Effect of Glucagon-Like Peptide-1 Receptor Agonists on the Risk of Non-Arteritic Anterior Ischemic Optic Neuropathy Among Older Adults with Type 2 Diabetes: A US. Medicare Active-Comparator New-User Cohort Study

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000966

Study ID

1000000966

DARWIN EU® study

No

Study countries

United States

Study description

This study aims to estimate the comparative effect of initiating a GLP-1RA versus alternative second-line glucose-lowering therapies—sodium–glucose cotransporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i)—on the risk of incident NAION among older adults with type 2 diabetes. We will conduct two parallel active-comparator, new-user cohort studies emulating separate head-to-head target trials. New use will be defined by a 12-month class-specific washout, and eligibility, exposure assignment, and follow-up will be aligned at the first prescription fill to avoid immortal time and ensure proper temporality. Follow-up will proceed under an as-treated framework until treatment discontinuation, switching, outcome occurrence, death, disenrollment, or end of data.

The study will use a 20% random sample of Medicare Fee-for-Service Parts A, B, and D claims, providing large-scale, nationally representative data suitable for evaluating the rare outcome of NAION in older adults. Analyses will estimate absolute and relative risks using standardized morbidity ratio (SMR) weighting to target the average treatment effect in the treated. SMR-weighted Aalen–Johansen cumulative incidence functions will provide adjusted risks accounting for competing mortality, complemented by SMR-weighted Cox models for hazard ratios. Secondary analyses will evaluate as-treated effects conditional on a second refill of the same drug class within days’ supply of the index prescription plus a grace period of 30 days, as well as intention-to-treat effects. Finally, sensitivity analyses will address outcome definitions, induction and latency windows, grace-period choices, propensity-score overlap, and unmeasured confounding.

Study status

Ongoing

Research institutions and networks

Institutions

University of North Carolina at Chapel Hill

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Institution

Contact details

Study institution contact

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Study contact

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Primary lead investigator

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 25/02/2026

Actual: 25/03/2026

Study start date
Planned: 25/03/2026

Actual: 25/03/2026

Data analysis start date
Planned: 25/03/2026

Actual: 25/03/2026

Date of final study report
Planned: 24/09/2027

Sources of funding

- No external funding

Study protocol

NAION_GLP1RA_ACNU HARPER PROTOCOL_2_23_26.pdf (1.14 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Active comparator new user cohort study

Main study objective:

To estimate the comparative effect of initiating GLP-1RA versus other second-line glucose-lowering therapies—specifically dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i)—on the risk of non-arteritic anterior ischemic optic neuropathy (NAION) among older adults with T2DM.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

OZEMPIC

RYBELSUS

WEGOVY

VICTOZA

SAXENDA

TRULICITY

MOUNJARO

JARDIANCE

INVOKANA

STEGLATRO

JANUVIA

Medicinal product name, other

FARXIGA

NESINA

TRADJENTA

SAXAGLIPTIN

Study drug International non-proprietary name (INN) or common name

EXENATIDE

LIRAGLUTIDE

LIXISENATIDE

ALBIGLUTIDE

DULAGLUTIDE

SEMAGLUTIDE

DAPAGLIFLOZIN

CANAGLIFLOZIN

EMPAGLIFLOZIN

ERTUGLIFLOZIN

ALOGLIPTIN

LINAGLIPTIN

SAXAGLIPTIN

SITAGLIPTIN

Anatomical Therapeutic Chemical (ATC) code

(A10BJ01) exenatide

exenatide

(A10BJ02) liraglutide

liraglutide

(A10BJ03) lixisenatide

lixisenatide

(A10BJ04) albiglutide

albiglutide

(A10BJ05) dulaglutide

dulaglutide

(A10BJ06) semaglutide

semaglutide

(A10BK01) dapagliflozin

dapagliflozin

(A10BK02) canagliflozin

canagliflozin

(A10BK03) empagliflozin

empagliflozin

(A10BK04) ertugliflozin

ertugliflozin

(A10BH01) sitagliptin

sitagliptin

(A10BH03) saxagliptin

saxagliptin

(A10BH04) alogliptin

alogliptin

(A10BH05) linagliptin

linagliptin

Medical condition to be studied

Optic neuropathy

Additional medical condition(s)

Non-Arteritic Anterior Ischemic Optic Neuropathy

Population studied

Short description of the study population

Fee-for-service Medicare beneficiaries age 66 or above with type 2 diabetes initiating either GLP1-RA, SGLT2i, or DPP4i after a 12 months washout period without any dispensed prescriptions for any of the drug classes and continuous Parts A, B, D enrollment, at least one claim with a type 2 diabetes code, and at least one ophthalmology or optometry encounter during the 12 months prior to drug initiation.

Exclusions:

• Diabetes mellitus other than type 2 diabetes

• Same-day initiation of both study drug classes

• GLP-1RA contraindications including pancreatitis, thyroid cancer, multiple endocrine neoplasia type 2, end-stage renal disease, dialysis dependence or renal replacement therapy

• Heart failure for GLP-1RA vs. DPP-4i cohort

• Bilateral blindness or legal blindness
• Prior ischemic optic neuropathy
• NAION mimickers (non-ischemic optic neuropathies
• Prior arteritic/systemic vasculitic conditions
• Empiric evaluation or treatment for suspected arteritic anterior ION

Age groups

- Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Setting

US fee-for-service Medicare population

Comparators

GLP1-RA, SGLT2i, DPP4i

Outcomes

First incident non-arteritic anterior ischemic optic neuropathy (NAION)

Data analysis plan

We will define exposure duration using pharmacy dispensing dates and days' supply. Continuous exposure is defined as sequential fills with ≤30-day allowable gaps (i.e., refill within days supply + 30 days grace period). Exposure episodes end on the earliest of treatment discontinuation, switching to the comparator class, initiation of the alternate study drug class, disenrollment, death, or end of data. For as-treated analyses, risk time is attributed to the

observed exposure episode; for intention-to-treat analyses, exposure is fixed at cohort entry. NAION follow-up begins after a 14-day induction lag period and ends 14 days after discontinuation or switching/augmenting (latent period). Propensity scores will be used for weighting the comparator cohorts (SGLT2i and DPP4i, respectively) to the GLP-1RA cohort to estimate tha average treatment effect in the treated (ATT).

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

US fee-for-service Medicare

Data sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Unknown