1. Title Page

Title	Risk of 4 obesity-related cancers after GLP-1 receptor agonist use
Research question & Objectives	Does the incident use of GLP-1 receptor agonists have an increased risk on the occurrence of endometrial, thyroid, pancreas or prostate cancer compared to DPP4 inhibitor use?
Protocol version	1
Last update date	24 April 2025
Contributors	**Primary investigator contact information:** Martin Russek, martin.russek@bfarm.de **Contributor names:** Dr.Britta Haenisch Dr.Nils Krüger Dr.Sebastian Schneeweiss Dr.Shirley V. Wang
Study registration	**Site:** HMA-EMA Catalog of RWD studies **Identifier:** TBD
Sponsor	**Organization:** n/a **Contact:** n/a
Conflict of interest	SVW has been an ad hoc consultant to Cytel Inc, ICA Group, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid Services. SS reports receiving grants from UCB Pharma and Bayer Pharma as well as personal fees from Aetion Inc

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2. Abstract

The GLP-1-receptor agonist (GLP-1RA) Liraglutide is authorised as a treatment for people with Type 2 diabetes. Randomised clinical trials (RCTs) including the LEADER trial have also shown cardioprotective effects of Liraglutide and other GLP-1RAs. An analysis of secondary outcomes of the LEADER trial has however also suggested an increased risk for any cancer after Liraglutide use. However, the study was not powered for this outcome.

This non-interventional study is aiming to emulate the LEADER trial using causal inference methodology on healthcare claims data, with a focus on the outcomes of

1) Endometrial cancer
2) Thyroid cancer
3) Pancreatic cancer
4) Prostate cancer

This emulation aims to replicate the exposures and eligibility criteria of the LEADER trial, which randomized patients with diabetes and high cardiovascular risk to liraglutide or placebo and evaluated the outcome of major adverse cardiovascular events (MACE). This study will benchmark results for the MACE outcome against the LEADER trial, expand to evaluate the cancer outcomes of interest, and expand the treatment group to include new users of any GLP-1RA. The control group consists of new users of DPP4 inhibitors (DPP4i), as an active comparator to emulate placebo assignment from the LEADER trial. Randomisation is emulated through propensity-score matching observations based on relevant covariates.

The LEADER trial has been successfully emulated previously for cardiovascular outcomes, with agreement of the effect estimates between original trial and emulation on pre-specified binary agreement metrics. Because new data have accrued and we have an expanded list of outcomes, we will re-benchmark the analysis of the primary cardiovascular outcome against LEADER with the new data, design, and analytic set up before expanding to emulation of hypothetical target trials that look at cancer outcomes, and evaluate GLP1-RA as a class rather than only liraglutide. Design choices in the current emulation are based on the prior study, with most operational definitions being adopted. However, there are some changes, most importantly the outcome, some updated covariate definitions, and more recent data accrual.

Sensitivity analyses changing the comparator group to SGLT2 inhibitors (SGLT2i), expanding the study population and changing the follow-up window will be conducted.

This exploratory study will investigate the feasibility of conducting studies on cancer outcomes with US-American claims data sources and the robustness of such studies with varying design choices.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason

4. Rationale and background

What is known about the condition and exposure:

Observational studies have investigated the relationship between GLP-1RAs and each of the 4 cancer types, with mixed results for each of the 4 cancer outcomes. Most of the studies however contain elements that lead to can suggest bias in the results, such as inappropriate comparison groups, implausible effect sizes and apparent effects on cancer development from day one.

For endometrial cancer, only long-term use was associated with an increased risk compared to sulfonylurea use in a UK-based study (Rothman et al, 2025); with fewer than 10.000 new GLP-1RA users, this study was however very underpowered for detecting even moderately large effects considering the incidence rate of endometrial cancer. On the other hand, a study investigating risks of 13 different obesity-related cancers (Dai 2025) found a reduced risk (HR 0.75 [95% CI, 0.57-0.99]) of endometrial cancer in new GLP-1RA users against non-users within a population eligible for anti-obesity medications. Comparisons against non-users are generally avoided, as those individuals treated with a drug could systematically differ from those that remain untreated. A recent study (Yen 2026) of GLP-1RA use in patients with endometrial hyperplasia showed a strong reduction in endometrial cancer risk when using GLP-1RAs in addition to progestins (HR 0.34 [95% CI, 0.27-0.44]). This study containing data from 2005 onwards did not adjust for calendar time in the analysis, meaning the strong effect can stem from improvements in treatment of endometrial hyperplasia as the use of GLP-1RA has been increasing over time. In another study investigating 9 obesity-related cancers (Lu 2025), there was an increased risk versus DPP4i use and no change in risk versus SGLT2i use. Kaplan-Meier plots of both of the latter studies show separation of survival curves from day one, indicating strong effect of treatment on the endometrial cancer risk right after initiation, which is biologically implausible and suggests bias due to different baseline risks between treatment and control group.

The risk of thyroid cancer was compared against different other diabetes medications and found either increased risks (Liang 2019, Funch 2021, Bezin 2023, Cheng 2024) or no change (Bea 2023, Lu 2025, Dai 2025, Baxter 2025, Sciscent 2026). Most of these studies were again underpowered to detect meaningful differences, had limited confounder adjustment, or made comparisons against metformin and insulin, which themselves have been suspected to affect cancer risks. The two studies with most power and appropriate control groups (Bea 2023 and Baxter 2025) have found no effect, which is not in line with a recent meta-analysis of randomised controlled trials (RCTs) which found a HR of 1.55 [1.05-2.27] (Silverii 2025), with effect sizes consistent between short-, medium- and long-term trials (< 1 year, 1-2 years, > 2 years).

For pancreatic cancer, increased risk (Faour 2025), decreased risk (Wang 2024, Wang 2025, Krishnan 2022, Ailawadi 2026, Kalathiya 2026, Ayoub 2024) and no change (Lu 2025, Dai 2025, Dankner 2023, Funch 2014, Funch 2019) have been estimated against different other diabetes medications. Many of those studies again compared against insulin or metformin and/or were underpowered. Of the 3 well-powered studies with appropriate comparator groups, 2 found a decreased risk while one found an increased risk, while a recent meta-analysis of RCTs found no change in risk (Wen 2025).

A decreased risk for prostate cancer compared to sulfonylurea use was found in an UK-based study (Lu 2022) comparing against sulfonylurea use and a Danish study comparing against basal Insulin (Skriver 2023), while no change versus DPP4i or SGLT2i was found by Lu 2025 and also versus non-use by Dai 2025.

There have been studies showing overexpression of GLP-1 receptors in endometrial, prostate and thyroid tumour cells, suggesting GLP-1RAs can play a role in later stages of cancer development, either as suppressor or promotor (Gier 2012, Zhang 2016, Bera 2025). Similarly, GLP-1RA were also found to reduce pancreatic cancer cell growth (Zhao 2020).

Both for DPP4i and SGLT2i, no overall effect on cancer risk was detected in meta-analyses of randomized controlled trials (Dicembrini 2020, Xu 2025), and neither were effects on the 4 individual cancers of interest in this study.

What is the expected contribution of this study?

Through the emulation of an existing RCT, which has been shown to lead to similar results for the primary outcomes, additional evidence on the risk of the four investigated cancer outcomes can be provided. Particularly, evidence will be based on comparisons against appropriate control population (DPP4i users), the active comparator new user design, appropriate handling of competing risks and sample sizes large enough for detecting meaningful changes in risk.

Sensitivity analyses will help evaluate how reliable evidence on cancer outcomes is in the given setting. Given remaining limitations inherent to the real-world data sources used (especially regarding time on treatment and follow-up durations), this study should be interpreted as exploratory rather than confirmatory.

5. Research question and objectives

Table 2 Primary and secondary research questions and objective

A. Primary research question and objective

Objective:	To evaluate the risk of four cancer outcomes after incident use of GLP-1RAs compared to incident use of DPP4 inhibitors among people with Type 2 diabetes
Hypothesis:	There is no increased risk of endometrial, thyroid, pancreatic or prostate cancer after incident use of GLP1-RAs compared to incident use of DPP4i.
Population ***(mention key inclusion-exclusion criteria):***	People over 50 with a diagnosis of Type 2 diabetes. For endometrial cancer restricted to women, for prostate cancer restricted to men.
Exposure:	GLP1-RAs
Comparator:	DPP4is
Outcome:	Primary: Incident diagnosis of 1) Endometrial cancer 2) Thyroid cancer 3) Pancreatic cancer

	4) Prostate cancer
Time *(when follow up begins and ends):*	Primary: 180 days after treatment initiation until first of outcome, death, other cancer diagnosis, disenrollment or end of study period
Setting:	Inpatient & outpatient for outcome
Main measure of effect:	Subdistribution hazard ratio

B. Secondary research question and objective 1

Objective:	To evaluate the risk of four cancer outcomes after incident use of GLP-1RAs compared to incident use of DPP4 inhibitors among people with Type 2 diabetes
Hypothesis:	There is no increased risk of endometrial, thyroid, pancreatic or prostate cancer after incident use of GLP1-RAs compared to incident use of DPP4i.
Population *(mention key inclusion-exclusion criteria):*	People over 50 with a diagnosis of Type 2 diabetes. For endometrial cancer restricted to women, for prostate cancer restricted to men.
Exposure:	Liraglutide
Comparator:	DPP4is
Outcome:	Incident diagnosis of 1) Endometrial cancer 2) Thyroid cancer 3) Pancreatic cancer 4) Prostate cancer
Time *(when follow up begins and ends):*	180 days after treatment initiation until first of outcome, death, other cancer diagnosis, disenrollment or end of study period
Setting:	Inpatient & outpatient for outcome
Main measure of effect:	Subdistribution hazard ratio

C. Secondary research question and objective 2

Objective:	To re-benchmark the LEADER trial emulation using the original outcome with updated covariates, comparator and longer data availability
Hypothesis:	Liraglutide use leads to a 13% reduction in risk for MACE
Population ***(mention key inclusion-exclusion criteria):***	People over 50 with a diagnosis of Type 2 diabetes.
Exposure:	Liraglutide
Comparator:	DPP4is
Outcome:	3-point major adverse cardiovascular events (MACE): Non-fatal myocardial infarction, non-fatal stroke, or CV mortality
Time ***(when follow up begins and ends):***	Day of treatment initiation until first of outcome, death, disenrollment or end of study period
Setting:	Inpatient & outpatient for outcome
Main measure of effect:	Hazard ratio

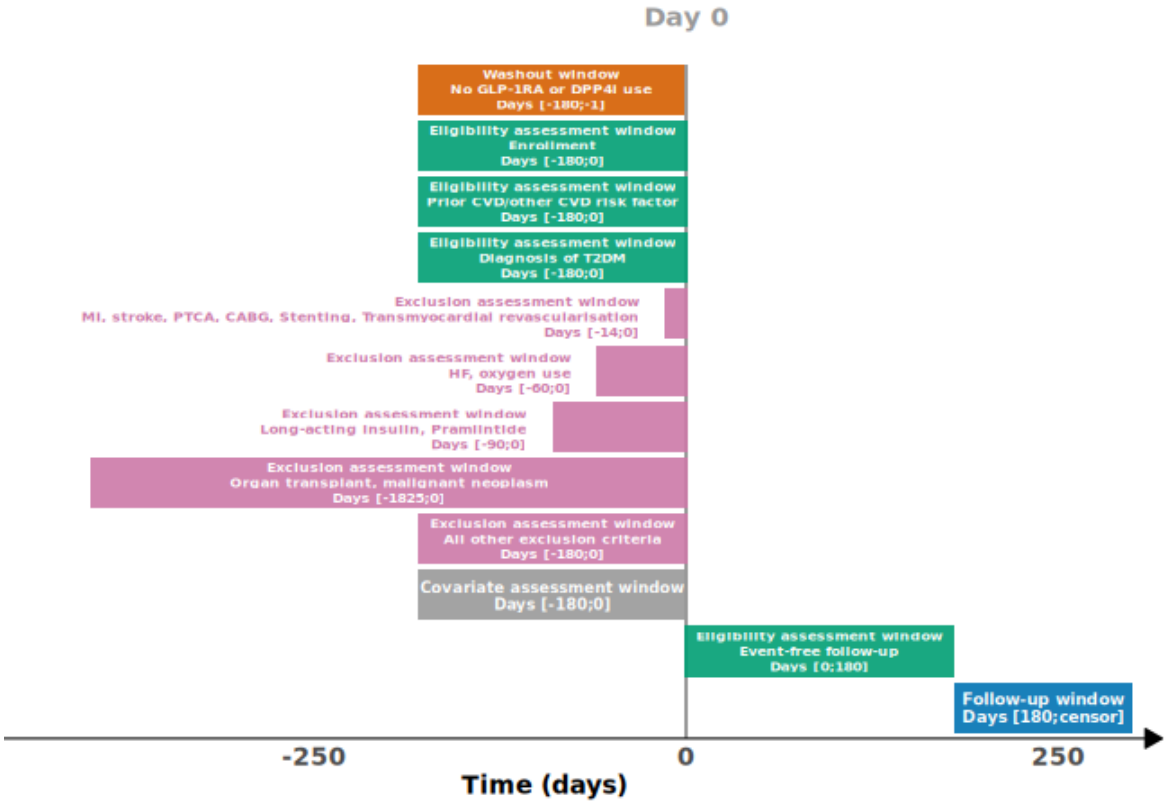
6. Research methods

6.1. Study design

Research design (e.g. cohort, case-control, etc.): Cohort study using active comparator new user (ACNU) design

Rationale for study design choice: The ACNU design is a standard approach in pharmacoepidemiology studies to reduce the risk of bias through confounding by indication. Use of cohort study rather than case-control as data is already collected, and thus case-control study does not have benefits but would lead to reduction in interpretability.

6.2. Study design diagram



*Follow-up for MACE will start at day 0 instead of day 180.

6.3. Setting

7.3.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Time 0 is chosen as the incident prescription of exposure (Liraglutide or GLP-1RA) or DPP4i. This is to emulate treatment assignment of the LEADER trial; the placebo group of the LEADER trial is replaced by DPP4i as an active comparator group. In a sensitivity analysis, the comparison is made with new users of SGLT2i instead of DPP4i.

Table 3 Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure (Liraglutide or all GLP-1RA)	Time 0	Single entry	Incident	[-180, -1]	n/a	RX		Any GLP-1RA or DPP4i (SGLT2i for sensitivity analysis)		
Comparator (DPP4i)	Time 0	Single entry	Incident	[-180, -1]	n/a	RX		Any GLP-1RA or DPP4i		
Comparator secondary (SGLT2i)	Time 0	Single entry	Incident	[-180, -1]	n/a	RX		Any GLP-1RA or SGLT2i		

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.3.2 Context and rationale for study inclusion criteria:

Inclusion criteria were chosen to emulate the inclusion criteria of the leader trial as closely as possible. For endometrial and prostate cancer outcome analyses, male and female gender are an additional inclusion criterion, respectively.

Refer to the original LEADER emulation (Wang 2023 and LEADER – Google Drive) for all inclusion criteria.

7.3.3 Context and rationale for study exclusion criteria

Exclusion criteria were chosen to emulate the exclusion criteria of the leader trial as closely as possible.

Refer to the original LEADER emulation for all exclusion criteria.

6.4. Variables

7.4.1 Context and rationale for exposure(s) of interest

Exposure of interest is Liraglutide, and GLP-1RA use in general – the LEADER trial investigated Liraglutide exclusively, but the outcomes of all GLP-1RAs are of interest in this study. DPP4i were chosen as an active comparator in the original trial emulation due to demonstrated null-effects in RCTs on cardiovascular outcomes, thereby

closely resembling a placebo. For the cancer outcomes, the evidence is not as clear, as no RCTs targeting these outcomes have been conducted, however a meta-analysis of RCTs with cancer as safety outcomes did not see any effect on the risk of the 4 cancer types of interest (Dicembrini 2020).

SGLT2i are chosen as comparator drug class for a sensitivity analysis as GLP-1RA and SGLT2i have proven cardioprotective effects and can lead to weight loss (Tong 2026) - changes in effect size compared to the primary analysis could hint at a mediatory effect of weight loss.

Sulfonylureas, another common comparator group, are linked to weight gain, making them a poor comparator for obesity-related cancer outcomes.

There are no requirements on dosage, formulation or administration of the medications.

Table 6. 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
GLP-1RA	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide	[-180, -1]	[0, inf]	n/a	RX	n/a	all	Any GLP-1RA or DPP4i (SGLT2i in sensitivity analysis) use		
Liraglutide	Liraglutide	[-180, -1]	[0, inf]	n/a	RX	n/a	all	Any GLP-1RA or DPP4i use		
DPP4i	Alogliptin Alogliptin/Metformin Alogliptin/Pioglitazone Dapagliflozin/Saxagliptin Empagliflozin/Linagliptin Empagliflozin/Linagliptin/Metformin Ertugliflozin/Sitagliptin Linagliptin Linagliptin/Metformin Saxagliptin Saxagliptin/Metformin Sitagliptin Sitagliptin/Metformin Sitagliptin/Simvastatin	[-180, -1]	[0, inf]	n/a	RX	n/a	all	Any GLP-1RA or DPP4i use		
SGLT2i	Canagliflozin, Canagliflozin/Metformin, Dapagliflozin,	[-180, -1]	[0, inf]	n/a	RX	n/a	all	Any GLP-1RA or		

	Dapagliflozin/Metformin, Empagliflozin, Empagliflozin/Metformin, Empagliflozin/Linagliptin, Empagliflozin/Linagliptin/Metformin, Ertugliflozin, Ertugliflozin/Metformin, Ertugliflozin/Sitagliptin							SGLT2i use		

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.2 Context and rationale for outcome(s) of interest

Outcomes are time to incident diagnosis for each cancer type, with any in- or outpatient diagnosis code for the specific cancer type defining the time of the outcome. For the MACE outcome, the definition is identical to that of the original LEADER emulation.

Table 7. 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 characteristics/ validation	Source of algorithm
Endometrial cancer	Timo to any diagnosis code (ICD9 182.0, 182.8; ICD10 C54.1, C54.8, C54.9)	Yes	Time-to-event	[-inf, 0]	IP, OP	ICD9, ICD10	Any	Liraglutide/GLP-1RA and DPP4i (Women only)	PPV 93%, Sensitivity 100%	Development and Validation of an Endometrial Cancer Algorithm in US Claims Data - Daniels - 2026 - Pharmacoepidemiology and Drug Safety - Wiley Online Library
Thyroid cancer	Time to any diagnosis code (193; C73)	Yes	Time-to-event	[-inf, 0]	IP, OP	ICD9, ICD10	Any	Liraglutide/GLP-1RA and DPP4i	n/a	GLP-1RA Use and Thyroid Cancer Risk | Diabetes | JAMA Otolaryngology–Head & Neck Surgery | JAMA Network
Pancreatic cancer	Time to inpatient diagnosis	Yes	Time-to-event	[-inf, 0]	IP, OP	ICD9, ICD10	Any	Liraglutide/GLP-1RA and DPP4i	PPV 78.0%, Sensitivity 86.6%	Identification of incident pancreatic cancer in Ontario administrative health data: A validation

	code (157; C25)									study - Wu - 2020 - Pharmacoepidemiology and Drug Safety - Wiley Online Library
Prostate cancer	Time to any diagnosis code (185; C61)	Yes	Time-to-event	[-inf, 0]	IP, OP	ICD9, ICD10	Any	Liraglutide/GLP-1RA and DPP4i (Men only)	n/a	Association of Glucagon-Like Peptide-1 Receptor Agonists With Cancer Risk in Older Adults With Type 2 Diabetes - Lu - Obesity - Wiley Online Library
MACE	Time to first of Myocardial infarction (410 excl 410.x2; I21), Stroke (430, 431, 433.x1, 434.x1, 436; I60, I61, I63, I67.89) or death	No	Time-to-event	[-180, 0]	IP (MI, Stroke)	ICD9, ICD10	Any (MI), Primary (Stroke)	Liraglutide and DPP4i	**For MI:** PPV 94% in Medicare claims data PPV 88.4% in commercially-insured population **For stroke:** PPV of 85% or higher for ischemic stroke PPV ranging from 80% to 98% for hemorrhagic stroke	Accuracy of medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records - ScienceDirect Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population - Wahl - 2010 - Pharmacoepidemiology and Drug Safety - Wiley Online Library A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data - Andrade - 2012 - Pharmacoepidemiology and Drug Safety - Wiley Online Library

										Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data - Roumie - 2008 - Pharmacoepidemiology and Drug Safety - Wiley Online Library

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.3 Context and rationale for follow up

Individuals are followed until the event of interest, death, or end of observation in the data, regardless of treatment adherence (as started analysis). A 180-day lag period is added at treatment initiation, as recommended by Pottegård et al (2018), to reduce the risk of protopathic bias. This is achieved by only including individuals that remain in the cohort without any event for at least 180 days, as done in previous literature (e.g. Baxter 2025, Lu 2022). Occurrence of death and other cancer diagnoses will be treated as a competing event.

For the MACE outcome, the follow-up is identical to the primary analysis of the original emulation, corresponding to an as-treated analysis. The only exception is longer data availability.

Table 8. Operational Definitions of Follow Up (Cancer outcomes)

Follow up start	Day 180	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	
Date of death	Yes	Censored as competing event
End of observation in data	Yes	End of enrolment
Day X following index date *(specify day)*	No	

End of study period (specify date)	Yes	31 December 2023 (MarketScan); 31 December 2024 (Optum)
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	
Date of add to/switch from exposure *(specify algorithm)*	No	
Other date *(specify)*	Yes	Date of other cancer diagnosis censored as competing event

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

Table 9. Operational Definitions of Follow Up (MACE)

Follow up start	Day 0	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	
Date of death	Yes	Part of outcome definition
End of observation in data	Yes	End of enrolment
Day X following index date *(specify day)*	No	
End of study period (specify date)	Yes	31 December 2023 (MarketScan); 31 December 2024 (Optum)
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	Yes	60 day grace period & lag period
Date of add to/switch from exposure *(specify algorithm)*	Yes	Switch between exposure & comparator
Other date *(specify)*	Yes	Nursing home enrolment

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

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

Covariates were selected to cover most important known risk factors for the outcome, and factors associated with the choice of treatment, such as demographics, lifestyle, disease and treatment history, comedications and comorbidities.
See appendix (covariates.pdf) for the codebook for overall and outcome-specific covariates for the 4 cancer outcomes.

6.5. Data analysis

7.5.1 Context and rationale for analysis plan

Cancer outcomes:

Analysis will be performed using a Fine-Gray regression model on a propensity-score (PS) matched population. Individuals are matched based on their probability to be assigned to the exposure group, modelled by the covariates given in 7.4.4 through logistic regression models. Subdistribution hazards of the respective outcomes are then estimated for initiating exposure drug (Liraglutide/GLP-1RAs) versus DPP4i. Each of the 4 outcomes is analysed in a separate model.

As this is not a confirmatory analysis, no adjustment for multiple testing will be done. All confidence intervals will be reported on the 95% level.

MACE:

Analysis will be performed using a Cox proportional hazards model on a propensity-score (PS) matched population. Individuals are matched based on their probability to be assigned to the exposure group at baseline, modelled by the covariates given in 7.4.4 through logistic regression models. The hazard ratio for treatment with Liraglutide versus DPP4i will be provided.

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	GLP-1RA initiation does not increase the risk for any of the 4 cancers investigated
Exposure contrast:	Incident use of GLP-1RA vs Incident use of SPP4i
Outcome:	1) Endometrial cancer 2) Thyroid cancer 3) Pancreatic cancer 4) Prostate cancer
Analytic software:	AETION, R
Model(s): *(provide details or code)*	Fine-Gray model: Time to outcome modelled depending on exposure status at baseline, with death and other cancer diagnosis treated as a competing risk.

Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.*
	1:1 nearest neighbour PS matching, calliper 0.01 on the PS scale. PS is estimated and matching performed separately in the overall, men-only and women-only cohorts.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present.
Subgroup Analyses	*List all subgroups*
	None

B. Secondary analysis 1 (Cancer outcomes)

Hypothesis:	Liraglutide initiation does not increase the risk for any of the 4 cancers investigated
Exposure contrast:	Incident use of Liraglutide vs Incident use of DPP4i
Outcome:	1) Endometrial cancer 2) Thyroid cancer 3) Pancreatic cancer 4) Prostate cancer
Analytic software:	AETION, R
Model(s): *(provide details or code)*	Fine-Gray model: Time to outcome modelled depending on exposure status at baseline, with death and other cancer diagnosis treated as a competing risk.
Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.*
	1:1 nearest neighbour PS matching, calliper 0.01 on the PS scale. PS is estimated and matching performed separately in the overall, men-only and women-only cohorts.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present.
Subgroup Analyses	*List all subgroups*
	None

C. Secondary analysis 2 (MACE)

Hypothesis:	TODO
Exposure contrast:	Incident use of Liraglutide vs Incident use of DPP4i
Outcome:	MACE

Analytic software:	AETION, R
Model(s): *(provide details or code)*	Cox proportional hazards model: Time to outcome modelled depending on exposure status at baseline.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	1:1 nearest neighbour PS matching, calliper 0.01 on the PS scale.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present.
Subgroup Analyses	***List all subgroups***
	None

Table 11. Sensitivity analyses – rationale, strengths and limitations

Sensitivity analyses will be applied to the primary analysis only.

	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
Expand eligibility	Inclusion criterion 2 "Either Prior cardiovascular disease cohort or No Prior cardiovascular disease group", which is restricting the population to individuals with either prior cardiovascular disease or other cardiovascular risk factors, is replaced by the criterion Age >= 50 years at CED	To evaluate robustness of results in broader population	Larger generalizability, larger sample size	New population differs from target population of LEADER trial
Follow-up window	Only follow individuals for the first 180 days after cohort entry	Investigate systematic differences in outcome risks between groups. Within first 180 days no detectable effect of drugs on cancer outcomes are expected, so any differences in risk suggest bias in estimation	Ability to detect residual bias	As primary analysis includes 180 day gap period, impact of detectable biases in this sensitivity analysis on main analysis results not certain.
Handling of gap period	Rather than requiring 180 days of follow-up, any event (Death or cancer diagnosis) within 180 days after CED are censored as non-event.	Investigate impact of modelling choice on results	Requiring 180 days follow-up could lead to immortal time-bias if the risk of exiting the cohort within 180 days differs	Differential censoring rates between the groups within the first 180 days would lead to imbalanced groups when the outcome is assessed.

Change comparator group	Change from new users of DPP4i to new users of SGLT2i	See the effect of GLP-1RAs in comparison to another suitable active comparator drug	Reduced mediation by weight loss, as SGLT2i use also leads to weight loss	Any effect mediated through weight loss is less likely to be detected.

6.6. Data sources

The study is conducted using MarketScan and Optum claims data from the US.

7.6.1 Context and rationale for data sources

Reason for selection: Claims data contain all necessary information on exposure and outcome for this research question, and provide enough data to adjust for relevant confounders.

Strengths of data source(s): Both data sources contain large samples of the US population, with linked longitudinal data of healthcare claims including reimbursed prescriptions, in- and outpatient diagnoses including respective dates, as well as demographic information and death data.

Limitations of data source(s): Both data sources only include information for those periods in which individuals are enrolled with health insurances contributing to the respective data sources. There is no information on medications not reimbursed, and there is no guarantee reimbursed medications are used.

Data source provenance/curation: Information about Optum Clinformatics and Merative MarketScan can be found in data dictionaries and user guides that are provided to clients.

Table 12. Metadata about data sources and software

	Data 1	**Data 2**
Data Source(s):	Optum Clinformatics	Merative MarketScan
Study Period:	01 January 2010 – 31 December 2024	01 January 2013 – 31 December 2023
Eligible Cohort Entry Period:	01 January 2010 – 31 December 2024	01 January 2013 – 31 December 2023
Data Version (or date of last update):	23 October 2025	01 May 2025
Data sampling/extraction criteria:	n/a	n/a
Type(s) of data:	Healthcare claims	Healthcare claims
Data linkage:	n/a	n/a

Conversion to CDM*:	No	No
Software for data management:	Aetion Evidence Platform® (2025)	Aetion Evidence Platform® (2025)

*CDM = Common Data Model

6.7. Data management

Tracking data: The Data Use Agreement (DUA) Custodian (Principal Investigator) and the Division Operations Manager (Winta Tekle) are responsible for receiving and creating a record of new data associated with the given request. The Operations Manager is responsible for all indexing and archiving of documents and electronic media related to data that the Division receives and will log data location, data contents, and associated DUA and Institutional Review Board (IRB) numbers in the Division's centralized tracking system.

Handling and storage: In-scope data will be stored utilizing Mass General Brigham approved information systems – i.e., Division servers and Mass General Brigham network storage.

Archiving: Data retention and any removal will be executed by the Division Operations Manager (Winta Tekle) and Data Manager (Todd MacGarvey). The Division follows Mass General Brigham enterprise record retention policies and follow the terms of the agreement through which the in-scope data was received.

Information security: The Division follows Mass General Brigham's Enterprise Information Security Program (EISP). The EISP helps by providing assurance that Mass General Brigham information and information systems are protected from unauthorized access, use, disclosure, duplication, 60 modification, or destruction in order to maintain their confidentiality, integrity, and availability. To that end, the EISP policies, standards and procedures create an information security framework that is aligned with the recommendations of the International Organization for Standardization's (ISO) publication 27001 and the National Institute of Standards and Technology's (NIST) publication 800-53 Family of Controls and MGB regulatory and legal requirements (as a HIPAA covered entity). Mass General Brigham workforce members are required to complete new workforce privacy and information security training upon hire and annually thereafter. Refresh training is provided as appropriate.

Mass General Brigham workforce members are required to review and sign a Confidentiality Agreement upon hire and annually thereafter. Additionally, we follow Enterprise Information Security and Privacy policies, including Managing Workforce Members Information Security Responsibilities Policy, which was developed to help assure that Mass General Brigham workforce members are competent and eligible to support the information security responsibilities associated with their role. Mass General Brigham workforce, including Division staff, are required to comply with Enterprise Information Security and Privacy Policies.

Facilities: The research team uses a highly secure, state-of-the-art, computing facility housed at Mass General Brigham's Corporate Data Centers in Needham and Marlborough, Massachusetts as well as Amazon Web Services (AWS). We maintain redundant storage for maximal data integrity and high-speed data access.

The Division uses Mass General Brigham corporate provisioned servers to analyze and store data in connection with this project. There are strict access controls enforced by technical means to ensure that only study staff who have been approved to conduct data analyses and contracted data engineers are able to access data (e.g., Mass General Brigham Authentication (Active Directory) utilized; auditing, logging, and monitoring enabled; firewalls enabled; etc.). All Division servers used in

this study are accessible to only authorized staff only through the MGB network and utilizing VPN as appropriate (i.e., users must be on the network and logged into VPN to access). Mass General Brigham has a network information security monitoring team and in-scope servers are enrolled in enterprise security tools (e.g., vulnerability scanning service, antivirus, etc.).

The Division also uses AWS. In-scope AWS services / resources have undergone review and assessment by Mass General Brigham's Information Security Risk Assessment Team/ InfoSec Risk Management Team as required and in alignment with NIST 800-30: Guide for Conducting Risk Assessments. In-scope AWS servers are for our exclusive use (reserved instances), are covered under our organization's Business Associate Agreement with AWS. In-scope servers are housed in anonymous facilities that are not branded as AWS facilities. Physical access is strictly controlled both at the perimeter and at building ingress points by professional security staff utilizing video surveillance, intrusion detection systems, and other electronic means.

Security attributes and controls for the Division's use of in-scope AWS in connection with this project include: encryption at rest and in transit (industry standard AES-256 encryption, SSL/TSL), anti-malware, latest OS updates and patches as well as anti-virus; multi-factor authentication (MFA), Identity and Access Management, including SSO; auditing and logging; principle of least privilege, including for traffic and ports (e.g., deny all default configurations), use of VPC enabled Step functions, etc.; separation between environments; minimum necessary (out of the box AWS roles are not used as they can be overly permissive); all data would reside in the US domestic regions – use only US east HIPAA compliant region; performance monitoring enabled and reviewed as per internal processes; passwords compliant with enterprise password policy and, as appropriate, more protective password requirements; etc. Our Division's AWS use is also subject to ongoing evaluation and monitoring as well – e.g., vulnerability scanning and management, access review, etc.

A data file list will be maintained in Amazon S3 and tracked through Cloudtrail and Cloudwatch. Reporting of data file availability for any file stored in an S3 bucket will be controlled by MGB

Amazon EC2, Amazon EBS, and Amazon VPC are integrated with AWS CloudTrail, a service that provides a record of actions taken by a user, role, or an AWS service in Amazon EC2, Amazon EBS, and Amazon VPC. CloudTrail captures all API calls for Amazon EC2, Amazon EBS, and Amazon VPC as events, including calls from the console and from code calls to the APIs. MGB IT/security staff have full access to CloudTrail to ensure that CloudTrail monitoring is available at all times. Amazon CloudWatch Events delivers a near-real-time stream of system events that describe changes in AWS resources. Amazon CloudTrail can log, continuously monitor, and retain account activity related to actions across the MGB AWS infrastructure. CloudTrail provides event history of MGB AWS account activity. This event history simplifies security analysis, resource change tracking, and troubleshooting and complies with requirements to ensure the data file inventory is controlled by MGB.

Backups: Backups are created using industry recognized Cryptographic mechanisms (e.g., 256-bit AES encryption) as appropriate and required. Data are backed up within the MGB network from the MGB Needham data center to the MGB Marlborough data center via replication/mirroring and volumelevel snapshots. AWS Backup supports both instance-level backups as Amazon Machine Images (AMIs) and volume-level backups as separate snapshots based on the resource tags. AMIs allow MGB IT and security staff to create backups of all S3 and EC2 instances.

In addition to the safeguards listed above, the Division follows enterprise privacy and information security policies and maintains internally procedures in connection with this project to safeguard the data in connection with this project as appropriate and required including: Physical Security and Environmental Controls for Electronic Information Policy; IT Access Control Standards for Users policy; Safeguarding Fax Copiers Printers Telephone Use and Pagers; Physical Removal and Transport of Protected Health Information and Personal Information policy, etc.

6.8. *Quality control*

Senior Programmers and Research Specialists perform QA/QC on raw or common data model converted data via SAS/R/Aetion software. The protocol will be iteratively developed and pre-specified data checks including feasibility counts and balance on baseline covariates will be conducted with outputs reviewed by MGB team members. Team members will review code lists to ensure fidelity to intended algorithms.

6.9. *Study size and feasibility*

As this is an exploratory analysis, no formal power assessment will be conducted.

7. Limitation of the methods

Due to the lack of randomisation in Real-World Data studies, any causal interpretation of results has to rely on untestable assumptions, such as the lack of unmeasured confounding. While this study adjusts for may baseline covariates, many factors influencing the outcome probabilities cannot be captured in administrative claims data, such as dietary habits. However, those factors are unlikely to influence the choice between GLP-1RA and DPP4i without mediation by health status, which is well-covered in the two data sources.

Follow-up time in US-based claims data sources can be shorter than necessary to detect outcomes with long detection times, such as cancer. This study might therefore underestimate cancer risks and will mostly detect effect on later stages of tumour development and faster-growing cancer types.

There have been no validation studies on measuring thyroid or prostate cancer in claims data, however there is no reason to expect large differences in measurement characteristics from those of endometrial and pancreatic cancer when using the same outcome algorithms.

8. Protection of human subjects

This study has been approved by the Brigham and Women's Hospital Institutional Review Board.

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10. Appendices

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