08 November 2023

Data analysis plan

Title: Association between exposure to GLP-1 receptor agonists and risk of suicide-related and self-harm-related events

Version 1.6

Administrative details of the data analysis	
Substance(s)	GLP-1 receptor agonists
Condition/ADR(s)	Suicide-related and self-harm-related and events (suicidal ideation, self-injurious ideation, self-injury/self-harm, suicide attempt, completed suicide)
Short title of topic	Suicide-related and self-harm-related events and GLP-1 receptor agonists
Regulatory procedure	Safety signal

1. Rationale and background

Suicide-related events, including ideation, attempt, and completed suicide, are an important drug safety issue. Therapies implicated as risk factors for suicidal outcomes include antidepressants (Barbui et al., 2009; Fergusson et al., 2005), anticonvulsants (Mula & Hesdorffer, 2011) interferon (Fragoso et al., 2010; Lucaciu & Dumitrascu, 2015) and hormonal contraceptives (Skovlund et al., 2018), among others. However, the strength of the evidence for some of these associations remains uncertain.

Currently, there is an ongoing signal of suicidal ideation and self-injurious ideation after exposure to liraglutide and semaglutide. These substances are glucagon-like peptide-1 (GLP-1) receptor agonists which are known as incretin mimetics because they act by increasing insulin release from the pancreas in response to food. Liraglutide is authorized for weight management in adult and adolescent patients aged ≥12 years and for the treatment of adults, adolescents, and children >10 years of age with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.[1] Semaglutide is authorized for the treatment of adult patients with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise and for weight loss and weight maintenance in adults who have a body mass index (BMI) ≥30 kg/m² (obesity) or a BMI between 27 kg/m² and <30 kg/m² (overweight).[2] Suicidal behaviour is not currently listed as a side effect in the EU product information for any GLP-1 receptor agonists. However, the FDA prescribing information for liraglutide includes a warning regarding suicidal behaviour and ideation.[3]

Weight control failure has been related to suicidal ideation, particularly among overweight and obese adolescents. (Ju et al., 2016) Obesity and diabetes are associated with multiple comorbidities (Guh et al., 2009; Zheng et al., 2018), premature mortality (Flegal et al., 2013; Zheng et al., 2018), and impaired health-related quality of life (Garner et al., 2012; Zheng et al., 2018). Studies suggest that diabetic patients and obese individuals have a higher prevalence of neuropsychiatric disorders, such as depression, compared to the general population (Khaledi et al., 2019; Luppino et al., 2010; Roy & Lloyd, 2012; Scott et al., 2008; Zhao et al., 2009). It has been indicated that incretin-based therapies may have neuropsychiatric effects given the presence of glucagon-like peptide-1 (GLP-1) receptors in the central nervous system. (Gamble et al., 2018)

To support the evaluation of the signal, a study is proposed to assess whether there is an association between exposure to GLP-1 receptor agonists and increased risk of recorded suicide-related and self-harm-related events among patients with type 2 diabetes mellitus (T2DM) when compared to patients who are prescribed alternative treatment (i.e., SGLT-2 inhibitors). Of note, it is of interest for the signal evaluation to investigate the effect of the entire class of GLP-1 receptor agonists. This study will be conducted using the UK IMRD database as the events of interest are not well-captured in other databases.

It is worth noting that the limited sample size of new users of GLP-1 receptor agonist patients with a history of obesity but not history of T2DM precludes the conduct of a study with a focus on this population.

[1] EMA. Victoza | European Medicines Agency (europa.eu)
[2] EMA. Ozempic | European Medicines Agency (europa.eu)
[3] FDA. SAXENDA (liraglutide).

2. Research question and objectives

Is the use of GLP-1 receptor agonists associated with an increased risk of suicide-related and self-harm-related events when compared to patients who are prescribed SGLT-2 inhibitors among T2DM patients?

3. Research methods

3.1. Study design

Comparative cohort design (active comparator, new user design).

3.2. Data sources

The following database will be used: IQVIA™ Medical Research Data (IMRD) UK. A brief description of this database is provided in Annex 1.

3.3. Setting and study population

The population eligible for the study will consist of patients:

- registered with a GP-practice covered by IQVIA™ Medical research data (IMRD),
- who initiated treatment with GLP-1 receptor agonists or SGLT-2 inhibitors (new users) during the study period,
- who had not used GLP-1 receptor agonists or SGLT-2 inhibitors before index-date (i.e., date of index treatment initiation and the start of follow-up in the study),
- with at least one year (365 days) of recorded medical history prior to index-date,
- with at least one diagnosis of T2DM before index-date,
- with no history of suicide-related or self-harm-related events prior to index-date,
- who have been treated with biguanides (e.g., metformin, which is considered first-line anti-diabetic treatment according to NICE guidelines (NICE, 2022)) before index-date.

No exclusion will be applied according to age.

3.4. Study period

The study period will cover from the first use of SGLT-2 inhibitors on the database (i.e., **01 March 2013**) onwards to most recent data available (**01 June 2023**). Although the first use of GLP-1 receptor agonists dates to August 2009 in the IMRD, we opted to include only the period in which both treatments were available, thus patients would have had the option to receive either treatment.

3.5. Variables

Exposure: Exposures of interest will consist of GLP-1 receptor agonists (**target group**) and SGLT-2 inhibitors (**comparator group**).

In the UK, NICE clinical guidelines (NICE, 2022) recommend use of SGLT-2 inhibitors after metformin and at least one other oral antidiabetic. GLP-1 receptor agonists are only recommended when triple therapy with metformin and two other oral antidiabetics are not effective, contraindicated or not tolerated. GLP-1 receptor agonists should replace one of the combination components, and it is indicated to T2DM adults:

- who have a BMI of ≥35 Kg/m^2 or other medical problems associated with obesity, or
- who have a BMI <35 Kg/m^2 for whom insulin therapy is not an option or weight loss would benefit other obesity related comorbidities.

New users of GLP-1 receptor agonists or SGLT-2 inhibitors will be identified based on the date of first prescription in the database (**index-date**).

Exposures will be identified through keyword search of prescriptions recorded in the description, generic name or product name fields. Detailed list of codes is provided in **Annex 2**.

Products containing GLP-1 receptor agonists or SGLT-2 inhibitors are combined under each corresponding treatment arm. The GLP-1 receptor agonists arm includes the following substances: liraglutide (alone and in combination with insulin), semaglutide, dulaglutide, exenatide and lixisenatide. The SGLT-2 inhibitor arm includes the following substances: dapagliflozin (alone or in combination with metformin or saxagliptin), empagliflozin (alone or in combination with metformin or linagliptin), canagliflozin (alone or in combination with metformin) and ertugliflozin. **Outcome**: The primary outcome will consist of a composite endpoint which will include the first recorded occurrence of any of the following events:

(a) suicide-related events which encompassed codes related to suicidal ideation, attempted suicide, intentional overdose/self-poisoning, completed suicide.

(b) self-harm-related events which covered codes in which intention of self-harm is clearly specified (e.g., deliberate self-harm/self-injury, self-inflicted harm, self-injurious behaviour) to differentiate from unintentional/accidental harm. The complete list of clinical terms and READ codes which will be used to identify these events are provided in Annex 2.

Potential confounding factors:

Analyses will account for the following baseline covariates measured before index date:

- Sociodemographic: age, sex, and deprivation index
- History of:
    - obesity
    - depression (included bipolar disorder or cyclothymia) or treatment for depression
    - anxiety or treatment for anxiety
    - schizophrenia/psychosis
    - dementia
    - malignancy
    - cardiovascular diseases (myocardial infarction, cerebrovascular disease, congestive heart failure)
    - kidney disease
    - smoking

- alcohol and substance abuse

- Prior anti-diabetic treatments before index date other than biguanide (metformin)

3.6. Statistical analysis

3.6.1. Descriptive analysis

Descriptive analyses will be performed to describe the study cohorts at baseline in terms of demographic characteristics, baseline comorbidities and medication history of anti-diabetic and psychiatric treatments.

3.6.2. Main statistical analysis

Inverse probability of treatment weighting (IPTW)

Inverse probability of treatment weighting (IPTW) will be used to render the assignment of study treatments independent of the measured covariates, thus minimising the potential confounding effect of these covariates. Using IPTW, the average treatment effect in the entire study population can be estimated, assuming that all important confounding variables have been accounted for. For each observation in the study population, the IPTW is the inverse of the probability of receiving the observed treatment conditional on all variables considered sufficient for confounding adjustment. In order to stabilize the weights (i.e., less extreme weights, that are closer to one), the numerator of one is replaced by the marginal probability of receiving the observed treatment in the study population (i.e., the proportion of observations in the study population with the respective treatment).(Hernan & Robins, 2006) All analyses (e.g., estimation of survival curves and hazard ratios) can be then conducted in the re-weighted population without additional confounding adjustment (such as introducing covariates in regression models). To account for weighting the population (essentially multiplying observations by the weight coefficient) robust standard error estimators will be used.

The distribution of co-variates before and after weighting will be compared between the two treatment arms by calculating and plotting standardized mean differences. For each variable, the standardized mean difference is the difference in mean (for continuous variables) or proportion (for binary variables) between the two treatment arms, divided by the squared mean variance of the variable in the two treatment arms.(Austin, 2011)

Intention-to-treat (ITT) analysis

For the main analysis, we will apply an **intention-to-treat (ITT)** approach. Patients will be followed from the date of study treatment initiation until the earliest of first outcome event date, transfer out date, date of death or date of last data collection. Patients are classified according to treatment initiated at baseline and any outcome event occurring during follow-up will be attributed to baseline treatment regardless treatment change. Intercurrent events that may occur during follow-up are assumed to have no effect on risk of the outcome (i.e., the risk of experiencing the outcome among individuals remaining in the analysis over the course of follow-up is representative of the risk among censored individuals).

Incidence rates

IRs will be calculated as the number of events occurring during follow-up divided by the total person-time in each treatment-arm. IRs will be presented as number of events per 100 person-years.

Cumulative incidences

Survival (i.e., the proportion of the patients included at baseline who have not yet experienced a suicide-related or a self-harm-related event) over the course of follow-up will be estimated by treatment arm using the product-limit method.(Bland & Altman, 1998) The cumulative incidence will be calculated as the complement of survival (i.e., the proportion of the patients included at baseline who have experienced a suicide-related or a self-harm-related event) at each follow-up time and will be presented as number of events per 100 patients.

Cox proportional hazard model

Hazard ratios of suicide-related and self-harm-related events associated with treatment of interest (GLP-1 receptor agonists) versus comparator (SGLT-2 inhibitors) will be estimated using a Cox proportional hazards model.

3.6.3. Sensitivity analysis

The following sensitivity analyses will be performed to test the validity of the underlying assumptions and to test the robustness of the study findings:

- **Assessing separately component parts of the outcome:** The component parts of the composite endpoint will be assessed separately: (a) only suicide-related events, and (b) only self-harm-related events.
- **Applying asymmetric PS trimming (Stürmer trimming method):** Patients with extreme PS will be excluded from the study, among whom unmeasured confounding may be more likely. (Sturmer et al., 2010)
- **Restricting the sample to a cohort of "low-risk" patients:** Patients with a history of psychiatric conditions (depression, anxiety and psychosis) will be excluded and analysis will be conducted in a cohort of "low-risk" patients.
- **Applying "on-treatment" (OT) approach:** In this analysis patients will be followed only as long as they continue the baseline treatment (i.e., censoring follow-up at baseline treatment discontinuation). Assuming that treatment discontinuation is independent of the risk of suicide-related and self-harm-related events, this analysis will estimate the treatment effect had patients remained on the baseline treatment for the entire follow-up. Patients will be censored at the earliest of these events: end of index-treatment, crossing over to the alternative treatment arm, first outcome event date, transfer out date, date of death or at the end of the study period.

3.6.4. Sample size

The sample size will be driven by the availability of individuals with exposures and outcomes within each database and no *a priori* sample size requirement will be stipulated.

Analyses will be done using SAS Enterprise Guide 7.1 software.

3.7. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

3.8. Limitations of the research methods

We will study the entire class of GLP-1 receptor agonists combined (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide and teduglutide). We will not assess the two individual substances related to the safety signal (liraglutide and semaglutide) separately because of sample size constraints. The PRAC is aware of this and has accepted it as a limitation.

Exposure is misclassified in ITT analyses if a large proportion of study participants change the baseline treatment early during follow up. An alternative to ITT is to follow study participants only as long as they remain on the baseline treatment. Therefore, we will conduct such an "on-treatment" analysis as sensitivity analysis. In OT analyses, the exposure is correctly classified, however censoring patients when they interrupt the baseline treatment could introduce selection bias, if risk factors for the outcome are reasons for interrupting treatment - i.e., informative censoring, or the risk of experiencing the outcome would have been different among those censored (had they been observed) compared to those remaining in the study. Our analyses assume that censoring is random (not informative). If the probability of interrupting the treatment is mainly increased by risk factors for the outcome, then the selection bias may create an inverse association between exposure and outcome.

A certain degree of outcome misclassification may be present in our study. Accurate and complete ascertainment of suicidal attempts and completed suicide in electronic health records presents challenges (Hall, 2009; Salmeron et al., 2013; Swain et al., 2019; Wijlaars et al., 2013). For example, suicide attempts (or suicidal ideation) may not always result in health care encounters. Absence of recorded clinical care is likely to be a major source of under ascertainment (i.e., false negatives). In addition, the health care practitioner must accurately describe the harm as intentional or accidental, which may not be clear sometimes; misclassification of intent can result in both false-positives and false-negatives, although false-negatives are expected to occur more frequently (Swain et al., 2019). The PRAC has acknowledged that the outcome of this study is suicide-related and intentional self-harm events and does not represent incidences of completed suicide.

To our knowledge, there is no data describing the accuracy of coding for suicide-related events or self-harm-related events such as suicidal ideation, self-harm ideation, intentional self-injury/self-harm, attempted suicide in the IMRD database. A study which assessed the validity of suicide recording in the UK THIN database found that the cause of death is incomplete even when free text entries are reviewed, therefore, any study of fatal, acute conditions would underestimate the rate of an event (Hall, 2009).

4. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database) will be removed prior to publication of the final study report. Additional cells may be redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

5. Management and reporting of adverse events/adverse reactions

Pursuant to the requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

6. Plans for disseminating and communicating study results

The analysis plan and study results will be published in EUPAS registries upon completion.

7. References

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Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

Annex 2 - Codelists

2.1 List of codes to identify study population:

20230807--FA_IMRD__T2DM_codes_trim

2.2 List of codes to identify antidiabetic treatment exposure:

Anti-diabetic Treatments:

Class	Code (EPHMRA ATC)
Insulins (including combinations)	A10C, A10D
Sulphonylureas (including combinations)	A10H, A10J2, A10K2
Thiazolidinediones (including combinations)	A10K
Biguanides (including combinations)	A10J
DPP-4 inhibitors (including combinations)	A10N, A10P5
SGLT-2 inhibitors (including combinations)	A10P
GLP-1 agonists (including combinations)	A10S, A10C9
Glinide	A10M
Other (acarbose, guar gum)	A10X, A10L

2.3 List of codes to identify outcome:

20230915_UK_IMRD_suicide_selfinjury_r

Note: "PHQ9 score - thoughts of suicide or self-harm" will be only used where the value associated with the code is between 1 and 3. The code is derived from a questionnaire aiming to assess severity of depression. "PHQ9 score - thoughts of suicide or self harm" is one of 9 questions with the following answer options: "0 - Not at all", "1 - Several days", "2 - More than half the days", "3 - Nearly every day".

2.4 List of codes to identify and define covariates

2.4.1 Obesity diagnosis

List of codes to identify obesity diagnoses:


obes_bin.csv

List of codes to identify BMI measurements:


obes_th.csv

Definition:

A patient will be considered to have had a recent history of obesity if at least one code from the list of obesity diagnoses above is recorded within 2 years before index-date or if they had a BMI measurement with value between 30 and 80 within 2 years before index-date.

2.4.2 Obesity treatment

List of codes to identify obesity treatments:


obes_rx_bin.csv

Definition:

A patient will be considered to have had a recent obesity treatment if at least one code from the list of obesity treatments above is recorded within 2 years before index-date.

2.4.3 Cancer

Lists of codes to identify cancer diagnoses and chemotherapy or radiotherapy procedures:


cancer_bin.csv


chimio_bin.csv


radio_bin.csv

Definition:

A patient will be considered to have had a history of cancer if at least one code from any of the lists above is recorded any time before index-date.

2.4.4 Renal disease

List of codes to identify renal disease diagnoses or dialysis procedures:


renal_bin.csv

Definition:

A patient will be considered to have had a history of renal disease if at least one code from the list above is recorded any time before index-date.

2.4.5 Myocardial infarction

List of codes to identify myocardial infarction diagnoses:

MI_bin.csv

Definition:

A patient will be considered to have had a recent myocardial infarction if at least one code from the list above is recorded within 2 years before index-date.

2.4.6 Congestive heart failure

List of codes to identify congestive heart failure diagnoses:

CHF_bin.csv

Definition:

A patient will be considered to have had a history of congestive heart failure if at least one code from the list above is recorded any time before index-date.

2.4.7 Cerebrovascular disease

List of codes to identify cerebrovascular disease diagnoses:

stroke_bin.csv

Definition:

A patient will be considered to have had a history of cerebrovascular disease if at least one code from the list above is recorded any time before index-date.

2.4.8 Anxiety diagnosis

List of codes to identify anxiety diagnoses:

anxi_bin.csv

Definition:

A patient will be considered to have had a history of anxiety if at least one code from the list above is recorded any time before index-date.

2.4.9 Anxiety treatment

List of codes to identify anxiolytic treatments:

anxi_rx_bin.csv

Definition:

A patient will be considered to have had a history of anxiolytic medication use if at least one code from the list above is recorded any time before index-date.

2.4.10 Depression diagnosis

List of codes to identify depression diagnoses:

depres_bin.csv

Definition:

A patient will be considered to have had a history of depression if at least one code from the list above is recorded any time before index-date.

2.4.11 Depression treatment

List of codes to identify anti-depressive medication:

depres_rx_bin.csv

Definition:

A patient will be considered to have had a history of anti-depressive medication use if at least one code from the list above is recorded any time before index-date.

2.4.12 Schizophrenia/Psychosis diagnosis

List of codes to identify schizophrenia diagnoses:

psycho_bin.csv

Definition:

A patient will be considered to have had a history of schizophrenia diagnosis if at least one code from the list above is recorded any time before index-date.

2.4.13 Stress related and adjustment disorders

List of codes to identify stress related diagnosis:

stress_bin.csv

Definition:

A patient will be considered to have had a history of stress disorders if at least one code from the list above is recorded any time before index-date.

2.4.14 Dementia diagnosis

List of codes to identify stress related diagnosis:

dement_bin.csv

Definition:

A patient will be considered to have had a history of stress of dementia if at least one code from the list above is recorded any time before index-date.

2.4.15 Substance (including alcohol) abuse

List of codes to identify substance abuse diagnoses:

subst_abus_bin.csv

List of codes to identify answer to individual AUDIT score questions:

AUDIT_q_th.csv

List of codes to identify short AUDIT score versions:

AUDIT_c_th.csv

List of codes to identify full AUDIT score:

AUDIT_f_th.csv

List of codes to identify weekly quantitative alcohol consumption measurements:

alc_cons_w_th.csv

List of codes to identify daily quantitative alcohol consumption measurements:

alc_cons_d_th.csv

Definition:

A patient will be considered to have had a recent history of substance abuse if at least one code from the list of substance abuse diagnoses above is recorded within 2 years before index-date or if they have had any of the following measurements within the same time window: (1) a score of 4 for the answer to an individual AUDIT question; (2) a score between 9 and 12 for answers to short AUDIT versions; (3) a score between 20 and 40 for answers to the full AUDIT version; (4) an alcohol consumption value between 35 unit, for females, or 50 units, for males, and 500 units per week or (5) an alcohol consumption value between 6 units, for females, or 8 units, for males, and 100 units per day.

2.4.16 Smoking

List of codes to identify recent smoking:

smoking_th.csv

Definition:

A patient will be considered a recent smoker if at least one code from the list above is recorded within 2 years before index-date, accompanied by either a missing value or a value higher than 0 (as some codes are accompanied by the number of cigarettes smoked per time unit).