

Risk of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) Following GLP-1 Receptor Agonist Use in Patients with Type 2 Diabetes Mellitus

A HARPER Study Protocol

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1. Abstract

Recently, the safety of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been questioned with respect to an increased risk of non-arteritic anterior ischemic optic neuropathy (NAION), a form of optic neuropathy which can cause acute blindness in adults. This concern was raised by a single referral-center study focused on semaglutide, and subsequent observational studies produced conflicting results. Given the severe and irreversible nature of NAION and the growing popularity of GLP-1 RAs, we aim to evaluate the previously observed safety signal with respect to NAION using a principled approach to study design and analysis. Therefore, we aim to conduct a non-randomized cohort study in the HealthVerity aggregated de-duplicated claims data source (January 2018 – June 2024) of the FDA Sentinel System's Real World Evidence Data Enterprise (RWE-DE) Commercial Network, augmented with several outcome validity-enhancing activities leveraging data linkages between insurance claims and electronic health records (EHRs) from two data sources: Mass General Brigham (MGB) and HealthVerity. This investigation is designed using the "PRocess guide for INferential studies using healthcare data from routine Clinical Practice to evaLuate causal Effects of Drugs" (PRINCIPILED) framework, which is a standard Sentinel process to conduct causal inferential studies of medication outcomes. This protocol outlines the specification and emulation of the target trial to answer the study question of interest.

2. Amendments and Updates

Version Date	Version Number	Section of Protocol	Reason
June 11, 2025	1.0		Initial publish
August 1, 2025	2.0	6.3.1, 6.4.4, 6.5.1	Clarifications and enhancements
September 2, 2025	3.0	Table 7, Table 9	Clarifications

3. Milestones

Table 1. Milestones and Timeline.

Milestone	Timeline
Initial Protocol	June 11, 2025

4. Rationale and Background

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have recently surged in popularity due to the expansion in their indication for chronic weight loss management in addition to the original indication for glucose control in patients with type 2 diabetes mellitus (T2DM). Some GLP-1 RAs have also demonstrated cardiovascular benefits in large cardiovascular outcome trials, leading to guideline recommendations as first-line medications in people with T2DM and established cardiovascular risk.¹⁻⁵

The safety profile of the GLP-1 RA class is generally well-characterized, with greater than 100,000 patient-years of clinical trial experience and millions of patient-years of post-marketing experience. The safety of GLP-1 RAs has been questioned recently with respect to the risk of non-arteritic anterior ischemic optic neuropathy (NAION),⁶⁻⁹ an ischemic damage occurring in the anterior portion of the optic nerve (AION), with acute, painless, unilateral loss of vision, which in the majority of patient does not improve with time.¹⁰⁻¹²

NAION is the most common cause of ION, and is most frequent in middle-aged (45 to 64 years) and older (over 64 years) individuals; NAION differs from arteritic AION (AAION), which is often secondary to vasculitis, in particular giant cell arteritis.⁶ In the United States, the estimated annual incidence of NAION ranges from 2.3 to 10.2/100,000 for the general population over 50 years old¹³⁻¹⁵ and 82/100,000 for the general population over 67 years old.¹⁶

The concern for an increased risk of NAION following the use of GLP-1 RAs was raised by a single referral-center study focused on semaglutide. The study found that semaglutide, compared with non-GLP-1 RA medications, was associated with a 4.3-fold increased risk of NAION in patients with T2DM and a 7.6-fold increased risk of NAION in patients with overweight or obesity, with the majority of events occurring within 12 months of drug initiation.⁶ Emerging evidence from subsequent cohort studies produced conflicting results. One investigation based on electronic health records from the TriNetX Analytics Network and not restricting to incident users of GLP-1 RA failed to find an increased risk of NAION among semaglutide users compared to users of non-GLP-1 RA glucose-lowering drugs or weight loss

medications.¹⁷ Additional two studies based on Scandinavian registries identified an elevation in the risk of NAION among people exposed to semaglutide, though one study did not restrict to GLP-1 RA incident users and did not use an active comparator,⁷ and the other study did not adjust for risk factors for NAION such as hemoglobin A1c (HbA1c) and body mass index (BMI).⁸ Two additional recently published studies evaluated the association between semaglutide and NAION. The former, Observational Health Data Sciences and Informatics (OHDSI) network, restricted the study population to people with T2DM on metformin monotherapy at baseline, thus excluding patients with more severe T2DM, and observed a moderate increase in risk among patients exposed to semaglutide.⁹ The latter, based on the TriNetX database failed to observe an association between semaglutide or overall GLP-1 RAs and NAION.¹⁸ Of note, all studies after the JAMA article by Hathaway and associates relied on claims-based diagnosis code algorithms to identify cases of NAION with unclear validity.

Given the severe and irreversible nature of NAION and the growing popularity of GLP-1 RA, we aim to evaluate the previously observed safety signal with respect to NAION using a principled approach to study design and analysis. Thus, we propose a non-randomized cohort study in the HealthVerity aggregated de-duplicated claims-EHR linked data source (January 2018 to June 2024) within the FDA Sentinel System's Real World Evidence Data Enterprise (RWE-DE) Commercial Network, augmented with several outcome validity-enhancing activities leveraging data linkages between insurance claims and electronic health records (EHRs) from two data sources, i.e., one development network site (MGB) and one commercial partner (HealthVerity). See **Appendix B** for more details on the validation study. In this non-randomized cohort study, we propose to 1) evaluate the entire class of GLP-1 RA, not only semaglutide, since we expect that the putative increase in risk of NAION may be related to the common mechanism of action of all GLP-1 RA medications (although we propose to also evaluate the association between individual GLP-1 RA medications and NAION in secondary analyses); and 2) restrict the study population to patients with T2DM who initiate treatment with GLP-1 RA or an alternative glucose-lowering medication, i.e., sodium-glucose cotransporter 2 inhibitors (SGLT2i), to reduce confounding through the use of a comparable active comparator with the same indication of use and similar line of treatment and expected access to health care (see **6.1. Study Design**); since an active comparator that is comparable to GLP-1 RA with respect to these elements does not exist in the setting of obesity treatment, the study population will focus on patients with T2DM, to increase study validity. This protocol follows the HARPER protocol template. [PMID: 36215113]

5. Research Question and Objectives

We will leverage the “PProcess guide for INferential studies using healthcare data from routine Clinical Practice to evaluate causal Effects of Drugs” (PRINCIPLED) framework¹⁹ to conduct the proposed study. Briefly, this framework features a pragmatic five step process (see **Figure 1**) that covers the range of considerations, including 1) formulating a well-defined causal question via specification of the target trial protocol, 2) describing the emulation of each component of the target trial

protocol and identifying fit-for-purpose data, 3) assessing expected precision and conducting diagnostic evaluations, 4) developing a plan for robustness assessments including deterministic sensitivity analyses, quantitative bias analyses, and net bias evaluation, and 5) conducting inferential analyses.

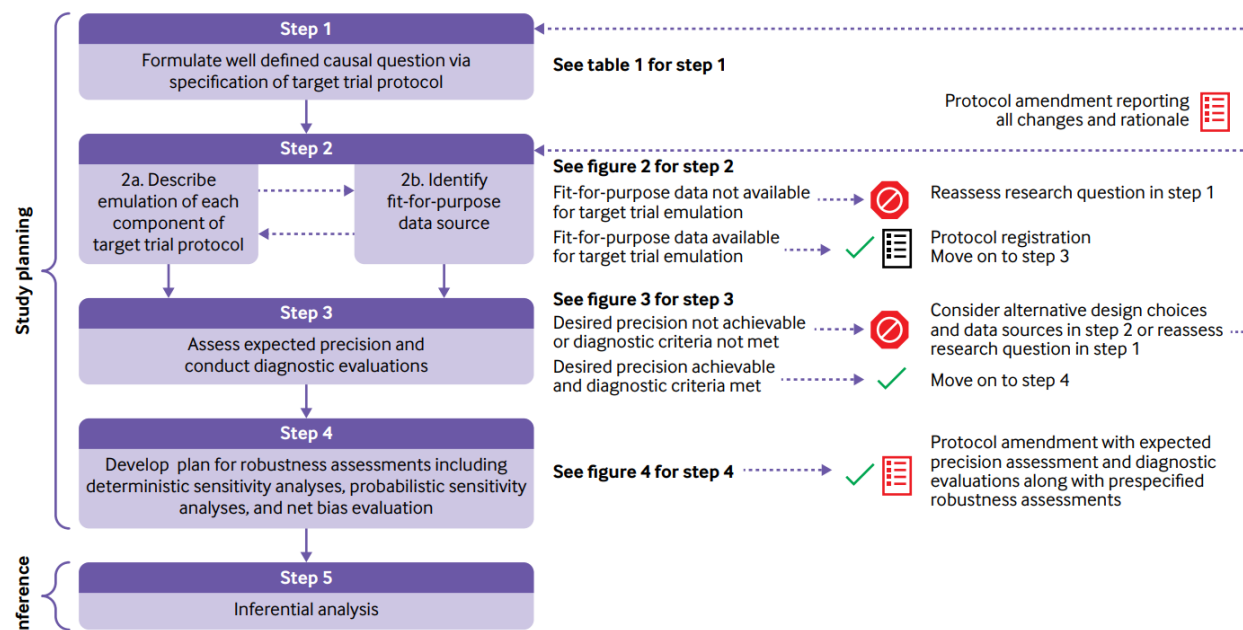


Figure 1. PRINCIPLED Process Overview.

Table 2 summarizes the causal question being asked in the current study via specification of a target trial protocol (Step 1 of the PRINCIPLED process).

Table 2. Step 1: Specification of the Target Trial Protocol.

Element	Specification of the Hypothetical Target Trial	Emulation Using Real-World Data Sources
Eligibility Criteria	January 2019* through June 2024, adult patients (age ≥ 18 years old) with type-2 diabetes mellitus, no use of study medications before randomization, no history of type 1 diabetes, secondary or gestational diabetes, stage 5 or end-stage kidney disease, acute or chronic pancreatitis, multiple endocrine neoplasia type 2 (MEN-2), ischemic optic neuropathy, optic atrophy, anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis and other causes of vasculitis, conditions associated with	Same as target trial operationalized using structured closed claims data

Element	Specification of the Hypothetical Target Trial	Emulation Using Real-World Data Sources
	potential misdiagnosis of NAION, cataract surgery or LASIK. Refer to Table 5 for a complete list of study exclusion criteria Continuous health plan enrollment for 12 months prior to treatment initiation	
Treatment Strategies	1. Initiation of GLP-1 RA (exenatide, liraglutide, semaglutide, dulaglutide, lixisenatide, or tirzepatide) 2. Initiation of SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin)	Same as target trial operationalized using pharmacy dispensing data
Treatment Assignment	Randomized, open label	Non-blinded initiation of a medication from either treatment group that is assumed to be random within levels of measured confounders
Follow-Up Start (Time 0)	The day after treatment assignment	Same as target trial
Follow-Up End	First of administrative end of follow-up (most recent data), loss to follow-up, death, or outcome occurrence, treatment discontinuation or switch (the latter only for per protocol effect)	Same as target trial
Primary Outcome	NAION, defined as an inpatient or outpatient encounter with an ophthalmologist or optometrist that resulted in an ICD-10-CM** diagnosis code of ischemic optic neuropathy (H47.01x).	Same as target trial The final operationalized outcome definition will be informed by ongoing outcome validation studies.
Causal Contrast	Per protocol effect (effect of staying on the treatment) Intent to treat effect (effect of being assigned to the treatment)	Observational analogue of per protocol effect Observational analogue of intent to treat effect

* While the data stream starts January 2018, this protocol requires 12 months of plan enrollment before the cohort entry date, which de facto limits the study eligibility to January 2019 going forward for the primary analysis.

** International Classification of Diseases, Tenth Revision, Clinical Modification.

6. Research Methods

Sections 6.1-6.5 correspond to Step 2a of the PRINCIPLED process, where we explicitly describe emulation of each component of the target trial protocol specified in Step 1.

6.1. Study Design

Research Design: New user active comparator cohort study emulating the above target trial embedded in longitudinal patient-level claims data from HealthVerity from January 2018 through June 2024.

Rationale for study design choice: This study design ensures patient populations with highly similar indications who are likely comparable in their profile of risk factor of the outcome and appropriate for evaluation of safety over the course of the treatment since initiation.

While an ideal target trial would include a placebo comparator, we propose to emulate a target trial comparing GLP-1 RA with an active comparator, i.e., SGLT2i, for the following reasons: 1) in clinical practice, a non-user comparator, which would more closely mimic placebo, would likely not ensure sufficient comparability with GLP-1 RA, due to the expected large differences in baseline risk for the outcome, healthcare surveillance, and key confounders for the association between GLP-1 RA and NAION, e.g., diabetes severity, cardiovascular risk, and BMI; 2) among the available glucose-lowering medications, SGLT2i share many common aspects with GLP-1 RA, including a similar positioning in the clinical guidelines for the treatment of T2DM, proven benefits for patients with cardiovascular and kidney disease, an established effect on weight loss reduction, and similar cost of treatment and expected access to health care. Due to these common elements, patients initiating GLP-1 RA and SGLT2i are expected to be more comparable with respect to many potential confounders and confounder proxies of the association between GLP-1 RA and NAION; 3) SGLT2i have not been previously associated with increased risk of NAION; nevertheless, findings from this investigation will be interpreted with caution, acknowledging that a hypothetical lack of difference in risk of NAION between GLP-1 RA and SGLT2i may still not entirely rule out a possible increase in risk of NAION associated with the use of GLP-1 RA (when compared to non-use).

6.2. Study Design Diagram

The study protocol and its longitudinal measurement definitions are visualized in **Figure 2**.

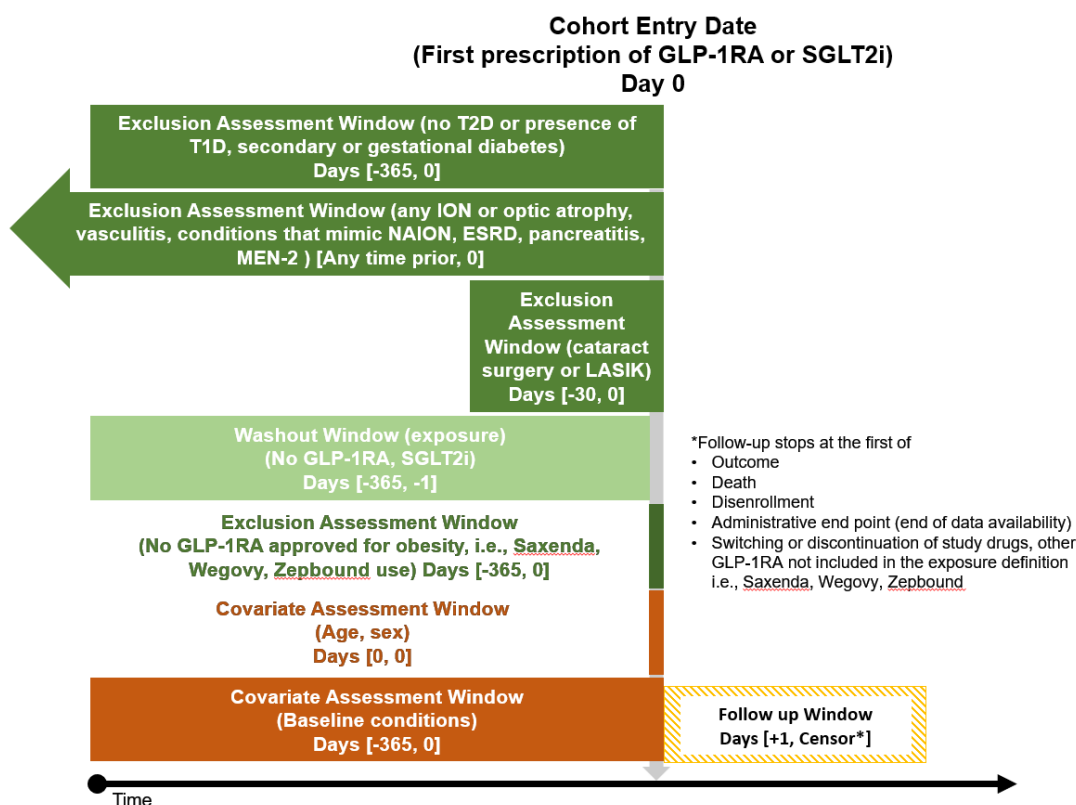


Figure 2. Visual Representation of Study Design.

GLP-1 RA: exenatide, liraglutide (Victoza), semaglutide (Ozempic, Rybelsus), dulaglutide, lixisenatide, tirzepatide (Mounjaro). Albiglutide not included in the definition of exposure to a GLP-1 RA because it was withdrawn from the United States market in 2017 (i.e., prior to the study period). Liraglutide 3.0 mg (Saxenda), semaglutide 2.4mg (Wegovy), or tirzepatide (Zepbound) are not included in the definition of exposure to a GLP-1 RA, as they are approved for the treatment of obesity).

6.3. Setting

6.3.1. Context and Rationale for Definition of Time 0 (and Other Primary Time Anchors) for Entry to the Study Population

Time 0 is the date of initiation of GLP-1 RA or SGLT2 inhibitors (SGLT2i) and the time when patients enter the study population.

Table 3. Operational Definition of Time 0 (Cohort Entry Date) and Other Primary Time Anchors.

Study Population Name(s)	Time Anchor Description (i.e., Time 0)	Number of Entries	Type of Entry	Washout Window	Care Setting ¹	Code Type ²	Diagnosis Position	Incident with Respect to...	Measurement Characteristic/ Validation	Source of Algorithm
Exposure: GLP-1 RA	Date of incident dispensing of GLP-1 RA or tirzepatide ³	Single	Incident	[-365, -1]	N/A	NDC ⁴	N/A	Any formulation of GLP-1 RA, tirzepatide, or SGLT2i ⁵	N/A	Investigator review of generic and/or brand names
Reference: SGLT2i	Date of incident dispensing of SGLT2i ⁶	Single	Incident	[-365, -1]	N/A	NDC ⁴	N/A	Any formulation of GLP-1 RA, tirzepatide, or SGLT2i ⁵	N/A	Investigator review of generic and/or brand names

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³GLP-1 RA: exenatide, liraglutide (Victoza), semaglutide (Ozempic, Rybelsus), dulaglutide, lixisenatide, tirzepatide (Mounjaro). Albiglutide not included in the definition of exposure to a GLP-1 RA because it was withdrawn from the United States market in 2017 (i.e., prior to the study period). Liraglutide 3.0 mg (Saxenda), semaglutide 2.4mg (Wegovy), or tirzepatide (Zepbound) are not included in the primary definition of exposure to a GLP-1 RA, as they are not approved for the treatment of type 2 diabetes mellitus (i.e., these products are only approved for the treatment of obesity).

⁴National Drug Code

⁵Incident with respect to: exenatide, liraglutide (Victoza or Saxenda), semaglutide (Ozempic, Rybelsus, or Wegovy), dulaglutide, lixisenatide, tirzepatide (Mounjaro or Zepbound), canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin

⁶SGLT2i: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin

6.3.2. Context and Rationale for Study Inclusion Criteria

We require 12 months medical and prescription enrolment coverage prior to time 0 with an enrolment gap of 30 days. Requiring 12 months of medical and prescription coverage ensures that patients have observable time in the data where contact with the healthcare system will allow capture of clinical codes to measure inclusion-exclusion criteria and baseline covariates. We restrict the population to patients with T2DM. See **Appendix A** for listing of structured codes for each study parameter.

Table 4. Operational Definitions of Inclusion Criteria.

Inclusion Criterion	Details	Order of Application	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Measurement Characteristic/Validation	Source for Algorithm
Observability related	Medical and prescription coverage (30 days maximum gaps allowed)	Before selection of cohort entry date	[-365, 0]	N/A	N/A	N/A	Exposure: GLP-1 RA Reference: SGLT2i	N/A	N/A
Type 2 Diabetes Mellitus (T2DM)		Before selection of cohort entry date	[-365, 0]	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator or review of clinical codes ⁵

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

⁴International Classification of Diseases, Tenth Revision, Clinical Modification

⁵These codes will be used in the context of a study design requiring the initiation of medications for T2DM (i.e., GLP-1 RA or SGLT2i, see Table 3) as the qualifying event for cohort entry. The co-occurrence of codes for T2DM + filled prescriptions for T2DM medications increases the specificity of the type 2 diagnosis definition.

6.3.3. Context and Rationale for Study Exclusion Criteria

We will exclude patients with type 1 diabetes or secondary or gestational diabetes since the focus of this query is on patients diagnosed with type 2 diabetes. Patients with conditions that might influence choice of SGLT2i or GLP-1 RA therapies and/or are associated with increased risk of ischemic complications, like NAION, will also be excluded. These conditions include end-stage kidney disease (ESKD), acute and chronic pancreatitis, and multiple endocrine neoplasia (MEN-2). We will exclude patients with a history of ischemic optic neuropathy or optic atrophy, to increase the specificity of the primary NAION outcome and to increase the likelihood that the NAION events observed during follow-up are incident cases. We will also exclude patients with history of ANCA and other causes of vasculitis, non-ION conditions that may be incorrectly coded as ION, and cataract surgery or LASIK [in the 30 days before the cohort entry date], to increase the specificity of the primary NAION outcome as these patients might have elevated risk of future NAION event which may not be attributable to the treatment. See **Appendix A** for listing of structured codes for each study parameter. Please note the final list of exclusion criteria aimed to increase the specificity of the primary NAION outcome will be informed by ongoing outcome validation studies (please see **Appendix B** for more details on the validation study).

Table 3. Operational Definitions of Exclusion Criteria.

Exclusion Criterion	Details	Order of Application	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Measurement Characteristic / Validation	Source for Algorithm
Type 1 Diabetes Mellitus (T1DM)	Pathophysiology and treatment differs in comparison to Type 2 Diabetes Mellitus (T2DM)	Before selection of cohort entry date	[-365, 0]	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Secondary or gestational diabetes	Pathophysiology and treatment differs in comparison to T2DM	Before selection of cohort entry date	[-365, 0]	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review or clinical codes
End stage kidney disease (ESKD)	Guidelines have varying recommendations on treatment with SGLT2i based on eGFR and dialysis has	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes

Exclusion Criterion	Details	Order of Application	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Measurement Characteristic / Validation	Source for Algorithm
	potential increased risk of NAION ^{20,21}								
Acute or chronic pancreatitis	Excluded. Evidence of rare association between GLP-1 RA exposure and risk might influence product selection ²²	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Multiple endocrine neoplasia type 2 (MEN-2)	Excluded as long acting GLP-1 RA are contraindicated in this population	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Ischemic optic neuropathy (ION)	Excluded to capture incident events during follow-up	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Optic atrophy	Excluded since ischemic optic neuropathy leads to optic atrophy	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes

Exclusion Criterion	Details	Order of Application	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Measurement Characteristic / Validation	Source for Algorithm
Anti-neutrophilic cytoplasmic autoantibody and other causes of vasculitis ⁵	Excluded as these patients have other potential causes of ischemic optic neuropathy	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Conditions associated with potential misdiagnosis of NAION ⁶	Excluded as these patients could be misdiagnosed as having NAION	Before selection of cohort entry date	Any time prior and including cohort entry date	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes
Cataract surgery or Laser-Assisted In Situ Keratomileusis (LASIK)	Excluded as these patients could be misdiagnosed as having NAION	Before selection of cohort entry date	[-30, 0]	Any	ICD-10-CM ⁴	Any	Exposure: GLP-1 RA Reference: SGLT2i	N/A	Investigator review of clinical codes

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

⁴International Classification of Diseases, Tenth Revision, Clinical Modification

⁵Includes giant cell arteritis, granulomatosis with polyangiitis/Wegener's granulomatosis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet's disease, urticarial vasculitis, Kawasaki disease, central nervous system vasculitis, rheumatoid vasculitis, polyarteritis nodosa, Takayasu arteritis, IgA vasculitis (Henoch-Schönlein purpura)

⁶Includes multiple sclerosis, neuromyelitis optica/Devic disease, other demyelinating diseases, optic neuritis, papilledema or pseudo papilledema, central or branch retinal artery occlusion, central or branch retinal vein occlusion, systemic shock, drusen of optic disc, optic neuropathies, syphilis, uveitis, other disorders of optic disc, optic nerve sheath hemorrhage, hypoplasia, and other disorders, disorders of optic chiasm, visual pathways, visual cortex, or optic nerve injury and disorders, benign or malignant tumors of the eye, orbit or brain, metastatic cancer

6.4. Variables

6.4.1. Context and Rationale for Exposure(s) of Interest

We focus on new initiators of drugs which are commonly used anti-diabetic drugs at similar stage of T2DM. This study design ensures homogenous patient population who are likely comparable and appropriate for evaluation of safety over the course of the treatment since initiation.

Algorithm to Define Duration of Exposure Effect: Assuming the effect of therapies lasts for 30 days after the days' supply, we allow 30 days gap between the dispensing (grace period) and also add 30 days at the end of days' supply of dispensing (exposure risk window).

Table 4. Operational Definitions of Exposure.

Exposure Group Name(s)	Details	Washout Window	Assessment Window	Care Setting ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Incident with Respect to...	Measurement Characteristics/ Validation	Source of Algorithm
Exposure	N/A	[-365, -1]	[1, censor]	N/A	NDC ⁴	N/A	Exposure: GLP-1 RA	Both drug classes or tirzepatide	N/A	Investigators review of generic names
Comparator	N/A	[-365, -1]	[1, censor]	N/A	NDC ⁴	N/A	Comparator: SGLT2i	Both drug classes or tirzepatide	N/A	Investigators review of generic names

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

⁴National Drug Code

6.4.2. Context and Rationale for Outcome(s) of Interest

Table 5. Operational Definitions of Outcome.

Outcome Name	Details	Primary Outcome?	Type of Outcome	Washout Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Measurement Characteristic/Validation	Source of Algorithm
NAION (defined as an ICD-10-CM ⁴ diagnosis code of ischemic optic neuropathy (ION), i.e., H47.01x), with an encounter with an ophthalmologist or optometrist within +/- 30 days	A validated definition developed by Hamedani et al.	Yes	Time-to-event	Any time prior to cohort entry	Any	ICD-10-CM ⁴ , ophthalmologist/optometrist specialist codes	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Positive Predicted Value of 75.8%	Hamedani et al. [PMID:38706093] <i>Note: The final operationalized outcome definition will be informed by ongoing outcome validation studies.</i>

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

⁴International Classification of Diseases, Tenth Revision, Clinical Modification

6.4.3. Context and Rationale for Follow-Up

We will conduct a per protocol analysis in the primary analysis.

Table 6. Operational Definitions of Follow-Up.

Follow-up start	1	
Follow-up end¹	Select all that apply	Specify
Date of outcome	Yes	Table 7
Date of death	Yes	As recorded in data sources
End of observation in data	Yes	Allow 30-day gaps in enrollment
Day X following cohort entry date (specify day)	No	-
End of study period (specify date)	Yes	Most recent data available
End of exposure (specify operational details, e.g., stockpiling algorithm, grace period)	Yes (only in the per protocol analysis)	Stockpiling algorithm: a stockpiling algorithm is used to account for dispensings with overlapping days of supply by adjusting the date of the subsequent overlapping dispensing. Episode gap: 30 days Episode extension: 30 days
Date of add to/switch from exposure (specify algorithm)	Yes (only in the per protocol analysis)	On the day of the switch
Initiation of non-cohort-defining GLP-1 RA s	Yes	Initiation of liraglutide 3.0 mg (Saxenda), semaglutide 2.4 mg (Wegovy), or tirzepatide (Zepbound)
Other date (specify)	N/A	N/A

¹ Follow-up ends at the first occurrence of any of the selected criteria that end follow up.

6.4.4. Context and Rationale for Pre-exposure Covariates (Confounding Variables and Effect Modifiers, e.g., Risk Factors, Comorbidities, Comedications)

We identified demographic, comorbidity, healthcare utilization, frailty, and markers of healthy behaviors (e.g., use of preventative services) as confounding variables of interest.

Table 7. Operational Definitions of Covariates: From Claims Data.

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Age	(Cohort entry year - year of birth)	Continuous	[0,0]	N/A	N/A	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	
Sex	Male, Female	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	
Region	Northeast, South, Midwest, West, Other, Missing, Invalid	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	
Calendar Year	Date of cohort entry	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	
Hypertension		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Hyperlipidemia		Binary	[-365, 0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Myocardial Infarction (MI)	Defined by acute MI/old MI	Binary	[-365, 0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Tobacco Use		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Desai RJ et al. ²³
Underweight or normal Weight (BMI < 25 kg/m ²)		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁴
Overweight (BMI 25-29.9 kg/m ²)		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁰
Obese (BMI 30-39.9 kg/m ²)		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁰
Severely Obese (BMI ≥ 40 kg/m ²)		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁰
Unspecified Obesity		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁰

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
No information on obesity or BMI		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Suissa K et al. ²⁰
Alcohol Abuse or Dependence		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002 and Investigators review of clinical codes
Cancer		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵
Stable Angina		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Unstable Angina		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵
Coronary Atherosclerosis		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Other Forms of Chronic Ischemic Heart Disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Coronary-Artery Bypass Grafting (CABG)/ Percutaneous		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Transluminal Coronary Angioplasty (PTCA)								Investigator review of codes
Any Stroke		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Transient Ischemic Attack		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Late Effects of Cerebrovascular Disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Valve Disorders		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Peripheral Vascular Disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Heart Failure		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Mahealani et al. ²⁶
Atrial Fibrillation		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
								packages/browse?at=refs%2Fheads%2Fcdersir_wp002 and RCT DUPLICATE Investigator review of codes
Other Cardiac Dysrhythmia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002 and RCT DUPLICATE Investigator review of codes
Cardiomyopathy		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Mahealani et al. ²²
Hypertensive Nephropathy		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Acute Kidney Injury		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Chronic Kidney Disease, Stage 1-2		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of codes
Chronic Kidney Disease, Stage 3-4		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Paik et al. ²⁷
Anemia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA	Investigators review of clinical codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
							Comparator: SGLT2i	
Miscellaneous renal disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Chronic obstructive pulmonary disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Obstructive Sleep Apnea		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Asthma		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Osteoporosis		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Osteoarthritis		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Falls		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Metabolic dysfunction-associated steatohepatitis (MASH) / Metabolic dysfunction associated fatty liver disease (MAFLD)		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Alzheimer's Disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Parkinson's Disease		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Other Dementia Types		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Psychosis		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of codes
Delirium		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Depression		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of codes
Anxiety		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of codes
Hypotension		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Deep Venous Thrombosis or Pulmonary Embolism		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Oedema		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Vertebral and Non-Vertebral Fractures		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Pneumonia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Frailty Score		Continuous	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Kim DH et al. ²⁸
Combined Comorbidity Score		Continuous	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Gagne J et al. ²⁹
Type 2 Diabetes Mellitus without		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Mention of Complications								Investigator review of codes
Diabetic Nephropathy		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Diabetes with Peripheral Circulatory Disorders		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Diabetic Foot		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Diabetic Neuropathy		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²¹ Investigator review of codes
Diabetic Retinopathy		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Type 2 Diabetes with Unspecified Complications		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Lower Limb Amputations		Binary	[-365,0]	Any	ICD-10-CM and CPT codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Hyperglycemia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of ICD-10 codes
Hypoglycemia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Hyperosmolar Hyperglycemic Nonketotic Syndrome		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Hypertriglyceridemia		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Glaucoma		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Cataract		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Pan retinal photocoagulation		Binary	[-365,0]	Any	ICD-10-CM and CPT codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Age-related macular degeneration		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Hemorrhage in the eye		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
History of vitrectomy		Binary	[-365,0]	Any	ICD-10-CM and/or CPT codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Vision impairment or loss		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Screening or vision or retinal eye examination		Binary	[-365,0]	Any	ICD-10-CM and/or CPT codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Ophthalmologist or optometrist visit		Binary	[-365,0]	Any	Provider specialty codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Urinary Tract or Genital Infection		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Number of Antidiabetic Drugs at cohort entry (with days-supply overlapping with CED)		Continuous	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	
Metformin Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Metformin Concomitant/ Current Use	1. Concomitant initiation is defined as patients who “start” the prescription on cohort entry day 2. Current use is defined as patients who have days’ supply overlapping cohort entry day	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Sulfonylureas Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Sulfonylurea’s Concomitant/ Current use	1. Concomitant initiation is defined as patients who “start” the	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
	prescription on cohort entry day 2. Current use is defined as patients who have days' supply overlapping cohort entry day							
Thiazolidinediones, Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Thiazolidinediones, Concomitant/ Current Use	1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day 2. Current use is	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
	defined as patients who have days' supply overlapping cohort entry day							
Alpha-Glucosidase Inhibitors, Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Alpha-Glucosidase Inhibitors, Concomitant/ Current Use	1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day 2. Current use is defined as patients who have days' supply overlapping cohort entry day	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Meglitinides, Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Meglitinides Concomitant/ Current Use	1. Concomitant initiation is defined as patients who “start” the prescription on cohort entry day 2. Current use is defined as patients who have days’ supply overlapping cohort entry day	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Amylin Analog, Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Amylin Analog, Concomitant/ Current Use	1. Concomitant initiation is defined as patients who “start” the prescription on cohort entry day 2. Current use is defined as patients who have days’ supply overlapping cohort entry day	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Insulin Any Use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Insulin Concomitant/ Current Use	1. Concomitant initiation is defined as patients who “start” the	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
	prescription on cohort entry day 2. Current use is defined as patients who have days' supply overlapping cohort entry day							
DPP-4i Any use		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
DPP-4i Concomitant/ Current Use	1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day 2. Current use is defined as patients	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
	who have days' supply overlapping cohort entry day							
SGLT2i Any Use (for GLP-1 RA vs. DPP-4i sensitivity analysis)		Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
SGLT2i Concomitant/ Current Use (for GLP-1 RA vs. DPP-4i sensitivity analysis)	1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day 2. Current use is defined as patients who have days' supply overlapping cohort entry day	Binary	[0,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Long-term use of insulin		Binary	[-365,0]	Any	ICD-10-CM	Any	Exposure: GLP-1 RA	Investigators review of clinical codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
							Comparator: SGLT2i	
Weight loss medications (not GLP-1 RA-based)	Benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine, naltrexone-bupropion, orlistat, phentermine-topiramate	Binary	[-365,-1]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of codes
Bariatric surgery		Binary	[-365,0]	Inpatient	ICD-10-PCS and CPT codes	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Madenci, Arin L., et al. ³⁰
Anticoagulants		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Antiarrhythmics		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Angiotensin Converting Enzyme (ACE) Inhibitors/Angiotensin		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Receptor Blockers (ARBs)								
Entresto		Binary	[-365, 0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Beta Blockers		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Calcium Channel Blockers		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Thiazides diuretics		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Loop diuretics		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Potassium-sparing diuretics		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Digoxin		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Non-Steroidal Anti-Inflammatory Drugs		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA	RCT DUPLICATE ²⁵

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
(NSAIDs) (without aspirin)							Comparator: SGLT2i	Investigator review of codes
Opioids		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Statins		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Other Lipid Lowering Drugs		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Gabapentinoids		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Antidepressants		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Antiosteoporosis Medications		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: DSGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Anxiolytics/ Hypnotics		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Antipsychotics	Both typical and atypical	Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Antiparkinsonian Medications		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Benzodiazepine		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Dementia Medications		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Amiodarone		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of codes
Phosphodiesterase type 5 inhibitors		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of codes
Oral corticosteroids		Binary	[-365,0]	N/A	NDC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Investigator review of codes
Number of Prescriptions		Continuous	[-365,0]	N/A		N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A
Number of Generics		Continuous	[-365,0]	N/A		N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Number of Hospital Visits		Continuous	[-365,0]	IP		N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A
Number of ED Visits		Continuous	[-365, 0]	ED	N/A	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A
Number of HbA1C Tests		Continuous	[-365, 0]	Any	LOINC	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Number of Metabolic/Creatinine Tests		Continuous	[-365, 0]	Any	LOINC	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Colonoscopy		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Fecal Occult Blood Test		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	Investigators review of clinical codes
Flu Vaccination		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Mammography	Only among females	Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Pap Smear Test	Only among female patients	Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002
Pneumococcal Vaccine		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Prostate Specific Antigen Test	Only among male patients	Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdersir_wp002 and RCT DUPLICATE ²⁵ Investigator choice of codes
Bone Mineral Density Test		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes
Metabolic or renal/creatinine panel test		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Source for Algorithm
Lipid test		Binary	[-365, 0]	Any	CPT, HCPCS	Any	Exposure: GLP-1 RA Comparator: SGLT2i	RCT DUPLICATE ²⁵ Investigator review of codes

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 8. Operational Definitions of Covariates: From Electronic Healthcare Record (EHR) Data.

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Handling of Missingness	Handling of Multiple Values Over Time
HbA1c	Based on structured EHRs	Continuous	[-365,0]	Any	LOINC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Serum Creatinine	Based on structured EHRs	Continuous	[-365,0]	Any	LOINC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Estimated glomerular filtration rate (eGFR)	Based on structured EHRs	Continuous	[-365,0]	Any	CKD-EPI creatinine equation ²³	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Low Density Lipoprotein (LDL)	Based on structured EHRs	Continuous	[-365,0]	Any	LOINC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Total Cholesterol	Based on structured EHRs	Continuous	[-365,0]	Any	LOINC	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be	Select closest value to the cohort entry date

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Handling of Missingness	Handling of Multiple Values Over Time
								investigated using smdi ⁴	
Body Mass Index (BMI) (Weight/Height)	Based on structured EHRs	Continuous	[-365,0]	Any	Sentinel Common Data Model Vitals Table	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Systolic Blood Pressure	Based on structured EHRs	Continuous	[-365,0]	Any	Sentinel Common Data Model Vitals Table	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Diastolic Blood Pressure	Based on structured EHRs	Continuous	[-365,0]	Any	Sentinel Common Data Model Vitals Table	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	Mechanism for missingness to be investigated using smdi ⁴	Select closest value to the cohort entry date
Tobacco Use	Based on structured EHRs	Binary	[-365,0]	Any	Sentinel Common Data Model Vitals Table	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A	Select closest value to the cohort entry date

Characteristic	Details	Type of Variable	Assessment Window	Care Settings ¹	Code Type ²	Diagnosis Position ³	Applied to Study Populations:	Handling of Missingness	Handling of Multiple Values Over Time
Total Number of EHR Encounters	Based on structured EHRs	Count	[-365, 0]	Any	Sentinel Common Data Model Tables	N/A	Exposure: GLP-1 RA Comparator: SGLT2i	N/A	Sum

¹IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

²See Appendix A for listing of clinical codes for each study parameter

³Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

⁴Structural Missing Data Investigations (SMDI)

6.5. Data Analysis

6.5.1. Context and Rationale for Analysis Plan

Primary analysis

We will use propensity score (PS) based fine-stratification weighting method with 50 strata for confounding adjustment by measured factors.³¹ PS will be estimated as the probability of initiating GLP-1 RA versus SGLT2i from fitting a multivariable logistic regression model including all baseline patient characteristics without further variable selection. Fifty strata will be created based on the distribution of PS in GLP-1 RA-treated patients, and SGLT2i initiators will be assigned into these strata based on their PS resulting in 50 strata. In the weighting step, SGLT2i initiators in each stratum will be weighted proportional to the number of GLP-1 RA patients to account for stratum membership and achieve balance. As diagnostics for PS models, we will evaluate distributional overlap, weight distribution, and individual covariate balance using standardized differences post-weighting. In the weighted population, we will estimate the hazard ratio including 95% confidence intervals for GLP-1 RA versus SGLT2i on NAION using a Cox proportional hazards model using a per protocol causal contrast (see **Section 6.4.3. Context and Rationale for Follow-Up**). An intent-to-treat causal contrast will be explored in sensitivity analyses (see **Table 10. Sensitivity Analyses: Rationale, Strengths, and Limitations**). While a per-protocol causal contrast censors study participants who may deviate from the initiated treatment regimen due to treatment discontinuation or switch during the follow-up, an intent-to-treat causal contrast disregards any changes to the initiated treatment during the follow-up and omits any censoring due to these reasons. The Cox proportional hazards models will be implemented with a Fine and Gray model statement to account for competing risk of death. Cumulative incidence at various time points during follow-up will be calculated using cumulative incidence functions³² to account for competing risk of death and will be reported stratified by treatment groups. Absolute risks, risk differences and risk ratios at specific follow-up intervals will be obtained from the cumulative incidences.

Assessment of unmeasured confounding and bias adjustment

In sensitivity analyses, to address that certain relevant risk factor information is not well captured in claims data (e.g., BMI, HbA1c, smoking), we will use the Sentinel Innovation Center-developed tools for expedited assessment of unmeasured confounding and bias adjustment (see **Table 10. Sensitivity Analyses: Rationale, Strengths, and Limitations**).³³⁻³⁶

First, we will conduct balance assessment for factors available for a subset of the population with EHR measurement. Among study participants with EHR information available, we will assess the balance in EHR measured risk factors (i.e., BMI, HbA1c, smoking) between exposure groups using standardized differences before and post-weighting.

Next, we will perform statistical adjustment for factors available for a subset of the population with EHR measurement using multiple imputations and raking weights.

Both approaches allow for leveraging rich confounder information available from a subset of the population to improve confounding adjustment. In prior studies, we have observed robust performance of these methods, even when information is only available in a small subset (around 20%), with respect to bias-variance trade-off when compared to an approach that ignores this confounding completely.^{34,35}

Table 9. Primary, Secondary, and Subgroup Analysis Specification.

Hypothesis:	GLP-1 RA use increases the risk of NAION compared to SGLT2i use
Exposure Contrast:	GLP-1 RA vs. SGLT2i
Outcome:	NAION
Analytic Software:	SAS, R
Model(s): (provide details or code)	R packages: smdi, mice, MatchThem, marginaffects
Confounding Adjustment Method	Propensity score fine stratification
Missing Data Methods	Multiple imputations with random forests
Subgroup Analyses	List all subgroups
	1. Age (<65, >=65 or alternative categories to be determined based on the age distribution observed in HealthVerity dataset) 2. Sex (Male/Female) 3. Cardiovascular disease (CVD)¹ 4. BMI categories (guided by data source availability) 5. A1c categories (guided by data source availability) 6. Insulin use at baseline 7. Smoking (guided by data source availability) 8. Obstructive sleep apnea 9. Diabetic retinopathy 10. Glaucoma² 11. Calendar time (before and after June 30, 2021), to account for potential differences in GLP-1 RA new users before and after the approval of semaglutide (Wegovy) for an indication of obesity/overweight 12. Individual GLP-1 RA drugs 13. Baseline use of DPP-4 inhibitors³

¹CVD defined as myocardial infarction, angina (stable and unstable), coronary atherosclerosis, other forms of chronic ischemic heart disease, Coronary-Artery Bypass Grafting (CABG)/ Percutaneous Transluminal Coronary Angioplasty (PTCA), heart failure, stroke, peripheral vascular disease.

²We expect 5-6% of the population to have history of glaucoma. Depending on size of the study population, glaucoma may be combined with diabetic retinopathy into one subgroup analysis labelled as "Ophthalmologic conditions".

³For this subgroup analysis, patients initiating GLP-1 RA or SGLT2i without baseline use of DPP-4 inhibitors will be censored at initiation of DPP-4 inhibitors during follow-up.

Table 10. Sensitivity Analyses: Rationale, Strengths, and Limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Baseline window	Decrease baseline window to 6 months for claims measurements	Greater representation the claims recorded confounding variables that may have a stronger association with the exposure and the outcome of interest due to their close proximity with the cohort entry date.	Greater representation of important clinical variables, which may have a stronger association with the exposure and the outcome of interest due to their close proximity with the cohort entry date.	Important claims information recorded in distant past (>180 days before) may be missed
Gap between dispensations (grace period) and exposure risk window	Increase gap between the dispensation (grace period) and exposure risk window to 60 days	Greater capture of true exposure to injectable medications, which may be characterized by gaps between dispensations >30 days	Less degree of exposure misclassification due to exposure underestimation	More degree of exposure misclassification compared to the primary analysis, due to exposure overestimation
Follow-up end (Intent to treat effect)	Omission of censoring at treatment discontinuation or switch, to follow an Intent to treat effect (effect of being assigned to the treatment)	To address potential informative censoring	Not prone to informative censoring	More prone to exposure misclassification compared to the primary analysis, due to exposure overestimation
Control outcome	Pneumococcal or influenza vaccine as a negative control outcome; gastrointestinal adverse events as a positive	Net bias analysis	Enables the detection of bias in the primary analysis, assuming shared confounding structure	N/A

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
	control outcome			
Expanded GLP-1 exposure definition ¹	Primary GLP-1 RA exposure definition will be updated through the inclusion of GLP-1 RA approved for obesity, i.e., liraglutide 3.0 mg (Saxenda), semaglutide 2.4mg (Wegovy), or tirzepatide (Zepbound)	To assess NAION risk in patients with T2DM exposed to GLP-1 RA approved for weight-loss.	Includes users of GLP-1 RAs approved for obesity and used at weight-lowering (high) doses of GLP-1 RA. These users are not included in the primary GLP-1 RA exposure definition.	More prone to confounding by indication compared to the primary analysis
Secondary comparator group	GLP-1 RA will be compared to an alternative comparator group, i.e., dipeptidyl peptidase-4 inhibitors	To test the robustness of the primary findings with respect to the use of an alternative comparator to SGLT2i.	Enables the evaluation of the association between GLP-1 RA and NAION with respect to a comparator, i.e., DPP-4i, which has a different mechanism of action compared to SGLT2i and may therefore be differently associated with NAION.	More prone to confounding by indication compared to the primary analysis
Assessment of unmeasured confounding and bias adjustment	Assessment of unmeasured confounding and bias adjustment through the Sentinel Innovation Center-developed tools	To explore and account for potential residual confounding due to certain relevant risk factor information not being well captured in claims data (e.g., BMI,	Enables to explore and account for potential residual confounding	Relies on imputed information

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
		HbA1c, smoking),		
Quantitative bias analysis for outcome misclassification	Assessment of outcome misclassification and bias adjustment through quantitative bias analysis based on the outcome validation study	To explore the impact of outcome misclassification on effect estimates generated in primary analysis	Enables to explore and account for potential outcome misclassification	N/A

¹ For this sensitivity analysis, we will also conduct subgroup analyses stratified by categories of BMI (obesity), as captured by ICD-10-CM diagnoses among people with recorded BMI (obesity) codes.

N/A: not applicable

6.6. Data Sources

6.6.1. Context and Rationale for Data Sources

This section corresponds to Step 2b of the PRINCIPLED framework: selecting fit-for-purpose data.

Two key considerations for determining fitness-for-purpose of data sources are data relevance and data reliability.

For determination of relevance and reliability, we consider the context of Sentinel where most of the data come from insurance claims, and ancillary sources (including electronic health records) provide opportunities for augmentation. Relevance and reliability determination depends on a series of questions focused on measurement characteristics of four variable types central to the research question of interest in insurance claims data: eligibility criteria, outcome, treatment, and key confounders. For the current question, as NAION is a rare event with an estimated incidence rate in claims data of 5 per 10,000 as identified in a claims data analysis among people with T2DM using SGLT2i (See **Section 6.9. Study Size and Feasibility**), we will conduct the main analysis in insurance claims data from the FDA Sentinel System's Real-World Evidence Data Enterprise (RWE-DE) Commercial Network (HealthVerity), independently of the presence of linked EHR information. However, as the outcome of interest (NAION)³⁷ and important confounders (HbA1c, BMI, smoking) are deemed to be insufficiently measured in claims data, we will also conduct validity enhancing activities using insurance claims linked with electronic health records. Specifically, we will (1) conduct two endpoint validation studies in two different study data sources (MGB and HealthVerity), and (2) use the Sentinel Innovation Center-developed tools for expedited assessment of unmeasured confounding and bias adjustment³³⁻³⁶ leveraging insurance claims linked with electronic health records in HealthVerity.

Within Sentinel, data quality evaluations are performed upstream when converting raw data from contributing sources to the Sentinel Common Data Model (SCDM)—which is then used for all subsequent analyses.

Data Source Provenance/Curation:

Table 11. Metadata About Data Sources and Software.

Data Source(s):	HealthVerity closed medical and pharmacy claims data linked to EHRs from the following three sources: • Inovalon Medical and Pharmacy Claims • Veradigm EHR • Source 42 EHR and clinical notes for 10,000 patients
Study Period:	January 1, 2018 - June 30, 2024; HealthVerity
Eligible Cohort Entry Period:	January 1, 2019 - June 30, 2024; HealthVerity
Data Version (or Date of Last Update):	HealthVerity ETL 3
Data Sampling/Extraction Criteria:	Treatment of interest criteria include: • Patients with a documented treatment of GLP-1 RA, SGLT2i, DPP-4i • Continuous medical and pharmacy enrollment for 6 months prior to first documented treatment of interest (as above)
Type(s) of Data:	Medical claims; electronic health records (EHRs)
Data Linkage:	EHR data linked with insurance claims data
Conversion to CDM:	Sentinel Common Data Model 8.1.0 ³⁸
Software for Data Management:	SAS

6.7. Data Management

N/A

6.8. Quality Control

HealthVerity ETL 3 will be approved using a standard Sentinel Quality Assurance review process.³⁹

6.9. Study Size and Feasibility

TBD; this study corresponds to Step 4 of the PRINCIPLED process and will be populated in the amended protocol along with any study adaptations as required.

7. Limitation of the Methods

TBD

8. Protection of Human Subjects

This Sentinel project is a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.^{40,41}

9. Reporting of Adverse Events

N/A

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11. Appendices

11.1. Appendix A. List of Medical Codes Used to Define Clinical Concepts in this Study

Please refer to the attached spreadsheet for a complete list of medical codes used to define concepts in this analysis.

11.2. Appendix B. Identifying Newly Diagnosed Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) in Insurance Claims Data: Validation Standard Operating Procedure (SOP)

Please refer to the attached document for detailed explanation of the validation study.