028507
Relative Change (%) at 3 Months after Intervention 1	-1.02	(-1.32, -0.71)	0.028217	0.028507
Absolute Change at 4 Months after Intervention 1	-0.000386	(-0.000505, -0.000267)	0.028241	0.028627
Relative Change (%) at 4 Months after Intervention 1	-1.35	(-1.75, -0.95)	0.028241	0.028627
Absolute Change at 5 Months after Intervention 1	-0.000483	(-0.000631, -0.000334)	0.028265	0.028747
Relative Change (%) at 5 Months after Intervention 1	-1.68	(-2.18, -1.18)	0.028265	0.028747
Absolute Change at 6 Months after Intervention 1	-0.000579	(-0.000758, -0.000401)	0.028288	0.028867
Relative Change (%) at 6 Months after Intervention 1	-2.01	(-2.60, -1.41)	0.028288	0.028867
Absolute Change at 7 Months after Intervention 1	-0.000676	(-0.000884, -0.000467)	0.028312	0.028988
Relative Change (%) at 7 Months after Intervention 1	-2.33	(-3.02, -1.64)	0.028312	0.028988
Absolute Change at 8 Months after Intervention 1	-0.000772	(-0.001010, -0.000534)	0.028335	0.029108
Relative Change (%) at 8 Months after Intervention 1	-2.65	(-3.44, -1.87)	0.028335	0.029108
Absolute Change at 9 Months after Intervention 1	-0.000869	(-0.001137, -0.000601)	0.028359	0.029228
Relative Change (%) at 9 Months after Intervention 1	-2.97	(-3.85, -2.09)	0.028359	0.029228
Absolute Change at 10 Months after Intervention 1	-0.000965	(-0.001263, -0.000668)	0.028383	0.029348
Relative Change (%) at 10 Months after Intervention 1	-3.29	(-4.26, -2.31)	0.028383	0.029348
Absolute Change at 11 Months after Intervention 1	-0.001062	(-0.001389, -0.000735)	0.028406	0.029468
Relative Change (%) at 11 Months after Intervention 1	-3.60	(-4.67, -2.54)	0.028406	0.029468
Absolute Change at 12 Months after Intervention 1	-0.001158	(-0.001515, -0.000801)	0.028430	0.029588
Relative Change (%) at 12 Months after Intervention 1	-3.92	(-5.07, -2.76)	0.028430	0.029588
Absolute Change at 13 Months after Intervention 1	-0.001255	(-0.001642, -0.000868)	0.028453	0.029708
Relative Change (%) at 13 Months after Intervention 1	-4.22	(-5.47, -2.98)	0.028453	0.029708
Absolute Change at 14 Months after Intervention 1	-0.001351	(-0.001768, -0.000935)	0.028477	0.029828
Relative Change (%) at 14 Months after Intervention 1	-4.53	(-5.87, -3.19)	0.028477	0.029828
Absolute Change at 15 Months after Intervention 1	-0.001448	(-0.001894, -0.001002)	0.028500	0.029948
Relative Change (%) at 15 Months after Intervention 1	-4.83	(-6.26, -3.41)	0.028500	0.029948
Absolute Change at 16 Months after Intervention 1	-0.001545	(-0.002021, -0.001068)	0.028524	0.030069
Relative Change (%) at 16 Months after Intervention 1	-5.14	(-6.65, -3.62)	0.028524	0.030069
Absolute Change at 17 Months after Intervention 1	-0.001641	(-0.002147, -0.001135)	0.028548	0.030189
Relative Change (%) at 17 Months after Intervention 1	-5.44	(-7.04, -3.84)	0.028548	0.030189
Absolute Change at 18 Months after Intervention 1	-0.001738	(-0.002273, -0.001202)	0.028571	0.030309
Relative Change (%) at 18 Months after Intervention 1	-5.73	(-7.42, -4.05)	0.028571	0.030309
Absolute Change at 19 Months after Intervention 1	-0.001834	(-0.002400, -0.001269)	0.028595	0.030429
Relative Change (%) at 19 Months after Intervention 1	-6.03	(-7.80, -4.26)	0.028595	0.030429
Absolute Change at 20 Months after Intervention 1	-0.001931	(-0.002526, -0.001335)	0.028618	0.030549
Relative Change (%) at 20 Months after Intervention 1	-6.32	(-8.17, -4.46)	0.028618	0.030549
Absolute Change at 21 Months after Intervention 1	-0.002027	(-0.002652, -0.001402)	0.028642	0.030669
Relative Change (%) at 21 Months after Intervention 1	-6.61	(-8.55, -4.67)	0.028642	0.030669
Absolute Change at 22 Months after Intervention 1	-0.002124	(-0.002778, -0.001469)	0.028666	0.030789
Relative Change (%) at 22 Months after Intervention 1	-6.90	(-8.92, -4.88)	0.028666	0.030789
Absolute Change at 23 Months after Intervention 1	-0.002220	(-0.002905, -0.001536)	0.028689	0.030909
Relative Change (%) at 23 Months after Intervention 1	-7.18	(-9.29, -5.08)	0.028689	0.030909
Absolute Change at 24 Months after Intervention 1	-0.002317	(-0.003031, -0.001603)	0.028713	0.031030
Relative Change (%) at 24 Months after Intervention 1	-7.47	(-9.65, -5.28)	0.028713	0.031030
Absolute Change at 25 Months after Intervention 1	-0.002413	(-0.003157, -0.001669)	0.028736	0.031150
Relative Change (%) at 25 Months after Intervention 1	-7.75	(-10.01, -5.48)	0.028736	0.031150
Absolute Change at 26 Months after Intervention 1	-0.002510	(-0.003284, -0.001736)	0.028760	0.031270
Relative Change (%) at 26 Months after Intervention 1	-8.03	(-10.37, -5.68)	0.028760	0.031270
Absolute Change at 27 Months after Intervention 1	-0.002606	(-0.003410, -0.001803)	0.028784	0.031390
Relative Change (%) at 27 Months after Intervention 1	-8.30	(-10.73, -5.88)	0.028784	0.031390
Absolute Change at 27 Months after Intervention 1	-0.002606	(-0.003410, -0.001803)	0.028784	0.031390
Relative Change (%) at 27 Months after Intervention 1	-8.30	(-10.73, -5.88)	0.028784	0.031390

¹The 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 Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020¹



¹The 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 61. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 59)²			
Intercept	0.154877	(0.154252, 0.155503)	<.001
Baseline trend	-0.000241	(-0.000266, -0.000215)	<.001
Level Change (After Intervention 1)	-0.002233	(-0.003349, -0.001118)	<.001
Trend Change (After Intervention 1)	-0.000091	(-0.000150, -0.000033)	0.003
Most Parsimonious Final Model Parameters (df = 59)^{2,3}			
Intercept	0.154877	(0.154252, 0.155503)	<.001
Baseline trend	-0.000241	(-0.000266, -0.000215)	<.001
Level Change (After Intervention 1)	-0.002233	(-0.003349, -0.001118)	<.001
Trend Change (After Intervention 1)	-0.000091	(-0.000150, -0.000033)	0.003

¹The 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.

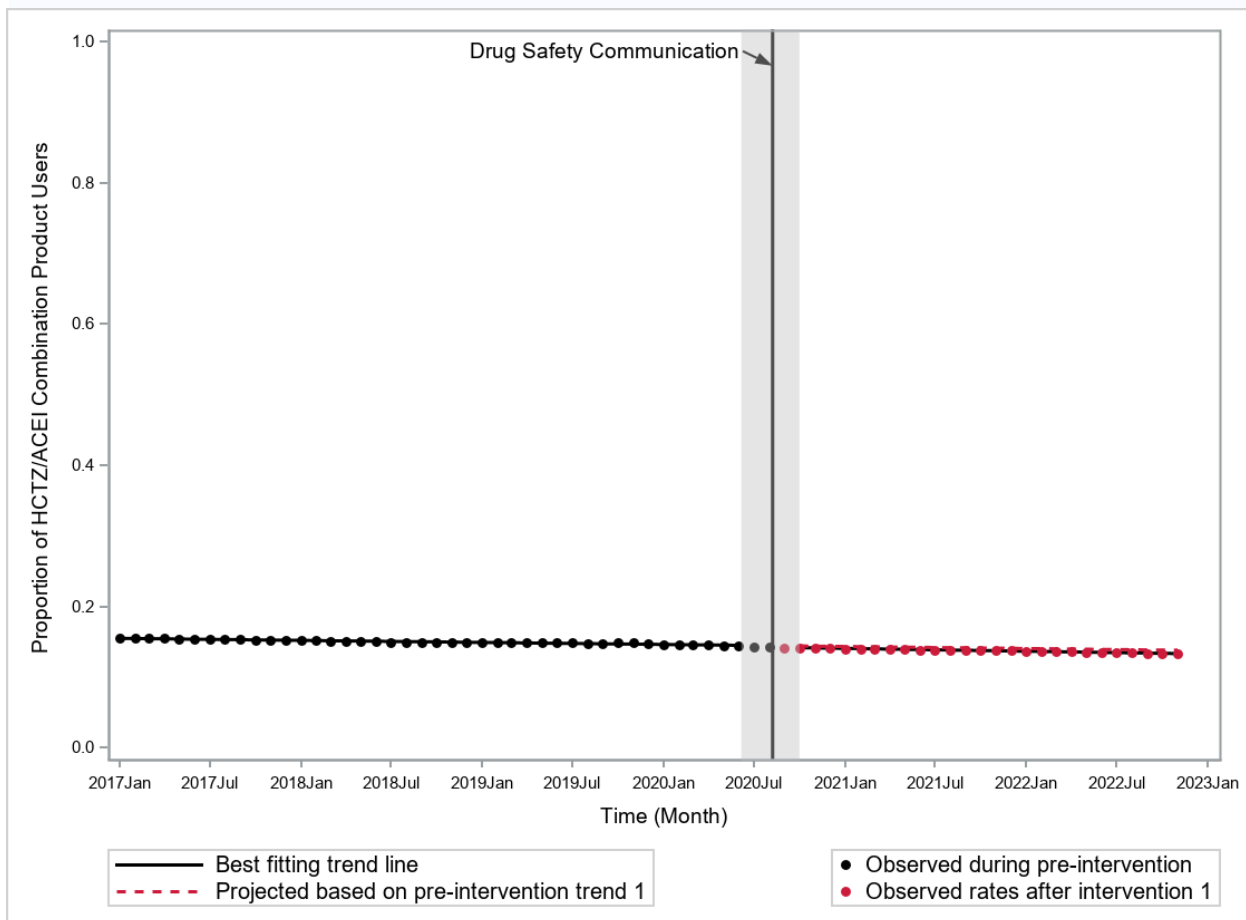
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 62. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.002416	(-0.003598, -0.001233)	0.141398	0.143814
Relative Change (%) at 2 Months after Intervention 1	-1.68	(-2.50, -0.86)	0.141398	0.143814
Absolute Change at 3 Months after Intervention 1	-0.002507	(-0.003669, -0.001346)	0.141067	0.143574
Relative Change (%) at 3 Months after Intervention 1	-1.75	(-2.55, -0.94)	0.141067	0.143574
Absolute Change at 4 Months after Intervention 1	-0.002598	(-0.003741, -0.001455)	0.140735	0.143333
Relative Change (%) at 4 Months after Intervention 1	-1.81	(-2.60, -1.02)	0.140735	0.143333
Absolute Change at 5 Months after Intervention 1	-0.002690	(-0.003817, -0.001562)	0.140403	0.143093
Relative Change (%) at 5 Months after Intervention 1	-1.88	(-2.66, -1.10)	0.140403	0.143093
Absolute Change at 6 Months after Intervention 1	-0.002781	(-0.003896, -0.001666)	0.140071	0.142852
Relative Change (%) at 6 Months after Intervention 1	-1.95	(-2.72, -1.18)	0.140071	0.142852
Absolute Change at 7 Months after Intervention 1	-0.002872	(-0.003977, -0.001767)	0.139740	0.142612
Relative Change (%) at 7 Months after Intervention 1	-2.01	(-2.78, -1.25)	0.139740	0.142612
Absolute Change at 8 Months after Intervention 1	-0.002963	(-0.004061, -0.001866)	0.139408	0.142371
Relative Change (%) at 8 Months after Intervention 1	-2.08	(-2.84, -1.32)	0.139408	0.142371
Absolute Change at 9 Months after Intervention 1	-0.003055	(-0.004149, -0.001961)	0.139076	0.142131
Relative Change (%) at 9 Months after Intervention 1	-2.15	(-2.91, -1.39)	0.139076	0.142131
Absolute Change at 10 Months after Intervention 1	-0.003146	(-0.004239, -0.002053)	0.138744	0.141890
Relative Change (%) at 10 Months after Intervention 1	-2.22	(-2.97, -1.46)	0.138744	0.141890
Absolute Change at 11 Months after Intervention 1	-0.003237	(-0.004333, -0.002141)	0.138412	0.141650
Relative Change (%) at 11 Months after Intervention 1	-2.29	(-3.05, -1.53)	0.138412	0.141650
Absolute Change at 12 Months after Intervention 1	-0.003328	(-0.004430, -0.002227)	0.138081	0.141409
Relative Change (%) at 12 Months after Intervention 1	-2.35	(-3.12, -1.59)	0.138081	0.141409
Absolute Change at 13 Months after Intervention 1	-0.003420	(-0.004530, -0.002310)	0.137749	0.141169
Relative Change (%) at 13 Months after Intervention 1	-2.42	(-3.19, -1.65)	0.137749	0.141169
Absolute Change at 14 Months after Intervention 1	-0.003511	(-0.004632, -0.002390)	0.137417	0.140928
Relative Change (%) at 14 Months after Intervention 1	-2.49	(-3.27, -1.71)	0.137417	0.140928
Absolute Change at 15 Months after Intervention 1	-0.003602	(-0.004738, -0.002466)	0.137085	0.140688
Relative Change (%) at 15 Months after Intervention 1	-2.56	(-3.35, -1.77)	0.137085	0.140688
Absolute Change at 16 Months after Intervention 1	-0.003693	(-0.004847, -0.002540)	0.136754	0.140447
Relative Change (%) at 16 Months after Intervention 1	-2.63	(-3.43, -1.83)	0.136754	0.140447
Absolute Change at 17 Months after Intervention 1	-0.003785	(-0.004958, -0.002612)	0.136422	0.140207
Relative Change (%) at 17 Months after Intervention 1	-2.70	(-3.52, -1.88)	0.136422	0.140207
Absolute Change at 18 Months after Intervention 1	-0.003876	(-0.005071, -0.002681)	0.136090	0.139966
Relative Change (%) at 18 Months after Intervention 1	-2.77	(-3.60, -1.94)	0.136090	0.139966
Absolute Change at 19 Months after Intervention 1	-0.003967	(-0.005187, -0.002747)	0.135758	0.139726
Relative Change (%) at 19 Months after Intervention 1	-2.84	(-3.69, -1.99)	0.135758	0.139726
Absolute Change at 20 Months after Intervention 1	-0.004059	(-0.005305, -0.002812)	0.135427	0.139485
Relative Change (%) at 20 Months after Intervention 1	-2.91	(-3.78, -2.04)	0.135427	0.139485
Absolute Change at 21 Months after Intervention 1	-0.004150	(-0.005426, -0.002874)	0.135095	0.139245
Relative Change (%) at 21 Months after Intervention 1	-2.98	(-3.87, -2.09)	0.135095	0.139245
Absolute Change at 22 Months after Intervention 1	-0.004241	(-0.005548, -0.002934)	0.134763	0.139004
Relative Change (%) at 22 Months after Intervention 1	-3.05	(-3.97, -2.13)	0.134763	0.139004
Absolute Change at 23 Months after Intervention 1	-0.004332	(-0.005672, -0.002992)	0.134431	0.138764
Relative Change (%) at 23 Months after Intervention 1	-3.12	(-4.06, -2.18)	0.134431	0.138764
Absolute Change at 24 Months after Intervention 1	-0.004424	(-0.005798, -0.003049)	0.134100	0.138523
Relative Change (%) at 24 Months after Intervention 1	-3.19	(-4.16, -2.23)	0.134100	0.138523
Absolute Change at 25 Months after Intervention 1	-0.004515	(-0.005925, -0.003104)	0.133768	0.138283
Relative Change (%) at 25 Months after Intervention 1	-3.26	(-4.26, -2.27)	0.133768	0.138283
Absolute Change at 26 Months after Intervention 1	-0.004606	(-0.006054, -0.003158)	0.133436	0.138042
Relative Change (%) at 26 Months after Intervention 1	-3.34	(-4.36, -2.31)	0.133436	0.138042
Absolute Change at 27 Months after Intervention 1	-0.004697	(-0.006184, -0.003210)	0.133104	0.137802
Relative Change (%) at 27 Months after Intervention 1	-3.41	(-4.46, -2.36)	0.133104	0.137802
Absolute Change at 27 Months after Intervention 1	-0.004697	(-0.006184, -0.003210)	0.133104	0.137802
Relative Change (%) at 27 Months after Intervention 1	-3.41	(-4.46, -2.36)	0.133104	0.137802

¹The 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.

Figure 31. 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 with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 63. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.004429	(0.004151, 0.004706)	<.001
Baseline trend	-0.000032	(-0.000043, -0.000022)	<.001
Level Change (After Intervention 1)	0.000053	(-0.000171, 0.000278)	0.636
Trend Change (After Intervention 1)	-0.000001	(-0.000025, 0.000024)	0.965
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.004420	(0.004203, 0.004637)	<.001
Baseline trend	-0.000031	(-0.000037, -0.000026)	<.001

¹The 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.

²Maximum 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.

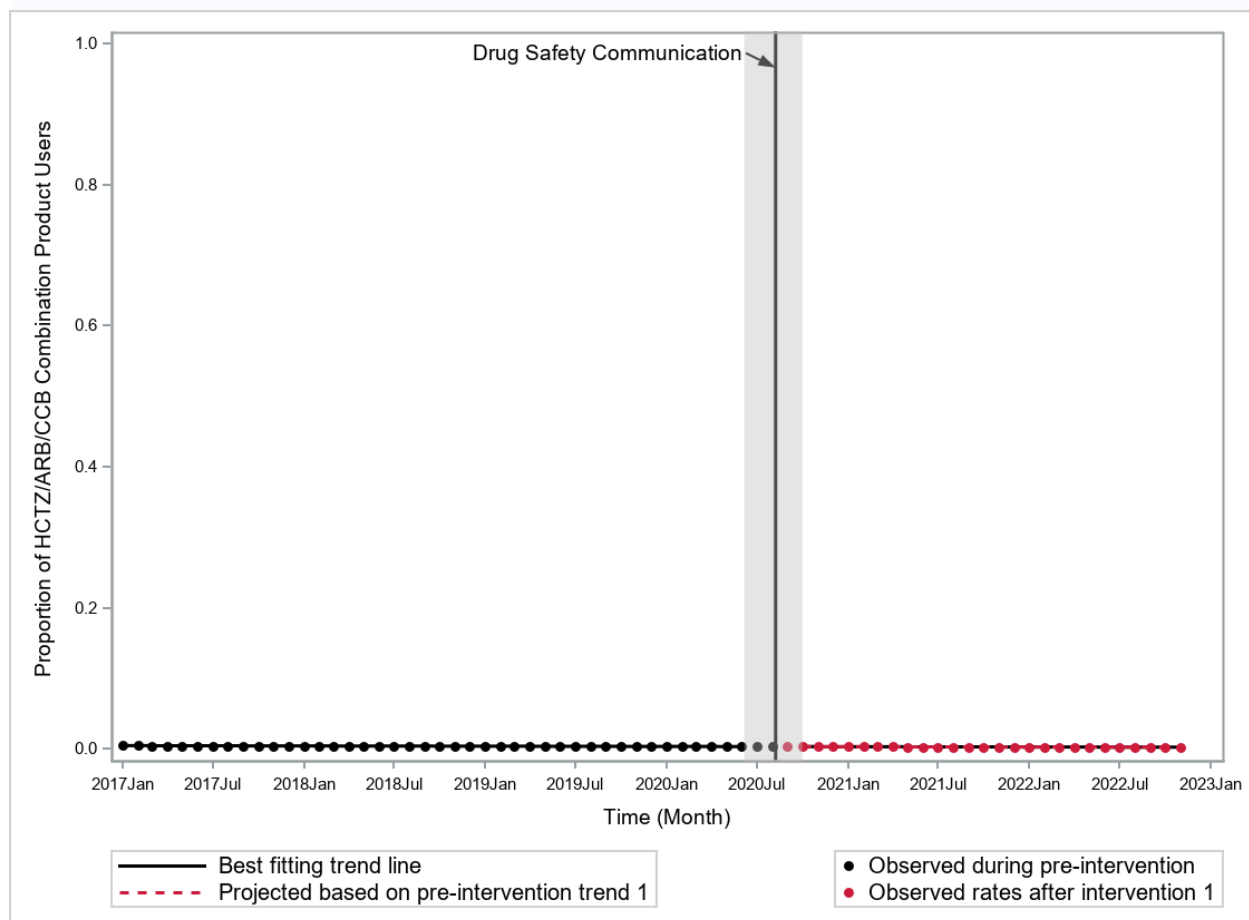
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table b4. 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 with History of Skin Cancer after August 8, 2020¹ 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	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)	0.002975	0.002975
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.002975	0.002975
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002944	0.002944
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.002944	0.002944
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002912	0.002912
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.002912	0.002912
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002881	0.002881
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.002881	0.002881
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002849	0.002849
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.002849	0.002849
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002818	0.002818
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.002818	0.002818
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002787	0.002787
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.002787	0.002787
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002755	0.002755
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.002755	0.002755
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002724	0.002724
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.002724	0.002724
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002692	0.002692
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.002692	0.002692
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002661	0.002661
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.002661	0.002661
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002630	0.002630
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.002630	0.002630
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002598	0.002598
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.002598	0.002598
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002567	0.002567
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.002567	0.002567
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002535	0.002535
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.002535	0.002535
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002504	0.002504
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.002504	0.002504
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002472	0.002472
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.002472	0.002472
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002441	0.002441
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.002441	0.002441
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002410	0.002410
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.002410	0.002410
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002378	0.002378
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.002378	0.002378
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002347	0.002347
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.002347	0.002347
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002315	0.002315
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.002315	0.002315
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002284	0.002284
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.002284	0.002284
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002253	0.002253
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.002253	0.002253
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002221	0.002221
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.002221	0.002221
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.002190	0.002190
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.002190	0.002190

¹The 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.

Figure 32. 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 with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 65. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 60)²			
Intercept	0.260376	(0.247175, 0.273577)	<.001
Baseline trend	-0.001578	(-0.002082, -0.001073)	<.001
Level Change (After Intervention 1)	-0.001091	(-0.009860, 0.007679)	0.804
Trend Change (After Intervention 1)	0.001418	(0.000152, 0.002684)	0.029
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.258175	(0.242386, 0.273963)	<.001
Baseline trend	-0.001524	(-0.002102, -0.000946)	<.001
Trend Change (After Intervention 1)	0.001373	(-0.000033, 0.002779)	0.056

¹The 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.

²Maximum 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.

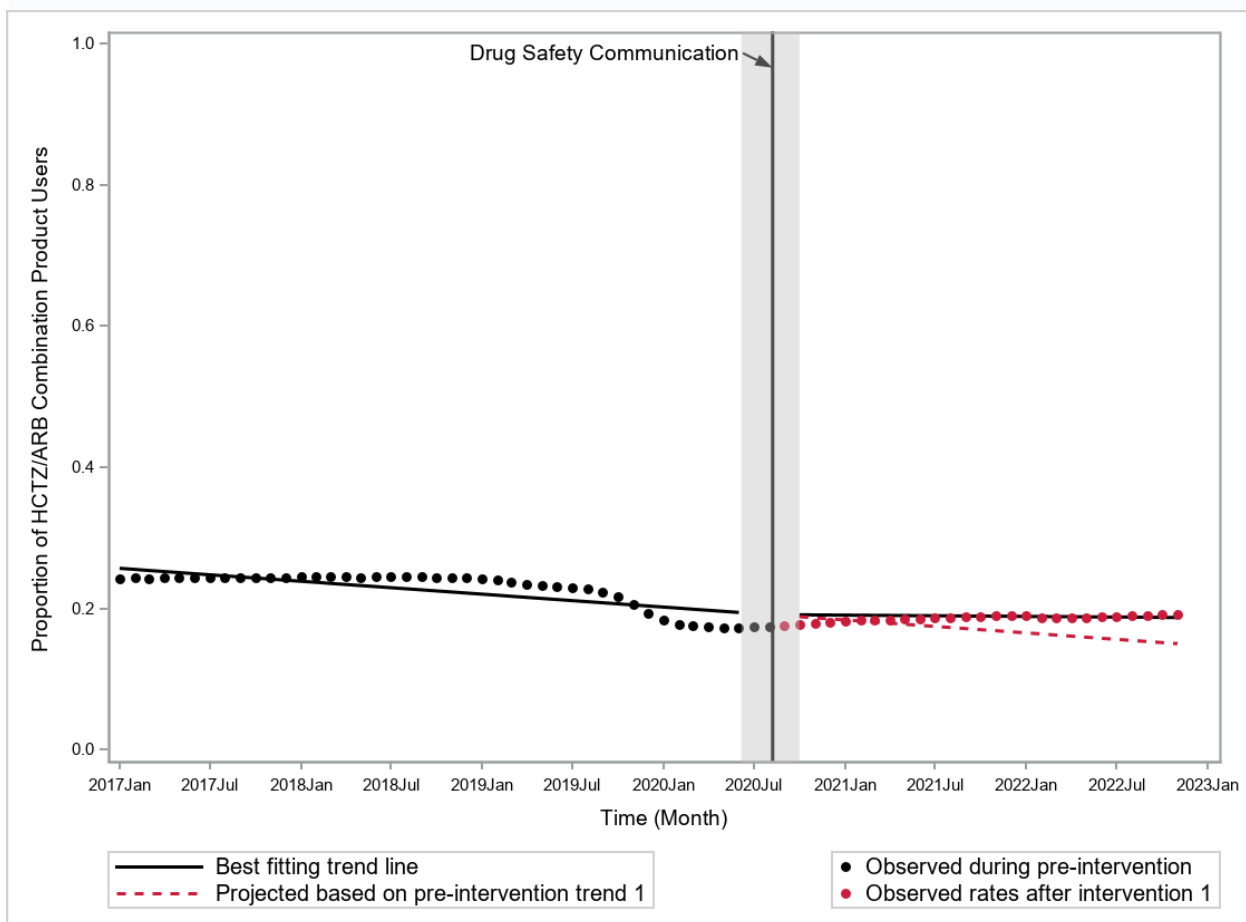
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 66. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.002746	(-0.000136, 0.005628)	0.190811	0.188066
Relative Change (%) at 2 Months after Intervention 1	1.46	(-0.18, 3.10)	0.190811	0.188066
Absolute Change at 3 Months after Intervention 1	0.004119	(-0.000204, 0.008442)	0.190660	0.186541
Relative Change (%) at 3 Months after Intervention 1	2.21	(-0.28, 4.69)	0.190660	0.186541
Absolute Change at 4 Months after Intervention 1	0.005492	(-0.000272, 0.011256)	0.190509	0.185017
Relative Change (%) at 4 Months after Intervention 1	2.97	(-0.38, 6.32)	0.190509	0.185017
Absolute Change at 5 Months after Intervention 1	0.006865	(-0.000340, 0.014070)	0.190358	0.183493
Relative Change (%) at 5 Months after Intervention 1	3.74	(-0.50, 7.98)	0.190358	0.183493
Absolute Change at 6 Months after Intervention 1	0.008238	(-0.000408, 0.016884)	0.190207	0.181969
Relative Change (%) at 6 Months after Intervention 1	4.53	(-0.62, 9.67)	0.190207	0.181969
Absolute Change at 7 Months after Intervention 1	0.009611	(-0.000476, 0.019698)	0.190056	0.180445
Relative Change (%) at 7 Months after Intervention 1	5.33	(-0.74, 11.40)	0.190056	0.180445
Absolute Change at 8 Months after Intervention 1	0.010984	(-0.000545, 0.022512)	0.189905	0.178921
Relative Change (%) at 8 Months after Intervention 1	6.14	(-0.88, 13.16)	0.189905	0.178921
Absolute Change at 9 Months after Intervention 1	0.012357	(-0.000613, 0.025326)	0.189753	0.177397
Relative Change (%) at 9 Months after Intervention 1	6.97	(-1.02, 14.96)	0.189753	0.177397
Absolute Change at 10 Months after Intervention 1	0.013730	(-0.000681, 0.028140)	0.189602	0.175873
Relative Change (%) at 10 Months after Intervention 1	7.81	(-1.18, 16.79)	0.189602	0.175873
Absolute Change at 11 Months after Intervention 1	0.015103	(-0.000749, 0.030954)	0.189451	0.174349
Relative Change (%) at 11 Months after Intervention 1	8.66	(-1.34, 18.66)	0.189451	0.174349
Absolute Change at 12 Months after Intervention 1	0.016476	(-0.000817, 0.033768)	0.189300	0.172824
Relative Change (%) at 12 Months after Intervention 1	9.53	(-1.51, 20.58)	0.189300	0.172824
Absolute Change at 13 Months after Intervention 1	0.017848	(-0.000885, 0.036582)	0.189149	0.171300
Relative Change (%) at 13 Months after Intervention 1	10.42	(-1.69, 22.53)	0.189149	0.171300
Absolute Change at 14 Months after Intervention 1	0.019221	(-0.000953, 0.039396)	0.188998	0.169776
Relative Change (%) at 14 Months after Intervention 1	11.32	(-1.88, 24.53)	0.188998	0.169776
Absolute Change at 15 Months after Intervention 1	0.020594	(-0.001021, 0.042210)	0.188847	0.168252
Relative Change (%) at 15 Months after Intervention 1	12.24	(-2.08, 26.57)	0.188847	0.168252
Absolute Change at 16 Months after Intervention 1	0.021967	(-0.001089, 0.045024)	0.188695	0.166728
Relative Change (%) at 16 Months after Intervention 1	13.18	(-2.30, 28.65)	0.188695	0.166728
Absolute Change at 17 Months after Intervention 1	0.023340	(-0.001157, 0.047838)	0.188544	0.165204
Relative Change (%) at 17 Months after Intervention 1	14.13	(-2.52, 30.78)	0.188544	0.165204
Absolute Change at 18 Months after Intervention 1	0.024713	(-0.001225, 0.050652)	0.188393	0.163680
Relative Change (%) at 18 Months after Intervention 1	15.10	(-2.76, 32.96)	0.188393	0.163680
Absolute Change at 19 Months after Intervention 1	0.026086	(-0.001293, 0.053466)	0.188242	0.162156
Relative Change (%) at 19 Months after Intervention 1	16.09	(-3.01, 35.19)	0.188242	0.162156
Absolute Change at 20 Months after Intervention 1	0.027459	(-0.001361, 0.056280)	0.188091	0.160632
Relative Change (%) at 20 Months after Intervention 1	17.09	(-3.28, 37.47)	0.188091	0.160632
Absolute Change at 21 Months after Intervention 1	0.028832	(-0.001429, 0.059094)	0.187940	0.159107
Relative Change (%) at 21 Months after Intervention 1	18.12	(-3.56, 39.80)	0.187940	0.159107
Absolute Change at 22 Months after Intervention 1	0.030205	(-0.001497, 0.061908)	0.187788	0.157583
Relative Change (%) at 22 Months after Intervention 1	19.17	(-3.86, 42.19)	0.187788	0.157583
Absolute Change at 23 Months after Intervention 1	0.031578	(-0.001565, 0.064722)	0.187637	0.156059
Relative Change (%) at 23 Months after Intervention 1	20.23	(-4.17, 44.64)	0.187637	0.156059
Absolute Change at 24 Months after Intervention 1	0.032951	(-0.001634, 0.067536)	0.187486	0.154535
Relative Change (%) at 24 Months after Intervention 1	21.32	(-4.49, 47.14)	0.187486	0.154535
Absolute Change at 25 Months after Intervention 1	0.034324	(-0.001702, 0.070350)	0.187335	0.153011
Relative Change (%) at 25 Months after Intervention 1	22.43	(-4.84, 49.70)	0.187335	0.153011
Absolute Change at 26 Months after Intervention 1	0.035697	(-0.001770, 0.073164)	0.187184	0.151487
Relative Change (%) at 26 Months after Intervention 1	23.56	(-5.20, 52.33)	0.187184	0.151487
Absolute Change at 27 Months after Intervention 1	0.037070	(-0.001838, 0.075978)	0.187033	0.149963
Relative Change (%) at 27 Months after Intervention 1	24.72	(-5.59, 55.02)	0.187033	0.149963
Absolute Change at 27 Months after Intervention 1	0.037070	(-0.001838, 0.075978)	0.187033	0.149963
Relative Change (%) at 27 Months after Intervention 1	24.72	(-5.59, 55.02)	0.187033	0.149963

¹The 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.

Figure 1. 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 with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 67. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.020325	(0.020247, 0.020403)	<.001
Baseline trend	-0.000067	(-0.000070, -0.000063)	<.001
Level Change (After Intervention 1)	-0.000093	(-0.000234, 0.000048)	0.193
Trend Change (After Intervention 1)	0.000009	(0.000002, 0.000016)	0.016
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.020325	(0.020247, 0.020403)	<.001
Baseline trend	-0.000067	(-0.000070, -0.000063)	<.001
Level Change (After Intervention 1)	-0.000093	(-0.000234, 0.000048)	0.193
Trend Change (After Intervention 1)	0.000009	(0.000002, 0.000016)	0.016

¹The 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.

²Maximum 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.

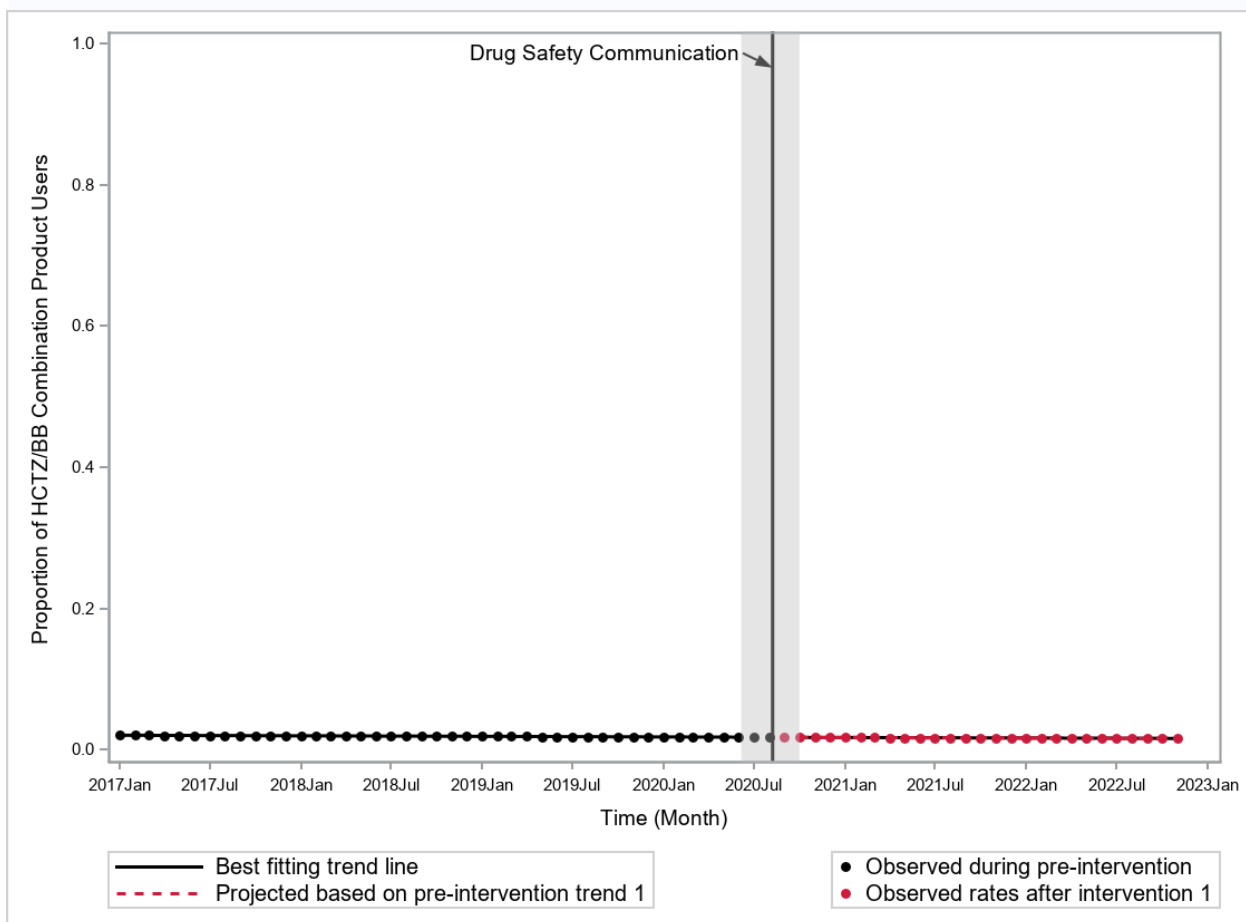
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 68. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.000075	(-0.000209, 0.000058)	0.017190	0.017265
Relative Change (%) at 2 Months after Intervention 1	-0.44	(-1.21, 0.34)	0.017190	0.017265
Absolute Change at 3 Months after Intervention 1	-0.000067	(-0.000198, 0.000065)	0.017132	0.017199
Relative Change (%) at 3 Months after Intervention 1	-0.39	(-1.15, 0.37)	0.017132	0.017199
Absolute Change at 4 Months after Intervention 1	-0.000058	(-0.000187, 0.000072)	0.017074	0.017132
Relative Change (%) at 4 Months after Intervention 1	-0.34	(-1.09, 0.42)	0.017074	0.017132
Absolute Change at 5 Months after Intervention 1	-0.000049	(-0.000177, 0.000079)	0.017017	0.017066
Relative Change (%) at 5 Months after Intervention 1	-0.29	(-1.03, 0.46)	0.017017	0.017066
Absolute Change at 6 Months after Intervention 1	-0.000040	(-0.000167, 0.000086)	0.016959	0.016999
Relative Change (%) at 6 Months after Intervention 1	-0.24	(-0.98, 0.51)	0.016959	0.016999
Absolute Change at 7 Months after Intervention 1	-0.000031	(-0.000157, 0.000094)	0.016901	0.016933
Relative Change (%) at 7 Months after Intervention 1	-0.18	(-0.93, 0.56)	0.016901	0.016933
Absolute Change at 8 Months after Intervention 1	-0.000022	(-0.000148, 0.000103)	0.016844	0.016866
Relative Change (%) at 8 Months after Intervention 1	-0.13	(-0.87, 0.61)	0.016844	0.016866
Absolute Change at 9 Months after Intervention 1	-0.000014	(-0.000139, 0.000112)	0.016786	0.016800
Relative Change (%) at 9 Months after Intervention 1	-0.08	(-0.83, 0.66)	0.016786	0.016800
Absolute Change at 10 Months after Intervention 1	-0.000005	(-0.000130, 0.000121)	0.016728	0.016733
Relative Change (%) at 10 Months after Intervention 1	-0.03	(-0.78, 0.72)	0.016728	0.016733
Absolute Change at 11 Months after Intervention 1	0.000004	(-0.000122, 0.000130)	0.016671	0.016667
Relative Change (%) at 11 Months after Intervention 1	0.02	(-0.73, 0.78)	0.016671	0.016667
Absolute Change at 12 Months after Intervention 1	0.000013	(-0.000115, 0.000140)	0.016613	0.016600
Relative Change (%) at 12 Months after Intervention 1	0.08	(-0.69, 0.85)	0.016613	0.016600
Absolute Change at 13 Months after Intervention 1	0.000022	(-0.000107, 0.000151)	0.016555	0.016534
Relative Change (%) at 13 Months after Intervention 1	0.13	(-0.65, 0.91)	0.016555	0.016534
Absolute Change at 14 Months after Intervention 1	0.000031	(-0.000100, 0.000161)	0.016498	0.016467
Relative Change (%) at 14 Months after Intervention 1	0.19	(-0.61, 0.98)	0.016498	0.016467
Absolute Change at 15 Months after Intervention 1	0.000039	(-0.000094, 0.000172)	0.016440	0.016401
Relative Change (%) at 15 Months after Intervention 1	0.24	(-0.57, 1.05)	0.016440	0.016401
Absolute Change at 16 Months after Intervention 1	0.000048	(-0.000087, 0.000184)	0.016382	0.016334
Relative Change (%) at 16 Months after Intervention 1	0.30	(-0.54, 1.13)	0.016382	0.016334
Absolute Change at 17 Months after Intervention 1	0.000057	(-0.000081, 0.000195)	0.016325	0.016268
Relative Change (%) at 17 Months after Intervention 1	0.35	(-0.50, 1.20)	0.016325	0.016268
Absolute Change at 18 Months after Intervention 1	0.000066	(-0.000076, 0.000207)	0.016267	0.016201
Relative Change (%) at 18 Months after Intervention 1	0.41	(-0.47, 1.28)	0.016267	0.016201
Absolute Change at 19 Months after Intervention 1	0.000075	(-0.000070, 0.000220)	0.016209	0.016134
Relative Change (%) at 19 Months after Intervention 1	0.46	(-0.44, 1.36)	0.016209	0.016134
Absolute Change at 20 Months after Intervention 1	0.000084	(-0.000065, 0.000232)	0.016152	0.016068
Relative Change (%) at 20 Months after Intervention 1	0.52	(-0.41, 1.45)	0.016152	0.016068
Absolute Change at 21 Months after Intervention 1	0.000092	(-0.000060, 0.000245)	0.016094	0.016001
Relative Change (%) at 21 Months after Intervention 1	0.58	(-0.38, 1.53)	0.016094	0.016001
Absolute Change at 22 Months after Intervention 1	0.000101	(-0.000055, 0.000258)	0.016036	0.015935
Relative Change (%) at 22 Months after Intervention 1	0.64	(-0.35, 1.62)	0.016036	0.015935
Absolute Change at 23 Months after Intervention 1	0.000110	(-0.000051, 0.000271)	0.015979	0.015868
Relative Change (%) at 23 Months after Intervention 1	0.69	(-0.33, 1.71)	0.015979	0.015868
Absolute Change at 24 Months after Intervention 1	0.000119	(-0.000046, 0.000284)	0.015921	0.015802
Relative Change (%) at 24 Months after Intervention 1	0.75	(-0.30, 1.81)	0.015921	0.015802
Absolute Change at 25 Months after Intervention 1	0.000128	(-0.000042, 0.000298)	0.015863	0.015735
Relative Change (%) at 25 Months after Intervention 1	0.81	(-0.28, 1.90)	0.015863	0.015735
Absolute Change at 26 Months after Intervention 1	0.000137	(-0.000038, 0.000311)	0.015805	0.015669
Relative Change (%) at 26 Months after Intervention 1	0.87	(-0.25, 1.99)	0.015805	0.015669
Absolute Change at 27 Months after Intervention 1	0.000145	(-0.000034, 0.000325)	0.015748	0.015602
Relative Change (%) at 27 Months after Intervention 1	0.93	(-0.23, 2.09)	0.015748	0.015602
Absolute Change at 27 Months after Intervention 1	0.000145	(-0.000034, 0.000325)	0.015748	0.015602
Relative Change (%) at 27 Months after Intervention 1	0.93	(-0.23, 2.09)	0.015748	0.015602

¹The 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.

Figure 34. Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 69. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.000044	(0.000038, 0.000050)	<.001
Baseline trend	-0.000001	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000014	(-0.000021, -0.000007)	<.001
Trend Change (After Intervention 1)	0.000000	(-0.000001, 0.000001)	0.728
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.000043	(0.000039, 0.000048)	<.001
Baseline trend	-0.000000	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000014	(-0.000020, -0.000007)	<.001

¹The 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.

²Maximum 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.

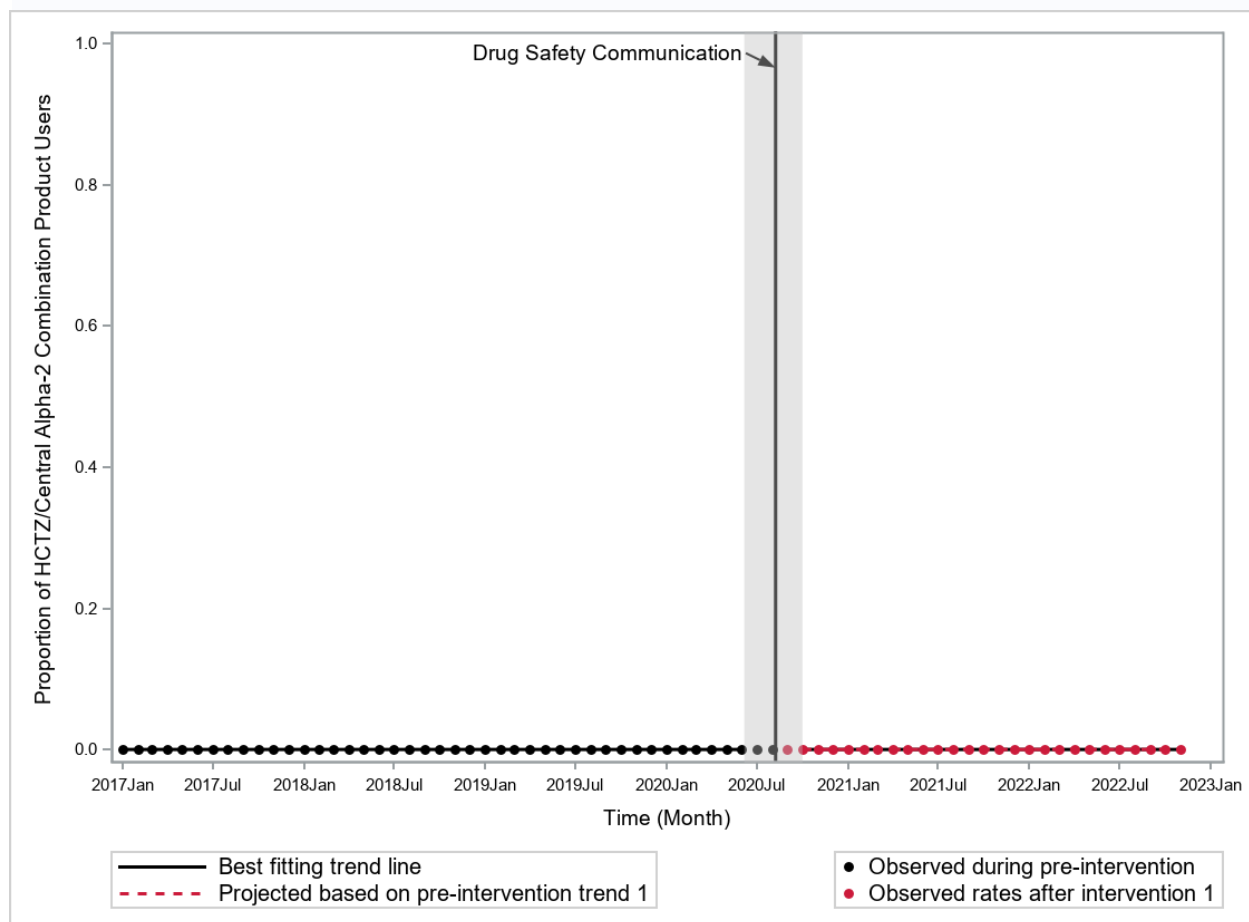
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 70. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.000014	(-0.000021, -0.000006)	0.000007	0.000021
Relative Change (%) at 2 Months after Intervention 1	-64.95	(-88.06, -41.85)	0.000007	0.000021
Absolute Change at 3 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000007	0.000021
Relative Change (%) at 3 Months after Intervention 1	-66.49	(-89.48, -43.50)	0.000007	0.000021
Absolute Change at 4 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000006	0.000020
Relative Change (%) at 4 Months after Intervention 1	-68.10	(-90.96, -45.24)	0.000006	0.000020
Absolute Change at 5 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000006	0.000020
Relative Change (%) at 5 Months after Intervention 1	-69.79	(-92.51, -47.07)	0.000006	0.000020
Absolute Change at 6 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000005	0.000019
Relative Change (%) at 6 Months after Intervention 1	-71.57	(-94.12, -49.01)	0.000005	0.000019
Absolute Change at 7 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000005	0.000019
Relative Change (%) at 7 Months after Intervention 1	-73.44	(-95.82, -51.05)	0.000005	0.000019
Absolute Change at 8 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000004	0.000018
Relative Change (%) at 8 Months after Intervention 1	-75.41	(-97.61, -53.20)	0.000004	0.000018
Absolute Change at 9 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000004	0.000018
Relative Change (%) at 9 Months after Intervention 1	-77.48	(-99.52, -55.45)	0.000004	0.000018
Absolute Change at 10 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000003	0.000017
Relative Change (%) at 10 Months after Intervention 1	-79.68	(-101.57, -57.79)	0.000003	0.000017
Absolute Change at 11 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000003	0.000017
Relative Change (%) at 11 Months after Intervention 1	-82.00	(-103.78, -60.22)	0.000003	0.000017
Absolute Change at 12 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000003	0.000016
Relative Change (%) at 12 Months after Intervention 1	-84.46	(-106.21, -62.72)	0.000003	0.000016
Absolute Change at 13 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000002	0.000016
Relative Change (%) at 13 Months after Intervention 1	-87.08	(-108.90, -65.26)	0.000002	0.000016
Absolute Change at 14 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000002	0.000015
Relative Change (%) at 14 Months after Intervention 1	-89.86	(-111.92, -67.80)	0.000002	0.000015
Absolute Change at 15 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000001	0.000015
Relative Change (%) at 15 Months after Intervention 1	-92.83	(-115.37, -70.29)	0.000001	0.000015
Absolute Change at 16 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000001	0.000014
Relative Change (%) at 16 Months after Intervention 1	-96.00	(-119.33, -72.67)	0.000001	0.000014
Absolute Change at 17 Months after Intervention 1	-0.000014	(-0.000021, -0.000006)	0.000000	0.000014
Relative Change (%) at 17 Months after Intervention 1	-99.39	(-123.93, -74.85)	0.000000	0.000014
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
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
Relative Change (%) at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 28 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 28 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A

¹The 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.

Figure 35. 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 with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 71. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 57)²			
Intercept	0.329995	(0.328969, 0.331022)	<.001
Baseline trend	-0.000841	(-0.000881, -0.000802)	<.001
Level Change (After Intervention 1)	0.000321	(-0.000995, 0.001636)	0.627
Trend Change (After Intervention 1)	0.000130	(0.000032, 0.000227)	0.010
Most Parsimonious Final Model Parameters (df = 58)^{2,3}			
Intercept	0.329944	(0.328922, 0.330966)	<.001
Baseline trend	-0.000838	(-0.000875, -0.000801)	<.001
Trend Change (After Intervention 1)	0.000138	(0.000043, 0.000234)	0.005

¹The 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.

²Maximum 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.

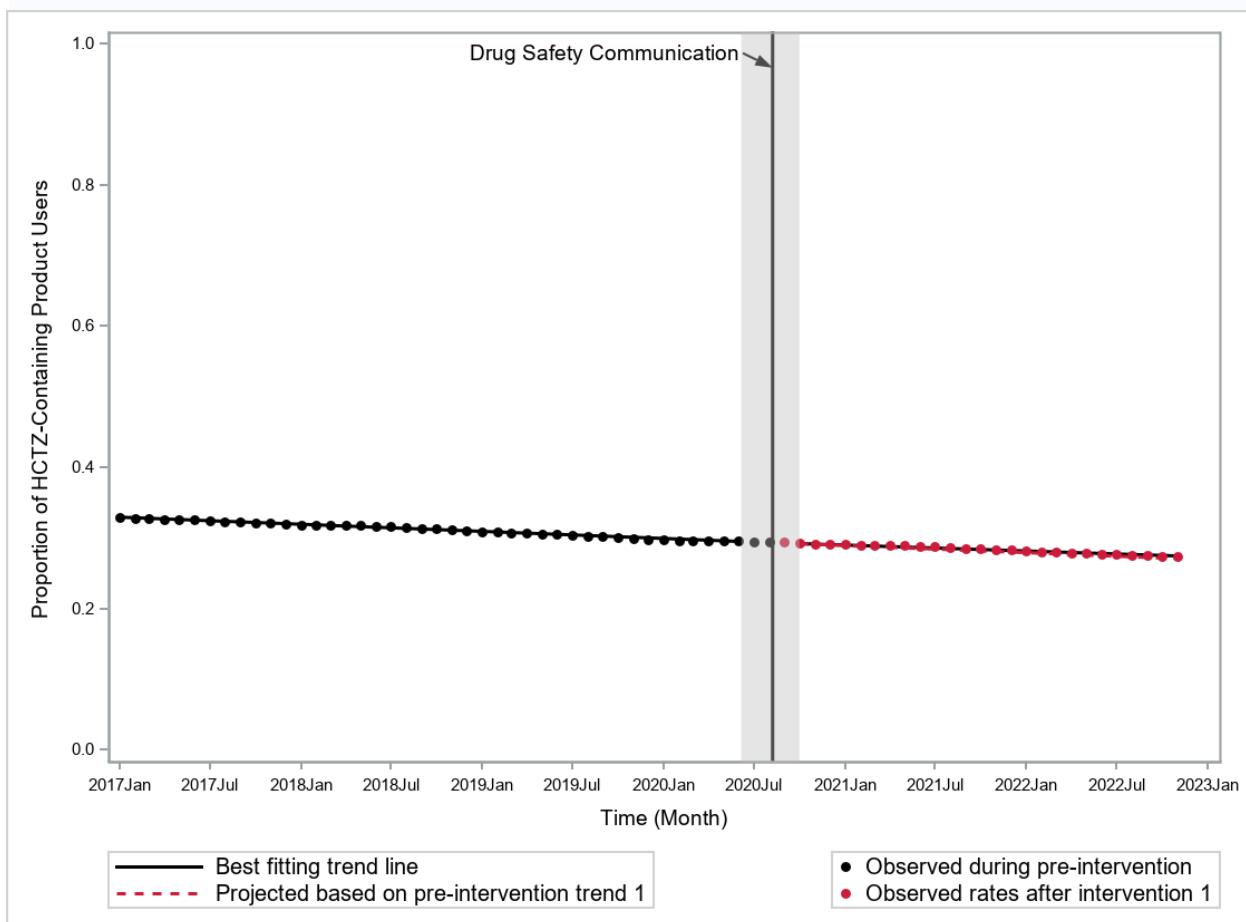
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 72. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.000276	(0.000068, 0.000485)	0.291678	0.291401
Relative Change (%) at 2 Months after Intervention 1	0.09	(0.02, 0.17)	0.291678	0.291401
Absolute Change at 3 Months after Intervention 1	0.000415	(0.000102, 0.000727)	0.290978	0.290563
Relative Change (%) at 3 Months after Intervention 1	0.14	(0.03, 0.25)	0.290978	0.290563
Absolute Change at 4 Months after Intervention 1	0.000553	(0.000136, 0.000970)	0.290278	0.289725
Relative Change (%) at 4 Months after Intervention 1	0.19	(0.05, 0.34)	0.290278	0.289725
Absolute Change at 5 Months after Intervention 1	0.000691	(0.000170, 0.001212)	0.289579	0.288887
Relative Change (%) at 5 Months after Intervention 1	0.24	(0.06, 0.42)	0.289579	0.288887
Absolute Change at 6 Months after Intervention 1	0.000829	(0.000204, 0.001455)	0.288879	0.288050
Relative Change (%) at 6 Months after Intervention 1	0.29	(0.07, 0.51)	0.288879	0.288050
Absolute Change at 7 Months after Intervention 1	0.000968	(0.000238, 0.001697)	0.288179	0.287212
Relative Change (%) at 7 Months after Intervention 1	0.34	(0.08, 0.59)	0.288179	0.287212
Absolute Change at 8 Months after Intervention 1	0.001106	(0.000272, 0.001940)	0.287480	0.286374
Relative Change (%) at 8 Months after Intervention 1	0.39	(0.09, 0.68)	0.287480	0.286374
Absolute Change at 9 Months after Intervention 1	0.001244	(0.000306, 0.002182)	0.286780	0.285536
Relative Change (%) at 9 Months after Intervention 1	0.44	(0.11, 0.77)	0.286780	0.285536
Absolute Change at 10 Months after Intervention 1	0.001382	(0.000340, 0.002425)	0.286081	0.284698
Relative Change (%) at 10 Months after Intervention 1	0.49	(0.12, 0.85)	0.286081	0.284698
Absolute Change at 11 Months after Intervention 1	0.001521	(0.000374, 0.002667)	0.285381	0.283860
Relative Change (%) at 11 Months after Intervention 1	0.54	(0.13, 0.94)	0.285381	0.283860
Absolute Change at 12 Months after Intervention 1	0.001659	(0.000408, 0.002910)	0.284681	0.283022
Relative Change (%) at 12 Months after Intervention 1	0.59	(0.14, 1.03)	0.284681	0.283022
Absolute Change at 13 Months after Intervention 1	0.001797	(0.000442, 0.003152)	0.283982	0.282184
Relative Change (%) at 13 Months after Intervention 1	0.64	(0.15, 1.12)	0.283982	0.282184
Absolute Change at 14 Months after Intervention 1	0.001935	(0.000476, 0.003394)	0.283282	0.281347
Relative Change (%) at 14 Months after Intervention 1	0.69	(0.17, 1.21)	0.283282	0.281347
Absolute Change at 15 Months after Intervention 1	0.002074	(0.000510, 0.003637)	0.282582	0.280509
Relative Change (%) at 15 Months after Intervention 1	0.74	(0.18, 1.30)	0.282582	0.280509
Absolute Change at 16 Months after Intervention 1	0.002212	(0.000545, 0.003879)	0.281883	0.279671
Relative Change (%) at 16 Months after Intervention 1	0.79	(0.19, 1.39)	0.281883	0.279671
Absolute Change at 17 Months after Intervention 1	0.002350	(0.000579, 0.004122)	0.281183	0.278833
Relative Change (%) at 17 Months after Intervention 1	0.84	(0.20, 1.48)	0.281183	0.278833
Absolute Change at 18 Months after Intervention 1	0.002488	(0.000613, 0.004364)	0.280483	0.277995
Relative Change (%) at 18 Months after Intervention 1	0.90	(0.22, 1.57)	0.280483	0.277995
Absolute Change at 19 Months after Intervention 1	0.002627	(0.000647, 0.004607)	0.279784	0.277157
Relative Change (%) at 19 Months after Intervention 1	0.95	(0.23, 1.67)	0.279784	0.277157
Absolute Change at 20 Months after Intervention 1	0.002765	(0.000681, 0.004849)	0.279084	0.276319
Relative Change (%) at 20 Months after Intervention 1	1.00	(0.24, 1.76)	0.279084	0.276319
Absolute Change at 21 Months after Intervention 1	0.002903	(0.000715, 0.005092)	0.278385	0.275481
Relative Change (%) at 21 Months after Intervention 1	1.05	(0.25, 1.85)	0.278385	0.275481
Absolute Change at 22 Months after Intervention 1	0.003041	(0.000749, 0.005334)	0.277685	0.274644
Relative Change (%) at 22 Months after Intervention 1	1.11	(0.27, 1.95)	0.277685	0.274644
Absolute Change at 23 Months after Intervention 1	0.003180	(0.000783, 0.005577)	0.276985	0.273806
Relative Change (%) at 23 Months after Intervention 1	1.16	(0.28, 2.04)	0.276985	0.273806
Absolute Change at 24 Months after Intervention 1	0.003318	(0.000817, 0.005819)	0.276286	0.272968
Relative Change (%) at 24 Months after Intervention 1	1.22	(0.29, 2.14)	0.276286	0.272968
Absolute Change at 25 Months after Intervention 1	0.003456	(0.000851, 0.006062)	0.275586	0.272130
Relative Change (%) at 25 Months after Intervention 1	1.27	(0.31, 2.23)	0.275586	0.272130
Absolute Change at 26 Months after Intervention 1	0.003594	(0.000885, 0.006304)	0.274886	0.271292
Relative Change (%) at 26 Months after Intervention 1	1.32	(0.32, 2.33)	0.274886	0.271292
Absolute Change at 27 Months after Intervention 1	0.003733	(0.000919, 0.006546)	0.274187	0.270454
Relative Change (%) at 27 Months after Intervention 1	1.38	(0.33, 2.43)	0.274187	0.270454
Absolute Change at 27 Months after Intervention 1	0.003733	(0.000919, 0.006546)	0.274187	0.270454
Relative Change (%) at 27 Months after Intervention 1	1.38	(0.33, 2.43)	0.274187	0.270454

¹The 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.

Figure 36. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 73. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.932213	(0.931512, 0.932914)	<.001
Baseline trend	-0.000439	(-0.000467, -0.000411)	<.001
Level Change (After Intervention 1)	0.002366	(0.001164, 0.003568)	<.001
Trend Change (After Intervention 1)	0.000185	(0.000123, 0.000248)	<.001
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.932213	(0.931512, 0.932914)	<.001
Baseline trend	-0.000439	(-0.000467, -0.000411)	<.001
Level Change (After Intervention 1)	0.002366	(0.001164, 0.003568)	<.001
Trend Change (After Intervention 1)	0.000185	(0.000123, 0.000248)	<.001

¹The 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.

²Maximum 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.

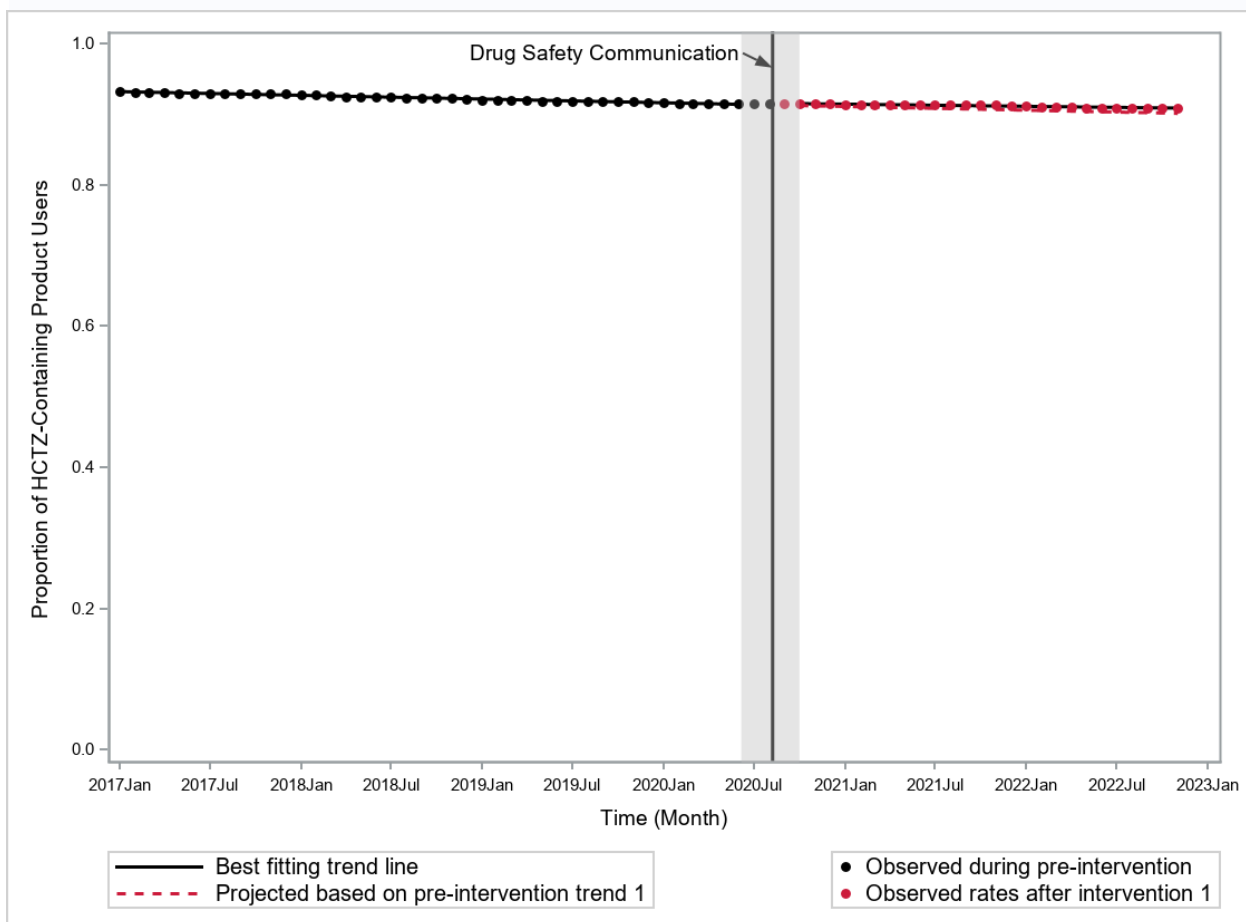
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 74. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.002737	(0.001547, 0.003926)	0.914754	0.912018
Relative Change (%) at 2 Months after Intervention 1	0.30	(0.17, 0.43)	0.914754	0.912018
Absolute Change at 3 Months after Intervention 1	0.002922	(0.001751, 0.004092)	0.914501	0.911579
Relative Change (%) at 3 Months after Intervention 1	0.32	(0.19, 0.45)	0.914501	0.911579
Absolute Change at 4 Months after Intervention 1	0.003107	(0.001952, 0.004262)	0.914247	0.911140
Relative Change (%) at 4 Months after Intervention 1	0.34	(0.21, 0.47)	0.914247	0.911140
Absolute Change at 5 Months after Intervention 1	0.003293	(0.002150, 0.004435)	0.913993	0.910701
Relative Change (%) at 5 Months after Intervention 1	0.36	(0.24, 0.49)	0.913993	0.910701
Absolute Change at 6 Months after Intervention 1	0.003478	(0.002345, 0.004611)	0.913740	0.910262
Relative Change (%) at 6 Months after Intervention 1	0.38	(0.26, 0.51)	0.913740	0.910262
Absolute Change at 7 Months after Intervention 1	0.003663	(0.002536, 0.004790)	0.913486	0.909823
Relative Change (%) at 7 Months after Intervention 1	0.40	(0.28, 0.53)	0.913486	0.909823
Absolute Change at 8 Months after Intervention 1	0.003849	(0.002724, 0.004973)	0.913232	0.909384
Relative Change (%) at 8 Months after Intervention 1	0.42	(0.30, 0.55)	0.913232	0.909384
Absolute Change at 9 Months after Intervention 1	0.004034	(0.002908, 0.005159)	0.912978	0.908945
Relative Change (%) at 9 Months after Intervention 1	0.44	(0.32, 0.57)	0.912978	0.908945
Absolute Change at 10 Months after Intervention 1	0.004219	(0.003089, 0.005349)	0.912725	0.908506
Relative Change (%) at 10 Months after Intervention 1	0.46	(0.34, 0.59)	0.912725	0.908506
Absolute Change at 11 Months after Intervention 1	0.004404	(0.003267, 0.005542)	0.912471	0.908067
Relative Change (%) at 11 Months after Intervention 1	0.49	(0.36, 0.61)	0.912471	0.908067
Absolute Change at 12 Months after Intervention 1	0.004590	(0.003441, 0.005739)	0.912217	0.907627
Relative Change (%) at 12 Months after Intervention 1	0.51	(0.38, 0.63)	0.912217	0.907627
Absolute Change at 13 Months after Intervention 1	0.004775	(0.003612, 0.005938)	0.911964	0.907188
Relative Change (%) at 13 Months after Intervention 1	0.53	(0.40, 0.66)	0.911964	0.907188
Absolute Change at 14 Months after Intervention 1	0.004960	(0.003780, 0.006141)	0.911710	0.906749
Relative Change (%) at 14 Months after Intervention 1	0.55	(0.42, 0.68)	0.911710	0.906749
Absolute Change at 15 Months after Intervention 1	0.005146	(0.003945, 0.006346)	0.911456	0.906310
Relative Change (%) at 15 Months after Intervention 1	0.57	(0.43, 0.70)	0.911456	0.906310
Absolute Change at 16 Months after Intervention 1	0.005331	(0.004107, 0.006555)	0.911202	0.905871
Relative Change (%) at 16 Months after Intervention 1	0.59	(0.45, 0.72)	0.911202	0.905871
Absolute Change at 17 Months after Intervention 1	0.005516	(0.004267, 0.006766)	0.910949	0.905432
Relative Change (%) at 17 Months after Intervention 1	0.61	(0.47, 0.75)	0.910949	0.905432
Absolute Change at 18 Months after Intervention 1	0.005702	(0.004424, 0.006980)	0.910695	0.904993
Relative Change (%) at 18 Months after Intervention 1	0.63	(0.49, 0.77)	0.910695	0.904993
Absolute Change at 19 Months after Intervention 1	0.005887	(0.004579, 0.007196)	0.910441	0.904554
Relative Change (%) at 19 Months after Intervention 1	0.65	(0.51, 0.80)	0.910441	0.904554
Absolute Change at 20 Months after Intervention 1	0.006072	(0.004731, 0.007414)	0.910188	0.904115
Relative Change (%) at 20 Months after Intervention 1	0.67	(0.52, 0.82)	0.910188	0.904115
Absolute Change at 21 Months after Intervention 1	0.006258	(0.004882, 0.007634)	0.909934	0.903676
Relative Change (%) at 21 Months after Intervention 1	0.69	(0.54, 0.85)	0.909934	0.903676
Absolute Change at 22 Months after Intervention 1	0.006443	(0.005030, 0.007856)	0.909680	0.903237
Relative Change (%) at 22 Months after Intervention 1	0.71	(0.56, 0.87)	0.909680	0.903237
Absolute Change at 23 Months after Intervention 1	0.006628	(0.005177, 0.008080)	0.909427	0.902798
Relative Change (%) at 23 Months after Intervention 1	0.73	(0.57, 0.90)	0.909427	0.902798
Absolute Change at 24 Months after Intervention 1	0.006814	(0.005322, 0.008305)	0.909173	0.902359
Relative Change (%) at 24 Months after Intervention 1	0.76	(0.59, 0.92)	0.909173	0.902359
Absolute Change at 25 Months after Intervention 1	0.006999	(0.005466, 0.008532)	0.908919	0.901920
Relative Change (%) at 25 Months after Intervention 1	0.78	(0.61, 0.95)	0.908919	0.901920
Absolute Change at 26 Months after Intervention 1	0.007184	(0.005609, 0.008760)	0.908665	0.901481
Relative Change (%) at 26 Months after Intervention 1	0.80	(0.62, 0.97)	0.908665	0.901481
Absolute Change at 27 Months after Intervention 1	0.007370	(0.005750, 0.008989)	0.908412	0.901042
Relative Change (%) at 27 Months after Intervention 1	0.82	(0.64, 1.00)	0.908412	0.901042
Absolute Change at 27 Months after Intervention 1	0.007370	(0.005750, 0.008989)	0.908412	0.901042
Relative Change (%) at 27 Months after Intervention 1	0.82	(0.64, 1.00)	0.908412	0.901042

¹The 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.

Figure 37. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 75. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.000523	(0.000503, 0.000542)	<.001
Baseline trend	-0.000006	(-0.000007, -0.000006)	<.001
Level Change (After Intervention 1)	0.000025	(-0.000007, 0.000057)	0.128
Trend Change (After Intervention 1)	0.000001	(-0.000001, 0.000003)	0.338
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.000519	(0.000502, 0.000536)	<.001
Baseline trend	-0.000006	(-0.000007, -0.000006)	<.001
Level Change (After Intervention 1)	0.000032	(0.000004, 0.000061)	0.028

¹The 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.

²Maximum 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.

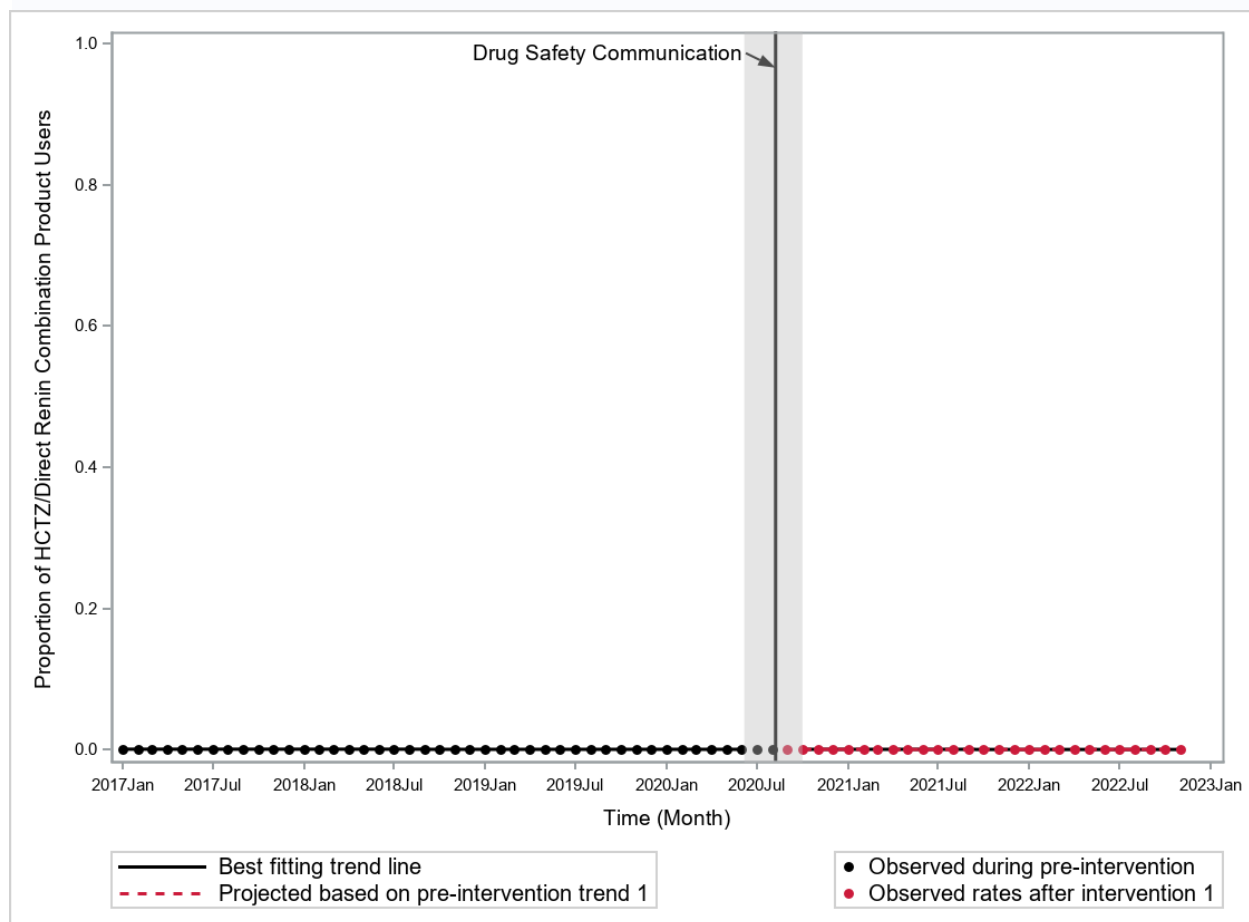
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 76. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.000032	(0.000004, 0.000061)	0.000260	0.000228
Relative Change (%) at 2 Months after Intervention 1	14.20	(0.48, 27.91)	0.000260	0.000228
Absolute Change at 3 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000254	0.000221
Relative Change (%) at 3 Months after Intervention 1	14.60	(0.43, 28.78)	0.000254	0.000221
Absolute Change at 4 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000247	0.000215
Relative Change (%) at 4 Months after Intervention 1	15.03	(0.36, 29.70)	0.000247	0.000215
Absolute Change at 5 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000241	0.000209
Relative Change (%) at 5 Months after Intervention 1	15.49	(0.29, 30.68)	0.000241	0.000209
Absolute Change at 6 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000235	0.000202
Relative Change (%) at 6 Months after Intervention 1	15.97	(0.21, 31.73)	0.000235	0.000202
Absolute Change at 7 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000229	0.000196
Relative Change (%) at 7 Months after Intervention 1	16.49	(0.12, 32.85)	0.000229	0.000196
Absolute Change at 8 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000222	0.000190
Relative Change (%) at 8 Months after Intervention 1	17.04	(0.01, 34.06)	0.000222	0.000190
Absolute Change at 9 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000216	0.000184
Relative Change (%) at 9 Months after Intervention 1	17.62	(-0.11, 35.35)	0.000216	0.000184
Absolute Change at 10 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000210	0.000177
Relative Change (%) at 10 Months after Intervention 1	18.25	(-0.25, 36.75)	0.000210	0.000177
Absolute Change at 11 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000203	0.000171
Relative Change (%) at 11 Months after Intervention 1	18.93	(-0.41, 38.26)	0.000203	0.000171
Absolute Change at 12 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000197	0.000165
Relative Change (%) at 12 Months after Intervention 1	19.66	(-0.59, 39.90)	0.000197	0.000165
Absolute Change at 13 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000191	0.000158
Relative Change (%) at 13 Months after Intervention 1	20.44	(-0.80, 41.68)	0.000191	0.000158
Absolute Change at 14 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000184	0.000152
Relative Change (%) at 14 Months after Intervention 1	21.29	(-1.05, 43.63)	0.000184	0.000152
Absolute Change at 15 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000178	0.000146
Relative Change (%) at 15 Months after Intervention 1	22.22	(-1.34, 45.77)	0.000178	0.000146
Absolute Change at 16 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000172	0.000139
Relative Change (%) at 16 Months after Intervention 1	23.23	(-1.68, 48.13)	0.000172	0.000139
Absolute Change at 17 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000165	0.000133
Relative Change (%) at 17 Months after Intervention 1	24.33	(-2.08, 50.74)	0.000165	0.000133
Absolute Change at 18 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000159	0.000127
Relative Change (%) at 18 Months after Intervention 1	25.55	(-2.55, 53.64)	0.000159	0.000127
Absolute Change at 19 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000153	0.000120
Relative Change (%) at 19 Months after Intervention 1	26.89	(-3.11, 56.89)	0.000153	0.000120
Absolute Change at 20 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000146	0.000114
Relative Change (%) at 20 Months after Intervention 1	28.38	(-3.79, 60.55)	0.000146	0.000114
Absolute Change at 21 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000140	0.000108
Relative Change (%) at 21 Months after Intervention 1	30.05	(-4.62, 64.71)	0.000140	0.000108
Absolute Change at 22 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000134	0.000101
Relative Change (%) at 22 Months after Intervention 1	31.92	(-5.62, 69.47)	0.000134	0.000101
Absolute Change at 23 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000127	0.000095
Relative Change (%) at 23 Months after Intervention 1	34.05	(-6.87, 74.97)	0.000127	0.000095
Absolute Change at 24 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000121	0.000089
Relative Change (%) at 24 Months after Intervention 1	36.48	(-8.42, 81.38)	0.000121	0.000089
Absolute Change at 25 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000115	0.000082
Relative Change (%) at 25 Months after Intervention 1	39.28	(-10.40, 88.96)	0.000115	0.000082
Absolute Change at 26 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000108	0.000076
Relative Change (%) at 26 Months after Intervention 1	42.55	(-12.95, 98.05)	0.000108	0.000076
Absolute Change at 27 Months after Intervention 1	0.000032	(0.000004, 0.000061)	0.000102	0.000070
Relative Change (%) at 27 Months after Intervention 1	46.41	(-16.31, 109.13)	0.000102	0.000070
Relative Change (%) at 27 Months after Intervention 1	46.41	(-16.31, 109.13)	0.000102	0.000070

¹The 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.

Figure 38. Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 77. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.366949	(0.352253, 0.381645)	<.001
Baseline trend	0.002002	(0.001455, 0.002549)	<.001
Level Change (After Intervention 1)	0.004068	(-0.006489, 0.014625)	0.444
Trend Change (After Intervention 1)	-0.001744	(-0.003060, -0.000429)	0.010
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.366494	(0.350972, 0.382015)	<.001
Baseline trend	0.002051	(0.001486, 0.002615)	<.001
Trend Change (After Intervention 1)	-0.001684	(-0.003063, -0.000304)	0.018

¹The 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.

²Maximum 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.

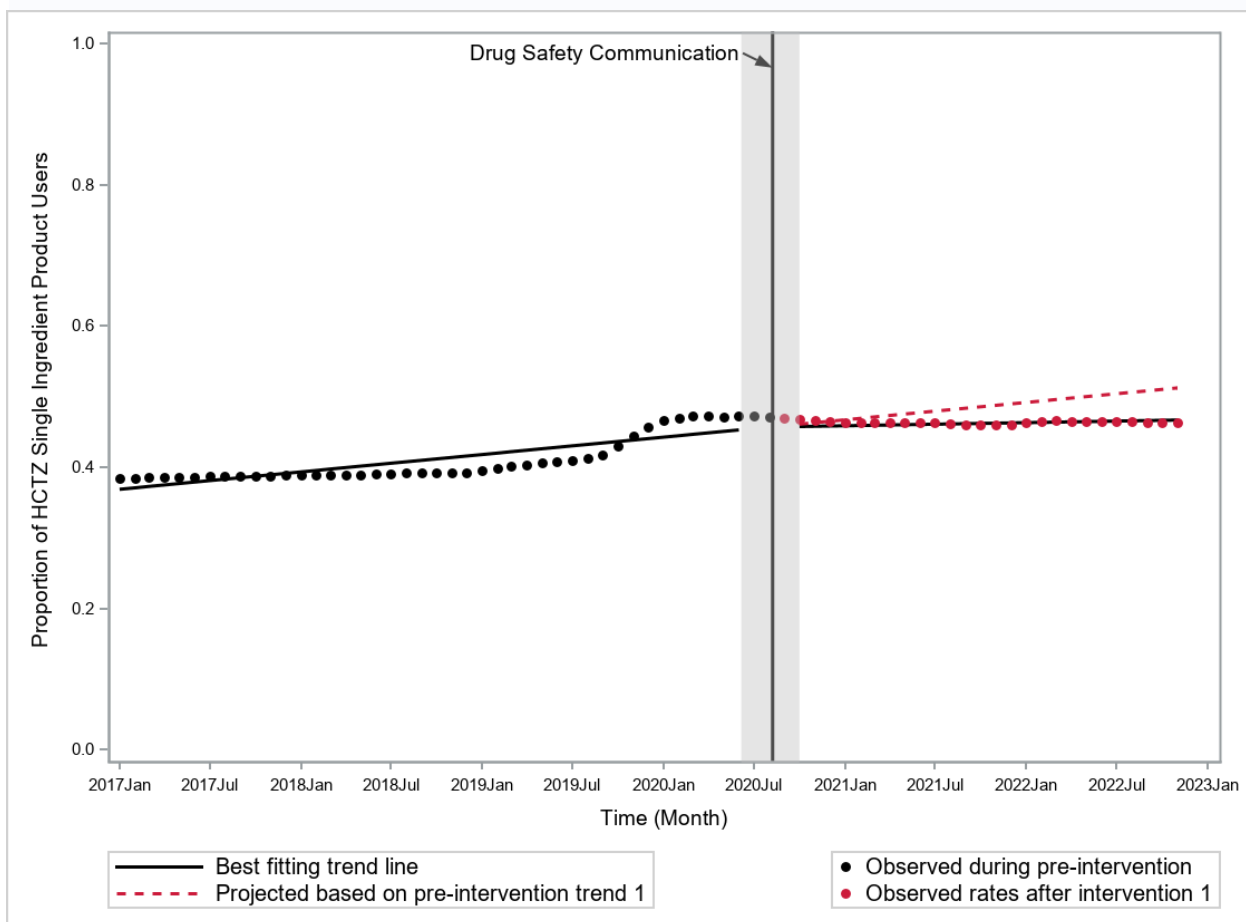
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 78. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.003368	(-0.006127, -0.000608)	0.457451	0.460819
Relative Change (%) at 2 Months after Intervention 1	-0.73	(-1.31, -0.15)	0.457451	0.460819
Absolute Change at 3 Months after Intervention 1	-0.005051	(-0.009191, -0.000912)	0.457818	0.462869
Relative Change (%) at 3 Months after Intervention 1	-1.09	(-1.95, -0.23)	0.457818	0.462869
Absolute Change at 4 Months after Intervention 1	-0.006735	(-0.012254, -0.001216)	0.458185	0.464920
Relative Change (%) at 4 Months after Intervention 1	-1.45	(-2.59, -0.30)	0.458185	0.464920
Absolute Change at 5 Months after Intervention 1	-0.008419	(-0.015318, -0.001520)	0.458551	0.466970
Relative Change (%) at 5 Months after Intervention 1	-1.80	(-3.23, -0.38)	0.458551	0.466970
Absolute Change at 6 Months after Intervention 1	-0.010103	(-0.018382, -0.001824)	0.458918	0.469021
Relative Change (%) at 6 Months after Intervention 1	-2.15	(-3.85, -0.46)	0.458918	0.469021
Absolute Change at 7 Months after Intervention 1	-0.011786	(-0.021445, -0.002128)	0.459285	0.471071
Relative Change (%) at 7 Months after Intervention 1	-2.50	(-4.47, -0.53)	0.459285	0.471071
Absolute Change at 8 Months after Intervention 1	-0.013470	(-0.024509, -0.002432)	0.459652	0.473122
Relative Change (%) at 8 Months after Intervention 1	-2.85	(-5.09, -0.61)	0.459652	0.473122
Absolute Change at 9 Months after Intervention 1	-0.015154	(-0.027572, -0.002735)	0.460018	0.475172
Relative Change (%) at 9 Months after Intervention 1	-3.19	(-5.69, -0.68)	0.460018	0.475172
Absolute Change at 10 Months after Intervention 1	-0.016838	(-0.030636, -0.003039)	0.460385	0.477223
Relative Change (%) at 10 Months after Intervention 1	-3.53	(-6.30, -0.76)	0.460385	0.477223
Absolute Change at 11 Months after Intervention 1	-0.018522	(-0.033700, -0.003343)	0.460752	0.479273
Relative Change (%) at 11 Months after Intervention 1	-3.86	(-6.89, -0.84)	0.460752	0.479273
Absolute Change at 12 Months after Intervention 1	-0.020205	(-0.036763, -0.003647)	0.461119	0.481324
Relative Change (%) at 12 Months after Intervention 1	-4.20	(-7.48, -0.91)	0.461119	0.481324
Absolute Change at 13 Months after Intervention 1	-0.021889	(-0.039827, -0.003951)	0.461485	0.483374
Relative Change (%) at 13 Months after Intervention 1	-4.53	(-8.07, -0.99)	0.461485	0.483374
Absolute Change at 14 Months after Intervention 1	-0.023573	(-0.042891, -0.004255)	0.461852	0.485425
Relative Change (%) at 14 Months after Intervention 1	-4.86	(-8.65, -1.06)	0.461852	0.485425
Absolute Change at 15 Months after Intervention 1	-0.025257	(-0.045954, -0.004559)	0.462219	0.487476
Relative Change (%) at 15 Months after Intervention 1	-5.18	(-9.23, -1.14)	0.462219	0.487476
Absolute Change at 16 Months after Intervention 1	-0.026940	(-0.049018, -0.004863)	0.462586	0.489526
Relative Change (%) at 16 Months after Intervention 1	-5.50	(-9.80, -1.21)	0.462586	0.489526
Absolute Change at 17 Months after Intervention 1	-0.028624	(-0.052081, -0.005167)	0.462952	0.491577
Relative Change (%) at 17 Months after Intervention 1	-5.82	(-10.36, -1.29)	0.462952	0.491577
Absolute Change at 18 Months after Intervention 1	-0.030308	(-0.055145, -0.005471)	0.463319	0.493627
Relative Change (%) at 18 Months after Intervention 1	-6.14	(-10.92, -1.36)	0.463319	0.493627
Absolute Change at 19 Months after Intervention 1	-0.031992	(-0.058209, -0.005775)	0.463686	0.495678
Relative Change (%) at 19 Months after Intervention 1	-6.45	(-11.47, -1.44)	0.463686	0.495678
Absolute Change at 20 Months after Intervention 1	-0.033675	(-0.061272, -0.006079)	0.464053	0.497728
Relative Change (%) at 20 Months after Intervention 1	-6.77	(-12.02, -1.51)	0.464053	0.497728
Absolute Change at 21 Months after Intervention 1	-0.035359	(-0.064336, -0.006383)	0.464420	0.499779
Relative Change (%) at 21 Months after Intervention 1	-7.07	(-12.56, -1.59)	0.464420	0.499779
Absolute Change at 22 Months after Intervention 1	-0.037043	(-0.067399, -0.006687)	0.464786	0.501829
Relative Change (%) at 22 Months after Intervention 1	-7.38	(-13.10, -1.66)	0.464786	0.501829
Absolute Change at 23 Months after Intervention 1	-0.038727	(-0.070463, -0.006991)	0.465153	0.503880
Relative Change (%) at 23 Months after Intervention 1	-7.69	(-13.64, -1.73)	0.465153	0.503880
Absolute Change at 24 Months after Intervention 1	-0.040411	(-0.073527, -0.007295)	0.465520	0.505930
Relative Change (%) at 24 Months after Intervention 1	-7.99	(-14.17, -1.81)	0.465520	0.505930
Absolute Change at 25 Months after Intervention 1	-0.042094	(-0.076590, -0.007599)	0.465887	0.507981
Relative Change (%) at 25 Months after Intervention 1	-8.29	(-14.69, -1.88)	0.465887	0.507981
Absolute Change at 26 Months after Intervention 1	-0.043778	(-0.079654, -0.007902)	0.466253	0.510031
Relative Change (%) at 26 Months after Intervention 1	-8.58	(-15.21, -1.95)	0.466253	0.510031
Absolute Change at 27 Months after Intervention 1	-0.045462	(-0.082717, -0.008206)	0.466620	0.512082
Relative Change (%) at 27 Months after Intervention 1	-8.88	(-15.73, -2.03)	0.466620	0.512082
Absolute Change at 27 Months after Intervention 1	-0.045462	(-0.082717, -0.008206)	0.466620	0.512082
Relative Change (%) at 27 Months after Intervention 1	-8.88	(-15.73, -2.03)	0.466620	0.512082

¹The 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.

Figure 39. Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 79. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.134513	(0.133499, 0.135527)	<.001
Baseline trend	-0.000416	(-0.000450, -0.000381)	<.001
Level Change (After Intervention 1)	0.000719	(-0.000049, 0.001486)	0.066
Trend Change (After Intervention 1)	0.000075	(0.000002, 0.000147)	0.043
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.134513	(0.133499, 0.135527)	<.001
Baseline trend	-0.000416	(-0.000450, -0.000381)	<.001
Level Change (After Intervention 1)	0.000719	(-0.000049, 0.001486)	0.066
Trend Change (After Intervention 1)	0.000075	(0.000002, 0.000147)	0.043

¹The 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.

²Maximum 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.

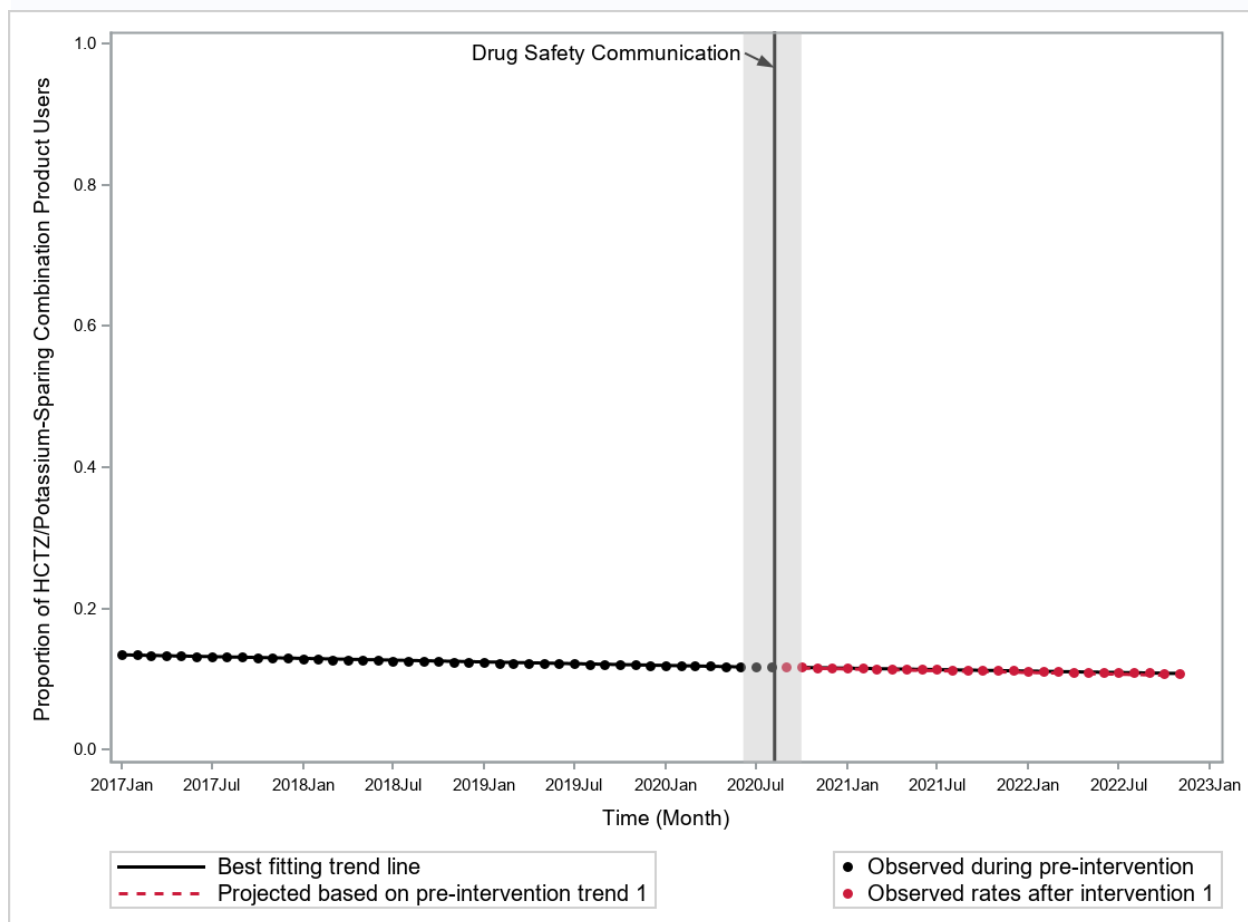
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 80. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.000868	(-0.000035, 0.001772)	0.116257	0.115389
Relative Change (%) at 2 Months after Intervention 1	0.75	(-0.04, 1.54)	0.116257	0.115389
Absolute Change at 3 Months after Intervention 1	0.000943	(0.000006, 0.001881)	0.115916	0.114973
Relative Change (%) at 3 Months after Intervention 1	0.82	(0.00, 1.64)	0.115916	0.114973
Absolute Change at 4 Months after Intervention 1	0.001018	(0.000040, 0.001996)	0.115575	0.114557
Relative Change (%) at 4 Months after Intervention 1	0.89	(0.03, 1.75)	0.115575	0.114557
Absolute Change at 5 Months after Intervention 1	0.001093	(0.000069, 0.002117)	0.115234	0.114142
Relative Change (%) at 5 Months after Intervention 1	0.96	(0.05, 1.86)	0.115234	0.114142
Absolute Change at 6 Months after Intervention 1	0.001168	(0.000092, 0.002243)	0.114893	0.113726
Relative Change (%) at 6 Months after Intervention 1	1.03	(0.07, 1.98)	0.114893	0.113726
Absolute Change at 7 Months after Intervention 1	0.001242	(0.000112, 0.002372)	0.114552	0.113310
Relative Change (%) at 7 Months after Intervention 1	1.10	(0.09, 2.11)	0.114552	0.113310
Absolute Change at 8 Months after Intervention 1	0.001317	(0.000128, 0.002506)	0.114211	0.112894
Relative Change (%) at 8 Months after Intervention 1	1.17	(0.10, 2.23)	0.114211	0.112894
Absolute Change at 9 Months after Intervention 1	0.001392	(0.000141, 0.002642)	0.113871	0.112479
Relative Change (%) at 9 Months after Intervention 1	1.24	(0.11, 2.36)	0.113871	0.112479
Absolute Change at 10 Months after Intervention 1	0.001467	(0.000152, 0.002781)	0.113530	0.112063
Relative Change (%) at 10 Months after Intervention 1	1.31	(0.12, 2.50)	0.113530	0.112063
Absolute Change at 11 Months after Intervention 1	0.001541	(0.000160, 0.002923)	0.113189	0.111647
Relative Change (%) at 11 Months after Intervention 1	1.38	(0.12, 2.64)	0.113189	0.111647
Absolute Change at 12 Months after Intervention 1	0.001616	(0.000166, 0.003066)	0.112848	0.111231
Relative Change (%) at 12 Months after Intervention 1	1.45	(0.13, 2.78)	0.112848	0.111231
Absolute Change at 13 Months after Intervention 1	0.001691	(0.000170, 0.003211)	0.112507	0.110816
Relative Change (%) at 13 Months after Intervention 1	1.53	(0.13, 2.92)	0.112507	0.110816
Absolute Change at 14 Months after Intervention 1	0.001766	(0.000173, 0.003358)	0.112166	0.110400
Relative Change (%) at 14 Months after Intervention 1	1.60	(0.13, 3.07)	0.112166	0.110400
Absolute Change at 15 Months after Intervention 1	0.001840	(0.000175, 0.003506)	0.111825	0.109984
Relative Change (%) at 15 Months after Intervention 1	1.67	(0.13, 3.21)	0.111825	0.109984
Absolute Change at 16 Months after Intervention 1	0.001915	(0.000176, 0.003655)	0.111484	0.109569
Relative Change (%) at 16 Months after Intervention 1	1.75	(0.13, 3.36)	0.111484	0.109569
Absolute Change at 17 Months after Intervention 1	0.001990	(0.000175, 0.003805)	0.111143	0.109153
Relative Change (%) at 17 Months after Intervention 1	1.82	(0.13, 3.52)	0.111143	0.109153
Absolute Change at 18 Months after Intervention 1	0.002065	(0.000174, 0.003956)	0.110802	0.108737
Relative Change (%) at 18 Months after Intervention 1	1.90	(0.13, 3.67)	0.110802	0.108737
Absolute Change at 19 Months after Intervention 1	0.002139	(0.000172, 0.004107)	0.110461	0.108321
Relative Change (%) at 19 Months after Intervention 1	1.98	(0.13, 3.83)	0.110461	0.108321
Absolute Change at 20 Months after Intervention 1	0.002214	(0.000169, 0.004259)	0.110120	0.107906
Relative Change (%) at 20 Months after Intervention 1	2.05	(0.12, 3.98)	0.110120	0.107906
Absolute Change at 21 Months after Intervention 1	0.002289	(0.000166, 0.004412)	0.109779	0.107490
Relative Change (%) at 21 Months after Intervention 1	2.13	(0.12, 4.14)	0.109779	0.107490
Absolute Change at 22 Months after Intervention 1	0.002364	(0.000162, 0.004566)	0.109438	0.107074
Relative Change (%) at 22 Months after Intervention 1	2.21	(0.11, 4.30)	0.109438	0.107074
Absolute Change at 23 Months after Intervention 1	0.002439	(0.000157, 0.004720)	0.109097	0.106658
Relative Change (%) at 23 Months after Intervention 1	2.29	(0.11, 4.47)	0.109097	0.106658
Absolute Change at 24 Months after Intervention 1	0.002513	(0.000153, 0.004874)	0.108756	0.106243
Relative Change (%) at 24 Months after Intervention 1	2.37	(0.10, 4.63)	0.108756	0.106243
Absolute Change at 25 Months after Intervention 1	0.002588	(0.000147, 0.005029)	0.108415	0.105827
Relative Change (%) at 25 Months after Intervention 1	2.45	(0.09, 4.80)	0.108415	0.105827
Absolute Change at 26 Months after Intervention 1	0.002663	(0.000142, 0.005184)	0.108074	0.105411
Relative Change (%) at 26 Months after Intervention 1	2.53	(0.08, 4.97)	0.108074	0.105411
Absolute Change at 27 Months after Intervention 1	0.002738	(0.000136, 0.005339)	0.107733	0.104995
Relative Change (%) at 27 Months after Intervention 1	2.61	(0.08, 5.14)	0.107733	0.104995
Absolute Change at 27 Months after Intervention 1	0.002738	(0.000136, 0.005339)	0.107733	0.104995
Relative Change (%) at 27 Months after Intervention 1	2.61	(0.08, 5.14)	0.107733	0.104995

¹The 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.

Figure 40. Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 81. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.382341	(0.380264, 0.384419)	<.001
Baseline trend	-0.001035	(-0.001107, -0.000963)	<.001
Level Change (After Intervention 1)	0.003032	(0.001392, 0.004672)	<.001
Trend Change (After Intervention 1)	0.000050	(-0.000101, 0.000201)	0.513
Most Parsimonious Final Model Parameters (df = 64)^{2,3}			
Intercept	0.382076	(0.380147, 0.384005)	<.001
Baseline trend	-0.001018	(-0.001067, -0.000968)	<.001
Level Change (After Intervention 1)	0.003092	(0.001471, 0.004714)	<.001

¹The 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.

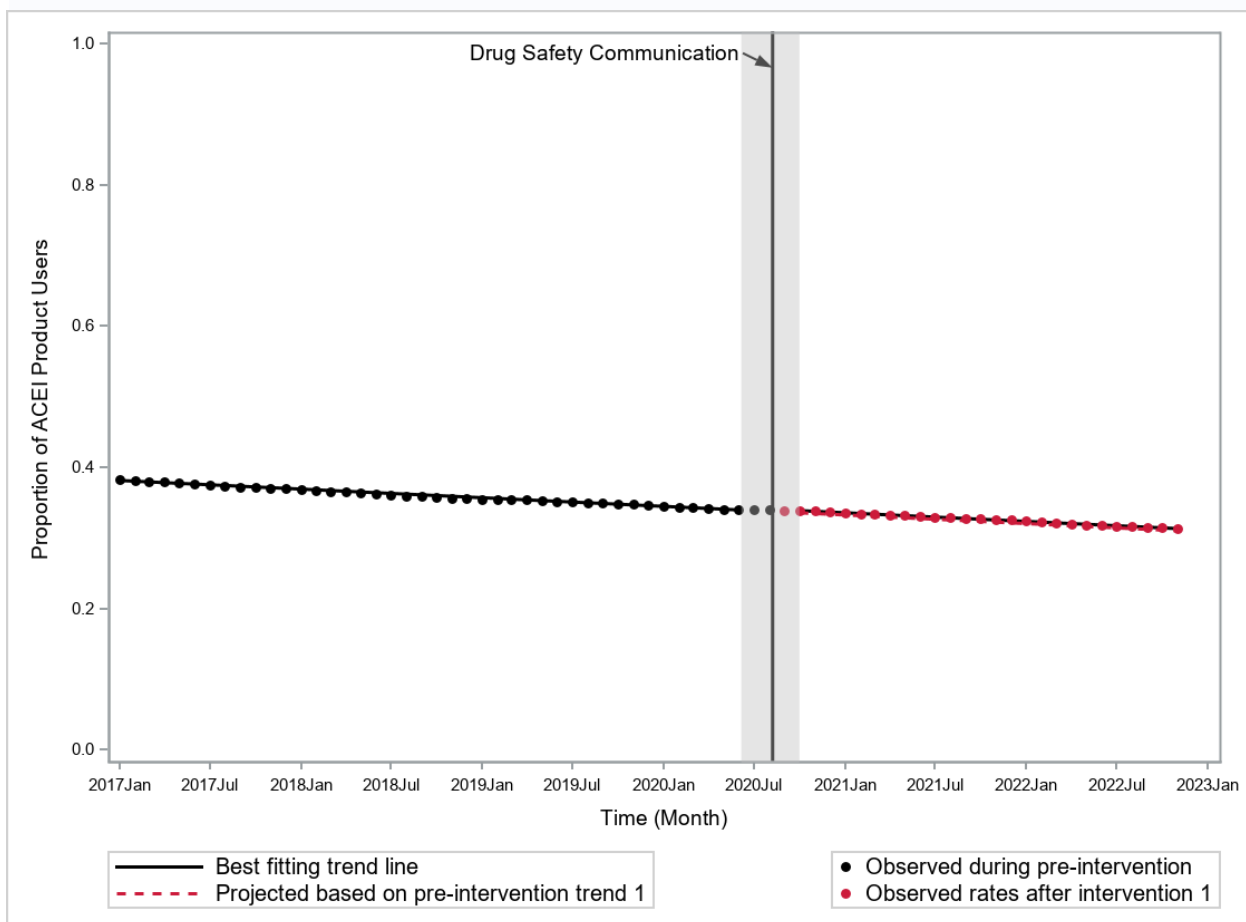
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 82. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.003092	(0.001462, 0.004723)	0.338354	0.335261
Relative Change (%) at 2 Months after Intervention 1	0.92	(0.43, 1.41)	0.338354	0.335261
Absolute Change at 3 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.337336	0.334243
Relative Change (%) at 3 Months after Intervention 1	0.93	(0.43, 1.42)	0.337336	0.334243
Absolute Change at 4 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.336318	0.333226
Relative Change (%) at 4 Months after Intervention 1	0.93	(0.44, 1.42)	0.336318	0.333226
Absolute Change at 5 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.335300	0.332208
Relative Change (%) at 5 Months after Intervention 1	0.93	(0.44, 1.42)	0.335300	0.332208
Absolute Change at 6 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.334283	0.331190
Relative Change (%) at 6 Months after Intervention 1	0.93	(0.44, 1.43)	0.334283	0.331190
Absolute Change at 7 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.333265	0.330173
Relative Change (%) at 7 Months after Intervention 1	0.94	(0.44, 1.43)	0.333265	0.330173
Absolute Change at 8 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.332247	0.329155
Relative Change (%) at 8 Months after Intervention 1	0.94	(0.44, 1.44)	0.332247	0.329155
Absolute Change at 9 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.331230	0.328137
Relative Change (%) at 9 Months after Intervention 1	0.94	(0.44, 1.44)	0.331230	0.328137
Absolute Change at 10 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.330212	0.327119
Relative Change (%) at 10 Months after Intervention 1	0.95	(0.44, 1.45)	0.330212	0.327119
Absolute Change at 11 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.329194	0.326102
Relative Change (%) at 11 Months after Intervention 1	0.95	(0.44, 1.45)	0.329194	0.326102
Absolute Change at 12 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.328176	0.325084
Relative Change (%) at 12 Months after Intervention 1	0.95	(0.45, 1.46)	0.328176	0.325084
Absolute Change at 13 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.327159	0.324066
Relative Change (%) at 13 Months after Intervention 1	0.95	(0.45, 1.46)	0.327159	0.324066
Absolute Change at 14 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.326141	0.323049
Relative Change (%) at 14 Months after Intervention 1	0.96	(0.45, 1.47)	0.326141	0.323049
Absolute Change at 15 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.325123	0.322031
Relative Change (%) at 15 Months after Intervention 1	0.96	(0.45, 1.47)	0.325123	0.322031
Absolute Change at 16 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.324106	0.321013
Relative Change (%) at 16 Months after Intervention 1	0.96	(0.45, 1.48)	0.324106	0.321013
Absolute Change at 17 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.323088	0.319995
Relative Change (%) at 17 Months after Intervention 1	0.97	(0.45, 1.48)	0.323088	0.319995
Absolute Change at 18 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.322070	0.318978
Relative Change (%) at 18 Months after Intervention 1	0.97	(0.45, 1.49)	0.322070	0.318978
Absolute Change at 19 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.321053	0.317960
Relative Change (%) at 19 Months after Intervention 1	0.97	(0.46, 1.49)	0.321053	0.317960
Absolute Change at 20 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.320035	0.316942
Relative Change (%) at 20 Months after Intervention 1	0.98	(0.46, 1.49)	0.320035	0.316942
Absolute Change at 21 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.319017	0.315925
Relative Change (%) at 21 Months after Intervention 1	0.98	(0.46, 1.50)	0.319017	0.315925
Absolute Change at 22 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.317999	0.314907
Relative Change (%) at 22 Months after Intervention 1	0.98	(0.46, 1.50)	0.317999	0.314907
Absolute Change at 23 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.316982	0.313889
Relative Change (%) at 23 Months after Intervention 1	0.99	(0.46, 1.51)	0.316982	0.313889
Absolute Change at 24 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.315964	0.312872
Relative Change (%) at 24 Months after Intervention 1	0.99	(0.46, 1.51)	0.315964	0.312872
Absolute Change at 25 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.314946	0.311854
Relative Change (%) at 25 Months after Intervention 1	0.99	(0.46, 1.52)	0.314946	0.311854
Absolute Change at 26 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.313929	0.310836
Relative Change (%) at 26 Months after Intervention 1	0.99	(0.46, 1.52)	0.313929	0.310836
Absolute Change at 27 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.312911	0.309818
Relative Change (%) at 27 Months after Intervention 1	1.00	(0.47, 1.53)	0.312911	0.309818
Absolute Change at 27 Months after Intervention 1	0.003092	(0.001462, 0.004723)	0.312911	0.309818
Relative Change (%) at 27 Months after Intervention 1	1.00	(0.47, 1.53)	0.312911	0.309818

¹The 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.

Figure 41. Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 83. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 61)²			
Intercept	0.396474	(0.394387, 0.398561)	<.001
Baseline trend	0.000092	(0.000016, 0.000168)	0.019
Level Change (After Intervention 1)	0.002496	(0.000277, 0.004716)	0.028
Trend Change (After Intervention 1)	0.000199	(0.000033, 0.000365)	0.020
Most Parsimonious Final Model Parameters (df = 61)^{2,3}			
Intercept	0.396474	(0.394387, 0.398561)	<.001
Baseline trend	0.000092	(0.000016, 0.000168)	0.019
Level Change (After Intervention 1)	0.002496	(0.000277, 0.004716)	0.028
Trend Change (After Intervention 1)	0.000199	(0.000033, 0.000365)	0.020

¹The 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.

²Maximum 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.

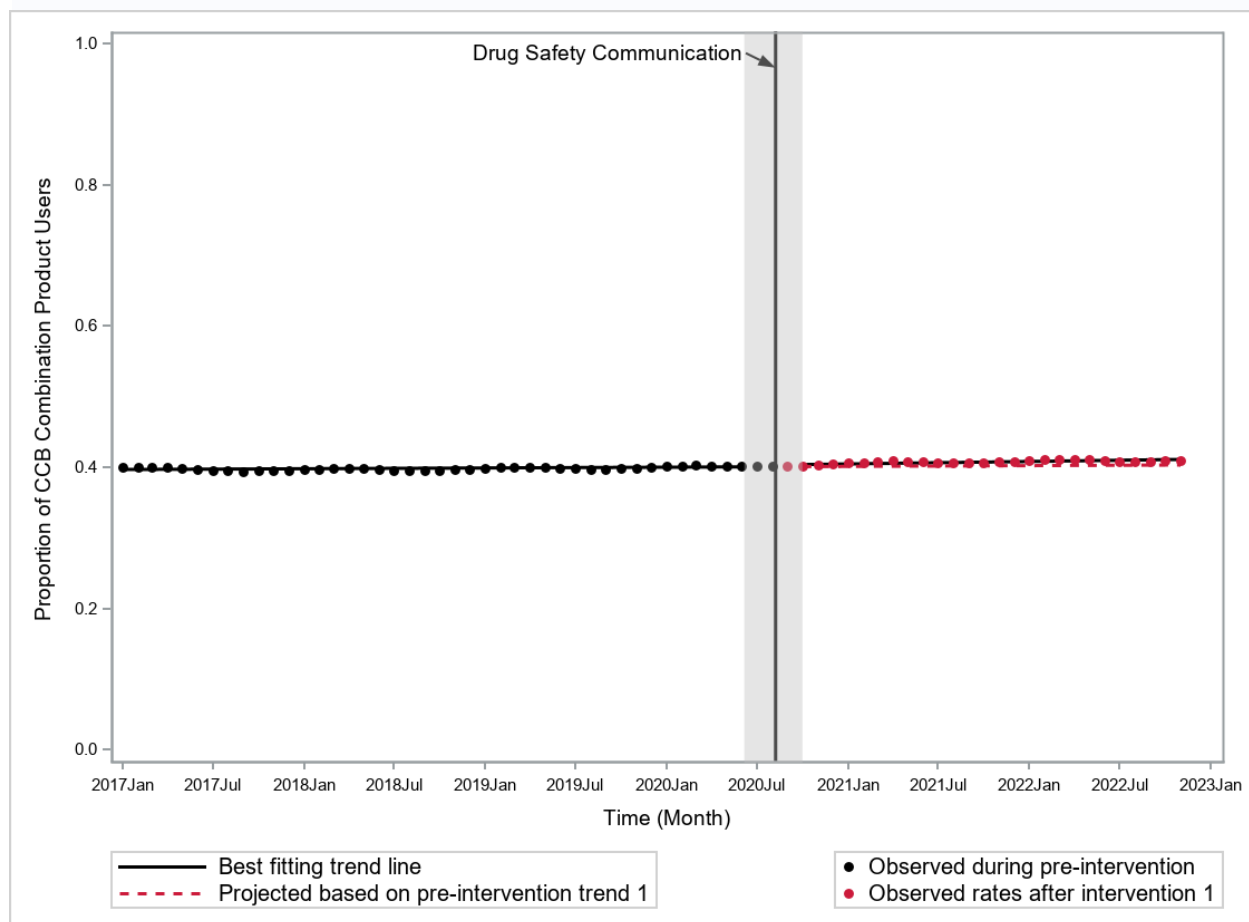
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 84. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	0.002894	(0.000431, 0.005358)	0.403595	0.400700
Relative Change (%) at 2 Months after Intervention 1	0.72	(0.10, 1.34)	0.403595	0.400700
Absolute Change at 3 Months after Intervention 1	0.003093	(0.000588, 0.005599)	0.403886	0.400792
Relative Change (%) at 3 Months after Intervention 1	0.77	(0.14, 1.40)	0.403886	0.400792
Absolute Change at 4 Months after Intervention 1	0.003292	(0.000732, 0.005853)	0.404176	0.400884
Relative Change (%) at 4 Months after Intervention 1	0.82	(0.18, 1.46)	0.404176	0.400884
Absolute Change at 5 Months after Intervention 1	0.003491	(0.000865, 0.006118)	0.404467	0.400976
Relative Change (%) at 5 Months after Intervention 1	0.87	(0.21, 1.53)	0.404467	0.400976
Absolute Change at 6 Months after Intervention 1	0.003691	(0.000986, 0.006395)	0.404758	0.401068
Relative Change (%) at 6 Months after Intervention 1	0.92	(0.24, 1.60)	0.404758	0.401068
Absolute Change at 7 Months after Intervention 1	0.003890	(0.001097, 0.006682)	0.405049	0.401160
Relative Change (%) at 7 Months after Intervention 1	0.97	(0.27, 1.67)	0.405049	0.401160
Absolute Change at 8 Months after Intervention 1	0.004089	(0.001199, 0.006978)	0.405340	0.401251
Relative Change (%) at 8 Months after Intervention 1	1.02	(0.29, 1.75)	0.405340	0.401251
Absolute Change at 9 Months after Intervention 1	0.004288	(0.001293, 0.007282)	0.405631	0.401343
Relative Change (%) at 9 Months after Intervention 1	1.07	(0.31, 1.82)	0.405631	0.401343
Absolute Change at 10 Months after Intervention 1	0.004487	(0.001379, 0.007594)	0.405922	0.401435
Relative Change (%) at 10 Months after Intervention 1	1.12	(0.34, 1.90)	0.405922	0.401435
Absolute Change at 11 Months after Intervention 1	0.004686	(0.001459, 0.007912)	0.406213	0.401527
Relative Change (%) at 11 Months after Intervention 1	1.17	(0.35, 1.98)	0.406213	0.401527
Absolute Change at 12 Months after Intervention 1	0.004885	(0.001532, 0.008237)	0.406503	0.401619
Relative Change (%) at 12 Months after Intervention 1	1.22	(0.37, 2.06)	0.406503	0.401619
Absolute Change at 13 Months after Intervention 1	0.005084	(0.001600, 0.008567)	0.406794	0.401711
Relative Change (%) at 13 Months after Intervention 1	1.27	(0.39, 2.14)	0.406794	0.401711
Absolute Change at 14 Months after Intervention 1	0.005283	(0.001664, 0.008901)	0.407085	0.401803
Relative Change (%) at 14 Months after Intervention 1	1.31	(0.40, 2.23)	0.407085	0.401803
Absolute Change at 15 Months after Intervention 1	0.005482	(0.001723, 0.009240)	0.407376	0.401895
Relative Change (%) at 15 Months after Intervention 1	1.36	(0.42, 2.31)	0.407376	0.401895
Absolute Change at 16 Months after Intervention 1	0.005681	(0.001779, 0.009583)	0.407667	0.401986
Relative Change (%) at 16 Months after Intervention 1	1.41	(0.43, 2.40)	0.407667	0.401986
Absolute Change at 17 Months after Intervention 1	0.005880	(0.001831, 0.009929)	0.407958	0.402078
Relative Change (%) at 17 Months after Intervention 1	1.46	(0.44, 2.48)	0.407958	0.402078
Absolute Change at 18 Months after Intervention 1	0.006079	(0.001880, 0.010278)	0.408249	0.402170
Relative Change (%) at 18 Months after Intervention 1	1.51	(0.45, 2.57)	0.408249	0.402170
Absolute Change at 19 Months after Intervention 1	0.006278	(0.001926, 0.010629)	0.408540	0.402262
Relative Change (%) at 19 Months after Intervention 1	1.56	(0.46, 2.66)	0.408540	0.402262
Absolute Change at 20 Months after Intervention 1	0.006477	(0.001970, 0.010983)	0.408831	0.402354
Relative Change (%) at 20 Months after Intervention 1	1.61	(0.47, 2.74)	0.408831	0.402354
Absolute Change at 21 Months after Intervention 1	0.006676	(0.002011, 0.011340)	0.409121	0.402446
Relative Change (%) at 21 Months after Intervention 1	1.66	(0.48, 2.83)	0.409121	0.402446
Absolute Change at 22 Months after Intervention 1	0.006875	(0.002051, 0.011698)	0.409412	0.402538
Relative Change (%) at 22 Months after Intervention 1	1.71	(0.49, 2.92)	0.409412	0.402538
Absolute Change at 23 Months after Intervention 1	0.007074	(0.002089, 0.012058)	0.409703	0.402630
Relative Change (%) at 23 Months after Intervention 1	1.76	(0.50, 3.01)	0.409703	0.402630
Absolute Change at 24 Months after Intervention 1	0.007273	(0.002125, 0.012420)	0.409994	0.402721
Relative Change (%) at 24 Months after Intervention 1	1.81	(0.51, 3.10)	0.409994	0.402721
Absolute Change at 25 Months after Intervention 1	0.007472	(0.002160, 0.012783)	0.410285	0.402813
Relative Change (%) at 25 Months after Intervention 1	1.85	(0.52, 3.19)	0.410285	0.402813
Absolute Change at 26 Months after Intervention 1	0.007671	(0.002194, 0.013148)	0.410576	0.402905
Relative Change (%) at 26 Months after Intervention 1	1.90	(0.52, 3.28)	0.410576	0.402905
Absolute Change at 27 Months after Intervention 1	0.007870	(0.002226, 0.013514)	0.410867	0.402997
Relative Change (%) at 27 Months after Intervention 1	1.95	(0.53, 3.37)	0.410867	0.402997
Absolute Change at 27 Months after Intervention 1	0.007870	(0.002226, 0.013514)	0.410867	0.402997
Relative Change (%) at 27 Months after Intervention 1	1.95	(0.53, 3.37)	0.410867	0.402997

¹The 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.

Figure 1. Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 85. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 61)²			
Intercept	0.207728	(0.207045, 0.208411)	<.001
Baseline trend	-0.000275	(-0.000300, -0.000250)	<.001
Level Change (After Intervention 1)	-0.000829	(-0.001647, -0.000011)	0.047
Trend Change (After Intervention 1)	-0.000040	(-0.000092, 0.000012)	0.132
Most Parsimonious Final Model Parameters (df = 61)^{2,3}			
Intercept	0.207728	(0.207045, 0.208411)	<.001
Baseline trend	-0.000275	(-0.000300, -0.000250)	<.001
Level Change (After Intervention 1)	-0.000829	(-0.001647, -0.000011)	0.047
Trend Change (After Intervention 1)	-0.000040	(-0.000092, 0.000012)	0.132

¹The 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.

²Maximum 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.

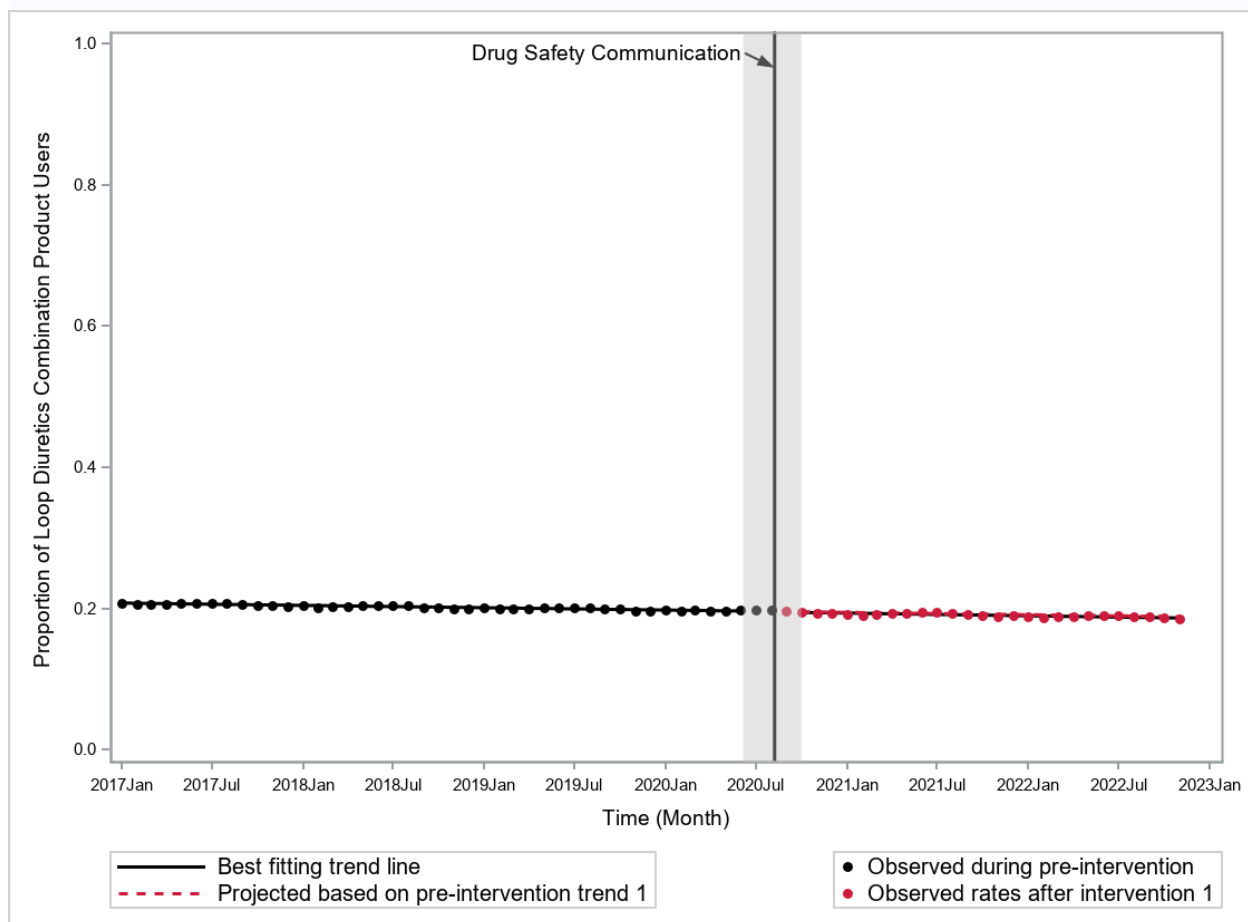
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 86. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.000908	(-0.001691, -0.000126)	0.194166	0.195075
Relative Change (%) at 2 Months after Intervention 1	-0.47	(-0.87, -0.07)	0.194166	0.195075
Absolute Change at 3 Months after Intervention 1	-0.000948	(-0.001726, -0.000171)	0.193851	0.194800
Relative Change (%) at 3 Months after Intervention 1	-0.49	(-0.88, -0.09)	0.193851	0.194800
Absolute Change at 4 Months after Intervention 1	-0.000988	(-0.001764, -0.000212)	0.193536	0.194525
Relative Change (%) at 4 Months after Intervention 1	-0.51	(-0.91, -0.11)	0.193536	0.194525
Absolute Change at 5 Months after Intervention 1	-0.001028	(-0.001806, -0.000250)	0.193221	0.194250
Relative Change (%) at 5 Months after Intervention 1	-0.53	(-0.93, -0.13)	0.193221	0.194250
Absolute Change at 6 Months after Intervention 1	-0.001068	(-0.001851, -0.000285)	0.192907	0.193974
Relative Change (%) at 6 Months after Intervention 1	-0.55	(-0.95, -0.15)	0.192907	0.193974
Absolute Change at 7 Months after Intervention 1	-0.001108	(-0.001900, -0.000316)	0.192592	0.193699
Relative Change (%) at 7 Months after Intervention 1	-0.57	(-0.98, -0.16)	0.192592	0.193699
Absolute Change at 8 Months after Intervention 1	-0.001148	(-0.001952, -0.000344)	0.192277	0.193424
Relative Change (%) at 8 Months after Intervention 1	-0.59	(-1.01, -0.18)	0.192277	0.193424
Absolute Change at 9 Months after Intervention 1	-0.001188	(-0.002007, -0.000369)	0.191962	0.193149
Relative Change (%) at 9 Months after Intervention 1	-0.61	(-1.04, -0.19)	0.191962	0.193149
Absolute Change at 10 Months after Intervention 1	-0.001227	(-0.002064, -0.000390)	0.191647	0.192874
Relative Change (%) at 10 Months after Intervention 1	-0.64	(-1.07, -0.20)	0.191647	0.192874
Absolute Change at 11 Months after Intervention 1	-0.001267	(-0.002125, -0.000409)	0.191332	0.192599
Relative Change (%) at 11 Months after Intervention 1	-0.66	(-1.10, -0.22)	0.191332	0.192599
Absolute Change at 12 Months after Intervention 1	-0.001307	(-0.002189, -0.000426)	0.191017	0.192324
Relative Change (%) at 12 Months after Intervention 1	-0.68	(-1.14, -0.22)	0.191017	0.192324
Absolute Change at 13 Months after Intervention 1	-0.001347	(-0.002254, -0.000440)	0.190702	0.192049
Relative Change (%) at 13 Months after Intervention 1	-0.70	(-1.17, -0.23)	0.190702	0.192049
Absolute Change at 14 Months after Intervention 1	-0.001387	(-0.002322, -0.000452)	0.190387	0.191774
Relative Change (%) at 14 Months after Intervention 1	-0.72	(-1.21, -0.24)	0.190387	0.191774
Absolute Change at 15 Months after Intervention 1	-0.001427	(-0.002392, -0.000462)	0.190072	0.191499
Relative Change (%) at 15 Months after Intervention 1	-0.75	(-1.25, -0.24)	0.190072	0.191499
Absolute Change at 16 Months after Intervention 1	-0.001467	(-0.002464, -0.000470)	0.189757	0.191224
Relative Change (%) at 16 Months after Intervention 1	-0.77	(-1.28, -0.25)	0.189757	0.191224
Absolute Change at 17 Months after Intervention 1	-0.001507	(-0.002537, -0.000476)	0.189442	0.190949
Relative Change (%) at 17 Months after Intervention 1	-0.79	(-1.32, -0.25)	0.189442	0.190949
Absolute Change at 18 Months after Intervention 1	-0.001547	(-0.002612, -0.000481)	0.189127	0.190674
Relative Change (%) at 18 Months after Intervention 1	-0.81	(-1.37, -0.26)	0.189127	0.190674
Absolute Change at 19 Months after Intervention 1	-0.001586	(-0.002688, -0.000485)	0.188812	0.190399
Relative Change (%) at 19 Months after Intervention 1	-0.83	(-1.41, -0.26)	0.188812	0.190399
Absolute Change at 20 Months after Intervention 1	-0.001626	(-0.002765, -0.000488)	0.188497	0.190124
Relative Change (%) at 20 Months after Intervention 1	-0.86	(-1.45, -0.26)	0.188497	0.190124
Absolute Change at 21 Months after Intervention 1	-0.001666	(-0.002843, -0.000489)	0.188182	0.189848
Relative Change (%) at 21 Months after Intervention 1	-0.88	(-1.49, -0.26)	0.188182	0.189848
Absolute Change at 22 Months after Intervention 1	-0.001706	(-0.002923, -0.000489)	0.187867	0.189573
Relative Change (%) at 22 Months after Intervention 1	-0.90	(-1.54, -0.26)	0.187867	0.189573
Absolute Change at 23 Months after Intervention 1	-0.001746	(-0.003003, -0.000489)	0.187552	0.189298
Relative Change (%) at 23 Months after Intervention 1	-0.92	(-1.58, -0.26)	0.187552	0.189298
Absolute Change at 24 Months after Intervention 1	-0.001786	(-0.003084, -0.000487)	0.187237	0.189023
Relative Change (%) at 24 Months after Intervention 1	-0.94	(-1.63, -0.26)	0.187237	0.189023
Absolute Change at 25 Months after Intervention 1	-0.001826	(-0.003166, -0.000485)	0.186923	0.188748
Relative Change (%) at 25 Months after Intervention 1	-0.97	(-1.67, -0.26)	0.186923	0.188748
Absolute Change at 26 Months after Intervention 1	-0.001866	(-0.003249, -0.000482)	0.186608	0.188473
Relative Change (%) at 26 Months after Intervention 1	-0.99	(-1.72, -0.26)	0.186608	0.188473
Absolute Change at 27 Months after Intervention 1	-0.001905	(-0.003332, -0.000479)	0.186293	0.188198
Relative Change (%) at 27 Months after Intervention 1	-1.01	(-1.76, -0.26)	0.186293	0.188198
Absolute Change at 27 Months after Intervention 1	-0.001905	(-0.003332, -0.000479)	0.186293	0.188198
Relative Change (%) at 27 Months after Intervention 1	-1.01	(-1.76, -0.26)	0.186293	0.188198

¹The 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.

Figure 43. Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 87. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.047078	(0.046611, 0.047545)	<.001
Baseline trend	0.000061	(0.000044, 0.000079)	<.001
Level Change (After Intervention 1)	-0.000448	(-0.001050, 0.000153)	0.141
Trend Change (After Intervention 1)	0.000116	(0.000077, 0.000155)	<.001
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.047078	(0.046611, 0.047545)	<.001
Baseline trend	0.000061	(0.000044, 0.000079)	<.001
Level Change (After Intervention 1)	-0.000448	(-0.001050, 0.000153)	0.141
Trend Change (After Intervention 1)	0.000116	(0.000077, 0.000155)	<.001

¹The 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.

²Maximum 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.

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

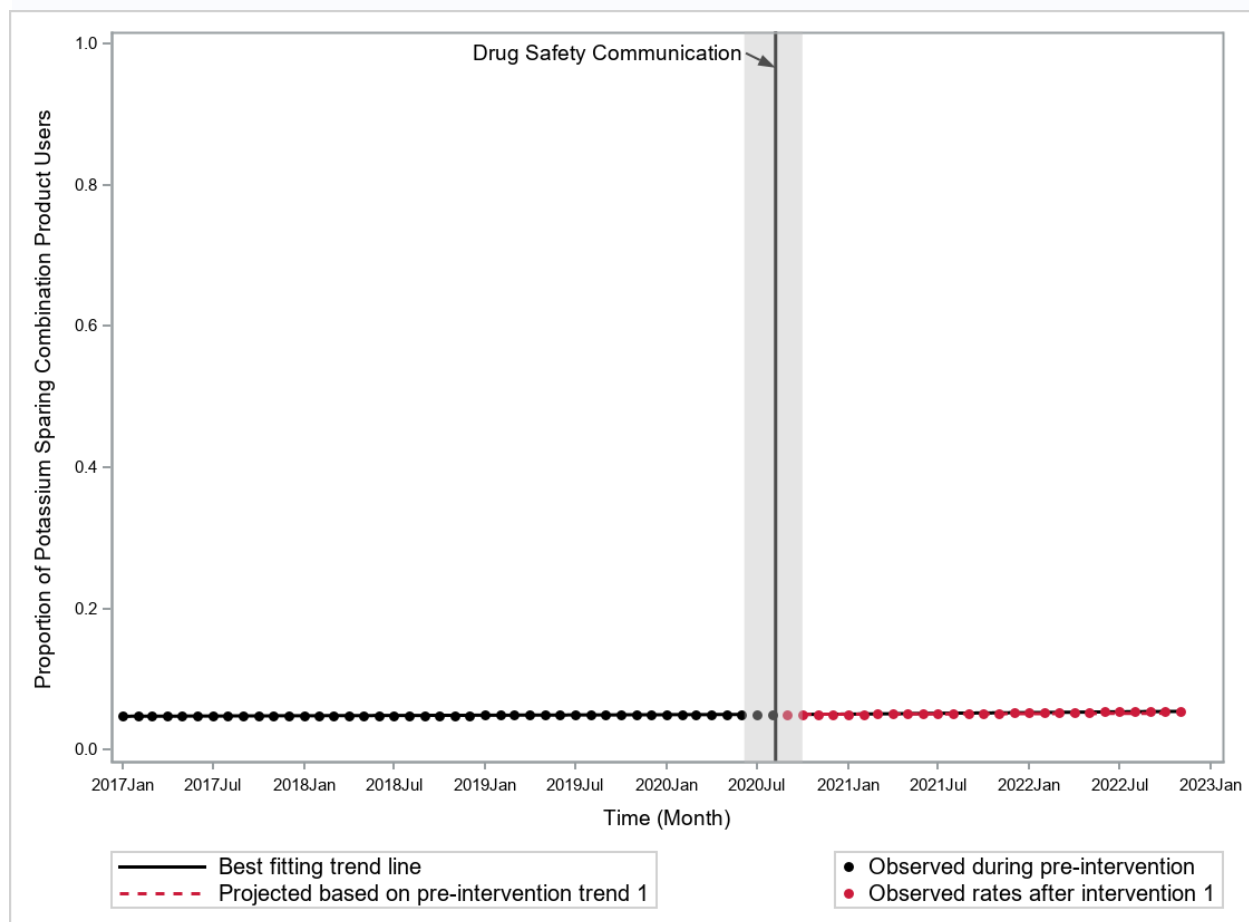
Table 88. Absolute and Relative Changes in Proportion of Potassium-Sparing Diuretics Users among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer after August 8, 2020¹ Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	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	-0.000216	(-0.000796, 0.000364)	0.049685	0.049901
Relative Change (%) at 2 Months after Intervention 1	-0.43	(-1.59, 0.73)	0.049685	0.049901
Absolute Change at 3 Months after Intervention 1	-0.000100	(-0.000678, 0.000478)	0.049862	0.049962
Relative Change (%) at 3 Months after Intervention 1	-0.20	(-1.36, 0.95)	0.049862	0.049962
Absolute Change at 4 Months after Intervention 1	0.000016	(-0.000563, 0.000594)	0.050039	0.050024
Relative Change (%) at 4 Months after Intervention 1	0.03	(-1.13, 1.19)	0.050039	0.050024
Absolute Change at 5 Months after Intervention 1	0.000132	(-0.000450, 0.000714)	0.050217	0.050085
Relative Change (%) at 5 Months after Intervention 1	0.26	(-0.90, 1.43)	0.050217	0.050085
Absolute Change at 6 Months after Intervention 1	0.000248	(-0.000340, 0.000836)	0.050394	0.050146
Relative Change (%) at 6 Months after Intervention 1	0.49	(-0.68, 1.67)	0.050394	0.050146
Absolute Change at 7 Months after Intervention 1	0.000364	(-0.000233, 0.000960)	0.050571	0.050208
Relative Change (%) at 7 Months after Intervention 1	0.72	(-0.47, 1.92)	0.050571	0.050208
Absolute Change at 8 Months after Intervention 1	0.000480	(-0.000128, 0.001087)	0.050749	0.050269
Relative Change (%) at 8 Months after Intervention 1	0.95	(-0.26, 2.17)	0.050749	0.050269
Absolute Change at 9 Months after Intervention 1	0.000596	(-0.000025, 0.001216)	0.050926	0.050330
Relative Change (%) at 9 Months after Intervention 1	1.18	(-0.06, 2.43)	0.050926	0.050330
Absolute Change at 10 Months after Intervention 1	0.000712	(0.000076, 0.001348)	0.051104	0.050392
Relative Change (%) at 10 Months after Intervention 1	1.41	(0.13, 2.69)	0.051104	0.050392
Absolute Change at 11 Months after Intervention 1	0.000828	(0.000174, 0.001481)	0.051281	0.050453
Relative Change (%) at 11 Months after Intervention 1	1.64	(0.33, 2.95)	0.051281	0.050453
Absolute Change at 12 Months after Intervention 1	0.000944	(0.000271, 0.001617)	0.051458	0.050515
Relative Change (%) at 12 Months after Intervention 1	1.87	(0.51, 3.22)	0.051458	0.050515
Absolute Change at 13 Months after Intervention 1	0.001060	(0.000366, 0.001754)	0.051636	0.050576
Relative Change (%) at 13 Months after Intervention 1	2.10	(0.70, 3.49)	0.051636	0.050576
Absolute Change at 14 Months after Intervention 1	0.001176	(0.000459, 0.001892)	0.051813	0.050637
Relative Change (%) at 14 Months after Intervention 1	2.32	(0.88, 3.77)	0.051813	0.050637
Absolute Change at 15 Months after Intervention 1	0.001292	(0.000551, 0.002032)	0.051990	0.050699
Relative Change (%) at 15 Months after Intervention 1	2.55	(1.05, 4.04)	0.051990	0.050699
Absolute Change at 16 Months after Intervention 1	0.001408	(0.000642, 0.002174)	0.052168	0.050760
Relative Change (%) at 16 Months after Intervention 1	2.77	(1.23, 4.32)	0.052168	0.050760
Absolute Change at 17 Months after Intervention 1	0.001524	(0.000731, 0.002316)	0.052345	0.050821
Relative Change (%) at 17 Months after Intervention 1	3.00	(1.40, 4.60)	0.052345	0.050821
Absolute Change at 18 Months after Intervention 1	0.001640	(0.000820, 0.002460)	0.052522	0.050883
Relative Change (%) at 18 Months after Intervention 1	3.22	(1.57, 4.88)	0.052522	0.050883
Absolute Change at 19 Months after Intervention 1	0.001756	(0.000907, 0.002604)	0.052700	0.050944
Relative Change (%) at 19 Months after Intervention 1	3.45	(1.73, 5.16)	0.052700	0.050944
Absolute Change at 20 Months after Intervention 1	0.001872	(0.000994, 0.002749)	0.052877	0.051005
Relative Change (%) at 20 Months after Intervention 1	3.67	(1.90, 5.44)	0.052877	0.051005
Absolute Change at 21 Months after Intervention 1	0.001988	(0.001080, 0.002895)	0.053055	0.051067
Relative Change (%) at 21 Months after Intervention 1	3.89	(2.06, 5.73)	0.053055	0.051067
Absolute Change at 22 Months after Intervention 1	0.002104	(0.001165, 0.003042)	0.053232	0.051128
Relative Change (%) at 22 Months after Intervention 1	4.11	(2.22, 6.01)	0.053232	0.051128
Absolute Change at 23 Months after Intervention 1	0.002220	(0.001250, 0.003190)	0.053409	0.051190
Relative Change (%) at 23 Months after Intervention 1	4.34	(2.38, 6.30)	0.053409	0.051190
Absolute Change at 24 Months after Intervention 1	0.002336	(0.001334, 0.003337)	0.053587	0.051251
Relative Change (%) at 24 Months after Intervention 1	4.56	(2.53, 6.58)	0.053587	0.051251
Absolute Change at 25 Months after Intervention 1	0.002452	(0.001417, 0.003486)	0.053764	0.051312
Relative Change (%) at 25 Months after Intervention 1	4.78	(2.69, 6.87)	0.053764	0.051312
Absolute Change at 26 Months after Intervention 1	0.002568	(0.001501, 0.003635)	0.053941	0.051374
Relative Change (%) at 26 Months after Intervention 1	5.00	(2.84, 7.15)	0.053941	0.051374
Absolute Change at 27 Months after Intervention 1	0.002684	(0.001583, 0.003784)	0.054119	0.051435
Relative Change (%) at 27 Months after Intervention 1	5.22	(3.00, 7.44)	0.054119	0.051435
Absolute Change at 27 Months after Intervention 1	0.002684	(0.001583, 0.003784)	0.054119	0.051435
Relative Change (%) at 27 Months after Intervention 1	5.22	(3.00, 7.44)	0.054119	0.051435

¹The 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 44. Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 89. 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 with History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 55)²			
Intercept	0.024221	(0.023905, 0.024537)	<.001
Baseline trend	0.000042	(0.000029, 0.000054)	<.001
Level Change (After Intervention 1)	-0.000469	(-0.000974, 0.000036)	0.068
Trend Change (After Intervention 1)	-0.000063	(-0.000092, -0.000034)	<.001
Most Parsimonious Final Model Parameters (df = 55)^{2,3}			
Intercept	0.024221	(0.023905, 0.024537)	<.001
Baseline trend	0.000042	(0.000029, 0.000054)	<.001
Level Change (After Intervention 1)	-0.000469	(-0.000974, 0.000036)	0.068
Trend Change (After Intervention 1)	-0.000063	(-0.000092, -0.000034)	<.001

¹The 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.

²Maximum 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.

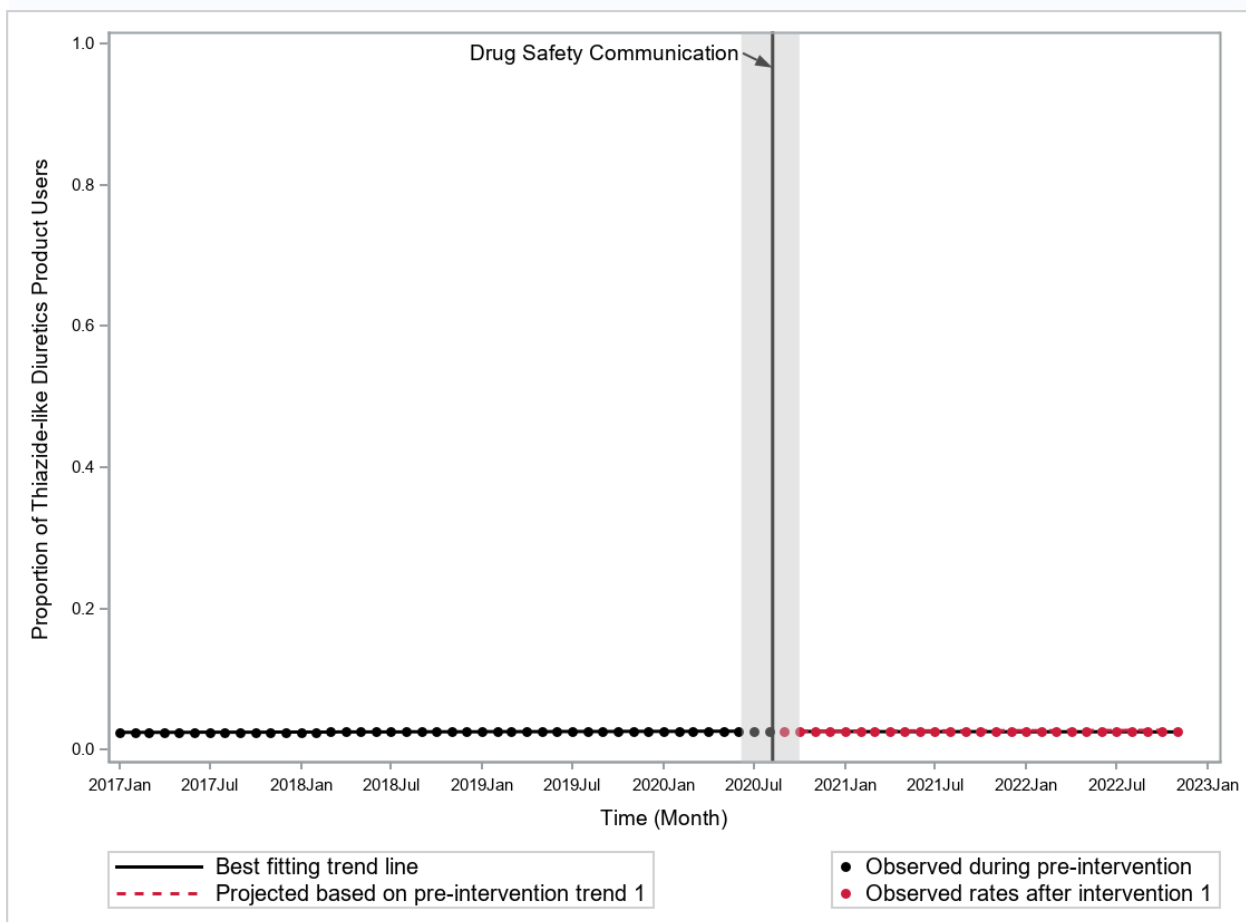
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 90. 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 with History of Skin Cancer after August 8, 2020¹ 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	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	-0.000595	(-0.001153, -0.000036)	0.025543	0.026138
Relative Change (%) at 2 Months after Intervention 1	-2.28	(-4.39, -0.16)	0.025543	0.026138
Absolute Change at 3 Months after Intervention 1	-0.000658	(-0.001210, -0.000106)	0.025521	0.026179
Relative Change (%) at 3 Months after Intervention 1	-2.51	(-4.59, -0.43)	0.025521	0.026179
Absolute Change at 4 Months after Intervention 1	-0.000721	(-0.001268, -0.000174)	0.025500	0.026221
Relative Change (%) at 4 Months after Intervention 1	-2.75	(-4.80, -0.70)	0.025500	0.026221
Absolute Change at 5 Months after Intervention 1	-0.000784	(-0.001327, -0.000240)	0.025479	0.026263
Relative Change (%) at 5 Months after Intervention 1	-2.98	(-5.02, -0.95)	0.025479	0.026263
Absolute Change at 6 Months after Intervention 1	-0.000847	(-0.001388, -0.000306)	0.025458	0.026304
Relative Change (%) at 6 Months after Intervention 1	-3.22	(-5.23, -1.20)	0.025458	0.026304
Absolute Change at 7 Months after Intervention 1	-0.000910	(-0.001451, -0.000369)	0.025436	0.026346
Relative Change (%) at 7 Months after Intervention 1	-3.45	(-5.46, -1.45)	0.025436	0.026346
Absolute Change at 8 Months after Intervention 1	-0.000973	(-0.001514, -0.000431)	0.025415	0.026388
Relative Change (%) at 8 Months after Intervention 1	-3.69	(-5.69, -1.69)	0.025415	0.026388
Absolute Change at 9 Months after Intervention 1	-0.001036	(-0.001580, -0.000492)	0.025394	0.026429
Relative Change (%) at 9 Months after Intervention 1	-3.92	(-5.92, -1.92)	0.025394	0.026429
Absolute Change at 10 Months after Intervention 1	-0.001099	(-0.001647, -0.000551)	0.025372	0.026471
Relative Change (%) at 10 Months after Intervention 1	-4.15	(-6.16, -2.15)	0.025372	0.026471
Absolute Change at 11 Months after Intervention 1	-0.001162	(-0.001715, -0.000608)	0.025351	0.026513
Relative Change (%) at 11 Months after Intervention 1	-4.38	(-6.40, -2.37)	0.025351	0.026513
Absolute Change at 12 Months after Intervention 1	-0.001225	(-0.001785, -0.000664)	0.025330	0.026554
Relative Change (%) at 12 Months after Intervention 1	-4.61	(-6.64, -2.58)	0.025330	0.026554
Absolute Change at 13 Months after Intervention 1	-0.001288	(-0.001856, -0.000719)	0.025308	0.026596
Relative Change (%) at 13 Months after Intervention 1	-4.84	(-6.89, -2.79)	0.025308	0.026596
Absolute Change at 14 Months after Intervention 1	-0.001351	(-0.001929, -0.000772)	0.025287	0.026638
Relative Change (%) at 14 Months after Intervention 1	-5.07	(-7.15, -2.99)	0.025287	0.026638
Absolute Change at 15 Months after Intervention 1	-0.001414	(-0.002003, -0.000825)	0.025266	0.026679
Relative Change (%) at 15 Months after Intervention 1	-5.30	(-7.41, -3.19)	0.025266	0.026679
Absolute Change at 16 Months after Intervention 1	-0.001477	(-0.002078, -0.000876)	0.025244	0.026721
Relative Change (%) at 16 Months after Intervention 1	-5.53	(-7.67, -3.38)	0.025244	0.026721
Absolute Change at 17 Months after Intervention 1	-0.001540	(-0.002154, -0.000925)	0.025223	0.026763
Relative Change (%) at 17 Months after Intervention 1	-5.75	(-7.94, -3.57)	0.025223	0.026763
Absolute Change at 18 Months after Intervention 1	-0.001603	(-0.002231, -0.000974)	0.025202	0.026804
Relative Change (%) at 18 Months after Intervention 1	-5.98	(-8.21, -3.75)	0.025202	0.026804
Absolute Change at 19 Months after Intervention 1	-0.001666	(-0.002309, -0.001022)	0.025180	0.026846
Relative Change (%) at 19 Months after Intervention 1	-6.20	(-8.48, -3.93)	0.025180	0.026846
Absolute Change at 20 Months after Intervention 1	-0.001729	(-0.002388, -0.001069)	0.025159	0.026888
Relative Change (%) at 20 Months after Intervention 1	-6.43	(-8.75, -4.11)	0.025159	0.026888
Absolute Change at 21 Months after Intervention 1	-0.001792	(-0.002468, -0.001115)	0.025138	0.026929
Relative Change (%) at 21 Months after Intervention 1	-6.65	(-9.03, -4.28)	0.025138	0.026929
Absolute Change at 22 Months after Intervention 1	-0.001855	(-0.002549, -0.001160)	0.025116	0.026971
Relative Change (%) at 22 Months after Intervention 1	-6.88	(-9.31, -4.45)	0.025116	0.026971
Absolute Change at 23 Months after Intervention 1	-0.001918	(-0.002630, -0.001205)	0.025095	0.027013
Relative Change (%) at 23 Months after Intervention 1	-7.10	(-9.59, -4.61)	0.025095	0.027013
Absolute Change at 24 Months after Intervention 1	-0.001981	(-0.002712, -0.001249)	0.025074	0.027054
Relative Change (%) at 24 Months after Intervention 1	-7.32	(-9.87, -4.77)	0.025074	0.027054
Absolute Change at 25 Months after Intervention 1	-0.002044	(-0.002795, -0.001292)	0.025052	0.027096
Relative Change (%) at 25 Months after Intervention 1	-7.54	(-10.15, -4.93)	0.025052	0.027096
Absolute Change at 26 Months after Intervention 1	-0.002107	(-0.002878, -0.001335)	0.025031	0.027138
Relative Change (%) at 26 Months after Intervention 1	-7.76	(-10.44, -5.09)	0.025031	0.027138
Absolute Change at 27 Months after Intervention 1	-0.002170	(-0.002962, -0.001377)	0.025010	0.027179
Relative Change (%) at 27 Months after Intervention 1	-7.98	(-10.72, -5.24)	0.025010	0.027179
Absolute Change at 27 Months after Intervention 1	-0.002170	(-0.002962, -0.001377)	0.025010	0.027179
Relative Change (%) at 27 Months after Intervention 1	-7.98	(-10.72, -5.24)	0.025010	0.027179

¹The 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.

Figure 45. Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 91. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 59)²			
Intercept	0.198359	(0.197455, 0.199263)	<.001
Baseline trend	-0.000269	(-0.000306, -0.000232)	<.001
Level Change (After Intervention 1)	-0.003797	(-0.005415, -0.002180)	<.001
Trend Change (After Intervention 1)	-0.000198	(-0.000282, -0.000114)	<.001
Most Parsimonious Final Model Parameters (df = 59)^{2,3}			
Intercept	0.198359	(0.197455, 0.199263)	<.001
Baseline trend	-0.000269	(-0.000306, -0.000232)	<.001
Level Change (After Intervention 1)	-0.003797	(-0.005415, -0.002180)	<.001
Trend Change (After Intervention 1)	-0.000198	(-0.000282, -0.000114)	<.001

¹The 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.

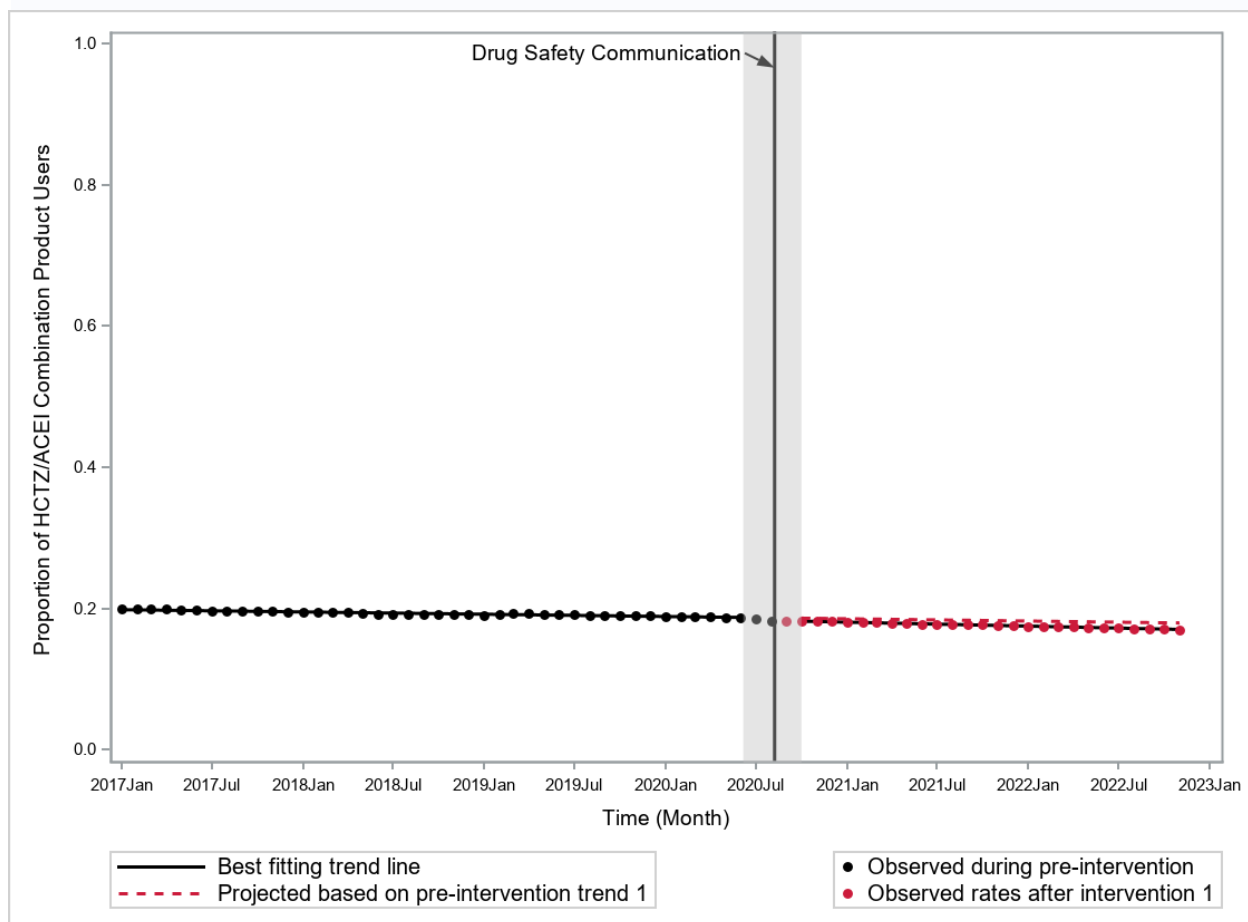
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 92. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	-0.004193	(-0.005773, -0.002614)	0.181795	0.185988
Relative Change (%) at 2 Months after Intervention 1	-2.25	(-3.10, -1.41)	0.181795	0.185988
Absolute Change at 3 Months after Intervention 1	-0.004391	(-0.005943, -0.002840)	0.181328	0.185719
Relative Change (%) at 3 Months after Intervention 1	-2.36	(-3.19, -1.54)	0.181328	0.185719
Absolute Change at 4 Months after Intervention 1	-0.004589	(-0.006116, -0.003062)	0.180861	0.185450
Relative Change (%) at 4 Months after Intervention 1	-2.47	(-3.29, -1.66)	0.180861	0.185450
Absolute Change at 5 Months after Intervention 1	-0.004787	(-0.006294, -0.003280)	0.180394	0.185181
Relative Change (%) at 5 Months after Intervention 1	-2.59	(-3.39, -1.78)	0.180394	0.185181
Absolute Change at 6 Months after Intervention 1	-0.004985	(-0.006477, -0.003494)	0.179927	0.184913
Relative Change (%) at 6 Months after Intervention 1	-2.70	(-3.49, -1.90)	0.179927	0.184913
Absolute Change at 7 Months after Intervention 1	-0.005183	(-0.006663, -0.003703)	0.179461	0.184644
Relative Change (%) at 7 Months after Intervention 1	-2.81	(-3.59, -2.02)	0.179461	0.184644
Absolute Change at 8 Months after Intervention 1	-0.005381	(-0.006855, -0.003907)	0.178994	0.184375
Relative Change (%) at 8 Months after Intervention 1	-2.92	(-3.70, -2.14)	0.178994	0.184375
Absolute Change at 9 Months after Intervention 1	-0.005579	(-0.007051, -0.004107)	0.178527	0.184106
Relative Change (%) at 9 Months after Intervention 1	-3.03	(-3.81, -2.25)	0.178527	0.184106
Absolute Change at 10 Months after Intervention 1	-0.005777	(-0.007252, -0.004302)	0.178060	0.183837
Relative Change (%) at 10 Months after Intervention 1	-3.14	(-3.93, -2.36)	0.178060	0.183837
Absolute Change at 11 Months after Intervention 1	-0.005975	(-0.007457, -0.004492)	0.177593	0.183568
Relative Change (%) at 11 Months after Intervention 1	-3.25	(-4.04, -2.47)	0.177593	0.183568
Absolute Change at 12 Months after Intervention 1	-0.006173	(-0.007667, -0.004678)	0.177126	0.183299
Relative Change (%) at 12 Months after Intervention 1	-3.37	(-4.16, -2.57)	0.177126	0.183299
Absolute Change at 13 Months after Intervention 1	-0.006371	(-0.007882, -0.004859)	0.176659	0.183030
Relative Change (%) at 13 Months after Intervention 1	-3.48	(-4.28, -2.68)	0.176659	0.183030
Absolute Change at 14 Months after Intervention 1	-0.006569	(-0.008101, -0.005036)	0.176193	0.182761
Relative Change (%) at 14 Months after Intervention 1	-3.59	(-4.41, -2.78)	0.176193	0.182761
Absolute Change at 15 Months after Intervention 1	-0.006766	(-0.008324, -0.005209)	0.175726	0.182492
Relative Change (%) at 15 Months after Intervention 1	-3.71	(-4.53, -2.88)	0.175726	0.182492
Absolute Change at 16 Months after Intervention 1	-0.006964	(-0.008551, -0.005377)	0.175259	0.182223
Relative Change (%) at 16 Months after Intervention 1	-3.82	(-4.66, -2.98)	0.175259	0.182223
Absolute Change at 17 Months after Intervention 1	-0.007162	(-0.008782, -0.005542)	0.174792	0.181954
Relative Change (%) at 17 Months after Intervention 1	-3.94	(-4.80, -3.08)	0.174792	0.181954
Absolute Change at 18 Months after Intervention 1	-0.007360	(-0.009017, -0.005704)	0.174325	0.181685
Relative Change (%) at 18 Months after Intervention 1	-4.05	(-4.93, -3.17)	0.174325	0.181685
Absolute Change at 19 Months after Intervention 1	-0.007558	(-0.009254, -0.005862)	0.173858	0.181416
Relative Change (%) at 19 Months after Intervention 1	-4.17	(-5.07, -3.26)	0.173858	0.181416
Absolute Change at 20 Months after Intervention 1	-0.007756	(-0.009495, -0.006017)	0.173391	0.181148
Relative Change (%) at 20 Months after Intervention 1	-4.28	(-5.21, -3.36)	0.173391	0.181148
Absolute Change at 21 Months after Intervention 1	-0.007954	(-0.009739, -0.006169)	0.172925	0.180879
Relative Change (%) at 21 Months after Intervention 1	-4.40	(-5.35, -3.45)	0.172925	0.180879
Absolute Change at 22 Months after Intervention 1	-0.008152	(-0.009985, -0.006319)	0.172458	0.180610
Relative Change (%) at 22 Months after Intervention 1	-4.51	(-5.49, -3.54)	0.172458	0.180610
Absolute Change at 23 Months after Intervention 1	-0.008350	(-0.010234, -0.006466)	0.171991	0.180341
Relative Change (%) at 23 Months after Intervention 1	-4.63	(-5.64, -3.62)	0.171991	0.180341
Absolute Change at 24 Months after Intervention 1	-0.008548	(-0.010485, -0.006611)	0.171524	0.180072
Relative Change (%) at 24 Months after Intervention 1	-4.75	(-5.78, -3.71)	0.171524	0.180072
Absolute Change at 25 Months after Intervention 1	-0.008746	(-0.010738, -0.006753)	0.171057	0.179803
Relative Change (%) at 25 Months after Intervention 1	-4.86	(-5.93, -3.80)	0.171057	0.179803
Absolute Change at 26 Months after Intervention 1	-0.008944	(-0.010993, -0.006894)	0.170590	0.179534
Relative Change (%) at 26 Months after Intervention 1	-4.98	(-6.08, -3.88)	0.170590	0.179534
Absolute Change at 27 Months after Intervention 1	-0.009142	(-0.011250, -0.007033)	0.170123	0.179265
Relative Change (%) at 27 Months after Intervention 1	-5.10	(-6.23, -3.97)	0.170123	0.179265
Absolute Change at 27 Months after Intervention 1	-0.009142	(-0.011250, -0.007033)	0.170123	0.179265
Relative Change (%) at 27 Months after Intervention 1	-5.10	(-6.23, -3.97)	0.170123	0.179265

¹The 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.

Figure 46. 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 with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 93. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.006078	(0.005716, 0.006440)	<.001
Baseline trend	-0.000036	(-0.000049, -0.000022)	<.001
Level Change (After Intervention 1)	0.000075	(-0.000184, 0.000335)	0.564
Trend Change (After Intervention 1)	-0.000013	(-0.000046, 0.000019)	0.419
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.006153	(0.005853, 0.006452)	<.001
Baseline trend	-0.000038	(-0.000046, -0.000031)	<.001

¹The 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.

²Maximum 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.

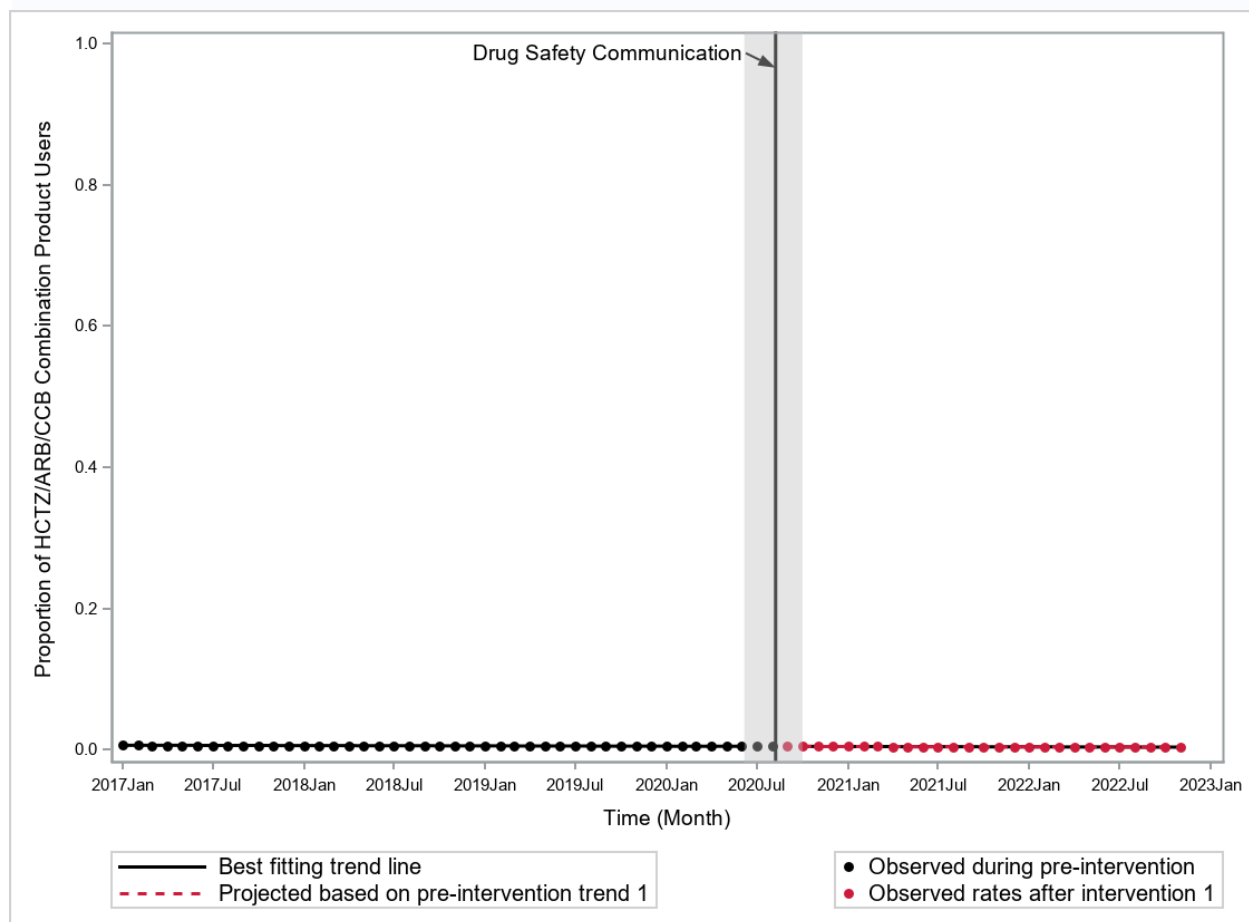
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 94. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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)	0.004384	0.004384
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.004384	0.004384
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004346	0.004346
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.004346	0.004346
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004307	0.004307
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.004307	0.004307
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004269	0.004269
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.004269	0.004269
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004230	0.004230
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.004230	0.004230
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004192	0.004192
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.004192	0.004192
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004154	0.004154
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.004154	0.004154
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004115	0.004115
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.004115	0.004115
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004077	0.004077
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.004077	0.004077
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004038	0.004038
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.004038	0.004038
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.004000	0.004000
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.004000	0.004000
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003961	0.003961
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.003961	0.003961
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003923	0.003923
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.003923	0.003923
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003885	0.003885
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.003885	0.003885
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003846	0.003846
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.003846	0.003846
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003808	0.003808
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.003808	0.003808
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003769	0.003769
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.003769	0.003769
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003731	0.003731
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.003731	0.003731
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003692	0.003692
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.003692	0.003692
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003654	0.003654
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.003654	0.003654
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003615	0.003615
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.003615	0.003615
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003577	0.003577
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.003577	0.003577
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003539	0.003539
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.003539	0.003539
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003500	0.003500
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.003500	0.003500
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003462	0.003462
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.003462	0.003462
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.003423	0.003423
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.003423	0.003423

¹The 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.

Figure 47. 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 with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 95. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 60)²			
Intercept	0.272525	(0.258523, 0.286528)	<.001
Baseline trend	-0.001633	(-0.002169, -0.001097)	<.001
Level Change (After Intervention 1)	-0.001662	(-0.011307, 0.007982)	0.731
Trend Change (After Intervention 1)	0.001823	(0.000471, 0.003174)	0.009
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.269267	(0.251824, 0.286710)	<.001
Baseline trend	-0.001549	(-0.002188, -0.000910)	<.001
Trend Change (After Intervention 1)	0.001719	(0.000163, 0.003274)	0.031

¹The 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.

²Maximum 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.

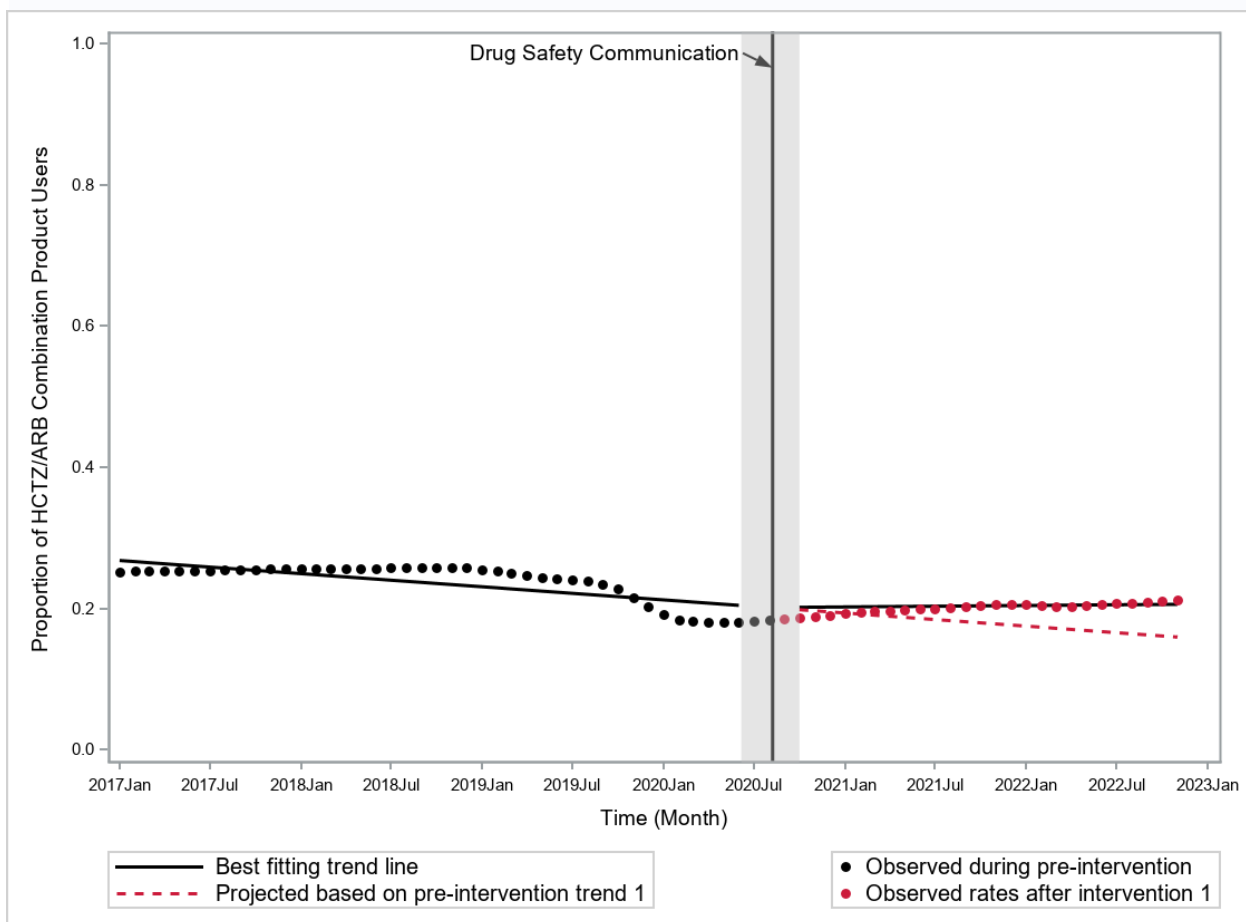
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 96. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.003437	(0.000255, 0.006619)	0.201453	0.198016
Relative Change (%) at 2 Months after Intervention 1	1.74	(0.00, 3.48)	0.201453	0.198016
Absolute Change at 3 Months after Intervention 1	0.005156	(0.000383, 0.009928)	0.201623	0.196467
Relative Change (%) at 3 Months after Intervention 1	2.62	(-0.02, 5.26)	0.201623	0.196467
Absolute Change at 4 Months after Intervention 1	0.006874	(0.000510, 0.013238)	0.201793	0.194918
Relative Change (%) at 4 Months after Intervention 1	3.53	(-0.03, 7.09)	0.201793	0.194918
Absolute Change at 5 Months after Intervention 1	0.008593	(0.000638, 0.016547)	0.201962	0.193370
Relative Change (%) at 5 Months after Intervention 1	4.44	(-0.06, 8.95)	0.201962	0.193370
Absolute Change at 6 Months after Intervention 1	0.010311	(0.000766, 0.019857)	0.202132	0.191821
Relative Change (%) at 6 Months after Intervention 1	5.38	(-0.09, 10.84)	0.202132	0.191821
Absolute Change at 7 Months after Intervention 1	0.012030	(0.000893, 0.023166)	0.202301	0.190272
Relative Change (%) at 7 Months after Intervention 1	6.32	(-0.13, 12.77)	0.202301	0.190272
Absolute Change at 8 Months after Intervention 1	0.013748	(0.001021, 0.026476)	0.202471	0.188723
Relative Change (%) at 8 Months after Intervention 1	7.28	(-0.18, 14.74)	0.202471	0.188723
Absolute Change at 9 Months after Intervention 1	0.015467	(0.001148, 0.029785)	0.202641	0.187174
Relative Change (%) at 9 Months after Intervention 1	8.26	(-0.23, 16.76)	0.202641	0.187174
Absolute Change at 10 Months after Intervention 1	0.017185	(0.001276, 0.033095)	0.202810	0.185625
Relative Change (%) at 10 Months after Intervention 1	9.26	(-0.29, 18.81)	0.202810	0.185625
Absolute Change at 11 Months after Intervention 1	0.018904	(0.001404, 0.036404)	0.202980	0.184076
Relative Change (%) at 11 Months after Intervention 1	10.27	(-0.37, 20.90)	0.202980	0.184076
Absolute Change at 12 Months after Intervention 1	0.020622	(0.001531, 0.039714)	0.203150	0.182527
Relative Change (%) at 12 Months after Intervention 1	11.30	(-0.45, 23.04)	0.203150	0.182527
Absolute Change at 13 Months after Intervention 1	0.022341	(0.001659, 0.043023)	0.203319	0.180978
Relative Change (%) at 13 Months after Intervention 1	12.34	(-0.54, 25.23)	0.203319	0.180978
Absolute Change at 14 Months after Intervention 1	0.024060	(0.001787, 0.046333)	0.203489	0.179429
Relative Change (%) at 14 Months after Intervention 1	13.41	(-0.64, 27.46)	0.203489	0.179429
Absolute Change at 15 Months after Intervention 1	0.025778	(0.001914, 0.049642)	0.203658	0.177880
Relative Change (%) at 15 Months after Intervention 1	14.49	(-0.75, 29.74)	0.203658	0.177880
Absolute Change at 16 Months after Intervention 1	0.027497	(0.002042, 0.052951)	0.203828	0.176331
Relative Change (%) at 16 Months after Intervention 1	15.59	(-0.88, 32.07)	0.203828	0.176331
Absolute Change at 17 Months after Intervention 1	0.029215	(0.002169, 0.056261)	0.203998	0.174782
Relative Change (%) at 17 Months after Intervention 1	16.72	(-1.02, 34.45)	0.203998	0.174782
Absolute Change at 18 Months after Intervention 1	0.030934	(0.002297, 0.059570)	0.204167	0.173234
Relative Change (%) at 18 Months after Intervention 1	17.86	(-1.16, 36.88)	0.204167	0.173234
Absolute Change at 19 Months after Intervention 1	0.032652	(0.002425, 0.062880)	0.204337	0.171685
Relative Change (%) at 19 Months after Intervention 1	19.02	(-1.33, 39.36)	0.204337	0.171685
Absolute Change at 20 Months after Intervention 1	0.034371	(0.002552, 0.066189)	0.204506	0.170136
Relative Change (%) at 20 Months after Intervention 1	20.20	(-1.50, 41.91)	0.204506	0.170136
Absolute Change at 21 Months after Intervention 1	0.036089	(0.002680, 0.069499)	0.204676	0.168587
Relative Change (%) at 21 Months after Intervention 1	21.41	(-1.69, 44.51)	0.204676	0.168587
Absolute Change at 22 Months after Intervention 1	0.037808	(0.002807, 0.072808)	0.204846	0.167038
Relative Change (%) at 22 Months after Intervention 1	22.63	(-1.90, 47.17)	0.204846	0.167038
Absolute Change at 23 Months after Intervention 1	0.039526	(0.002935, 0.076118)	0.205015	0.165489
Relative Change (%) at 23 Months after Intervention 1	23.88	(-2.12, 49.89)	0.205015	0.165489
Absolute Change at 24 Months after Intervention 1	0.041245	(0.003063, 0.079427)	0.205185	0.163940
Relative Change (%) at 24 Months after Intervention 1	25.16	(-2.36, 52.68)	0.205185	0.163940
Absolute Change at 25 Months after Intervention 1	0.042963	(0.003190, 0.082737)	0.205354	0.162391
Relative Change (%) at 25 Months after Intervention 1	26.46	(-2.62, 55.53)	0.205354	0.162391
Absolute Change at 26 Months after Intervention 1	0.044682	(0.003318, 0.086046)	0.205524	0.160842
Relative Change (%) at 26 Months after Intervention 1	27.78	(-2.89, 58.46)	0.205524	0.160842
Absolute Change at 27 Months after Intervention 1	0.046401	(0.003445, 0.089356)	0.205694	0.159293
Relative Change (%) at 27 Months after Intervention 1	29.13	(-3.19, 61.45)	0.205694	0.159293
Absolute Change at 27 Months after Intervention 1	0.046401	(0.003445, 0.089356)	0.205694	0.159293
Relative Change (%) at 27 Months after Intervention 1	29.13	(-3.19, 61.45)	0.205694	0.159293

¹The 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.

Figure 48. 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 with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 97. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 60)²			
Intercept	0.021701	(0.021618, 0.021783)	<.001
Baseline trend	-0.000074	(-0.000078, -0.000071)	<.001
Level Change (After Intervention 1)	0.000173	(0.000039, 0.000308)	0.013
Trend Change (After Intervention 1)	0.000012	(0.000004, 0.000019)	0.002
Most Parsimonious Final Model Parameters (df = 60)^{2,3}			
Intercept	0.021701	(0.021618, 0.021783)	<.001
Baseline trend	-0.000074	(-0.000078, -0.000071)	<.001
Level Change (After Intervention 1)	0.000173	(0.000039, 0.000308)	0.013
Trend Change (After Intervention 1)	0.000012	(0.000004, 0.000019)	0.002

¹The 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.

²Maximum 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.

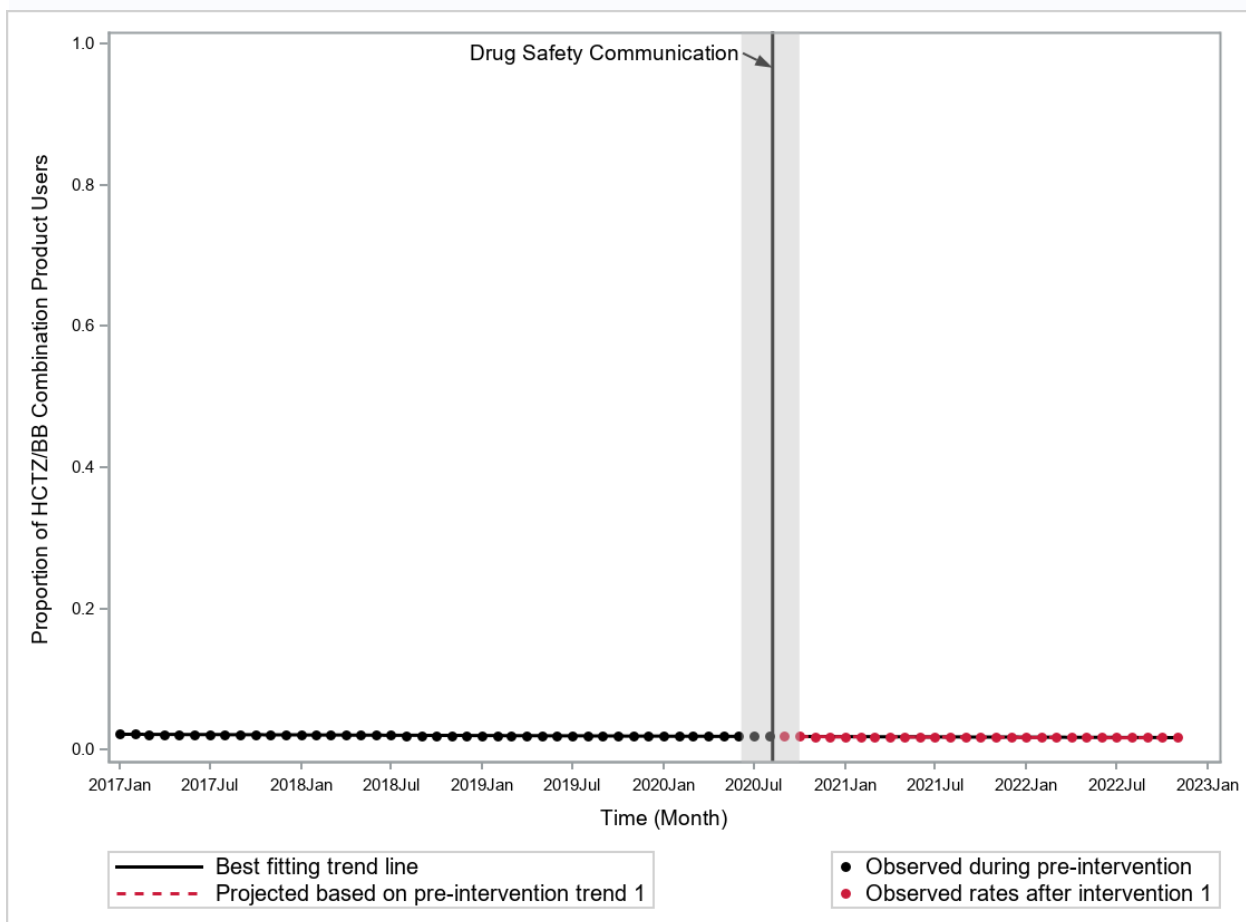
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 98. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.000197	(0.000051, 0.000342)	0.018472	0.018276
Relative Change (%) at 2 Months after Intervention 1	1.08	(0.28, 1.87)	0.018472	0.018276
Absolute Change at 3 Months after Intervention 1	0.000208	(0.000065, 0.000352)	0.018410	0.018201
Relative Change (%) at 3 Months after Intervention 1	1.14	(0.35, 1.94)	0.018410	0.018201
Absolute Change at 4 Months after Intervention 1	0.000220	(0.000078, 0.000362)	0.018347	0.018127
Relative Change (%) at 4 Months after Intervention 1	1.21	(0.42, 2.00)	0.018347	0.018127
Absolute Change at 5 Months after Intervention 1	0.000231	(0.000090, 0.000372)	0.018284	0.018053
Relative Change (%) at 5 Months after Intervention 1	1.28	(0.49, 2.07)	0.018284	0.018053
Absolute Change at 6 Months after Intervention 1	0.000243	(0.000102, 0.000383)	0.018221	0.017978
Relative Change (%) at 6 Months after Intervention 1	1.35	(0.56, 2.14)	0.018221	0.017978
Absolute Change at 7 Months after Intervention 1	0.000254	(0.000114, 0.000395)	0.018158	0.017904
Relative Change (%) at 7 Months after Intervention 1	1.42	(0.63, 2.21)	0.018158	0.017904
Absolute Change at 8 Months after Intervention 1	0.000266	(0.000126, 0.000406)	0.018095	0.017829
Relative Change (%) at 8 Months after Intervention 1	1.49	(0.70, 2.29)	0.018095	0.017829
Absolute Change at 9 Months after Intervention 1	0.000278	(0.000137, 0.000418)	0.018032	0.017755
Relative Change (%) at 9 Months after Intervention 1	1.56	(0.76, 2.37)	0.018032	0.017755
Absolute Change at 10 Months after Intervention 1	0.000289	(0.000148, 0.000431)	0.017969	0.017680
Relative Change (%) at 10 Months after Intervention 1	1.64	(0.82, 2.45)	0.017969	0.017680
Absolute Change at 11 Months after Intervention 1	0.000301	(0.000158, 0.000443)	0.017907	0.017606
Relative Change (%) at 11 Months after Intervention 1	1.71	(0.89, 2.53)	0.017907	0.017606
Absolute Change at 12 Months after Intervention 1	0.000312	(0.000168, 0.000456)	0.017844	0.017531
Relative Change (%) at 12 Months after Intervention 1	1.78	(0.95, 2.62)	0.017844	0.017531
Absolute Change at 13 Months after Intervention 1	0.000324	(0.000178, 0.000470)	0.017781	0.017457
Relative Change (%) at 13 Months after Intervention 1	1.86	(1.01, 2.70)	0.017781	0.017457
Absolute Change at 14 Months after Intervention 1	0.000335	(0.000187, 0.000484)	0.017718	0.017383
Relative Change (%) at 14 Months after Intervention 1	1.93	(1.06, 2.80)	0.017718	0.017383
Absolute Change at 15 Months after Intervention 1	0.000347	(0.000196, 0.000498)	0.017655	0.017308
Relative Change (%) at 15 Months after Intervention 1	2.00	(1.12, 2.89)	0.017655	0.017308
Absolute Change at 16 Months after Intervention 1	0.000359	(0.000205, 0.000512)	0.017592	0.017234
Relative Change (%) at 16 Months after Intervention 1	2.08	(1.17, 2.99)	0.017592	0.017234
Absolute Change at 17 Months after Intervention 1	0.000370	(0.000214, 0.000526)	0.017529	0.017159
Relative Change (%) at 17 Months after Intervention 1	2.16	(1.23, 3.09)	0.017529	0.017159
Absolute Change at 18 Months after Intervention 1	0.000382	(0.000222, 0.000541)	0.017466	0.017085
Relative Change (%) at 18 Months after Intervention 1	2.23	(1.28, 3.19)	0.017466	0.017085
Absolute Change at 19 Months after Intervention 1	0.000393	(0.000230, 0.000556)	0.017404	0.017010
Relative Change (%) at 19 Months after Intervention 1	2.31	(1.33, 3.29)	0.017404	0.017010
Absolute Change at 20 Months after Intervention 1	0.000405	(0.000238, 0.000572)	0.017341	0.016936
Relative Change (%) at 20 Months after Intervention 1	2.39	(1.38, 3.40)	0.017341	0.016936
Absolute Change at 21 Months after Intervention 1	0.000416	(0.000245, 0.000587)	0.017278	0.016861
Relative Change (%) at 21 Months after Intervention 1	2.47	(1.43, 3.50)	0.017278	0.016861
Absolute Change at 22 Months after Intervention 1	0.000428	(0.000253, 0.000603)	0.017215	0.016787
Relative Change (%) at 22 Months after Intervention 1	2.55	(1.48, 3.61)	0.017215	0.016787
Absolute Change at 23 Months after Intervention 1	0.000440	(0.000260, 0.000619)	0.017152	0.016713
Relative Change (%) at 23 Months after Intervention 1	2.63	(1.53, 3.73)	0.017152	0.016713
Absolute Change at 24 Months after Intervention 1	0.000451	(0.000267, 0.000635)	0.017089	0.016638
Relative Change (%) at 24 Months after Intervention 1	2.71	(1.58, 3.84)	0.017089	0.016638
Absolute Change at 25 Months after Intervention 1	0.000463	(0.000274, 0.000651)	0.017026	0.016564
Relative Change (%) at 25 Months after Intervention 1	2.79	(1.63, 3.96)	0.017026	0.016564
Absolute Change at 26 Months after Intervention 1	0.000474	(0.000281, 0.000668)	0.016963	0.016489
Relative Change (%) at 26 Months after Intervention 1	2.88	(1.68, 4.08)	0.016963	0.016489
Absolute Change at 27 Months after Intervention 1	0.000486	(0.000287, 0.000684)	0.016901	0.016415
Relative Change (%) at 27 Months after Intervention 1	2.96	(1.72, 4.20)	0.016901	0.016415
Absolute Change at 27 Months after Intervention 1	0.000486	(0.000287, 0.000684)	0.016901	0.016415
Relative Change (%) at 27 Months after Intervention 1	2.96	(1.72, 4.20)	0.016901	0.016415

¹The 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.

Figure 49. Proportion of Hydrochlorothiazide (HCTZ)-Beta Blocker Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 99. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.000030	(0.000026, 0.000034)	<.001
Baseline trend	-0.000000	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000006	(-0.000009, -0.000004)	<.001
Trend Change (After Intervention 1)	0.000000	(0.000000, 0.000001)	0.003
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.000030	(0.000026, 0.000034)	<.001
Baseline trend	-0.000000	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000006	(-0.000009, -0.000004)	<.001
Trend Change (After Intervention 1)	0.000000	(0.000000, 0.000001)	0.003

¹The 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.

²Maximum 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.

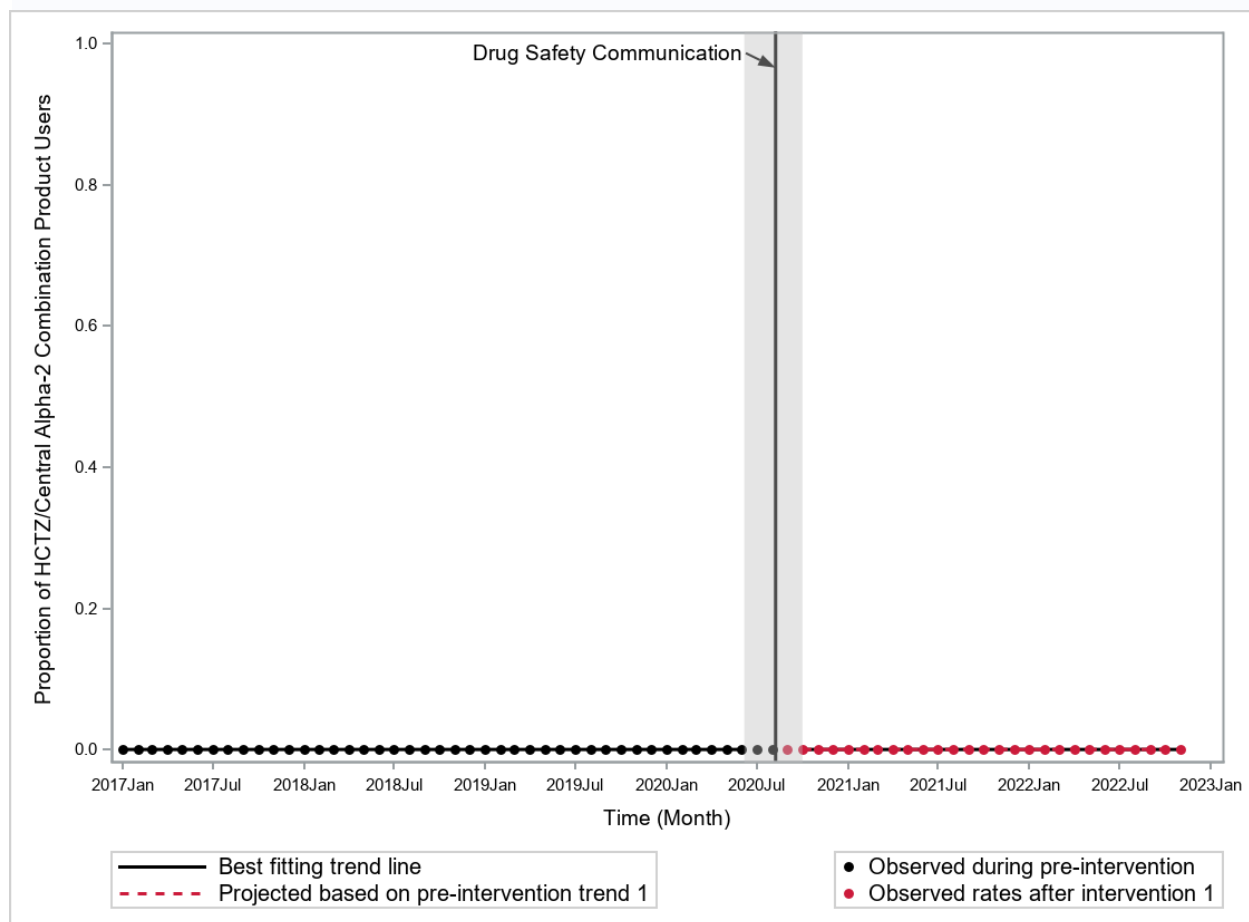
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 100. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	-0.000006	(-0.000009, -0.000003)	0.000002	0.000007
Relative Change (%) at 2 Months after Intervention 1	-75.96	(-118.82, -33.10)	0.000002	0.000007
Absolute Change at 3 Months after Intervention 1	-0.000005	(-0.000008, -0.000002)	0.000002	0.000007
Relative Change (%) at 3 Months after Intervention 1	-75.19	(-118.73, -31.64)	0.000002	0.000007
Absolute Change at 4 Months after Intervention 1	-0.000005	(-0.000008, -0.000002)	0.000002	0.000006
Relative Change (%) at 4 Months after Intervention 1	-74.30	(-118.75, -29.84)	0.000002	0.000006
Absolute Change at 5 Months after Intervention 1	-0.000004	(-0.000008, -0.000001)	0.000002	0.000006
Relative Change (%) at 5 Months after Intervention 1	-73.26	(-118.94, -27.58)	0.000002	0.000006
Absolute Change at 6 Months after Intervention 1	-0.000004	(-0.000007, -0.000001)	0.000002	0.000005
Relative Change (%) at 6 Months after Intervention 1	-72.04	(-119.40, -24.68)	0.000002	0.000005
Absolute Change at 7 Months after Intervention 1	-0.000004	(-0.000007, 0.000000)	0.000001	0.000005
Relative Change (%) at 7 Months after Intervention 1	-70.59	(-120.29, -20.88)	0.000001	0.000005
Absolute Change at 8 Months after Intervention 1	-0.000003	(-0.000007, 0.000001)	0.000001	0.000005
Relative Change (%) at 8 Months after Intervention 1	-68.82	(-121.85, -15.79)	0.000001	0.000005
Absolute Change at 9 Months after Intervention 1	-0.000003	(-0.000007, 0.000001)	0.000001	0.000004
Relative Change (%) at 9 Months after Intervention 1	-66.63	(-124.52, -8.73)	0.000001	0.000004
Absolute Change at 10 Months after Intervention 1	-0.000002	(-0.000006, 0.000002)	0.000001	0.000004
Relative Change (%) at 10 Months after Intervention 1	-63.84	(-129.07, 1.40)	0.000001	0.000004
Absolute Change at 11 Months after Intervention 1	-0.000002	(-0.000006, 0.000003)	0.000001	0.000003
Relative Change (%) at 11 Months after Intervention 1	-60.16	(-137.03, 16.70)	0.000001	0.000003
Absolute Change at 12 Months after Intervention 1	-0.000001	(-0.000006, 0.000003)	0.000001	0.000003
Relative Change (%) at 12 Months after Intervention 1	-55.11	(-151.56, 41.34)	0.000001	0.000003
Absolute Change at 13 Months after Intervention 1	-0.000001	(-0.000006, 0.000004)	0.000001	0.000002
Relative Change (%) at 13 Months after Intervention 1	-47.72	(-180.23, 84.78)	0.000001	0.000002
Absolute Change at 14 Months after Intervention 1	-0.000001	(-0.000006, 0.000005)	0.000001	0.000002
Relative Change (%) at 14 Months after Intervention 1	-35.89	(-244.39, 172.61)	0.000001	0.000002
Absolute Change at 15 Months after Intervention 1	0.000000	(-0.000006, 0.000005)	0.000001	0.000001
Relative Change (%) at 15 Months after Intervention 1	-13.89	(-423.53, 395.75)	0.000001	0.000001
Absolute Change at 16 Months after Intervention 1	0.000000	(-0.000005, 0.000006)	0.000001	0.000001
Relative Change (%) at 16 Months after Intervention 1	41.33	(-1215.96, 1298.63)	0.000001	0.000001
Absolute Change at 17 Months after Intervention 1	0.000001	(-0.000005, 0.000007)	0.000001	0.000000
Relative Change (%) at 17 Months after Intervention 1	436.03	(-21185.7, 22057.77)	0.000001	0.000000
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
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
Relative 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

¹The 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.

Figure 50. 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 with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 101. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.365621	(0.363472, 0.367769)	<.001
Baseline trend	-0.000650	(-0.000733, -0.000566)	<.001
Level Change (After Intervention 1)	0.001520	(-0.001641, 0.004682)	0.340
Trend Change (After Intervention 1)	-0.000040	(-0.000225, 0.000144)	0.663
Most Parsimonious Final Model Parameters (df = 54)^{2,3}			
Intercept	0.365481	(0.363757, 0.367205)	<.001
Baseline trend	-0.000635	(-0.000677, -0.000593)	<.001

¹The 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.

²Maximum 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.

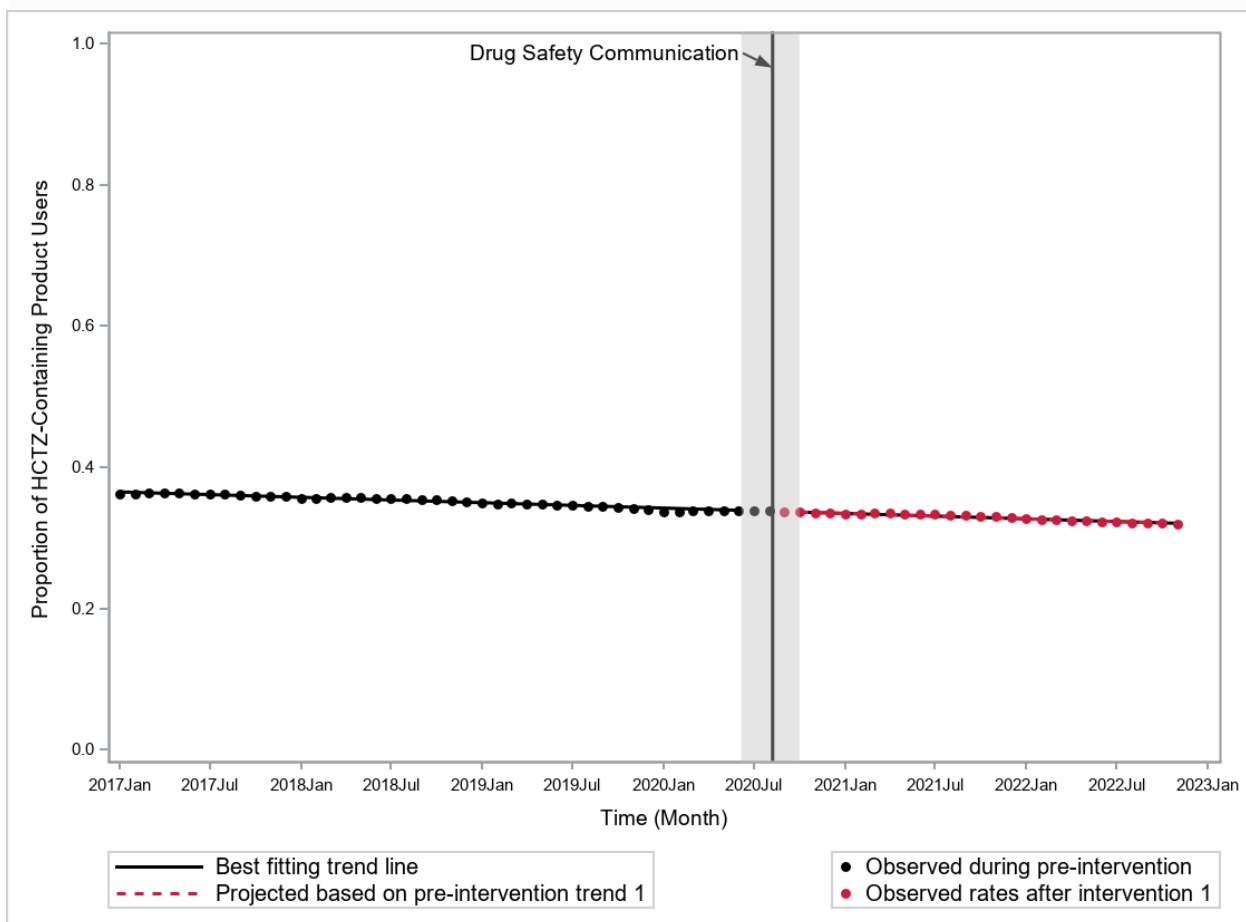
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 102. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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)	0.336279	0.336279
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.336279	0.336279
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.335645	0.335645
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.335645	0.335645
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.335010	0.335010
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.335010	0.335010
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.334375	0.334375
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.334375	0.334375
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.333740	0.333740
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.333740	0.333740
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.333105	0.333105
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.333105	0.333105
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.332470	0.332470
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.332470	0.332470
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.331836	0.331836
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.331836	0.331836
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.331201	0.331201
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.331201	0.331201
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.330566	0.330566
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.330566	0.330566
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.329931	0.329931
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.329931	0.329931
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.329296	0.329296
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.329296	0.329296
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.328661	0.328661
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.328661	0.328661
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.328027	0.328027
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.328027	0.328027
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.327392	0.327392
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.327392	0.327392
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.326757	0.326757
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.326757	0.326757
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.326122	0.326122
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.326122	0.326122
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.325487	0.325487
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.325487	0.325487
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.324853	0.324853
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.324853	0.324853
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.324218	0.324218
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.324218	0.324218
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.323583	0.323583
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.323583	0.323583
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.322948	0.322948
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.322948	0.322948
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.322313	0.322313
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.322313	0.322313
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.321678	0.321678
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.321678	0.321678
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.321044	0.321044
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.321044	0.321044
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.320409	0.320409
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.320409	0.320409
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.320409	0.320409

¹The 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.

Figure 51. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 103. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.943796	(0.943390, 0.944203)	<.001
Baseline trend	-0.000436	(-0.000452, -0.000420)	<.001
Level Change (After Intervention 1)	0.001576	(0.000864, 0.002288)	<.001
Trend Change (After Intervention 1)	0.000167	(0.000131, 0.000204)	<.001
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.943796	(0.943390, 0.944203)	<.001
Baseline trend	-0.000436	(-0.000452, -0.000420)	<.001
Level Change (After Intervention 1)	0.001576	(0.000864, 0.002288)	<.001
Trend Change (After Intervention 1)	0.000167	(0.000131, 0.000204)	<.001

¹The 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.

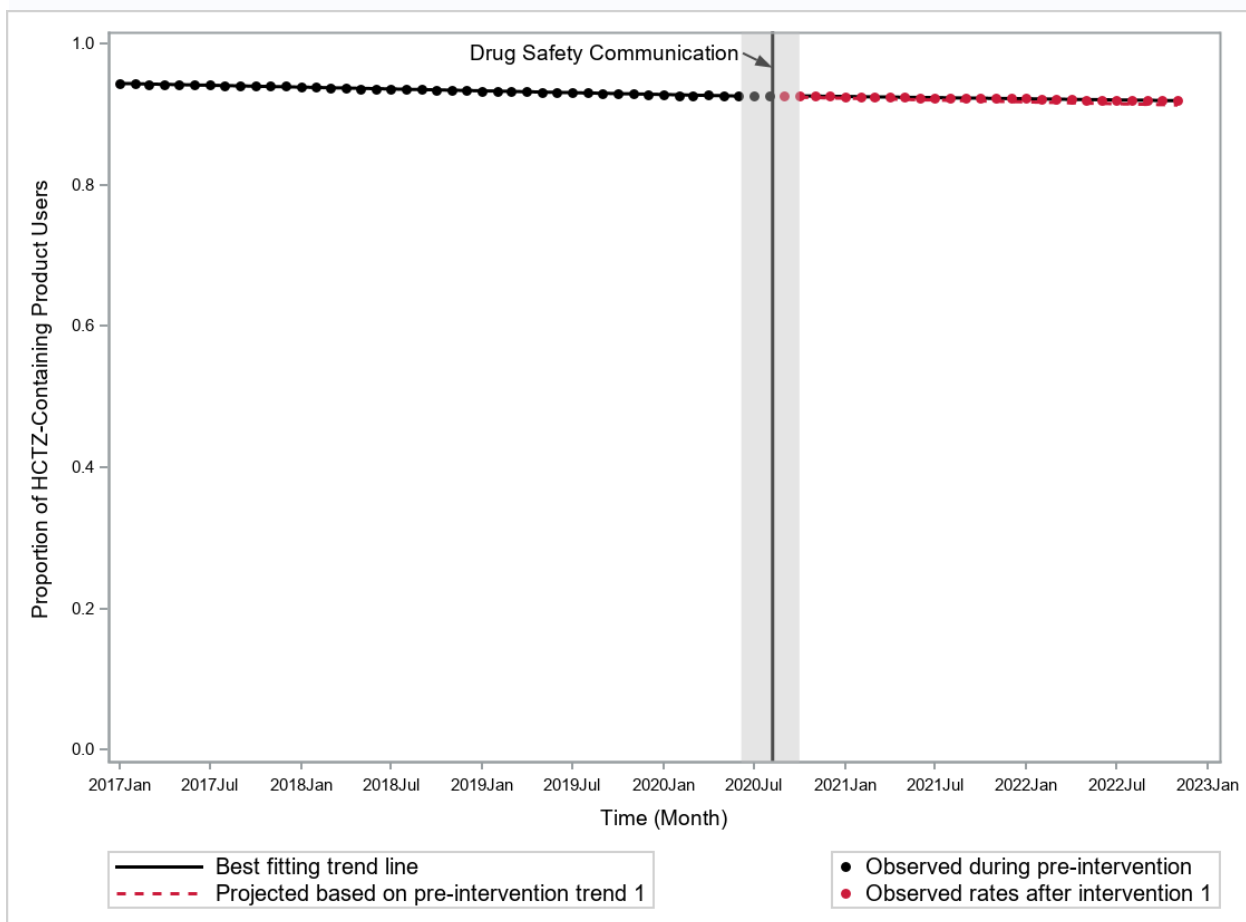
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 104. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.001910	(0.001212, 0.002609)	0.925652	0.923742
Relative Change (%) at 2 Months after Intervention 1	0.21	(0.13, 0.28)	0.925652	0.923742
Absolute Change at 3 Months after Intervention 1	0.002077	(0.001389, 0.002766)	0.925383	0.923306
Relative Change (%) at 3 Months after Intervention 1	0.22	(0.15, 0.30)	0.925383	0.923306
Absolute Change at 4 Months after Intervention 1	0.002245	(0.001565, 0.002924)	0.925115	0.922870
Relative Change (%) at 4 Months after Intervention 1	0.24	(0.17, 0.32)	0.925115	0.922870
Absolute Change at 5 Months after Intervention 1	0.002412	(0.001739, 0.003084)	0.924846	0.922434
Relative Change (%) at 5 Months after Intervention 1	0.26	(0.19, 0.33)	0.924846	0.922434
Absolute Change at 6 Months after Intervention 1	0.002579	(0.001911, 0.003247)	0.924577	0.921998
Relative Change (%) at 6 Months after Intervention 1	0.28	(0.21, 0.35)	0.924577	0.921998
Absolute Change at 7 Months after Intervention 1	0.002746	(0.002082, 0.003411)	0.924308	0.921562
Relative Change (%) at 7 Months after Intervention 1	0.30	(0.23, 0.37)	0.924308	0.921562
Absolute Change at 8 Months after Intervention 1	0.002914	(0.002250, 0.003577)	0.924040	0.921126
Relative Change (%) at 8 Months after Intervention 1	0.32	(0.24, 0.39)	0.924040	0.921126
Absolute Change at 9 Months after Intervention 1	0.003081	(0.002417, 0.003745)	0.923771	0.920690
Relative Change (%) at 9 Months after Intervention 1	0.33	(0.26, 0.41)	0.923771	0.920690
Absolute Change at 10 Months after Intervention 1	0.003248	(0.002581, 0.003915)	0.923502	0.920254
Relative Change (%) at 10 Months after Intervention 1	0.35	(0.28, 0.43)	0.923502	0.920254
Absolute Change at 11 Months after Intervention 1	0.003415	(0.002744, 0.004087)	0.923233	0.919818
Relative Change (%) at 11 Months after Intervention 1	0.37	(0.30, 0.44)	0.923233	0.919818
Absolute Change at 12 Months after Intervention 1	0.003583	(0.002905, 0.004260)	0.922965	0.919382
Relative Change (%) at 12 Months after Intervention 1	0.39	(0.32, 0.46)	0.922965	0.919382
Absolute Change at 13 Months after Intervention 1	0.003750	(0.003064, 0.004436)	0.922696	0.918946
Relative Change (%) at 13 Months after Intervention 1	0.41	(0.33, 0.48)	0.922696	0.918946
Absolute Change at 14 Months after Intervention 1	0.003917	(0.003221, 0.004613)	0.922427	0.918510
Relative Change (%) at 14 Months after Intervention 1	0.43	(0.35, 0.50)	0.922427	0.918510
Absolute Change at 15 Months after Intervention 1	0.004084	(0.003376, 0.004792)	0.922159	0.918074
Relative Change (%) at 15 Months after Intervention 1	0.44	(0.37, 0.52)	0.922159	0.918074
Absolute Change at 16 Months after Intervention 1	0.004251	(0.003530, 0.004972)	0.921890	0.917638
Relative Change (%) at 16 Months after Intervention 1	0.46	(0.38, 0.54)	0.921890	0.917638
Absolute Change at 17 Months after Intervention 1	0.004419	(0.003683, 0.005154)	0.921621	0.917202
Relative Change (%) at 17 Months after Intervention 1	0.48	(0.40, 0.56)	0.921621	0.917202
Absolute Change at 18 Months after Intervention 1	0.004586	(0.003834, 0.005338)	0.921352	0.916766
Relative Change (%) at 18 Months after Intervention 1	0.50	(0.42, 0.58)	0.921352	0.916766
Absolute Change at 19 Months after Intervention 1	0.004753	(0.003984, 0.005523)	0.921084	0.916331
Relative Change (%) at 19 Months after Intervention 1	0.52	(0.43, 0.60)	0.921084	0.916331
Absolute Change at 20 Months after Intervention 1	0.004920	(0.004132, 0.005709)	0.920815	0.915895
Relative Change (%) at 20 Months after Intervention 1	0.54	(0.45, 0.62)	0.920815	0.915895
Absolute Change at 21 Months after Intervention 1	0.005088	(0.004279, 0.005896)	0.920546	0.915459
Relative Change (%) at 21 Months after Intervention 1	0.56	(0.47, 0.64)	0.920546	0.915459
Absolute Change at 22 Months after Intervention 1	0.005255	(0.004426, 0.006084)	0.920277	0.915023
Relative Change (%) at 22 Months after Intervention 1	0.57	(0.48, 0.67)	0.920277	0.915023
Absolute Change at 23 Months after Intervention 1	0.005422	(0.004571, 0.006273)	0.920009	0.914587
Relative Change (%) at 23 Months after Intervention 1	0.59	(0.50, 0.69)	0.920009	0.914587
Absolute Change at 24 Months after Intervention 1	0.005589	(0.004715, 0.006463)	0.919740	0.914151
Relative Change (%) at 24 Months after Intervention 1	0.61	(0.52, 0.71)	0.919740	0.914151
Absolute Change at 25 Months after Intervention 1	0.005757	(0.004859, 0.006654)	0.919471	0.913715
Relative Change (%) at 25 Months after Intervention 1	0.63	(0.53, 0.73)	0.919471	0.913715
Absolute Change at 26 Months after Intervention 1	0.005924	(0.005002, 0.006846)	0.919203	0.913279
Relative Change (%) at 26 Months after Intervention 1	0.65	(0.55, 0.75)	0.919203	0.913279
Absolute Change at 27 Months after Intervention 1	0.006091	(0.005144, 0.007038)	0.918934	0.912843
Relative Change (%) at 27 Months after Intervention 1	0.67	(0.56, 0.77)	0.918934	0.912843
Absolute Change at 28 Months after Intervention 1	0.006091	(0.005144, 0.007038)	0.918934	0.912843
Relative Change (%) at 28 Months after Intervention 1	0.67	(0.56, 0.77)	0.918934	0.912843

¹The 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.

Figure 52. Proportion of Hydrochlorothiazide (HCTZ)-Containing Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 105. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.000494	(0.000445, 0.000543)	<.001
Baseline trend	-0.000008	(-0.000009, -0.000006)	<.001
Level Change (After Intervention 1)	0.000019	(-0.000006, 0.000045)	0.134
Trend Change (After Intervention 1)	0.000004	(0.000001, 0.000007)	0.012
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.000494	(0.000445, 0.000543)	<.001
Baseline trend	-0.000008	(-0.000009, -0.000006)	<.001
Level Change (After Intervention 1)	0.000019	(-0.000006, 0.000045)	0.134
Trend Change (After Intervention 1)	0.000004	(0.000001, 0.000007)	0.012

¹The 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.

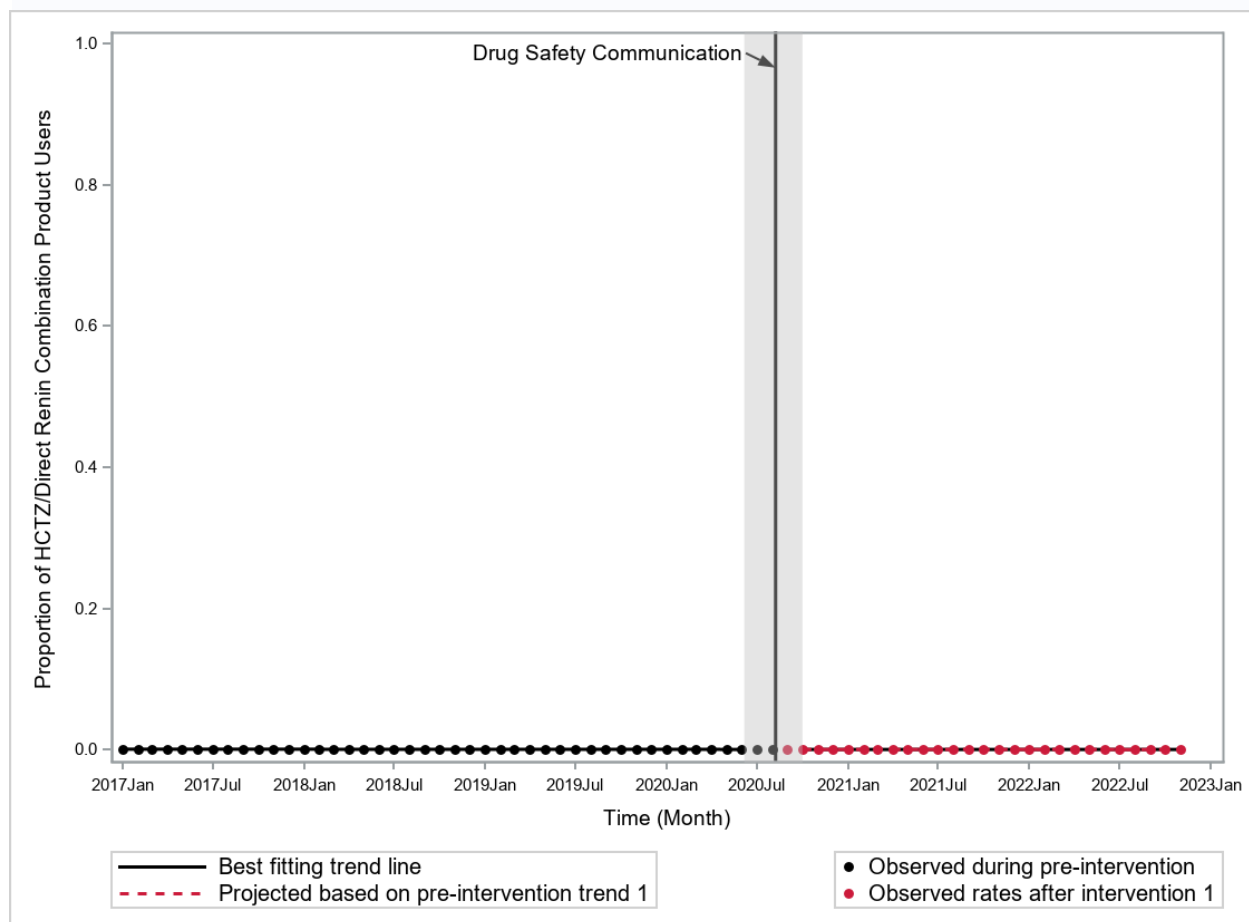
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 106. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.000027	(0.000000, 0.000053)	0.000174	0.000147
Relative Change (%) at 2 Months after Intervention 1	18.10	(-4.52, 40.72)	0.000174	0.000147
Absolute Change at 3 Months after Intervention 1	0.000030	(0.000002, 0.000058)	0.000170	0.000140
Relative Change (%) at 3 Months after Intervention 1	21.70	(-4.79, 48.18)	0.000170	0.000140
Absolute Change at 4 Months after Intervention 1	0.000034	(0.000004, 0.000063)	0.000166	0.000132
Relative Change (%) at 4 Months after Intervention 1	25.71	(-5.62, 57.04)	0.000166	0.000132
Absolute Change at 5 Months after Intervention 1	0.000038	(0.000006, 0.000069)	0.000162	0.000124
Relative Change (%) at 5 Months after Intervention 1	30.21	(-7.12, 67.53)	0.000162	0.000124
Absolute Change at 6 Months after Intervention 1	0.000041	(0.000008, 0.000075)	0.000158	0.000117
Relative Change (%) at 6 Months after Intervention 1	35.28	(-9.42, 79.98)	0.000158	0.000117
Absolute Change at 7 Months after Intervention 1	0.000045	(0.000009, 0.000081)	0.000154	0.000109
Relative Change (%) at 7 Months after Intervention 1	41.06	(-12.73, 94.85)	0.000154	0.000109
Absolute Change at 8 Months after Intervention 1	0.000049	(0.000010, 0.000087)	0.000150	0.000102
Relative Change (%) at 8 Months after Intervention 1	47.68	(-17.38, 112.75)	0.000150	0.000102
Absolute Change at 9 Months after Intervention 1	0.000052	(0.000011, 0.000093)	0.000147	0.000094
Relative Change (%) at 9 Months after Intervention 1	55.37	(-23.83, 134.57)	0.000147	0.000094
Absolute Change at 10 Months after Intervention 1	0.000056	(0.000012, 0.000100)	0.000143	0.000087
Relative Change (%) at 10 Months after Intervention 1	64.39	(-32.80, 161.58)	0.000143	0.000087
Absolute Change at 11 Months after Intervention 1	0.000060	(0.000013, 0.000106)	0.000139	0.000079
Relative Change (%) at 11 Months after Intervention 1	75.12	(-45.40, 195.65)	0.000139	0.000079
Absolute Change at 12 Months after Intervention 1	0.000063	(0.000014, 0.000113)	0.000135	0.000072
Relative Change (%) at 12 Months after Intervention 1	88.11	(-63.42, 239.63)	0.000135	0.000072
Absolute Change at 13 Months after Intervention 1	0.000067	(0.000015, 0.000119)	0.000131	0.000064
Relative Change (%) at 13 Months after Intervention 1	104.14	(-89.79, 298.07)	0.000131	0.000064
Absolute Change at 14 Months after Intervention 1	0.000071	(0.000015, 0.000126)	0.000127	0.000057
Relative Change (%) at 14 Months after Intervention 1	124.43	(-129.69, 378.55)	0.000127	0.000057
Absolute Change at 15 Months after Intervention 1	0.000074	(0.000016, 0.000132)	0.000123	0.000049
Relative Change (%) at 15 Months after Intervention 1	150.94	(-192.78, 494.65)	0.000123	0.000049
Absolute Change at 16 Months after Intervention 1	0.000078	(0.000017, 0.000139)	0.000120	0.000042
Relative Change (%) at 16 Months after Intervention 1	187.03	(-298.64, 672.70)	0.000120	0.000042
Absolute Change at 17 Months after Intervention 1	0.000082	(0.000017, 0.000146)	0.000116	0.000034
Relative Change (%) at 17 Months after Intervention 1	239.07	(-491.79, 969.92)	0.000116	0.000034
Absolute Change at 18 Months after Intervention 1	0.000085	(0.000018, 0.000153)	0.000112	0.000027
Relative Change (%) at 18 Months after Intervention 1	320.60	(-890.70, 1531.90)	0.000112	0.000027
Absolute Change at 19 Months after Intervention 1	0.000089	(0.000018, 0.000160)	0.000108	0.000019
Relative Change (%) at 19 Months after Intervention 1	466.62	(-1899.22, 2832.46)	0.000108	0.000019
Absolute Change at 20 Months after Intervention 1	0.000093	(0.000019, 0.000166)	0.000104	0.000012
Relative Change (%) at 20 Months after Intervention 1	803.72	(-5669.52, 7276.96)	0.000104	0.000012
Absolute Change at 21 Months after Intervention 1	0.000096	(0.000019, 0.000173)	0.000100	0.000004
Relative Change (%) at 21 Months after Intervention 1	2416.71	(-51572.0, 56405.38)	0.000100	0.000004
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
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
Relative 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

¹The 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.

Figure 53. Proportion of Hydrochlorothiazide (HCTZ)-Direct Renin Inhibitor Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 107. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.351571	(0.335919, 0.367223)	<.001
Baseline trend	0.002059	(0.001476, 0.002641)	<.001
Level Change (After Intervention 1)	0.005550	(-0.005784, 0.016884)	0.331
Trend Change (After Intervention 1)	-0.002102	(-0.003505, -0.000700)	0.004
Most Parsimonious Final Model Parameters (df = 63)^{2,3}			
Intercept	0.350943	(0.334147, 0.367739)	<.001
Baseline trend	0.002125	(0.001514, 0.002736)	<.001
Trend Change (After Intervention 1)	-0.002019	(-0.003511, -0.000526)	0.009

¹The 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.

²Maximum 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.

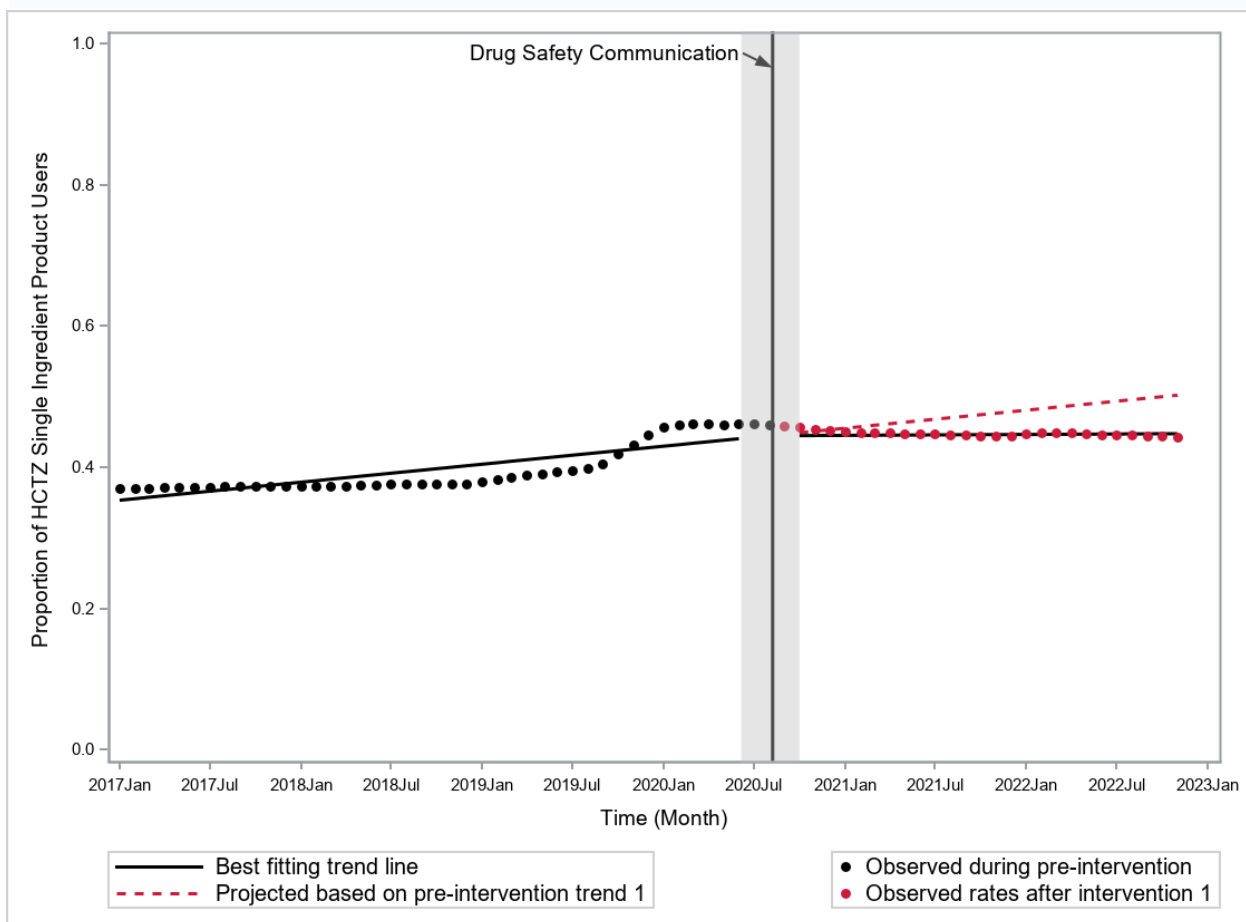
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 108. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	-0.004038	(-0.007022, -0.001053)	0.444648	0.448686
Relative Change (%) at 2 Months after Intervention 1	-0.90	(-1.54, -0.26)	0.444648	0.448686
Absolute Change at 3 Months after Intervention 1	-0.006056	(-0.010534, -0.001579)	0.444754	0.450811
Relative Change (%) at 3 Months after Intervention 1	-1.34	(-2.29, -0.39)	0.444754	0.450811
Absolute Change at 4 Months after Intervention 1	-0.008075	(-0.014045, -0.002106)	0.444861	0.452936
Relative Change (%) at 4 Months after Intervention 1	-1.78	(-3.04, -0.52)	0.444861	0.452936
Absolute Change at 5 Months after Intervention 1	-0.010094	(-0.017556, -0.002632)	0.444967	0.455061
Relative Change (%) at 5 Months after Intervention 1	-2.22	(-3.78, -0.65)	0.444967	0.455061
Absolute Change at 6 Months after Intervention 1	-0.012113	(-0.021067, -0.003159)	0.445073	0.457185
Relative Change (%) at 6 Months after Intervention 1	-2.65	(-4.52, -0.78)	0.445073	0.457185
Absolute Change at 7 Months after Intervention 1	-0.014132	(-0.024578, -0.003685)	0.445179	0.459310
Relative Change (%) at 7 Months after Intervention 1	-3.08	(-5.24, -0.91)	0.445179	0.459310
Absolute Change at 8 Months after Intervention 1	-0.016150	(-0.028089, -0.004211)	0.445285	0.461435
Relative Change (%) at 8 Months after Intervention 1	-3.50	(-5.96, -1.04)	0.445285	0.461435
Absolute Change at 9 Months after Intervention 1	-0.018169	(-0.031601, -0.004738)	0.445391	0.463560
Relative Change (%) at 9 Months after Intervention 1	-3.92	(-6.67, -1.17)	0.445391	0.463560
Absolute Change at 10 Months after Intervention 1	-0.020188	(-0.035112, -0.005264)	0.445497	0.465685
Relative Change (%) at 10 Months after Intervention 1	-4.34	(-7.37, -1.30)	0.445497	0.465685
Absolute Change at 11 Months after Intervention 1	-0.022207	(-0.038623, -0.005791)	0.445603	0.467810
Relative Change (%) at 11 Months after Intervention 1	-4.75	(-8.07, -1.42)	0.445603	0.467810
Absolute Change at 12 Months after Intervention 1	-0.024226	(-0.042134, -0.006317)	0.445709	0.469935
Relative Change (%) at 12 Months after Intervention 1	-5.16	(-8.76, -1.55)	0.445709	0.469935
Absolute Change at 13 Months after Intervention 1	-0.026244	(-0.045645, -0.006843)	0.445815	0.472059
Relative Change (%) at 13 Months after Intervention 1	-5.56	(-9.44, -1.68)	0.445815	0.472059
Absolute Change at 14 Months after Intervention 1	-0.028263	(-0.049156, -0.007370)	0.445921	0.474184
Relative Change (%) at 14 Months after Intervention 1	-5.96	(-10.12, -1.81)	0.445921	0.474184
Absolute Change at 15 Months after Intervention 1	-0.030282	(-0.052668, -0.007896)	0.446027	0.476309
Relative Change (%) at 15 Months after Intervention 1	-6.36	(-10.78, -1.93)	0.446027	0.476309
Absolute Change at 16 Months after Intervention 1	-0.032301	(-0.056179, -0.008423)	0.446133	0.478434
Relative Change (%) at 16 Months after Intervention 1	-6.75	(-11.45, -2.06)	0.446133	0.478434
Absolute Change at 17 Months after Intervention 1	-0.034320	(-0.059690, -0.008949)	0.446239	0.480559
Relative Change (%) at 17 Months after Intervention 1	-7.14	(-12.10, -2.18)	0.446239	0.480559
Absolute Change at 18 Months after Intervention 1	-0.036338	(-0.063201, -0.009476)	0.446345	0.482684
Relative Change (%) at 18 Months after Intervention 1	-7.53	(-12.75, -2.31)	0.446345	0.482684
Absolute Change at 19 Months after Intervention 1	-0.038357	(-0.066712, -0.010002)	0.446451	0.484808
Relative Change (%) at 19 Months after Intervention 1	-7.91	(-13.39, -2.43)	0.446451	0.484808
Absolute Change at 20 Months after Intervention 1	-0.040376	(-0.070224, -0.010528)	0.446557	0.486933
Relative Change (%) at 20 Months after Intervention 1	-8.29	(-14.03, -2.55)	0.446557	0.486933
Absolute Change at 21 Months after Intervention 1	-0.042395	(-0.073735, -0.011055)	0.446663	0.489058
Relative Change (%) at 21 Months after Intervention 1	-8.67	(-14.66, -2.68)	0.446663	0.489058
Absolute Change at 22 Months after Intervention 1	-0.044414	(-0.077246, -0.011581)	0.446769	0.491183
Relative Change (%) at 22 Months after Intervention 1	-9.04	(-15.28, -2.80)	0.446769	0.491183
Absolute Change at 23 Months after Intervention 1	-0.046432	(-0.080757, -0.012108)	0.446875	0.493308
Relative Change (%) at 23 Months after Intervention 1	-9.41	(-15.90, -2.92)	0.446875	0.493308
Absolute Change at 24 Months after Intervention 1	-0.048451	(-0.084268, -0.012634)	0.446982	0.495433
Relative Change (%) at 24 Months after Intervention 1	-9.78	(-16.52, -3.04)	0.446982	0.495433
Absolute Change at 25 Months after Intervention 1	-0.050470	(-0.087779, -0.013161)	0.447088	0.497558
Relative Change (%) at 25 Months after Intervention 1	-10.14	(-17.12, -3.17)	0.447088	0.497558
Absolute Change at 26 Months after Intervention 1	-0.052489	(-0.091291, -0.013687)	0.447194	0.499682
Relative Change (%) at 26 Months after Intervention 1	-10.50	(-17.72, -3.29)	0.447194	0.499682
Absolute Change at 27 Months after Intervention 1	-0.054508	(-0.094802, -0.014213)	0.447300	0.501807
Relative Change (%) at 27 Months after Intervention 1	-10.86	(-18.32, -3.41)	0.447300	0.501807
Absolute Change at 27 Months after Intervention 1	-0.054508	(-0.094802, -0.014213)	0.447300	0.501807
Relative Change (%) at 27 Months after Intervention 1	-10.86	(-18.32, -3.41)	0.447300	0.501807

¹The 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.

Figure 54. Proportion of Hydrochlorothiazide (HCTZ) Single Ingredient/Monotherapy Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 109. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 63)²			
Intercept	0.104652	(0.103467, 0.105838)	<.001
Baseline trend	-0.000345	(-0.000380, -0.000309)	<.001
Level Change (After Intervention 1)	0.000343	(-0.000300, 0.000986)	0.290
Trend Change (After Intervention 1)	0.000016	(-0.000054, 0.000087)	0.645
Most Parsimonious Final Model Parameters (df = 65)^{2,3}			
Intercept	0.104618	(0.103302, 0.105935)	<.001
Baseline trend	-0.000334	(-0.000359, -0.000309)	<.001

¹The 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.

²Maximum 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.

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

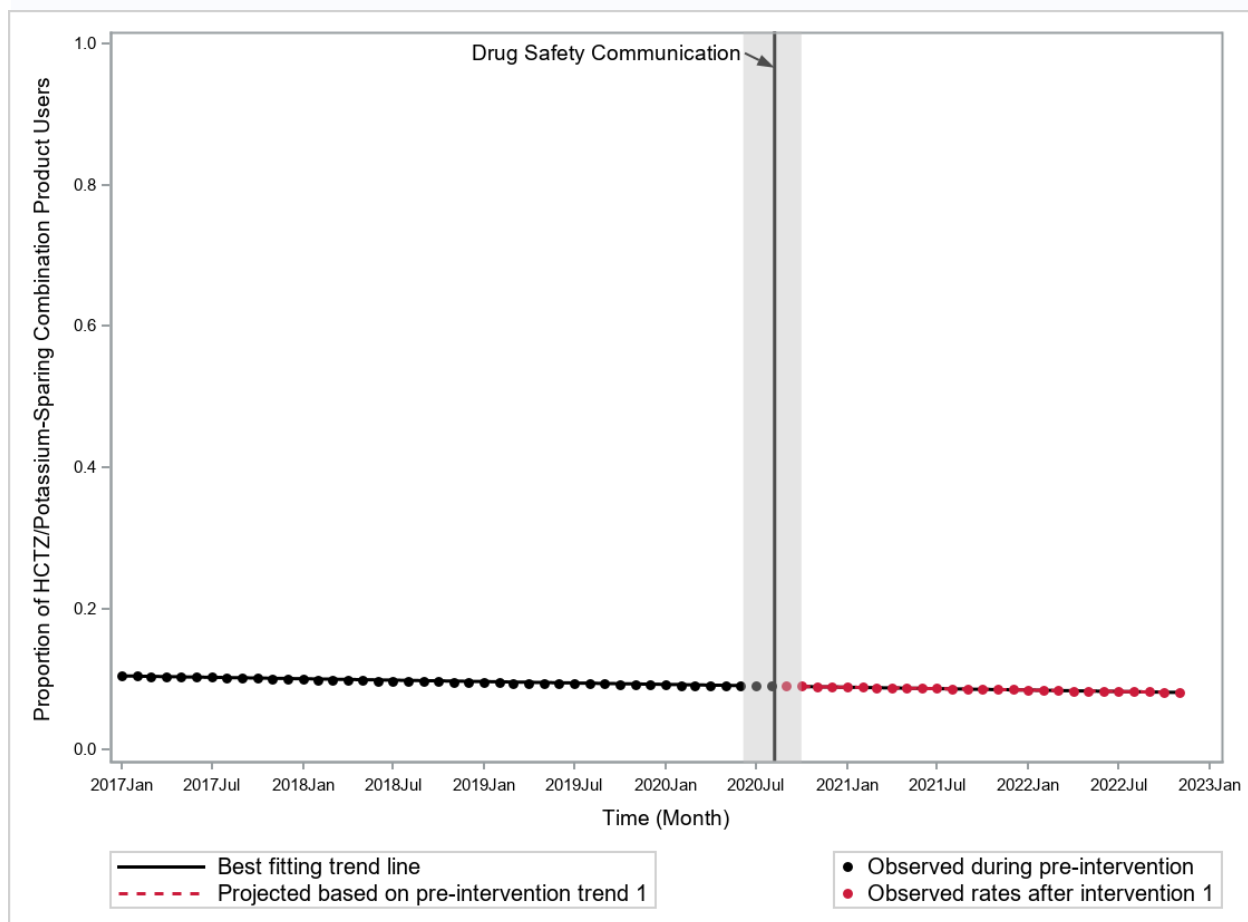
Table 110. Absolute and Relative Changes in Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer after August 8, 2020¹ Compared with Expected 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	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)	0.089251	0.089251
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.089251	0.089251
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088917	0.088917
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.088917	0.088917
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088582	0.088582
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.088582	0.088582
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.088248	0.088248
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.088248	0.088248
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087914	0.087914
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.087914	0.087914
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087580	0.087580
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.087580	0.087580
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.087246	0.087246
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.087246	0.087246
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086912	0.086912
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.086912	0.086912
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086578	0.086578
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.086578	0.086578
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.086244	0.086244
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.086244	0.086244
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085910	0.085910
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.085910	0.085910
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085576	0.085576
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.085576	0.085576
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.085242	0.085242
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.085242	0.085242
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084908	0.084908
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.084908	0.084908
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084573	0.084573
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.084573	0.084573
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.084239	0.084239
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.084239	0.084239
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083905	0.083905
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.083905	0.083905
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083571	0.083571
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.083571	0.083571
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.083237	0.083237
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.083237	0.083237
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082903	0.082903
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.082903	0.082903
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082569	0.082569
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.082569	0.082569
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.082235	0.082235
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.082235	0.082235
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081901	0.081901
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.081901	0.081901
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081567	0.081567
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.081567	0.081567
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.081233	0.081233
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.081233	0.081233
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.080899	0.080899
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.080899	0.080899
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.080899	0.080899

¹The 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 55. Proportion of Hydrochlorothiazide (HCTZ)-Potassium Sparing Diuretic Combination Product Users Among Number of Patients with Use of HCTZ-containing Products or Thiazide-like Diuretics with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 111. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 61)²			
Intercept	0.402057	(0.400931, 0.403183)	<.001
Baseline trend	-0.000637	(-0.000680, -0.000593)	<.001
Level Change (After Intervention 1)	0.003280	(0.001697, 0.004863)	<.001
Trend Change (After Intervention 1)	-0.000309	(-0.000403, -0.000215)	<.001
Most Parsimonious Final Model Parameters (df = 61)^{2,3}			
Intercept	0.402057	(0.400931, 0.403183)	<.001
Baseline trend	-0.000637	(-0.000680, -0.000593)	<.001
Level Change (After Intervention 1)	0.003280	(0.001697, 0.004863)	<.001
Trend Change (After Intervention 1)	-0.000309	(-0.000403, -0.000215)	<.001

¹The 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.

²Maximum 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.

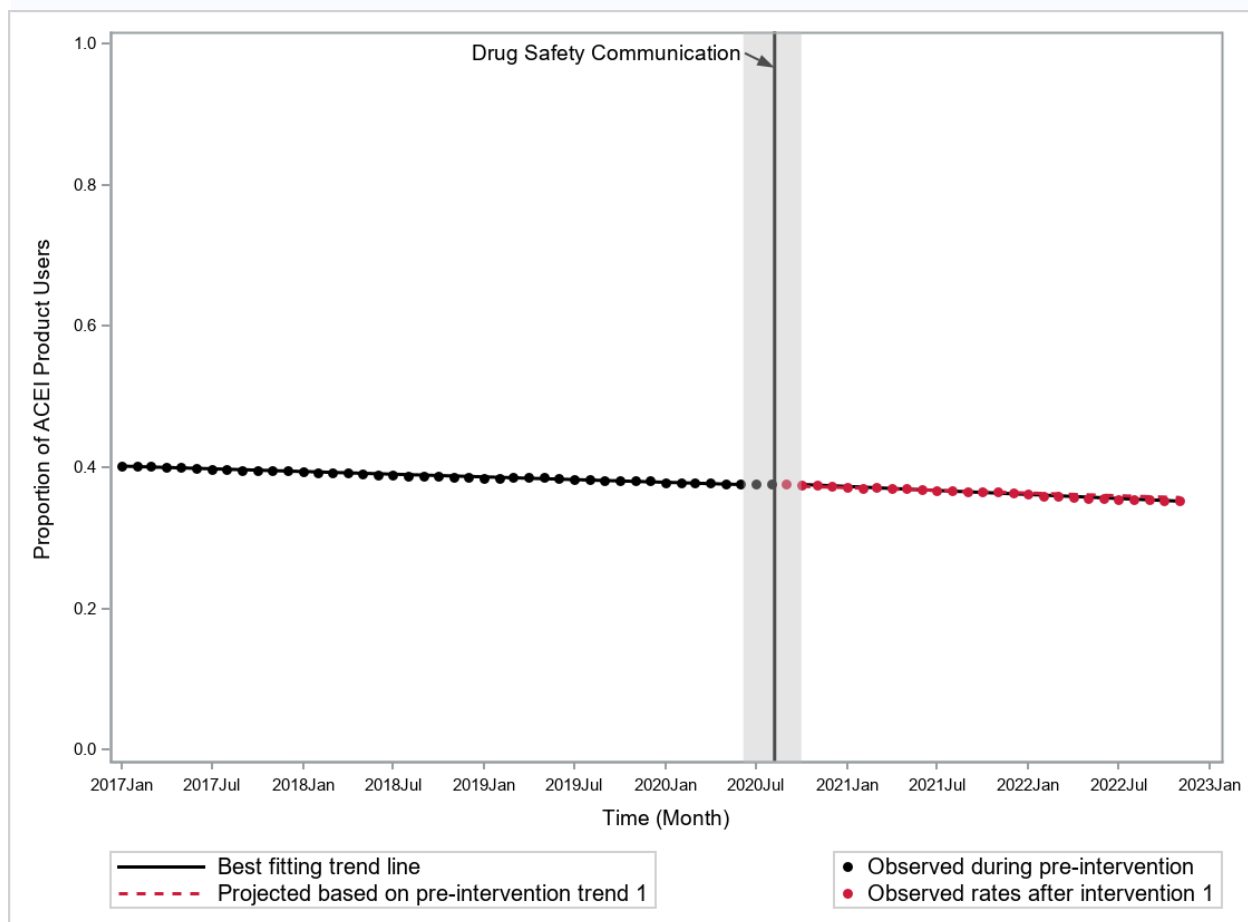
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 112. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.002662	(0.001015, 0.004309)	0.375437	0.372775
Relative Change (%) at 2 Months after Intervention 1	0.71	(0.27, 1.16)	0.375437	0.372775
Absolute Change at 3 Months after Intervention 1	0.002353	(0.000711, 0.003994)	0.374491	0.372138
Relative Change (%) at 3 Months after Intervention 1	0.63	(0.19, 1.07)	0.374491	0.372138
Absolute Change at 4 Months after Intervention 1	0.002044	(0.000402, 0.003685)	0.373546	0.371502
Relative Change (%) at 4 Months after Intervention 1	0.55	(0.11, 0.99)	0.373546	0.371502
Absolute Change at 5 Months after Intervention 1	0.001734	(0.000087, 0.003382)	0.372600	0.370865
Relative Change (%) at 5 Months after Intervention 1	0.47	(0.02, 0.91)	0.372600	0.370865
Absolute Change at 6 Months after Intervention 1	0.001425	(-0.000233, 0.003084)	0.371654	0.370229
Relative Change (%) at 6 Months after Intervention 1	0.38	(-0.06, 0.83)	0.371654	0.370229
Absolute Change at 7 Months after Intervention 1	0.001116	(-0.000558, 0.002791)	0.370708	0.369592
Relative Change (%) at 7 Months after Intervention 1	0.30	(-0.15, 0.76)	0.370708	0.369592
Absolute Change at 8 Months after Intervention 1	0.000807	(-0.000889, 0.002503)	0.369763	0.368956
Relative Change (%) at 8 Months after Intervention 1	0.22	(-0.24, 0.68)	0.369763	0.368956
Absolute Change at 9 Months after Intervention 1	0.000498	(-0.001224, 0.002220)	0.368817	0.368319
Relative Change (%) at 9 Months after Intervention 1	0.14	(-0.33, 0.60)	0.368817	0.368319
Absolute Change at 10 Months after Intervention 1	0.000189	(-0.001564, 0.001942)	0.367871	0.367683
Relative Change (%) at 10 Months after Intervention 1	0.05	(-0.43, 0.53)	0.367871	0.367683
Absolute Change at 11 Months after Intervention 1	-0.000120	(-0.001908, 0.001668)	0.366926	0.367046
Relative Change (%) at 11 Months after Intervention 1	-0.03	(-0.52, 0.45)	0.366926	0.367046
Absolute Change at 12 Months after Intervention 1	-0.000429	(-0.002257, 0.001398)	0.365980	0.366409
Relative Change (%) at 12 Months after Intervention 1	-0.12	(-0.62, 0.38)	0.365980	0.366409
Absolute Change at 13 Months after Intervention 1	-0.000738	(-0.002610, 0.001133)	0.365034	0.365773
Relative Change (%) at 13 Months after Intervention 1	-0.20	(-0.71, 0.31)	0.365034	0.365773
Absolute Change at 14 Months after Intervention 1	-0.001048	(-0.002966, 0.000871)	0.364089	0.365136
Relative Change (%) at 14 Months after Intervention 1	-0.29	(-0.81, 0.24)	0.364089	0.365136
Absolute Change at 15 Months after Intervention 1	-0.001357	(-0.003325, 0.000612)	0.363143	0.364500
Relative Change (%) at 15 Months after Intervention 1	-0.37	(-0.91, 0.17)	0.363143	0.364500
Absolute Change at 16 Months after Intervention 1	-0.001666	(-0.003688, 0.000357)	0.362197	0.363863
Relative Change (%) at 16 Months after Intervention 1	-0.46	(-1.01, 0.10)	0.362197	0.363863
Absolute Change at 17 Months after Intervention 1	-0.001975	(-0.004054, 0.000104)	0.361252	0.363227
Relative Change (%) at 17 Months after Intervention 1	-0.54	(-1.11, 0.03)	0.361252	0.363227
Absolute Change at 18 Months after Intervention 1	-0.002284	(-0.004422, -0.000146)	0.360306	0.362590
Relative Change (%) at 18 Months after Intervention 1	-0.63	(-1.22, -0.04)	0.360306	0.362590
Absolute Change at 19 Months after Intervention 1	-0.002593	(-0.004793, -0.000393)	0.359360	0.361953
Relative Change (%) at 19 Months after Intervention 1	-0.72	(-1.32, -0.11)	0.359360	0.361953
Absolute Change at 20 Months after Intervention 1	-0.002902	(-0.005166, -0.000639)	0.358415	0.361317
Relative Change (%) at 20 Months after Intervention 1	-0.80	(-1.43, -0.18)	0.358415	0.361317
Absolute Change at 21 Months after Intervention 1	-0.003211	(-0.005541, -0.000882)	0.357469	0.360680
Relative Change (%) at 21 Months after Intervention 1	-0.89	(-1.53, -0.25)	0.357469	0.360680
Absolute Change at 22 Months after Intervention 1	-0.003520	(-0.005918, -0.001123)	0.356523	0.360044
Relative Change (%) at 22 Months after Intervention 1	-0.98	(-1.64, -0.32)	0.356523	0.360044
Absolute Change at 23 Months after Intervention 1	-0.003830	(-0.006297, -0.001362)	0.355578	0.359407
Relative Change (%) at 23 Months after Intervention 1	-1.07	(-1.75, -0.38)	0.355578	0.359407
Absolute Change at 24 Months after Intervention 1	-0.004139	(-0.006677, -0.001600)	0.354632	0.358771
Relative Change (%) at 24 Months after Intervention 1	-1.15	(-1.85, -0.45)	0.354632	0.358771
Absolute Change at 25 Months after Intervention 1	-0.004448	(-0.007059, -0.001837)	0.353686	0.358134
Relative Change (%) at 25 Months after Intervention 1	-1.24	(-1.96, -0.52)	0.353686	0.358134
Absolute Change at 26 Months after Intervention 1	-0.004757	(-0.007442, -0.002072)	0.352741	0.357498
Relative Change (%) at 26 Months after Intervention 1	-1.33	(-2.07, -0.59)	0.352741	0.357498
Absolute Change at 27 Months after Intervention 1	-0.005066	(-0.007826, -0.002306)	0.351795	0.356861
Relative Change (%) at 27 Months after Intervention 1	-1.42	(-2.18, -0.65)	0.351795	0.356861
Absolute Change at 27 Months after Intervention 1	-0.005066	(-0.007826, -0.002306)	0.351795	0.356861
Relative Change (%) at 27 Months after Intervention 1	-1.42	(-2.18, -0.65)	0.351795	0.356861

¹The 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.

Figure 56. Proportion of Angiotensin Converting Enzyme Inhibitor (ACEi) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 113. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.369575	(0.369028, 0.370121)	<.001
Baseline trend	0.000669	(0.000647, 0.000691)	<.001
Level Change (After Intervention 1)	0.003400	(0.002399, 0.004401)	<.001
Trend Change (After Intervention 1)	-0.000302	(-0.000354, -0.000251)	<.001
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.369575	(0.369028, 0.370121)	<.001
Baseline trend	0.000669	(0.000647, 0.000691)	<.001
Level Change (After Intervention 1)	0.003400	(0.002399, 0.004401)	<.001
Trend Change (After Intervention 1)	-0.000302	(-0.000354, -0.000251)	<.001

¹The 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.

²Maximum 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.

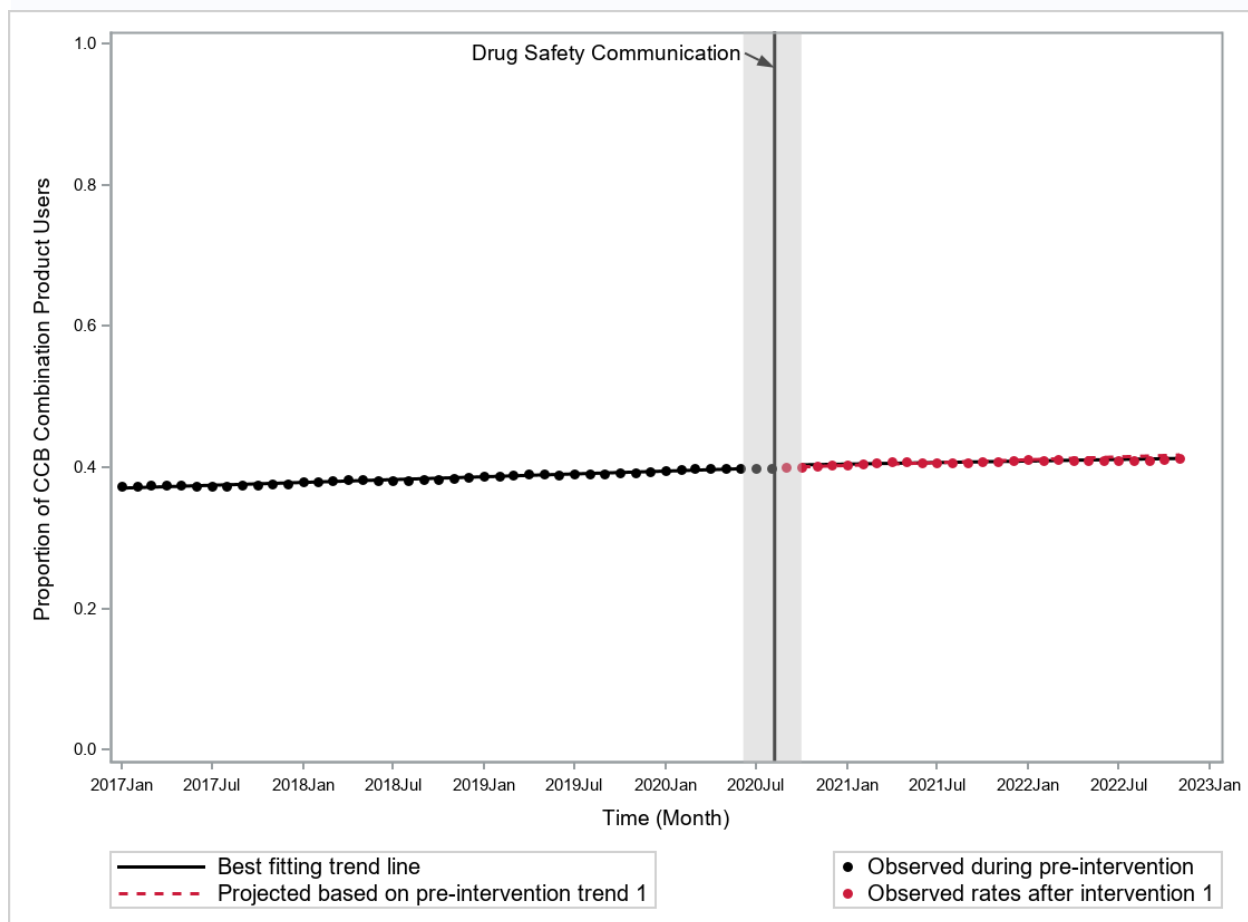
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 114. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.002795	(0.001855, 0.003735)	0.403134	0.400338
Relative Change (%) at 2 Months after Intervention 1	0.70	(0.46, 0.93)	0.403134	0.400338
Absolute Change at 3 Months after Intervention 1	0.002493	(0.001571, 0.003415)	0.403500	0.401007
Relative Change (%) at 3 Months after Intervention 1	0.62	(0.39, 0.85)	0.403500	0.401007
Absolute Change at 4 Months after Intervention 1	0.002191	(0.001284, 0.003097)	0.403867	0.401676
Relative Change (%) at 4 Months after Intervention 1	0.55	(0.32, 0.77)	0.403867	0.401676
Absolute Change at 5 Months after Intervention 1	0.001888	(0.000995, 0.002781)	0.404233	0.402345
Relative Change (%) at 5 Months after Intervention 1	0.47	(0.25, 0.69)	0.404233	0.402345
Absolute Change at 6 Months after Intervention 1	0.001586	(0.000703, 0.002469)	0.404599	0.403014
Relative Change (%) at 6 Months after Intervention 1	0.39	(0.17, 0.61)	0.404599	0.403014
Absolute Change at 7 Months after Intervention 1	0.001283	(0.000408, 0.002159)	0.404966	0.403682
Relative Change (%) at 7 Months after Intervention 1	0.32	(0.10, 0.54)	0.404966	0.403682
Absolute Change at 8 Months after Intervention 1	0.000981	(0.000110, 0.001852)	0.405332	0.404351
Relative Change (%) at 8 Months after Intervention 1	0.24	(0.03, 0.46)	0.405332	0.404351
Absolute Change at 9 Months after Intervention 1	0.000679	(-0.000190, 0.001548)	0.405699	0.405020
Relative Change (%) at 9 Months after Intervention 1	0.17	(-0.05, 0.38)	0.405699	0.405020
Absolute Change at 10 Months after Intervention 1	0.000376	(-0.000494, 0.001247)	0.406065	0.405689
Relative Change (%) at 10 Months after Intervention 1	0.09	(-0.12, 0.31)	0.406065	0.405689
Absolute Change at 11 Months after Intervention 1	0.000074	(-0.000800, 0.000948)	0.406431	0.406357
Relative Change (%) at 11 Months after Intervention 1	0.02	(-0.20, 0.23)	0.406431	0.406357
Absolute Change at 12 Months after Intervention 1	-0.000228	(-0.001110, 0.000653)	0.406798	0.407026
Relative Change (%) at 12 Months after Intervention 1	-0.06	(-0.27, 0.16)	0.406798	0.407026
Absolute Change at 13 Months after Intervention 1	-0.000531	(-0.001422, 0.000361)	0.407164	0.407695
Relative Change (%) at 13 Months after Intervention 1	-0.13	(-0.35, 0.09)	0.407164	0.407695
Absolute Change at 14 Months after Intervention 1	-0.000833	(-0.001737, 0.000071)	0.407531	0.408364
Relative Change (%) at 14 Months after Intervention 1	-0.20	(-0.42, 0.02)	0.407531	0.408364
Absolute Change at 15 Months after Intervention 1	-0.001135	(-0.002054, -0.000216)	0.407897	0.409033
Relative Change (%) at 15 Months after Intervention 1	-0.28	(-0.50, -0.05)	0.407897	0.409033
Absolute Change at 16 Months after Intervention 1	-0.001438	(-0.002375, -0.000501)	0.408264	0.409701
Relative Change (%) at 16 Months after Intervention 1	-0.35	(-0.58, -0.12)	0.408264	0.409701
Absolute Change at 17 Months after Intervention 1	-0.001740	(-0.002697, -0.000783)	0.408630	0.410370
Relative Change (%) at 17 Months after Intervention 1	-0.42	(-0.66, -0.19)	0.408630	0.410370
Absolute Change at 18 Months after Intervention 1	-0.002043	(-0.003022, -0.001063)	0.408996	0.411039
Relative Change (%) at 18 Months after Intervention 1	-0.50	(-0.73, -0.26)	0.408996	0.411039
Absolute Change at 19 Months after Intervention 1	-0.002345	(-0.003348, -0.001341)	0.409363	0.411708
Relative Change (%) at 19 Months after Intervention 1	-0.57	(-0.81, -0.33)	0.409363	0.411708
Absolute Change at 20 Months after Intervention 1	-0.002647	(-0.003677, -0.001618)	0.409729	0.412376
Relative Change (%) at 20 Months after Intervention 1	-0.64	(-0.89, -0.39)	0.409729	0.412376
Absolute Change at 21 Months after Intervention 1	-0.002950	(-0.004007, -0.001892)	0.410096	0.413045
Relative Change (%) at 21 Months after Intervention 1	-0.71	(-0.97, -0.46)	0.410096	0.413045
Absolute Change at 22 Months after Intervention 1	-0.003252	(-0.004339, -0.002165)	0.410462	0.413714
Relative Change (%) at 22 Months after Intervention 1	-0.79	(-1.05, -0.52)	0.410462	0.413714
Absolute Change at 23 Months after Intervention 1	-0.003554	(-0.004673, -0.002436)	0.410828	0.414383
Relative Change (%) at 23 Months after Intervention 1	-0.86	(-1.13, -0.59)	0.410828	0.414383
Absolute Change at 24 Months after Intervention 1	-0.003857	(-0.005008, -0.002706)	0.411195	0.415052
Relative Change (%) at 24 Months after Intervention 1	-0.93	(-1.20, -0.65)	0.411195	0.415052
Absolute Change at 25 Months after Intervention 1	-0.004159	(-0.005344, -0.002974)	0.411561	0.415720
Relative Change (%) at 25 Months after Intervention 1	-1.00	(-1.28, -0.72)	0.411561	0.415720
Absolute Change at 26 Months after Intervention 1	-0.004461	(-0.005681, -0.003242)	0.411928	0.416389
Relative Change (%) at 26 Months after Intervention 1	-1.07	(-1.36, -0.78)	0.411928	0.416389
Absolute Change at 27 Months after Intervention 1	-0.004764	(-0.006020, -0.003508)	0.412294	0.417058
Relative Change (%) at 27 Months after Intervention 1	-1.14	(-1.44, -0.84)	0.412294	0.417058
Absolute Change at 27 Months after Intervention 1	-0.004764	(-0.006020, -0.003508)	0.412294	0.417058
Relative Change (%) at 27 Months after Intervention 1	-1.14	(-1.44, -0.84)	0.412294	0.417058

¹The 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.

Figure 57. Proportion of Calcium Channel Blockers (CCB) Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 115. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 61)²			
Intercept	0.164132	(0.163480, 0.164785)	<.001
Baseline trend	-0.000180	(-0.000202, -0.000157)	<.001
Level Change (After Intervention 1)	0.000482	(-0.000226, 0.001190)	0.178
Trend Change (After Intervention 1)	-0.000183	(-0.000229, -0.000136)	<.001
Most Parsimonious Final Model Parameters (df = 61)^{2,3}			
Intercept	0.164132	(0.163480, 0.164785)	<.001
Baseline trend	-0.000180	(-0.000202, -0.000157)	<.001
Level Change (After Intervention 1)	0.000482	(-0.000226, 0.001190)	0.178
Trend Change (After Intervention 1)	-0.000183	(-0.000229, -0.000136)	<.001

¹The 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.

²Maximum 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.

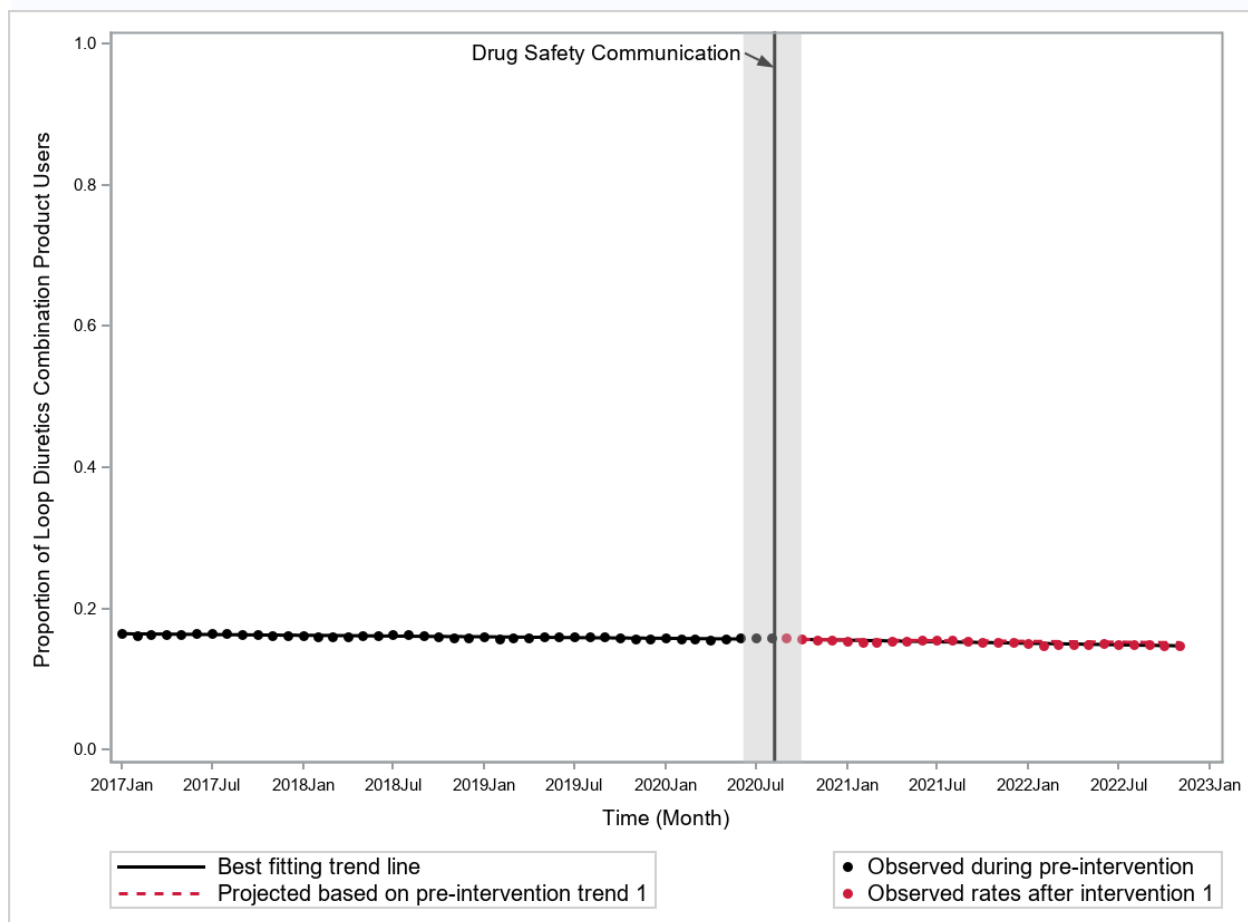
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 116. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	0.000117	(-0.000563, 0.000796)	0.155976	0.155860
Relative Change (%) at 2 Months after Intervention 1	0.07	(-0.36, 0.51)	0.155976	0.155860
Absolute Change at 3 Months after Intervention 1	-0.000066	(-0.000742, 0.000611)	0.155614	0.155680
Relative Change (%) at 3 Months after Intervention 1	-0.04	(-0.48, 0.39)	0.155614	0.155680
Absolute Change at 4 Months after Intervention 1	-0.000249	(-0.000926, 0.000429)	0.155251	0.155500
Relative Change (%) at 4 Months after Intervention 1	-0.16	(-0.59, 0.28)	0.155251	0.155500
Absolute Change at 5 Months after Intervention 1	-0.000431	(-0.001112, 0.000250)	0.154889	0.155320
Relative Change (%) at 5 Months after Intervention 1	-0.28	(-0.72, 0.16)	0.154889	0.155320
Absolute Change at 6 Months after Intervention 1	-0.000614	(-0.001302, 0.000074)	0.154526	0.155140
Relative Change (%) at 6 Months after Intervention 1	-0.40	(-0.84, 0.05)	0.154526	0.155140
Absolute Change at 7 Months after Intervention 1	-0.000797	(-0.001495, -0.000098)	0.154164	0.154960
Relative Change (%) at 7 Months after Intervention 1	-0.51	(-0.96, -0.07)	0.154164	0.154960
Absolute Change at 8 Months after Intervention 1	-0.000979	(-0.001691, -0.000268)	0.153801	0.154781
Relative Change (%) at 8 Months after Intervention 1	-0.63	(-1.09, -0.18)	0.153801	0.154781
Absolute Change at 9 Months after Intervention 1	-0.001162	(-0.001889, -0.000435)	0.153439	0.154601
Relative Change (%) at 9 Months after Intervention 1	-0.75	(-1.22, -0.28)	0.153439	0.154601
Absolute Change at 10 Months after Intervention 1	-0.001345	(-0.002091, -0.000599)	0.153076	0.154421
Relative Change (%) at 10 Months after Intervention 1	-0.87	(-1.35, -0.39)	0.153076	0.154421
Absolute Change at 11 Months after Intervention 1	-0.001527	(-0.002295, -0.000760)	0.152714	0.154241
Relative Change (%) at 11 Months after Intervention 1	-0.99	(-1.48, -0.50)	0.152714	0.154241
Absolute Change at 12 Months after Intervention 1	-0.001710	(-0.002501, -0.000920)	0.152351	0.154061
Relative Change (%) at 12 Months after Intervention 1	-1.11	(-1.62, -0.60)	0.152351	0.154061
Absolute Change at 13 Months after Intervention 1	-0.001893	(-0.002709, -0.001077)	0.151989	0.153881
Relative Change (%) at 13 Months after Intervention 1	-1.23	(-1.75, -0.71)	0.151989	0.153881
Absolute Change at 14 Months after Intervention 1	-0.002075	(-0.002919, -0.001232)	0.151626	0.153702
Relative Change (%) at 14 Months after Intervention 1	-1.35	(-1.89, -0.81)	0.151626	0.153702
Absolute Change at 15 Months after Intervention 1	-0.002258	(-0.003130, -0.001386)	0.151264	0.153522
Relative Change (%) at 15 Months after Intervention 1	-1.47	(-2.03, -0.91)	0.151264	0.153522
Absolute Change at 16 Months after Intervention 1	-0.002441	(-0.003344, -0.001538)	0.150901	0.153342
Relative Change (%) at 16 Months after Intervention 1	-1.59	(-2.17, -1.01)	0.150901	0.153342
Absolute Change at 17 Months after Intervention 1	-0.002624	(-0.003558, -0.001689)	0.150538	0.153162
Relative Change (%) at 17 Months after Intervention 1	-1.71	(-2.31, -1.11)	0.150538	0.153162
Absolute Change at 18 Months after Intervention 1	-0.002806	(-0.003774, -0.001838)	0.150176	0.152982
Relative Change (%) at 18 Months after Intervention 1	-1.83	(-2.46, -1.21)	0.150176	0.152982
Absolute Change at 19 Months after Intervention 1	-0.002989	(-0.003991, -0.001987)	0.149813	0.152802
Relative Change (%) at 19 Months after Intervention 1	-1.96	(-2.60, -1.31)	0.149813	0.152802
Absolute Change at 20 Months after Intervention 1	-0.003172	(-0.004209, -0.002134)	0.149451	0.152622
Relative Change (%) at 20 Months after Intervention 1	-2.08	(-2.75, -1.41)	0.149451	0.152622
Absolute Change at 21 Months after Intervention 1	-0.003354	(-0.004428, -0.002281)	0.149088	0.152443
Relative Change (%) at 21 Months after Intervention 1	-2.20	(-2.89, -1.51)	0.149088	0.152443
Absolute Change at 22 Months after Intervention 1	-0.003537	(-0.004647, -0.002426)	0.148726	0.152263
Relative Change (%) at 22 Months after Intervention 1	-2.32	(-3.04, -1.61)	0.148726	0.152263
Absolute Change at 23 Months after Intervention 1	-0.003720	(-0.004868, -0.002571)	0.148363	0.152083
Relative Change (%) at 23 Months after Intervention 1	-2.45	(-3.19, -1.71)	0.148363	0.152083
Absolute Change at 24 Months after Intervention 1	-0.003902	(-0.005089, -0.002716)	0.148001	0.151903
Relative Change (%) at 24 Months after Intervention 1	-2.57	(-3.33, -1.80)	0.148001	0.151903
Absolute Change at 25 Months after Intervention 1	-0.004085	(-0.005311, -0.002859)	0.147638	0.151723
Relative Change (%) at 25 Months after Intervention 1	-2.69	(-3.48, -1.90)	0.147638	0.151723
Absolute Change at 26 Months after Intervention 1	-0.004268	(-0.005533, -0.003002)	0.147276	0.151543
Relative Change (%) at 26 Months after Intervention 1	-2.82	(-3.63, -2.00)	0.147276	0.151543
Absolute Change at 27 Months after Intervention 1	-0.004450	(-0.005756, -0.003145)	0.146913	0.151364
Relative Change (%) at 27 Months after Intervention 1	-2.94	(-3.78, -2.10)	0.146913	0.151364
Absolute Change at 27 Months after Intervention 1	-0.004450	(-0.005756, -0.003145)	0.146913	0.151364
Relative Change (%) at 27 Months after Intervention 1	-2.94	(-3.78, -2.10)	0.146913	0.151364

¹The 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.

Figure 58. Proportion of Loop Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 117. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 60)²			
Intercept	0.046899	(0.046703, 0.047095)	<.001
Baseline trend	0.000214	(0.000206, 0.000222)	<.001
Level Change (After Intervention 1)	-0.000532	(-0.000894, -0.000170)	0.005
Trend Change (After Intervention 1)	0.000086	(0.000068, 0.000104)	<.001
Most Parsimonious Final Model Parameters (df = 60)^{2,3}			
Intercept	0.046899	(0.046703, 0.047095)	<.001
Baseline trend	0.000214	(0.000206, 0.000222)	<.001
Level Change (After Intervention 1)	-0.000532	(-0.000894, -0.000170)	0.005
Trend Change (After Intervention 1)	0.000086	(0.000068, 0.000104)	<.001

¹The 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.

²Maximum 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.

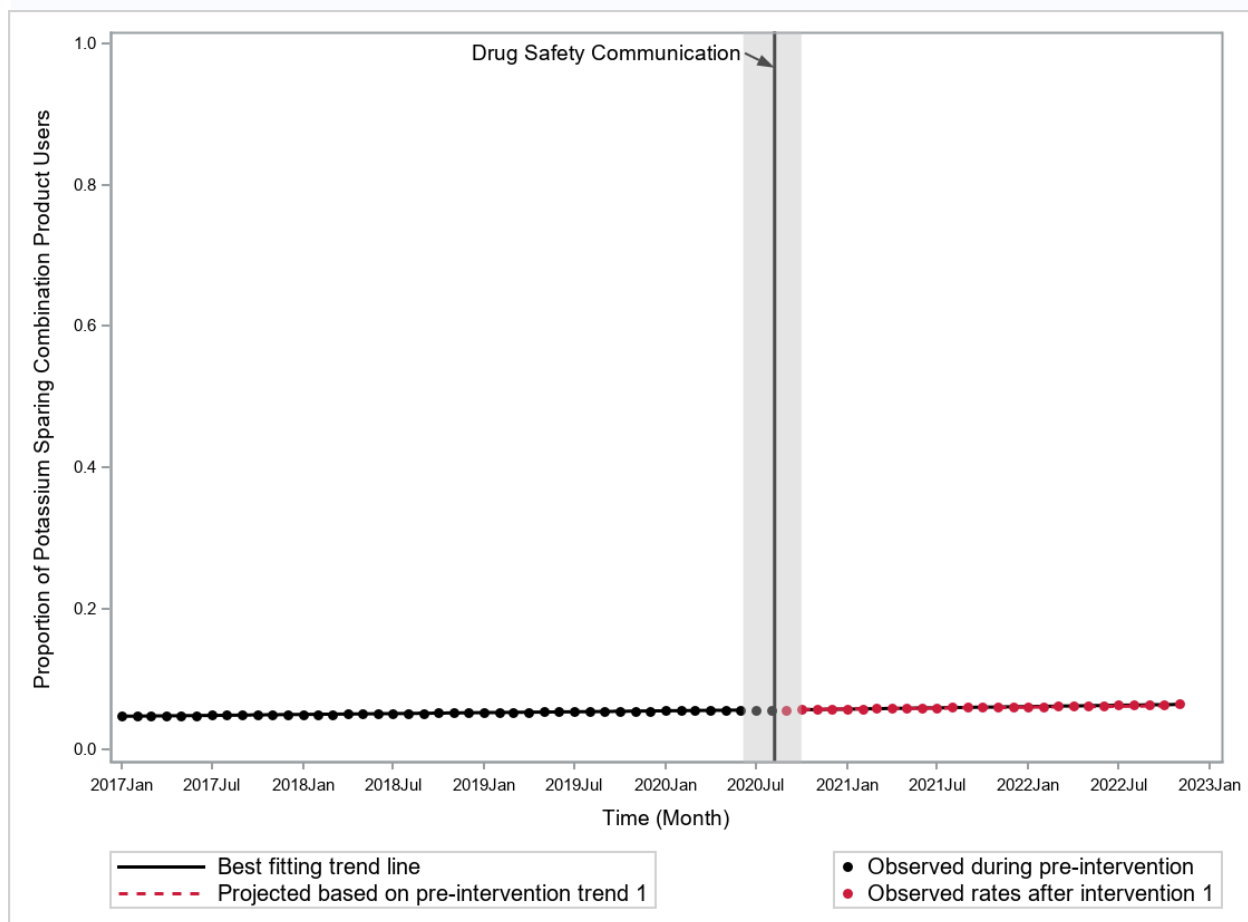
³Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 118. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	-0.000360	(-0.000703, -0.000017)	0.056380	0.056740
Relative Change (%) at 2 Months after Intervention 1	-0.63	(-1.24, -0.03)	0.056380	0.056740
Absolute Change at 3 Months after Intervention 1	-0.000274	(-0.000612, 0.000063)	0.056680	0.056954
Relative Change (%) at 3 Months after Intervention 1	-0.48	(-1.07, 0.11)	0.056680	0.056954
Absolute Change at 4 Months after Intervention 1	-0.000188	(-0.000521, 0.000144)	0.056979	0.057168
Relative Change (%) at 4 Months after Intervention 1	-0.33	(-0.91, 0.25)	0.056979	0.057168
Absolute Change at 5 Months after Intervention 1	-0.000103	(-0.000431, 0.000226)	0.057279	0.057382
Relative Change (%) at 5 Months after Intervention 1	-0.18	(-0.75, 0.39)	0.057279	0.057382
Absolute Change at 6 Months after Intervention 1	-0.000017	(-0.000342, 0.000308)	0.057579	0.057595
Relative Change (%) at 6 Months after Intervention 1	-0.03	(-0.59, 0.54)	0.057579	0.057595
Absolute Change at 7 Months after Intervention 1	0.000069	(-0.000254, 0.000392)	0.057879	0.057809
Relative Change (%) at 7 Months after Intervention 1	0.12	(-0.44, 0.68)	0.057879	0.057809
Absolute Change at 8 Months after Intervention 1	0.000155	(-0.000166, 0.000476)	0.058178	0.058023
Relative Change (%) at 8 Months after Intervention 1	0.27	(-0.29, 0.82)	0.058178	0.058023
Absolute Change at 9 Months after Intervention 1	0.000241	(-0.000080, 0.000562)	0.058478	0.058237
Relative Change (%) at 9 Months after Intervention 1	0.41	(-0.14, 0.97)	0.058478	0.058237
Absolute Change at 10 Months after Intervention 1	0.000327	(0.000005, 0.000649)	0.058778	0.058451
Relative Change (%) at 10 Months after Intervention 1	0.56	(0.01, 1.11)	0.058778	0.058451
Absolute Change at 11 Months after Intervention 1	0.000412	(0.000089, 0.000736)	0.059078	0.058665
Relative Change (%) at 11 Months after Intervention 1	0.70	(0.15, 1.26)	0.059078	0.058665
Absolute Change at 12 Months after Intervention 1	0.000498	(0.000172, 0.000825)	0.059377	0.058879
Relative Change (%) at 12 Months after Intervention 1	0.85	(0.29, 1.41)	0.059377	0.058879
Absolute Change at 13 Months after Intervention 1	0.000584	(0.000254, 0.000915)	0.059677	0.059093
Relative Change (%) at 13 Months after Intervention 1	0.99	(0.42, 1.55)	0.059677	0.059093
Absolute Change at 14 Months after Intervention 1	0.000670	(0.000335, 0.001005)	0.059977	0.059307
Relative Change (%) at 14 Months after Intervention 1	1.13	(0.56, 1.70)	0.059977	0.059307
Absolute Change at 15 Months after Intervention 1	0.000756	(0.000415, 0.001097)	0.060277	0.059521
Relative Change (%) at 15 Months after Intervention 1	1.27	(0.69, 1.85)	0.060277	0.059521
Absolute Change at 16 Months after Intervention 1	0.000842	(0.000494, 0.001189)	0.060576	0.059735
Relative Change (%) at 16 Months after Intervention 1	1.41	(0.82, 2.00)	0.060576	0.059735
Absolute Change at 17 Months after Intervention 1	0.000927	(0.000573, 0.001282)	0.060876	0.059949
Relative Change (%) at 17 Months after Intervention 1	1.55	(0.95, 2.15)	0.060876	0.059949
Absolute Change at 18 Months after Intervention 1	0.001013	(0.000650, 0.001376)	0.061176	0.060163
Relative Change (%) at 18 Months after Intervention 1	1.68	(1.07, 2.30)	0.061176	0.060163
Absolute Change at 19 Months after Intervention 1	0.001099	(0.000727, 0.001471)	0.061476	0.060377
Relative Change (%) at 19 Months after Intervention 1	1.82	(1.20, 2.45)	0.061476	0.060377
Absolute Change at 20 Months after Intervention 1	0.001185	(0.000804, 0.001566)	0.061775	0.060591
Relative Change (%) at 20 Months after Intervention 1	1.96	(1.32, 2.59)	0.061775	0.060591
Absolute Change at 21 Months after Intervention 1	0.001271	(0.000879, 0.001662)	0.062075	0.060804
Relative Change (%) at 21 Months after Intervention 1	2.09	(1.44, 2.74)	0.062075	0.060804
Absolute Change at 22 Months after Intervention 1	0.001357	(0.000955, 0.001758)	0.062375	0.061018
Relative Change (%) at 22 Months after Intervention 1	2.22	(1.55, 2.89)	0.062375	0.061018
Absolute Change at 23 Months after Intervention 1	0.001442	(0.001029, 0.001855)	0.062675	0.061232
Relative Change (%) at 23 Months after Intervention 1	2.36	(1.67, 3.04)	0.062675	0.061232
Absolute Change at 24 Months after Intervention 1	0.001528	(0.001103, 0.001953)	0.062974	0.061446
Relative Change (%) at 24 Months after Intervention 1	2.49	(1.78, 3.19)	0.062974	0.061446
Absolute Change at 25 Months after Intervention 1	0.001614	(0.001177, 0.002051)	0.063274	0.061660
Relative Change (%) at 25 Months after Intervention 1	2.62	(1.90, 3.34)	0.063274	0.061660
Absolute Change at 26 Months after Intervention 1	0.001700	(0.001251, 0.002149)	0.063574	0.061874
Relative Change (%) at 26 Months after Intervention 1	2.75	(2.01, 3.49)	0.063574	0.061874
Absolute Change at 27 Months after Intervention 1	0.001786	(0.001323, 0.002248)	0.063874	0.062088
Relative Change (%) at 27 Months after Intervention 1	2.88	(2.12, 3.64)	0.063874	0.062088
Absolute Change at 27 Months after Intervention 1	0.001786	(0.001323, 0.002248)	0.063874	0.062088
Relative Change (%) at 27 Months after Intervention 1	2.88	(2.12, 3.64)	0.063874	0.062088

¹The 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.

Figure 59. Proportion of Potassium-Sparing Diuretics Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

Table 119. 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 with no History of Skin Cancer after August 8, 2020¹

	Estimate	95% CI	Approximate Pr > t
Initial Model Parameters (df = 62)²			
Intercept	0.022752	(0.022467, 0.023038)	<.001
Baseline trend	0.000128	(0.000116, 0.000139)	<.001
Level Change (After Intervention 1)	-0.000508	(-0.000970, -0.000046)	0.032
Trend Change (After Intervention 1)	-0.000089	(-0.000114, -0.000064)	<.001
Most Parsimonious Final Model Parameters (df = 62)^{2,3}			
Intercept	0.022752	(0.022467, 0.023038)	<.001
Baseline trend	0.000128	(0.000116, 0.000139)	<.001
Level Change (After Intervention 1)	-0.000508	(-0.000970, -0.000046)	0.032
Trend Change (After Intervention 1)	-0.000089	(-0.000114, -0.000064)	<.001

¹The 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.

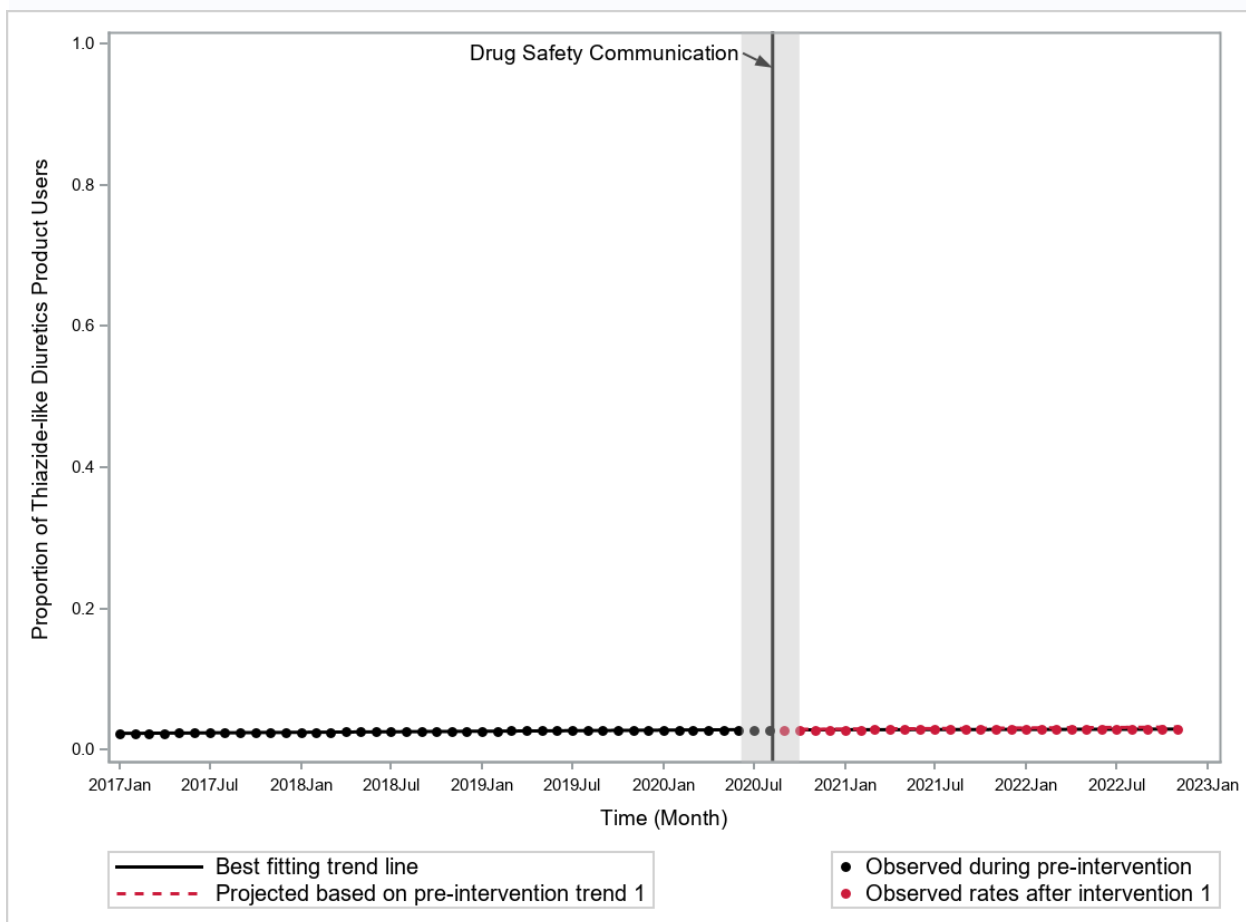
²Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

Table 120. 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 with no History of Skin Cancer after August 8, 2020¹ 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	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	-0.000686	(-0.001169, -0.000203)	0.027934	0.028620
Relative Change (%) at 2 Months after Intervention 1	-2.40	(-4.06, -0.73)	0.027934	0.028620
Absolute Change at 3 Months after Intervention 1	-0.000775	(-0.001251, -0.000298)	0.027973	0.028748
Relative Change (%) at 3 Months after Intervention 1	-2.70	(-4.33, -1.06)	0.027973	0.028748
Absolute Change at 4 Months after Intervention 1	-0.000864	(-0.001335, -0.000393)	0.028011	0.028875
Relative Change (%) at 4 Months after Intervention 1	-2.99	(-4.60, -1.39)	0.028011	0.028875
Absolute Change at 5 Months after Intervention 1	-0.000953	(-0.001421, -0.000485)	0.028050	0.029003
Relative Change (%) at 5 Months after Intervention 1	-3.29	(-4.87, -1.71)	0.028050	0.029003
Absolute Change at 6 Months after Intervention 1	-0.001042	(-0.001507, -0.000577)	0.028088	0.029130
Relative Change (%) at 6 Months after Intervention 1	-3.58	(-5.14, -2.02)	0.028088	0.029130
Absolute Change at 7 Months after Intervention 1	-0.001131	(-0.001595, -0.000667)	0.028127	0.029258
Relative Change (%) at 7 Months after Intervention 1	-3.87	(-5.41, -2.32)	0.028127	0.029258
Absolute Change at 8 Months after Intervention 1	-0.001220	(-0.001684, -0.000756)	0.028165	0.029386
Relative Change (%) at 8 Months after Intervention 1	-4.15	(-5.68, -2.62)	0.028165	0.029386
Absolute Change at 9 Months after Intervention 1	-0.001309	(-0.001775, -0.000844)	0.028204	0.029513
Relative Change (%) at 9 Months after Intervention 1	-4.44	(-5.96, -2.91)	0.028204	0.029513
Absolute Change at 10 Months after Intervention 1	-0.001398	(-0.001867, -0.000930)	0.028242	0.029641
Relative Change (%) at 10 Months after Intervention 1	-4.72	(-6.24, -3.20)	0.028242	0.029641
Absolute Change at 11 Months after Intervention 1	-0.001487	(-0.001960, -0.001015)	0.028281	0.029768
Relative Change (%) at 11 Months after Intervention 1	-5.00	(-6.52, -3.47)	0.028281	0.029768
Absolute Change at 12 Months after Intervention 1	-0.001576	(-0.002054, -0.001099)	0.028319	0.029896
Relative Change (%) at 12 Months after Intervention 1	-5.27	(-6.80, -3.74)	0.028319	0.029896
Absolute Change at 13 Months after Intervention 1	-0.001665	(-0.002150, -0.001181)	0.028358	0.030023
Relative Change (%) at 13 Months after Intervention 1	-5.55	(-7.09, -4.01)	0.028358	0.030023
Absolute Change at 14 Months after Intervention 1	-0.001754	(-0.002246, -0.001263)	0.028396	0.030151
Relative Change (%) at 14 Months after Intervention 1	-5.82	(-7.37, -4.27)	0.028396	0.030151
Absolute Change at 15 Months after Intervention 1	-0.001844	(-0.002344, -0.001343)	0.028435	0.030279
Relative Change (%) at 15 Months after Intervention 1	-6.09	(-7.66, -4.52)	0.028435	0.030279
Absolute Change at 16 Months after Intervention 1	-0.001933	(-0.002443, -0.001422)	0.028474	0.030406
Relative Change (%) at 16 Months after Intervention 1	-6.36	(-7.94, -4.77)	0.028474	0.030406
Absolute Change at 17 Months after Intervention 1	-0.002022	(-0.002543, -0.001500)	0.028512	0.030534
Relative Change (%) at 17 Months after Intervention 1	-6.62	(-8.23, -5.01)	0.028512	0.030534
Absolute Change at 18 Months after Intervention 1	-0.002111	(-0.002644, -0.001577)	0.028551	0.030661
Relative Change (%) at 18 Months after Intervention 1	-6.88	(-8.52, -5.25)	0.028551	0.030661
Absolute Change at 19 Months after Intervention 1	-0.002200	(-0.002746, -0.001654)	0.028589	0.030789
Relative Change (%) at 19 Months after Intervention 1	-7.14	(-8.81, -5.48)	0.028589	0.030789
Absolute Change at 20 Months after Intervention 1	-0.002289	(-0.002848, -0.001729)	0.028628	0.030916
Relative Change (%) at 20 Months after Intervention 1	-7.40	(-9.10, -5.71)	0.028628	0.030916
Absolute Change at 21 Months after Intervention 1	-0.002378	(-0.002951, -0.001804)	0.028666	0.031044
Relative Change (%) at 21 Months after Intervention 1	-7.66	(-9.39, -5.93)	0.028666	0.031044
Absolute Change at 22 Months after Intervention 1	-0.002467	(-0.003055, -0.001878)	0.028705	0.031171
Relative Change (%) at 22 Months after Intervention 1	-7.91	(-9.68, -6.15)	0.028705	0.031171
Absolute Change at 23 Months after Intervention 1	-0.002556	(-0.003160, -0.001952)	0.028743	0.031299
Relative Change (%) at 23 Months after Intervention 1	-8.17	(-9.97, -6.36)	0.028743	0.031299
Absolute Change at 24 Months after Intervention 1	-0.002645	(-0.003265, -0.002025)	0.028782	0.031427
Relative Change (%) at 24 Months after Intervention 1	-8.42	(-10.26, -6.58)	0.028782	0.031427
Absolute Change at 25 Months after Intervention 1	-0.002734	(-0.003371, -0.002097)	0.028820	0.031554
Relative Change (%) at 25 Months after Intervention 1	-8.66	(-10.55, -6.78)	0.028820	0.031554
Absolute Change at 26 Months after Intervention 1	-0.002823	(-0.003477, -0.002169)	0.028859	0.031682
Relative Change (%) at 26 Months after Intervention 1	-8.91	(-10.83, -6.99)	0.028859	0.031682
Absolute Change at 27 Months after Intervention 1	-0.002912	(-0.003584, -0.002240)	0.028897	0.031809
Relative Change (%) at 27 Months after Intervention 1	-9.15	(-11.12, -7.19)	0.028897	0.031809
Absolute Change at 27 Months after Intervention 1	-0.002912	(-0.003584, -0.002240)	0.028897	0.031809
Relative Change (%) at 27 Months after Intervention 1	-9.15	(-11.12, -7.19)	0.028897	0.031809

¹The 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.

Figure 60. Proportion of Thiazide-like Diuretics Product Users Among Number of Patients with Use of HCTZ-containing Products or Any Diuretics or Any Antihypertensives with no History of Skin Cancer Before and After August 8, 2020^{1,2}



¹The 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.

²The gray box indicates the timing of the anticipatory period, starting from June 6, 2020 (rounded to the nearest subsequent month) up to the month prior to the first intervention (August 8, 2020).

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 ¹
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

¹End 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
HCTZ single ingredient/monotherapy	
hydrochlorothiazide	hydrochlorothiazide
hydrochlorothiazide	Microzide
HCTZ combination products	
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
HCTZ ACE inhibitor combination	
benazepril HCl/hydrochlorothiazide	benazepril-hydrochlorothiazide

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

Non-Proprietary	Brand Name
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
HCTZ ARB combination	
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiiazid
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
HCTZ potassium sparing diuretics combination	
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
HCTZ beta blocker combination	
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
HCTZ ARB calcium channel blocker combination	
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
Chlorothiazide, Bendroflumethiazide, or Thiazide-like diuretics	
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide

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

Non-Proprietary	Brand Name
metolazone	metolazone
chlorothiazide	chlorothiazide
chlorothiazide	Diuril
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
Chlorothiazide	
chlorothiazide	chlorothiazide
chlorothiazide	Diuril
Bendroflumethiazide	
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
Thiazide-like diuretics	
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
ACE inhibitors	
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
Calcium channel blockers	
amlodipine benzoate	Katerzia
amlodipine besylate	amlodipine
amlodipine besylate	Norliqva
amlodipine besylate	Norvasc
amlodipine besylate/celecoxib	Consensi
diltiazem HCl	Cardizem
diltiazem HCl	Cardizem CD

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

Non-Proprietary	Brand Name
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
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
Potassium-sparing diuretics	
amiloride HCl	amiloride
eplerenone	eplerenone
eplerenone	Inspra
spironolactone	Aldactone
spironolactone	CaroSpir
spironolactone	spironolactone
triamterene	Dyrenium
triamterene	triamterene
Loop diuretics	
bumetanide	bumetanide
ethacrynic acid	Edecrin
ethacrynic acid	ethacrynic acid
furosemide	furosemide
furosemide	Lasix
torsemide	Demadex
torsemide	Soanz
torsemide	torsemide
Limited denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide or thiazide-like diuretics)	
aliskiren hemifumarate/hydrochlorothiazide	Tekturna HCT

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

Non-Proprietary	Brand Name
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 besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
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

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

Non-Proprietary	Brand Name
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
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 besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
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

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

Non-Proprietary	Brand Name
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
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

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

Non-Proprietary	Brand Name
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
amiloride HCl	amiloride
eplerenone	eplerenone
eplerenone	Inspra
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
ARB Generics	
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

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

Non-Proprietary	Brand Name
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
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

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

Non-Proprietary	Brand Name
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
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
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

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

Non-Proprietary	Brand Name
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
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
Beta Blockers Generic	
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

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

Non-Proprietary	Brand Name
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
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	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

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

Non-Proprietary	Brand Name
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
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/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
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

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

Non-Proprietary	Brand Name
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
propranolol HCl	propranolol
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	Sotylize
timolol maleate	timolol maleate
timolol maleate	timolol maleate
timolol maleate	timolol maleate

Appendix C.1. Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events	Multiple Events Group 1		Multiple Events Group 2		Multiple Events Group 3	
	Numerator: HCTZ-containing products		Numerator: HCTZ single ingredient/monotherapy		Numerator: ACEI + HCTZ	
	Multiple Events Composition (Primary)	denom_limited_no	denom_limited_no	denom_limited_no	denom_limited_no	denom_limited_no
	Multiple Events Composition (Secondary)	hctz_containing_all_no	hctz_mono_all_no	hctz_mono_all_no	hctz_acei_combo_no	hctz_acei_combo_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of any HCTZ-containing product; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ single ingredient; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ single ingredient; NO evidence of skin cancer in enrollment history	Number of patients with use of ACEI + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of ACEI + HCTZ combo product; NO evidence of skin cancer in enrollment history
	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	Start of primary episode (index date) to end of 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	First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
ITS Analysis	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode	1 adherent episode	1 adherent episode
	Categories for length of primary episode	N/A	N/A	N/A	N/A	N/A
	ITS Analysis 1A		ITS Analysis 2A		ITS Analysis 3A	
	Intervention date 8/8/2020		Intervention date 8/8/2020		Intervention date 8/8/2020	
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes	Yes	Yes
ITS Analysis	Interval length	Monthly	Monthly	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2	0.2	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	All available months between intervention date and data range end	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	No	No	No
	ITS Analysis 1B		ITS Analysis 2B		ITS Analysis 3B	
	Anticipatory/lag period from 6/1/2020 -		Anticipatory/lag period from 6/1/2020 -		Anticipatory/lag period from 6/1/2020 -	
ITS Analysis	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	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	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2	0.2	0.2	0.2
ITS Analysis	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	All available months between intervention date and data range end	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	No	No	No

Appendix C.1. Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events	Multiple Events Group 4		Multiple Events Group 5		Multiple Events Group 6	
	Numerator: ARB + HCTZ		Numerator: Potassium-sparing diuretic + HCTZ		Numerator: Beta blocker + HCTZ	
	Multiple Events Composition (Primary)	denom_limited_no	denom_limited_no	denom_limited_no	denom_limited_no	denom_limited_no
	Multiple Events Composition (Secondary)	hctz_arb_combo_no	hctz_potass_combo_no	hctz_potass_combo_no	hctz_beta_combo_no	hctz_beta_combo_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of ARB + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of potassium-sparing diuretic + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of potassium-sparing diuretic + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of beta blocker + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of beta blocker + HCTZ combo product; NO evidence of skin cancer in enrollment history
	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	Start of primary episode (index date) to end of 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	First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
ITS Analysis	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode	1 adherent episode	1 adherent episode
	Categories for length of primary episode	N/A	N/A	N/A	N/A	N/A
	ITS Analysis 4A		ITS Analysis 5A		ITS Analysis 6A	
	Intervention date 8/8/2020		Intervention date 8/8/2020		Intervention date 8/8/2020	
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes	Yes	Yes
ITS Analysis	Interval length	Monthly	Monthly	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2	0.2	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	All available months between intervention date and data range end	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	No	No	No
	ITS Analysis 4B		ITS Analysis 5B		ITS Analysis 6B	
	Anticipatory/lag period from 6/1/2020 -		Anticipatory/lag period from 6/1/2020 -		Anticipatory/lag period from 6/1/2020 -	
ITS Analysis	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data	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	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2	0.2	0.2	0.2
ITS Analysis	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	All available months between intervention date and data range end	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	No	No	No

Appendix C.1. Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events		Multiple Events Group 7 Numerator: ARB + CCB + HCTZ denom_limited_no hctz_arb_ccb_combo_no Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history Number of patients with use of ARB + CCB + HCTZ combo product; NO evidence of skin cancer in enrollment history Start of primary episode (index date) to end of primary episode First occurrence of secondary index 1 adherent episode N/A	Multiple Events Group 8 Numerator: Direct renin inhibitor + HCTZ denom_limited_no hctz_direct_no Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history Number of patients with use of direct renin inhibitor + HCTZ combo product; NO evidence of skin cancer in enrollment history Start of primary episode (index date) to end of primary episode First occurrence of secondary index 1 adherent episode N/A	Multiple Events Group 9 Numerator: Central alpha 2 agonist + HCTZ denom_limited_no hctz_central_no Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history Number of patients with use of central alpha 2 agonist + HCTZ combo product; NO evidence of skin cancer in enrollment history Start of primary episode (index date) to end of primary episode First occurrence of secondary index 1 adherent episode N/A
	Multiple Events Composition (Primary)			
	Multiple Events Composition (Secondary)			
	ITS Denominator			
	ITS Numerator			
	Observation window around primary episode			
	Secondary episode to use for time metrics			
	Minimum cutoff to be considered adherent			
Categories for length of primary episode				

ITS Analysis		ITS Analysis 7A Intervention date 8/8/2020 1/1/2017 - most recent available data N/A 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No	ITS Analysis 8A Intervention date 8/8/2020 1/1/2017 - most recent available data N/A 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No	ITS Analysis 9A Intervention date 8/8/2020 1/1/2017 - most recent available data N/A 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No
	Data range start, end			
	Anticipatory date period			
	Intervention date			
	Truncation of exposure episode at intervention date?			
	Interval length			
	p-value			
	Autoregression lag			
Autoregression model parameter cutoff				
Time points at which to report difference metrics				
Continuous enrollment required?				

ITS Analysis		ITS Analysis 7B Anticipatory/lag period from 6/1/2020 - 1/1/2017 - most recent available data 6/1/2020 - 10/1/2020 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No	ITS Analysis 8B Anticipatory/lag period from 6/1/2020 - 1/1/2017 - most recent available data 6/1/2020 - 10/1/2020 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No	ITS Analysis 9B Anticipatory/lag period from 6/1/2020 - 1/1/2017 - most recent available data 6/1/2020 - 10/1/2020 8/8/2020 Yes Monthly 0.05 12 (12 months) 0.2 All available months between intervention date and data range end No
	Data range start, end			
	Anticipatory/lag period			
	Intervention date			
	Truncation of exposure episode at intervention date?			
	Interval length			
	p-value			
	Autoregression lag			
Autoregression model parameter cutoff				
Time points at which to report difference metrics				
Continuous enrollment required?				

Appendix C.1. Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

		Multiple Events Group 10	Multiple Events Group 11	Multiple Events Group 12
		Numerator: HCTZ-containing products	Numerator: Chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Numerator: ACEIs (non-HCTZ combination)
Multiple Events	Multiple Events Composition (Primary)	denom_all	denom_all	denom_all
	Multiple Events Composition (Secondary)	hctz_containing_all	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	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 HCTZ-containing products	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	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	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode
		N/A	N/A	N/A
ITS Analysis	ITS Analysis 10A		ITS Analysis 11A	ITS Analysis 12A
	Intervention date 8/8/2020		Intervention date 8/8/2020	Intervention date 8/8/2020
	1/1/2017 - most recent available data		1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Data range start, end	N/A	N/A	N/A
	Anticipatory date period	8/8/2020	8/8/2020	8/8/2020
	Intervention date	Yes	Yes	Yes
	Truncation of exposure episode at intervention date?	Monthly	Monthly	Monthly
	Interval length	0.05	0.05	0.05
	p-value	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression lag	0.2	0.2	0.2
	Autoregression model parameter cutoff	All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
	Time points at which to report difference metrics	No	No	No
	Continuous enrollment required?			
ITS Analysis	ITS Analysis 10B		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	Anticipatory/lag period from 6/1/2020 - 10/1/2020
	1/1/2017 - most recent available data		1/1/2017 - most recent available data	1/1/2017 - most recent available data
	6/1/2020 - 10/1/2020		6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Data range start, end	8/8/2020	8/8/2020	8/8/2020
	Anticipatory/lag period	Yes	Yes	Yes
	Intervention date	Monthly	Monthly	Monthly
	Truncation of exposure episode at intervention date?	0.05	0.05	0.05
	Interval length	12 (12 months)	12 (12 months)	12 (12 months)
	p-value	0.2	0.2	0.2
	Autoregression lag	All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
	Autoregression model parameter cutoff	No	No	No
	Time points at which to report difference metrics			
	Continuous enrollment required?			

Appendix C.1. Specifications for Type 2, Interrupted Time Series Request, Skin Cancer History Analysis, Full Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events				
		Multiple Events Group 13	Multiple Events Group 14	Multiple Events Group 15
		Numerator: CCBs (non-HCTZ combination)	Numerator: Potassium-sparing diuretics (non-HCTZ combination)	Numerator: Loop diuretics
	Multiple Events Composition (Primary)	denom_all	denom_all	denom_all
	Multiple Events Composition (Secondary)	other_ccb	other_potass	other_loop
	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	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)	Number of patients with use of loop diuretics
	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	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	First occurrence of secondary index	
Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode	
Categories for length of primary episode	N/A	N/A	N/A	
ITS Analysis		ITS Analysis 13A	ITS Analysis 14A	ITS Analysis 15A
		Intervention date 8/8/2020	Intervention date 8/8/2020	Intervention date 8/8/2020
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	
ITS Analysis		ITS Analysis 13B	ITS Analysis 14B	ITS Analysis 15B
		Anticipatory/lag period from 6/1/2020 - 10/1/2020	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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)	
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	

N/A: Not applicable

Appendix C.2. Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events	Multiple Events Group 18		Multiple Events Group 19		Multiple Events Group 20	
	Numerator: HCTZ-containing products; NO evidence of skin cancer prior to dispensing		Numerator: HCTZ single ingredient/monotherapy; NO evidence of skin cancer prior to dispensing		Numerator: ACEI + HCTZ; NO evidence of skin cancer prior to dispensing	
	Multiple Events Composition (Primary)	denom_limited_no	Multiple Events Composition (Primary)	denom_limited_no	Multiple Events Composition (Primary)	denom_limited_no
	Multiple Events Composition (Secondary)	hctz_containing_all_no	Multiple Events Composition (Secondary)	hctz_mono_all_no	Multiple Events Composition (Secondary)	hctz_acei_combo_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of any HCTZ-containing product; NO evidence of skin cancer in enrollment history	ITS Numerator	Number of patients with use of HCTZ single ingredient; NO evidence of skin cancer in enrollment history	ITS Numerator	Number of patients with use of ACEI + HCTZ combo product; NO evidence of skin cancer in enrollment history
	Observation window around primary episode	Start of primary episode (index date) to end of primary episode	Observation window around primary episode	Start of primary episode (index date) to end of primary episode	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	Secondary episode to use for time metrics	First occurrence of secondary index	Secondary episode to use for time metrics	First occurrence of secondary index
ITS Analysis	Minimum cutoff to be considered adherent	1 adherent episode	Minimum cutoff to be considered adherent	1 adherent episode	Minimum cutoff to be considered adherent	1 adherent episode
	Categories for length of primary episode	N/A	Categories for length of primary episode	N/A	Categories for length of primary episode	N/A
	ITS Analysis 1A		ITS Analysis 2A		ITS Analysis 3A	
	Intervention date 8/8/2020		Intervention date 8/8/2020		Intervention date 8/8/2020	
	Data range start, end	1/1/2017 - most recent available data	Data range start, end	1/1/2017 - most recent available data	Data range start, end	1/1/2017 - most recent available data
	Anticipatory date period	N/A	Anticipatory date period	N/A	Anticipatory date period	N/A
	Intervention date	8/8/2020	Intervention date	8/8/2020	Intervention date	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Truncation of exposure episode at intervention date?	Yes	Truncation of exposure episode at intervention date?	Yes
ITS Analysis	Interval length	Monthly	Interval length	Monthly	Interval length	Monthly
	p-value	0.05	p-value	0.05	p-value	0.05
	Autoregression lag	12 (12 months)	Autoregression lag	12 (12 months)	Autoregression lag	12 (12 months)
	Autoregression model parameter cutoff	0.2	Autoregression model parameter cutoff	0.2	Autoregression model parameter cutoff	0.2
	Time points at which to report difference metrics	All available months between intervention date and data range end	Time points at which to report difference metrics	All available months between intervention date and data range end	Time points at which to report difference metrics	All available months between intervention date and data range end
	Continuous enrollment required?	No	Continuous enrollment required?	No	Continuous enrollment required?	No
	ITS Analysis 1B		ITS Analysis 2B		ITS Analysis 3B	
	Anticipatory/lag period from 6/1/2020 - 10/1/2020		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	Data range start, end	1/1/2017 - most recent available data	Data range start, end	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	Anticipatory/lag period	6/1/2020 - 10/1/2020	Anticipatory/lag period	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	Intervention date	8/8/2020	Intervention date	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Truncation of exposure episode at intervention date?	Yes	Truncation of exposure episode at intervention date?	Yes
	Interval length	Monthly	Interval length	Monthly	Interval length	Monthly
	p-value	0.05	p-value	0.05	p-value	0.05
	Autoregression lag	12 (12 months)	Autoregression lag	12 (12 months)	Autoregression lag	12 (12 months)
	Autoregression model parameter cutoff	0.2	Autoregression model parameter cutoff	0.2	Autoregression model parameter cutoff	0.2
ITS Analysis	Time points at which to report difference metrics	All available months between intervention date and data range end	Time points at which to report difference metrics	All available months between intervention date and data range end	Time points at which to report difference metrics	All available months between intervention date and data range end
	Continuous enrollment required?	No	Continuous enrollment required?	No	Continuous enrollment required?	No

Appendix C.2. Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsd1_v01)

		Multiple Events Group 21	Multiple Events Group 22	Multiple Events Group 23
		Numerator: ARB + HCTZ; NO evidence of skin cancer prior to dispensing	Numerator: Potassium-sparing diuretic + HCTZ; NO evidence of skin cancer prior to dispensing	Numerator: Beta blocker + HCTZ; NO evidence of skin cancer prior to dispensing
Multiple Events	Multiple Events Composition (Primary)	denom_limited_no	denom_limited_no	denom_limited_no
	Multiple Events Composition (Secondary)	hctz_arb_combo_no	hctz_potass_combo_no	hctz_beta_combo_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of ARB + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of potassium-sparing diuretic + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of beta blocker + HCTZ combo product; NO evidence of skin cancer in enrollment history
	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	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	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode
		Categories for length of primary episode	N/A	N/A
ITS Analysis			ITS Analysis 4A	ITS Analysis 5A
			Intervention date 8/8/2020	Intervention date 8/8/2020
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end
	Continuous enrollment required?	No	No	No
ITS Analysis			ITS Analysis 4B	ITS Analysis 5B
			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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end
	Continuous enrollment required?	No	No	No
ITS Analysis			ITS Analysis 6B	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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end
	Continuous enrollment required?	No	No	No

Appendix C.2. Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsd1_v01)

		Multiple Events Group 24	Multiple Events Group 25	Multiple Events Group 26
		Numerator: ARB + CCB + HCTZ; NO evidence of skin cancer prior to dispensing	Numerator: Direct renin inhibitor + HCTZ; NO evidence of skin cancer prior to dispensing	Numerator: Central alpha 2 agonist + HCTZ; NO evidence of skin cancer prior to dispensing
Multiple Events	Multiple Events Composition (Primary)	denom_limited_no	denom_limited_no	denom_limited_no
	Multiple Events Composition (Secondary)	hctz_arb_ccb_combo_no	hctz_direct_no	hctz_central_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of ARB + CCB + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of direct renin inhibitor + HCTZ combo product; NO evidence of skin cancer in enrollment history	Number of patients with use of central alpha 2 agonist + HCTZ combo product; NO evidence of skin cancer in enrollment history
	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	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	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode
		Categories for length of primary episode	N/A	N/A
ITS Analysis		ITS Analysis 7A	ITS Analysis 8A	ITS Analysis 9A
		Intervention date 8/8/2020	Intervention date 8/8/2020	Intervention date 8/8/2020
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end
	Continuous enrollment required?	No	No	No
ITS Analysis		ITS Analysis 7B	ITS Analysis 8B	ITS Analysis 9B
		Anticipatory/lag period from 6/1/2020 - 10/1/2020	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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end
	Continuous enrollment required?	No	No	No

Appendix C.2. Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsdp1_v01)

Multiple Events		Multiple Events Group 27 Numerator: HCTZ-containing products; NO evidence of skin cancer prior to dispensing	Multiple Events Group 28 Numerator: Chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer prior to dispensing	Multiple Events Group 29 Numerator: ACEIs (non-HCTZ combination); NO evidence of skin cancer prior to dispensing
	Multiple Events Composition (Primary)	denom_all_no	denom_all_no	denom_all_no
	Multiple Events Composition (Secondary)	hctz_containing_all_no	other_thiazide_plus_no	other_acei_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history
		Number of patients with use of HCTZ-containing products; NO evidence of skin cancer in enrollment history	Number of patients with use of chlorothiazide, bendroflumethiazide, or thiazide-like diuretics; NO evidence of skin cancer in enrollment history	Number of patients with use of ACEIs (non-HCTZ combination); NO evidence of skin cancer in enrollment history
	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	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	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode
Categories for length of primary episode	N/A	N/A	N/A	
ITS Analysis		ITS Analysis 10A Intervention date 8/8/2020	ITS Analysis 11A Intervention date 8/8/2020	ITS Analysis 12A Intervention date 8/8/2020
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	
ITS Analysis		ITS Analysis 10B Anticipatory/lag period from 6/1/2020 - 10/1/2020	ITS Analysis 11B Anticipatory/lag period from 6/1/2020 - 10/1/2020	ITS Analysis 12B 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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	

Appendix C.2. Specifications for Type 2, Interrupted Time Series Request, No Skin Cancer History Analysis, Limited Denominator (cder_mpl2p_wp058_nsd1_v01)

Multiple Events		Multiple Events Group 30 Numerator: CCBs (non-HCTZ combination); NO evidence of skin cancer prior to dispensing	Multiple Events Group 31 Numerator: ARBs (non-HCTZ combination); NO evidence of skin cancer prior to dispensing	Multiple Events Group 32 Numerator: Beta blockers (non-HCTZ combination); NO evidence of skin cancer prior to dispensing
	Multiple Events Composition (Primary)	denom_all_no	denom_all_no	denom_all_no
	Multiple Events Composition (Secondary)	other_ccb_no	other_arbs_no	other_bb_no
	ITS Denominator	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives; NO evidence of skin cancer in enrollment history
	ITS Numerator	Number of patients with use of CCBs (non-HCTZ combination); NO evidence of skin cancer in enrollment history	Number of patients with use of ARBs (non-HCTZ combination); NO evidence of skin cancer in enrollment history	Number of patients with use of beta blockers; NO evidence of skin cancer in enrollment history
	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	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	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode	1 adherent episode
Categories for length of primary episode	N/A	N/A	N/A	
ITS Analysis		ITS Analysis 13A Intervention date 8/8/2020	ITS Analysis 14A Intervention date 8/8/2020	ITS Analysis 15A Intervention date 8/8/2020
	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A	N/A
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	
ITS Analysis		ITS Analysis 13B Anticipatory/lag period from 6/1/2020 - 10/1/2020	ITS Analysis 14B Anticipatory/lag period from 6/1/2020 - 10/1/2020	ITS Analysis 15B 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	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	8/8/2020	8/8/2020	8/8/2020
	Truncation of exposure episode at intervention date?	Yes	Yes	Yes
	Interval length	Monthly	Monthly	Monthly
	p-value	0.05	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)	12 (12 months)
Autoregression model parameter cutoff	0.2	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	All available months between intervention date and data range end	
Continuous enrollment required?	No	No	No	

N/A: Not applicable