PASS INFORMATION

Title	Post-authorization Safety Study to Assess the Risk of Diabetic Ketoacidosis among Type 2 Diabetes Mellitus Patients Treated with Ertugliflozin Compared to Patients Treated with Other Antihyperglycemic Agents: Interim Report 2
Version identifier of the interim study report	001
Date of last version of the final study report	Not applicable
EU PAS register number	EUPAS31718
Active substance	Ertugliflozin Ertugliflozin + Metformin Hydrochloride Ertugliflozin + Sitagliptin
Medicinal product	STEGLATRO™ (ertugliflozin; ATC code A10BK04) SEGLUROMET™ (ertugliflozin/metformin; ATC code A10BD23) STEGLUJAN™ (ertugliflozin/sitagliptin; ATC code A10BD24)
Product reference	EMEA/H/C/004315 - Steglatro™ EMEA/H/C/004314 - Segluromet™ EMEA/H/C/004313 - Steglujan™
Procedure number	EMEA/H/C/004315/MEA/002.5 - Steglatro™ EMEA/H/C/004314/MEA/002.5 - Segluromet™ EMEA/H/C/004313/MEA/002.5 - Steglujan™
Marketing authorisation holder(s)	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Joint PASS	No

Research question and objectives	Preliminary analyses on the study population included as of 2 Aug 2022 were conducted to: 1. Assess the sample size (count and person-time) of new users of ertugliflozin and comparator antihyperglycemic agents (AHAs, based on data from the Innovation in Medical Evidence Development and Surveillance System Distributed Database, Optum Research Database, and Centers for Medicare & Medicaid Services Medicare Research Identifiable Files, 2. Describe the baseline characteristics of new users of ertugliflozin and comparator AHAs, and 3. Discuss the feasibility of reaching the required sample size via the stepwise data addition approach proposed in response to Interim Report 1 comments.
Country(-ies) of study	United States
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

1 ABSTRACT

Title

Post-authorization Safety Study to Assess the Risk of Diabetic Ketoacidosis among Type 2 Diabetes Mellitus Patients Treated with Ertugliflozin Compared to Patients Treated with Other Antihyperglycemic Agents: Interim Report 2

Keywords

ertugliflozin, antihyperglycemic agents, IMEDS framework, sample size, type 2 diabetes mellitus

Rationale and background

MSD has committed to the European Medicines Agency (EMA) to conduct *the Post-Authorization Safety Study (PASS) to Assess the Risk of Diabetic Ketoacidosis among Type 2 Diabetes Mellitus Patients Treated with Ertugliflozin Compared to Patients Treated with Other Antihyperglycemic Agents* (Protocol MK8835-062; EUPAS31718) to investigate the association of ertugliflozin use with diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients using the Innovation in Medical Evidence Development and Surveillance System (IMEDS) framework. As part of the study milestones, two interim reports were planned to be submitted (4Q 2021 and 4Q 2022). As requested in the Pharmacovigilance Risk Assessment Committee (PRAC) PASS Protocol Assessment Report dated 05 September 2019 (Section 11), these interim reports should provide preliminary analyses on the study population available at their respective reporting time, discuss the sample size, and consider inclusion of other database(s) if the sample size is not anticipated to reach the target number needed for the final analyses. This is Interim Report 2.

Objectives of Interim Report 2

Preliminary analyses on the study population included as of 2 Aug 2022 were conducted to:

1. Assess the sample size (count and person-time) of new users of ertugliflozin and comparator AHAs, based on data from the IMEDS Distributed Database (IMEDS-DD), Optum Research Database, and Centers for Medicare & Medicaid (CMS) Services Medicare Research Identifiable Files (RIFs),

2. Describe the baseline characteristics of new users of ertugliflozin and comparator AHAs, and

3. Discuss the feasibility of reaching the required sample size via the stepwise data addition approach proposed in response to Interim Report 1 comments.

Study design

A non-interventional cohort study using electronic healthcare data.

Setting

Predominantly community-dwelling individuals of all ages, commercially or publicly insured in health plans.

Subjects and study size, including dropouts

Three primary exposure cohorts of interest were defined as new users of: (1) ertugliflozin; (2) sulfonylureas (SU) or thiazolidinediones (TZD); and (3) incretin-based drugs. Each exposure cohort was defined as the set of patients who: had a first qualifying exposure to the cohort-defining drug(s), with the first exposure date (index date) occurring between 1 July 2018 and most recent available in each database; had at least 1 diagnosis of T2DM without any diagnosis of type 1 diabetes mellitus (T1DM) or gestational diabetes on or any time before the index date; and had no prior exposure to the cohort-defining drug(s) in the 6 months before the index date .

Variables and data sources

Variables: baseline demographics (age and sex), comorbidity burden (Charlson-Elixhauser combined comorbidity index), pre-existing comorbidities and diabetes-related complications (cerebrovascular disease, coronary heart disease, heart failure, myocardial infarction, peripheral vascular disease, stroke, hypertension, hyperlipidemia, hypoglycemia, hypovolemia, hypoxemia, obesity, pancreatitis, thyroid disorders, moderate or severe renal insufficiency, diabetic nephropathy, neuropathy, retinopathy, and amputation), AHA utilization by class, and health services utilization (number of unique medications, number of outpatient, inpatient, and emergency department visits).

Data sources: The preliminary analyses were conducted using data from the following sources: 1) the Reagan-Udall Foundation for the Food and Drug Administration (FDA)'s IMEDS-DD, 2) the Optum Research Database, and 3) the CMS Medicare RIFs. All three databases include previously or currently contributing datasets to the US FDA's Sentinel System, a national electronic system for active surveillance of medical product safety in the United States.

Results

A total of 2,196 new users and 2,235 new use episodes of ertugliflozin were identified between 1 July 2018 and 31 December 2021. Among the new use episodes, the mean age on the exposure index date was 62.9 years (SD=10.7 years), and of these, 15.2% initiated ertugliflozin as monotherapy. The most commonly utilized concomitant AHA class was metformin (61.7%), followed by dipeptidyl peptidase-4 inhibitors (31.5%) and SU (26.4%). The most common baseline comorbidities included hypertension (77.4%) and hyperlipidemia (75.6%). Individuals with a history of cardiovascular disease represented 29.4% of ertugliflozin new use episodes. Average follow-up for a new use episode of ertugliflozin and comparator ranged from 0.54 to 0.66 person-year, depending on the new user type (primary/incident) and comparator.

During the same study periods, there were 668,154 new users of SU or TZD and 622,290 new users of incretin-based drugs, of whom the demographic and clinical characteristics were comparable to those reported for comparison groups in observational studies of other SGLT2 inhibitors.

Discussion

Significant sample size gain after including the Optum Research Database and CMS Medicare RIFs as the additional data sources suggests successful implementation of the stepwise data addition proposed in the Interim Report 1. Nonetheless, the required study sample size is not expected to be reached to perform the final analyses if data are limited to the current data sources. Therefore, the Applicant seeks to include multi-state Medicaid data provided through the CMS Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) RIFs. In this way, the sample size is projected to expand substantially to support the final analyses.

Marketing Authorisation Holder(s)

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[a] PPD, who had been the co-investigator of the project since July 2018, replaced PPD as the PI starting November 2021.

2 LIST OF ABBREVIATIONS

AHA	Antihyperglycemic agents
CCAE	Merative™ MarketScan® Commercial Claims and Encounters Database
CDC	Centers for Disease Control and Prevention
CPT	Current Procedural Terminology
CVD	Cardiovascular disease
CVD-REAL	Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors
CMS	Centers for Medicare & Medicaid Services
CNODES	Canadian Network for Observational Drug Effect Studies
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase 4
EHR	Electronic health record
EMA	European Medicines Agency
EMPRISE	EMPagliflozin compaRative effectIveness and SafEty
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FISMA	Federal Information Security Management Act
GLP-1	Glucagon-like peptide-1
HbA_{1c}	Hemoglobin A_{1c}
HCPCS	Healthcare Common Procedure Coding System
HPHCI	Harvard Pilgrim Health Care Institute
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IMEDS	Innovation in Medical Evidence and Development Surveillance
IMEDS-DD	Innovation in Medical Evidence and Development Surveillance Distributed Database
IRB	Institutional Review Board
MDCR	Merative™ MarketScan® Medicare Supplemental Beneficiaries
MSD	Merck Sharp & Dohme, Corp.
NDC	National Drug Codes
PASS	Post-Authorization Safety Study
PCORnet	National Patient-Centered Clinical Research Network
QA	Quality assurance

QC	Quality control
RIF	Research Identifiable Files
SD	Standard deviation
SU	Sulfonylurea
SGLT2	Sodium-glucose cotransporter 2
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAF	Transformed Medicaid Statistical Information System Analytic File
T-MSIS	Transformed Medicaid Statistical Information System
TZD	Thiazolidinedione
US	United States
VRDC	Virtual Research Data Center
ZIP	Zone Improvement Plan

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Vendor/Collaborator	Innovation in Medical Evidence and Development Surveillance
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4 OTHER RESPONSIBLE PARTIES

Not applicable.

[b] PPD, who had been the co-investigator of the project since July 2018, replaced PPD as the PI starting November 2021.

5 MILESTONES OF MK8835-062

Milestone	Planned date	Actual date
Start of data collection of MK8835-062	1 July 2018	1 July 2018
End of data collection of MK8835-062	31 March 2024 *	
Registration in the EU PAS register	24 October 2019	17 October 2019
Feasibility assessment report	31 December 2020	7 December 2020
Interim report 1	31 December 2021	9 December 2021
Interim report 2	31 December 2022	
Final report of study results	31 October 2024 *	

*Due to the delay in receiving data from the Centers for Medicare & Medicaid Services, a 10-month extension for the final report is being requested. The newly proposed milestone date for the end of data collection and final report are 31 March 2024 and 31 October 2024, respectively.

6 RATIONALE AND BACKGROUND

Ertugliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Ertugliflozin products (including ertugliflozin, ertugliflozin/sitagliptin and ertugliflozin/metformin HCl) were approved in the US on 19 December 2017 and in Europe on 21 March 2018 for type 2 diabetes mellitus (T2DM) treatment to improve glycemic control in adults. As its marketing authorization holder, Merck Sharp & Dohme, Corp (MSD) has committed to the European Medicines Agency (EMA) to conduct the *Post-Authorization Safety Study (PASS) to Assess the Risk of Diabetic Ketoacidosis among Type 2 Diabetes Mellitus Patients Treated with Ertugliflozin Compared to Patients Treated with Other Antihyperglycemic Agents* (MK8835-062; EUPAS31718) to investigate the association of ertugliflozin use with diabetic ketoacidosis (DKA) among T2DM patients and more specifically, whether new use of ertugliflozin is associated with an increased risk of DKA, compared to new use of other non-SGLT2 inhibitor antihyperglycemic agents (AHAs), among T2DM patients using the Innovation in Medical Evidence Development and Surveillance System (IMEDS) Distributed Database (IMEDS-DD).

Per the Pharmacovigilance Risk Assessment Committee (PRAC) PASS Protocol Assessment Report dated 05 September 2019 (Section 11), two interim reports were requested to provide preliminary results on the study population available at the time of report submission and to assess the availability of ertugliflozin exposure in the database in order to conduct the final analysis planned for MK8835-062. The first interim report was submitted to the EMA on 9 December 2021. Findings of the Interim Report 1 indicated that the required study sample size would not be reached in time to perform the final analyses if data were limited to those from five regional and national health insurers in the IMEDS-DD. Recognizing this issue, MSD proposed a stepwise approach to inclusion of additional data sources.

The present report is the second interim report, in which the initial step of the stepwise data expansion was implemented by adding the two data sources proposed in the Interim Report 1 – the Optum Research Database and the Centers for Medicare & Medicaid Services (CMS) Medicare Research Identifiable Files (RIFs). This report assesses the availability of ertugliflozin exposure in the refreshed IMEDS-DD, Optum Research Database, and CMS Medicare RIFs altogether. All three databases include previously or currently contributing datasets to the US Food and Drug Administration (FDA)'s Sentinel System, a national electronic system for active surveillance of medical product safety in the US, established under the Sentinel Initiative [Ref. 5.4: 052TMC, 052WPW].

7 OBJECTIVES OF INTERIM REPORT 2

Preliminary analyses on the study population included as of 2 Aug 2022 were conducted to:

1. Assess the sample size (count and person-time) of new users of ertugliflozin and comparator AHAs, based on data from the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs,

2. Describe the baseline characteristics of new users of ertugliflozin and comparator AHAs, and

3. Discuss the feasibility of reaching the required sample size via the stepwise data addition approach proposed in response to Interim Report 1 comments.

8 AMENDMENTS AND UPDATES

None.

9 RESEARCH METHODS

9.1 Study design

A non-interventional cohort study using electronic healthcare data was conducted to describe the risk of DKA between new users of ertugliflozin and new users of other non-SGLT2 inhibitor AHAs among T2DM patients. Eligible AHA drug classes include sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists (hereinafter collectively referred to as "comparator AHAs"). These drug classes were chosen based on their similar place in therapy to ertugliflozin as the second-line treatment for T2DM and as the recommended 'add-on' medications to metformin [Ref. 5.4: 04YCLB, 052W8Y].

In this second interim report, three exposure groups of interest were defined as new users of: (1) ertugliflozin; (2) SU or TZD; and (3) incretin-based drugs (i.e., DPP-4 inhibitors, or GLP-1 receptor agonists). Each exposure cohort was defined as the set of patients who had at least one qualifying exposure for the cohort-defining drug(s), with a new use date (index date preceded by no evidence of use in the prior 183 days) occurring between 1 July 2018 and 31 December 2021 (or most recent available).

Unless otherwise specified, this study used outpatient pharmacy claims to define drug utilization and medical encounter claims to define existing conditions, medical history, or outcomes. National Drug Codes (NDCs) were used to identify individual medications. Diagnosis and procedure codes encoded in the following coding systems were used to identify individual medical conditions: International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM, ICD-10-CM), International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes.

9.2 Setting

The study utilized data from regional and national health insurers included in the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs. Health plan members enrolled with these insurers are predominately community-dwelling individuals and can be of all ages, commercially or publicly insured. All three databases include previously or currently contributing datasets to the US FDA's Sentinel System, a national electronic system for active surveillance of the safety of medical product safety in the US, established under the Sentinel Initiative [Ref. 5.4: 052TMC, 052WPW].

9.3 Subjects

This study included eligible patients who met the following inclusion and exclusion criteria in the analysis:

Inclusion criteria

- New users of ertugliflozin or new users of a comparator AHA beginning on 1 July 2018
- Age 18 years or older on the new initiation date (referred to as "index date") of ertugliflozin or a comparator AHA
- 6 or more months of continuous enrollment in medical and prescription drug insurance plans before the index date
- T2DM, evidenced by at least one qualifying diagnosis recorded in claims of any encounter type any time before or on the index date. Qualifying diagnoses include ICD-9-CM *250.x0 or 250.x2 Type II Diabetes Mellitus,* or ICD-10-CM E11.x *Type 2 Diabetes Mellitus*

Exclusion criteria

- Type 1 diabetes (T1DM) or gestational diabetes, evidenced by at least one qualifying diagnosis recorded in claims of any encounter type any time before or on the index date. Qualifying diagnoses include ICD-9-CM *250.x1 and 250.x3 Type I Diabetes Mellitus*, *648.8x Abnormal Glucose Tolerance of Mother Complicating Pregnancy Childbirth or the Puerperium*, ICD-10-CM *E10.x Type 1 Diabetes Mellitus*, and *O24.2x Gestational Diabetes Mellitus in Pregnancy*

- Initiation of insulin on the index date, defined as insulin initiation on the index date with no prior use any time before the index date (note: history of insulin use that discontinued before the index date or ongoing insulin use were allowed)

- Initiation of the opposite exposure (i.e., ertugliflozin new users starting a SU/TZD; ertugliflozin new users starting an incretin-based drug; or vice versa) on the index date

- History of DKA, evidenced by at least one qualifying discharge diagnosis of any position recorded in claims of inpatient encounters, any time before the index date. Qualifying diagnoses include ICD-9-CM *250.10 Type II Diabetes Mellitus with Ketoacidos*is, and ICD-10-CM *E11.1x Type II Diabetes Mellitus with Ketoacidosis*

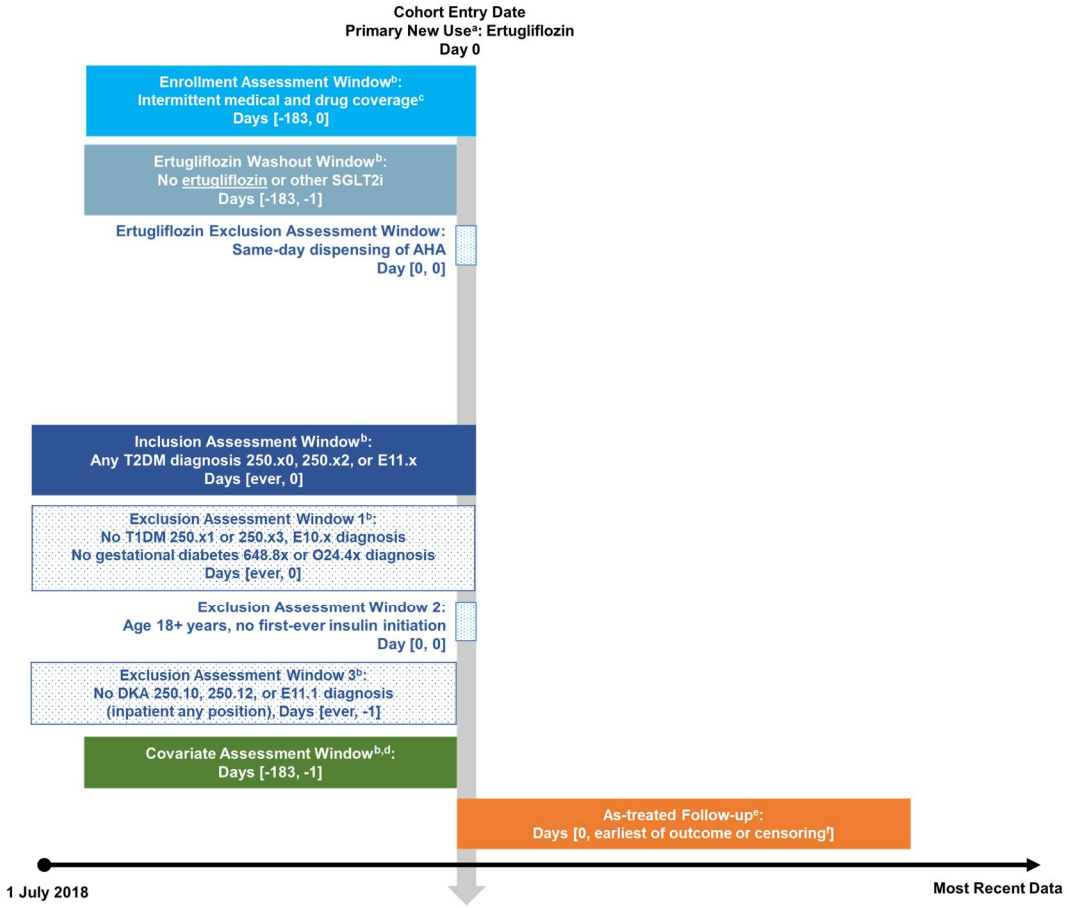
9.4 Variables

9.4.1 Exposure

The study population was classified into three new user groups based on exposure: 1) ertugliflozin, 2) SUs or TZDs, and 3) incretin-based drugs (i.e., DPP-4 inhibitors, or GLP-1 receptor agonists).

New user was defined as having a first exposure of the cohort-defining drug(s) (referred to as "index exposure"), but no prior use of the index exposure nor other non-ertugliflozin SGLT2 inhibitors in the 6 months before the index date. This was considered the "primary new user" definition (Figure 1).

Figure 1. Design Schematic for Primary New Users: Ertugliflozin Example



a. Index date (Day 0) was defined by date of the valid new use of ertugliflozin. Members were only allowed to enter the analytic cohort multiple times.

b. Assessment window might start before query start date 1 July 2018.

c. Up to 45-day gap in medical or prescription drug plan enrollment was allowed.

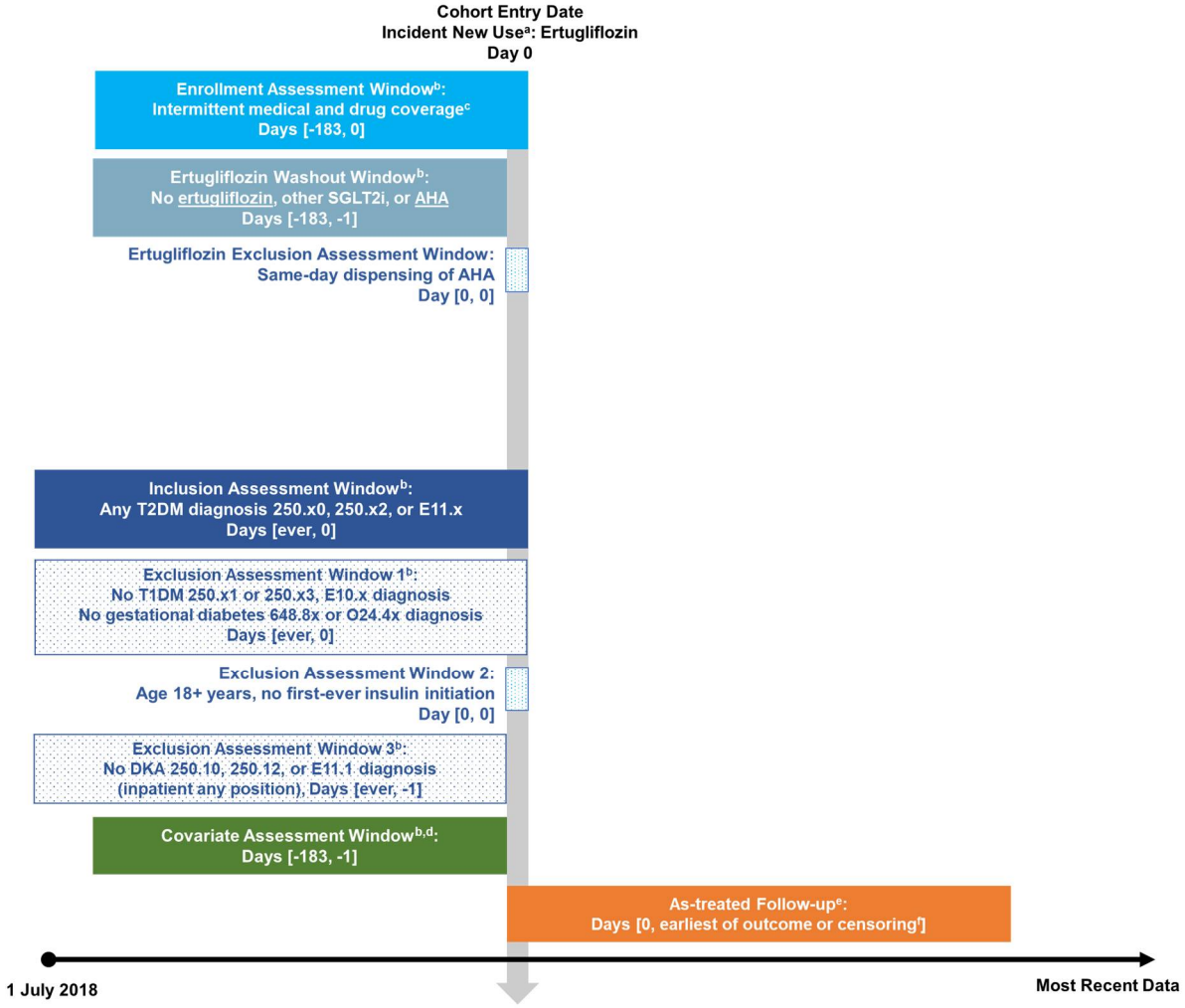
d. Except Day 0 assessment for: age, sex, calendar year, concomitant T2DM treatment, and number of concomitant unique drug use by class.

e. Dispensings with days of supply gap up to 30 days were bridged. An extension of 30 days was appended after the last dispensing.

f. Censoring criteria included discontinuation of the index exposure, initiation of AHA, other SGLT2i, first-ever insulin, disenrollment, end of data availability, recorded death.

Furthermore, we assessed the number of new users of ertugliflozin and comparators based on the "incident new user" definition, which required no prior use of SGLT2 inhibitors (including ertugliflozin), a comparator AHA (i.e., SU/TZD when comparing ertugliflozin with SU/TZD; or DPP-4 inhibitors/GLP-1 receptor agonists when comparing ertugliflozin with incretin-based drugs) in the 6 months before the index date (Figure 2).

Figure 2. Design Schematic for Incident New Users: Ertugliflozin Example



a. Index date (Day 0) was defined by date of the valid new use of ertugliflozin. Members were only allowed to enter the analytic cohort multiple times.

b. Assessment window might start before query start date 1 July 2018.

c. Up to 45-day gap in medical or prescription drug plan enrollment was allowed.

d. Except Day 0 assessment for: age, sex, calendar year, concomitant T2DM treatment, and number of concomitant unique drug use by class.

e. Dispensings with days of supply gap up to 30 days were bridged. An extension of 30 days was appended after the last dispensing.

f. Censoring criteria included discontinuation of the index exposure, initiation of AHA, other SGLT2i, first-ever insulin, disenrollment, end of data availability, recorded death.

A patient was allowed to contribute to more than one exposure group, as long as he/she qualified as a new user of that exposure category (i.e., index exposure). For example, if a TZD new user started on ertugliflozin after the end of the last dispensing's days of supply for the TZD, that patient would qualify as a new user of TZD and new user of ertugliflozin at the different time points.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Duration of use, including ertugliflozin and comparator AHAs, was established using the days supplied per dispensing recorded in pharmacy claims and a 30-day grace period. The study considered days of supply as evidence of the period in which a patient was covered for the dispensed medication. In the event of early refills, days of supply was stockpiled, and sum of days of supply of the two overlapping dispensings was newly assigned as the covered period. In the event of late refills, dispensings with a gap shorter than the grace period were bridged, and the exact number of days in the gap were considered in the duration of use calculation. For the last refill, the grace period was considered in the duration of use calculation to account for potential medication overstock or residual biologic effect remaining in the system. Duration of use was the total number of days summing the covered period, any dispensing gap(s) (if applicable), and the grace period.

9.4.2 Outcome

The study outcome was hospitalization for DKA, identified from principal discharge diagnosis of inpatient claims. Qualifying diagnoses included ICD-10-CM *E11.1x Type 2 Diabetes Mellitus with Ketoacidosis*. The admission date was used as the diagnosis date.

9.4.3 Covariates

This study examined baseline characteristics including demographics, AHA utilization, use of medications associated with DKA, comorbidity burden, pre-existing comorbidities, diabetic complications, and health services utilization. Unless otherwise specified, all characteristics were evaluated within the 6 months prior to the exposure index date (defined in Section 9.3 Subjects), and medical conditions were assessed using medical encounter claims from any care setting.

Table 1. List of Variables

Category	Covariates
Demographics	Age, sex, calendar year of cohort entry
Use of AHAs	Distribution of diabetes treatment by class (i.e., metformin, SU, TZD, alpha glucosidase or meglitinides, DPP-4 inhibitor, GLP-1 receptor agonist, SGLT2 inhibitor, and insulin)
Use of medications associated with DKA	Clozapine or olanzapine, lithium, terbutaline, oral corticosteroids, thiazides, pentamidine
Comorbidity burden	Charlson-Elixhauser combined comorbidity index [Ref. 5.4: 052TS6]
Pre-existing comorbidities	Acute illness (i.e., serious infection, trauma, acute febrile illness, or sepsis), surgical procedures, acute renal failure, cerebrovascular disease, coronary heart disease, heart failure, hyperlipidemia, hypertension, pancreatitis, hypovolemia, hypoxemia, myocardial infarction, obesity, peripheral vascular disease, stroke, thyroid disorders
Diabetic complications	Moderate to severe renal insufficiency (i.e., stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy, neuropathy, retinopathy, amputation
Health services utilization	Number of generic medications, unique pharmacological classes, dispensings, inpatient encounters, non-acute institutional encounters, emergency department encounters, ambulatory encounters, and other ambulatory* encounters

AHA: antihyperglycemic agent; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2.
** Other ambulatory encounters include other non-overnight ambulatory encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone, and email consultations.*

9.5 Data sources and measurement

This study employed the stepwise data expansion proposed in Interim Report 1 and was conducted using existing electronic health insurance claims data from IMEDS-DD and two additional sources – the Optum Research Database and the CMS Medicare RIFs. All three databases include previously or currently contributing datasets to the US FDA's Sentinel System, a national electronic system for active surveillance of medical product safety in the US, established under the Sentinel Initiative [Ref. 5.4: 052TMC, 052WPW].

9.5.1 Innovation in Medical Evidence Development and Surveillance System Distributed Database (IMEDS-DD)

IMEDS is a public-private partnership launched in 2017 by the Reagan-Udall Foundation for the FDA, an independent, non-for-profit organization created by the US Congress, to advance the US FDA's mission to modernize medical product development and safety. IMEDS provides a framework for private-sector entities (e.g., regulated industry, academic institutes)

to leverage the FDA Sentinel System, a national electronic system for active surveillance of medical product safety in the US, established under the Sentinel Initiative [26] [27]. The IMEDS-DD works with selected partners from the Sentinel Initiative, with Harvard Pilgrim Health Care Institute (HPHCI) serving as the IMEDS Analytic Center (IMEDS AC) and the Reagan-Udall Foundation as the IMEDS Operational Center, to provide real-world healthcare information on large patient populations in a timely manner, by facilitating efficient analyses of medical product safety evaluations.

The IMEDS-DD is largely comprised of current Sentinel data partners and is expected to be largely representative of the commercially insured population in US. At present, the IMEDS-DD has claims data available for research for over 95 million health plan members who have overlapping medical and pharmacy insurance coverage. The average enrollment length is similar to other claims databases of members with medical and pharmacy coverage - about 25% of patients have over three years of enrollment, and patients with chronic conditions such as diabetes and older members typically have longer than average enrollment periods within these databases. The Reagan-Udall Foundation for the FDA's IMEDS-DD, a subset of the FDA Sentinel Distributed Database, is expected to be largely representative of the commercially insured population in US.

This study included data from five national and regional health insurers of the IMEDS-DD in the US. All listed network partners have access to their respective claims data and provided input and feedback for the study.

Brief descriptions of the network partners are provided below:

- **Aetna, a CVS Health company** is one of the nation's leading healthcare benefits companies, serving ~48 million people with information and resources to help them make better-informed decisions about their health care. CVS Health Clinical Trial Services, Safety Surveillance & Collaboration (SS&C) team uses the research portion of the Aetna's medical, pharmacy, and laboratory results for the Commercial and Medicare Advantage health plans in IMEDS research. Aetna/ CVS Health became an FDA Sentinel Program data partner in 2010 and continues to be one of the largest contributors of data for public health purposes.

- **Harvard Pilgrim Health Care** is one of the country's premier health plans. It is large non-profit health plan with over 1 million diverse enrollees across New England. HPHCI is a research and academic partnership between Harvard Medical School and Harvard Pilgrim Health Care. HPHCI also participates in the IMEDS program as the IMEDS AC.

- **HealthCore, Inc.**, a wholly-owned subsidiary of Elevance Health, uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late phase research. The HealthCore Integrated Research Database is a proprietary, fully integrated, longitudinal claims database that combines medical, pharmacy, and laboratory information drawn from nearly 80 million unique individuals with medical coverage and nearly 62 million researchable lives with medical and pharmacy claims information since 2006. In addition, The HealthCore Integrated Research Environment has the ability to link the claims data in the HealthCore Integrated Research Database to complementary data sources, including inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, member and provider surveys, and point of care clinical data. Using these resources, HealthCore conducts a range of real-world research designed to meet client needs, including retrospective database studies, medical record review studies, cross-sectional and longitudinal patient and provider surveys, and prospective site-based studies, including pragmatic clinical trials.

- **HealthPartners Institute** (the Institute) is a 501c (3) nonprofit organization dedicated to conducting high-quality, public-domain health research, often in collaboration with other academic and research organizations throughout the world. The Institute employs 33 career research investigators and more than 400 clinician researchers and encompasses vast and varied areas of research. The Institute is linked to an integrated health care system that provides health insurance for more than 1 million members and health care for more than 1.2 million patients.

- **Humana/Humana Healthcare Research** is a health economics and outcomes research subsidiary of Humana, which focuses on treatment effectiveness, drug safety, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services. Humana/Humana Healthcare Research has been an active collaborator and Data Partner in the FDA Sentinel System, the Patient-Centered Outcomes Research Institute's National Patient-Centered Research Network, and several other Distributed Research Network initiatives. More than 28 million researchable lives are available for research within this health system since 2007. Humana’s geographic coverage for the IMEDS research population includes nearly every U.S. state and is predominantly a Medicare population.

9.5.2 Optum Research Database

To increase the study sample size, the Optum Research Database has been included as an additional data source.

Optum has access to a proprietary research database containing medical and pharmacy claims with linked enrollment information with data from as early as 1993 available for 70 million individuals with both medical and pharmacy benefit coverage. For 2020, data are available for approximately 13.2 million individuals with medical and pharmacy benefit coverage. On average, individuals are enrolled in the health plan for 2.6 years. The individuals covered by

this health plan are geographically diverse across the US and fairly representative of the US population.

9.5.3 Centers for Medicare & Medicaid Services (CMS) Medicare Research Identifiable Files (RIFs)

To further increase the study sample size, CMS Medicare RIFs have been included as an additional data source. This data source represents the publicly (or government-) insured population and was accessed directly via the CMS Virtual Research Data Center (VRDC) by analysts at the IMEDS AC.

Medicare provides health insurance to US residents aged 65 years and older, as well as to younger individuals in special populations. It is estimated that over 98% of adults aged 65 years and older are enrolled in Medicare, making Medicare data one of the richest sources of health services utilization information in the country. During 2010-2020, there were approximately 32 million Medicare fee-for-service (FFS) beneficiaries [Ref. 5.4: 085XR5]. Note that other data sources included in this study may also contribute claims for patients who are Medicare beneficiaries. Many of these patients are enrolled in Medicare Advantage plans, which are distinct from full Medicare FFS coverage. Hereafter, all specific references to CMS and Medicare data refer only to the FFS population.

9.5.4 Measurement

As with the prior analyses (feasibility assessment and the first interim analysis) conducted within the IMEDS framework, data extraction was performed locally, which means for this study: at the individual IMEDS-DD partner sites, Optum, and specifically for CMS Medicare RIFs at the IMEDS AC.

Like the Sentinel Distributed Database, the IMEDS framework uses the Sentinel Common Data Model [Ref. 5.4: 052TNG, 052Y0K] for standardization of demographic and clinical data elements and has routine analytic tools (i.e., reusable, modular SAS programs) in place to permit rapid queries, including descriptive analyses and complex methodologies (e.g., comparative analyses), across data sources. Specific information in the Sentinel Common Data Model includes, but is not limited to, the following types of data:

- *Enrollment* data: One record per covered individual per unique enrollment span is included in the Sentinel Common Data Model. Individuals are assigned a unique identifier by their insurer, which is linkable to all other data in the Sentinel Common Data Model. Due to changes in employment status, individuals may be enrolled multiple times with the same insurer, and the length of each given enrollment "span" may vary substantially. Each record in the enrollment file indicates the patient identifier, enrollment start and end dates, and whether the patient was enrolled in medical coverage, pharmacy coverage, or both during that range. Likewise, a final field indicates whether the data partner can request medical charts for a given patient during a given enrollment span.

- *Demographic* data, including birth date, sex, race/ethnicity, and the Zone Improvement Plan (ZIP) code of their most recently recorded primary residence. Data on race/ethnicity and ZIP code are available for some, but not all, of the data sources, and the level of completeness for these data for those network partners with such data varies.

- *Outpatient Pharmacy* dispensing data, including the date of each prescription dispensing, the NDC identifier associated with the dispensed product, the nominal days of supply, and the number of individual units (pills, tablets, vials, etc.) dispensed. Note that products purchased over the counter, or at some cash-only retail locations selling prescription drug products (e.g., through the Walmart Prescription Program) are not captured.

- *Medical encounter* data, including the healthcare provider most responsible for the encounter as well as the facility in which the encounter occurred and its ZIP code. Admission and discharge dates (if applicable) are also included, as is the encounter type (either an ambulatory visit, an emergency department visit, an inpatient hospital, a non-acute inpatient, or an otherwise unspecified ambulatory visit). Discharge disposition (alive, expired, or unknown) as well as discharge status (to where a patient was discharged) are also included for inpatient hospital stays and non-acute inpatient stays. Finally, laboratory data, are available for some, but not all, of the data partners; and the level of completeness for laboratory information for those network partners with such data varies [Ref. 5.4: 052WSP].

- *Diagnosis* data, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded with ICD-9-CM and ICD-10-CM codes. For inpatient hospital and non-acute inpatient stay encounters, the Sentinel Common Data Model includes the principal discharge diagnosis.

- *Procedure* data, including the procedure date, its associated encounter identifier, admission date, provider identifier, and encounter type. Procedures are coded as ICD-9-CM and ICD-10-PCS procedure codes, CPT categories II, III, or IV codes, as well as HCPCS levels II and III codes.

- *Death* data, including the date of death, source of death information, whether the death month and day were imputed, and the degree of confidence in the record (excellent, fair, poor). Among the IMEDS-DD network partners participating in this study, Optum Research Database, and CMS Medicare RIFs, six have death data and two have cause of death data [Ref. 5.4: 052X67]. Both death and cause of death data are substantially lagged (at least 2 years). Cause of death is coded as ICD-10-CM diagnosis codes.

Data contributing to the present preliminary analyses were converted into the Sentinel Common Data Model version 8.0 or above. The IMEDS network partners and Optum maintain their data in the Sentinel Common Data Model format, whereas the IMEDS AC transformed the CMS Medicare RIFs on the VRDC. A universal package with pre-specified parameter values using Sentinel Routine Querying Tool version 11.3.0 and additional programming was sent by the IMEDS AC to extract the study cohorts from and query all data sources.

9.6 Bias

Despite the data strengths of the IMEDS framework in scale and standardization (hence reproducibility), the potential for misclassification remains due to the use of diagnostic codes, drug claim codes, or procedure codes for identification of specific medical conditions. For example, a diagnosis code could be used to rule out a certain condition instead of indicating the presence of disease, or alternatively, a disease that is truly present might not be coded in the database. There is also a substantial underestimate of obesity, as this condition is often under-recorded in electronic health record (EHR) data or missing from electronic health insurance claims data. Further, analyses were limited to information obtained in the claims database of individual data sources; therefore, information on diagnoses, procedures, and prescriptions outside of the contracted health care systems underlying within individual data sources may not be captured. Lastly, we required all patients to have a minimum of 6 months of continuous enrollment available prior to their index date but since we examined all patient data available in the databases prior to the index date for their diabetes diagnosis during the study period, the duration of medical history available varied across patients. The detailed discussion is included in [Sec. 11.2].

9.7 Study size required to conduct MK8835-062

Study size required for MK8835-062 was provided in Section 7.5 of the study protocol (Protocol MK8835-062; EUPAS31718). Sample size estimates assuming different combinations of hazard ratio (HR), power, and DKA incidence rate in the comparator AHA new users are provided in Table 2. The calculations assumed two-sided tests at a significance level of 0.05 (or type I error of 0.05) for power to be 80% and 90% (or type II error of 0.20 and 0.10, respectively). The number of events and person-years were estimated for the matched sample after 1:1 propensity score matching. These results assumed proportional hazards and exponential survival times.

For example, in order to detect a HR of 2.0 or above in ertugliflozin users relative to comparator AHA for DKA, with targeted power of 80% and significance level of 0.05 in a two-sided test, a total of 66 DKA events from ertugliflozin and comparator AHA groups combined would be required. This can be achieved by 8,819 person-years of ertugliflozin new users matched to comparator AHA new users in a 1:1 ratio on propensity score, assuming a DKA incidence rate of 2.5 per 1,000 person-years among T2DM patients treated with comparator AHAs [Ref. 5.4: 052Y70, 052V37, 0576MY]. The sample size calculation presented here reflects estimates meeting assumed values of HRs and DKA incidence rate in T2DM patients treated with comparator AHAs. As the literature evolves, these assumptions may change over time. In general, when DKA incidence rate in T2DM patients treated with comparator AHAs increases, the required sample size to achieve the same power is expected to decrease, holding constant the total number of DKA cases needed for any pre-specified HR.

Table 2. Sample Size Calculation

Number of ertugliflozin-exposed person-years needed, by hazard ratios and incidence rate of diabetic ketoacidosis (DKA) in Type 2 diabetes mellitus patients treated with comparator AHAs							
Hazard Ratio	Power	Total DKA Events	DKA Incidence Rate (per 1,000 Person-Years)				
			0.5	1.0	1.5	2.0	2.5
2.5	80%	38	21,726	10,869	7,250	5,440	4,355
2.0	80%	66	44,019	22,019	14,686	11,019	8,819
1.5	80%	192	153,650	76,850	51,250	38,450	30,770
2.5	90%	51	29,158	14,588	9,730	7,302	5,844
2.0	90%	88	58,692	29,358	19,581	14,692	11,758
1.5	90%	256	204,868	102,468	68,334	51,268	41,028
The number of events and person-years are estimates for the matched sample after 1:1 propensity score matching. These results assume two-sided tests with significance level= 0.05, proportional hazards and exponential survival times.							

The above preliminary study size estimate remains valid, considering similar range of DKA incidence rates in T2DM patients treated with comparator AHAs reported by more recent literature [Ref. 5.4: 05LSHQ, 05LSH3].

The number of new users of ertugliflozin accumulated in the so far included data sources has been assessed in this interim report and compared with target sample size to determine whether additional database(s) or data partner(s) would be necessary to help reach the target number required to perform the final analyses.

9.8 Data transformation

9.8.1 Data management

As with the prior analyses (feasibility assessment and the first interim analysis) conducted within the IMEDS framework, data management was performed locally, which means for this study: at the individual IMEDS-DD partner sites, Optum, and specifically for CMS Medicare RIFs on the VRDC. All incorporated datasets were applied the same data management, privacy protection methods, and quality assurance procedures with the Sentinel Distributed Database [Ref. 5.4: 052WPT, 052WWP, 052XV9]. The Sentinel Distributed Database is compliant to the security requirements of the US Federal Information Security Management Act of 2002 (FISMA, specifically Moderate Risk Security Controls, as specified in the National Institute of Standards and Technology Special Publication 800-53) and has implemented policies and procedures to ensure the utmost data security, including an annual assessment process to ensure compliance.

As noted, the IMEDS framework operates on a minimum necessary basis [Ref. 5.4: 052TNG, 052WY2] and implements a secure distributed querying environment to enable safe distribution of analytic queries, data transfer, and document storage. Queries are sent securely by the IMEDS AC, and data responses are securely

returned using a web-based distributed querying application (PopMedNet) [Ref. 5.4: 052X99, 052VKQ] administered by the HPHCI. In this approach, data remain behind each data source's local firewall, and the data owners maintain physical and operational control of their data. In most cases, query results are returned to the web portal in aggregate form. All communications between the web portal and the application use HTTP/SSL/TLS connections to securely transfer queries and results. In this study, queries against the CMS Medicare RIFs were conducted locally within the IMEDS AC at the HPHCI.

The IMEDS framework employs the Sentinel Common Data Model [Ref. 5.4: 052TNG, 052Y0K] to allow data standardization across data sources. Only data elements of Sentinel Common Data Model are available for queries, including demographics, health plan enrollment, diagnoses, procedures, and outpatient pharmacy dispensing records. During query execution, analytic programs based on SAS software were used. Data management and conversion of the Sentinel Common Data Model to analysis variables were performed using SAS software version 9.4 and above (SAS Institute, Inc., Cary, North Carolina).

For quality assurance of datasets incorporated into the IMEDS framework, refer to [Sec. 9.10]

As described in more detail in Section 10.1.1 Protection of Human Subjects, this study was subject to research ethics review by an Institutional Review Board/Independent Ethics Committee (IRB/IEC). Non-interventional studies using administrative claims data typically post no direct risk of harm to patients. Therefore, this study was determined as exempt from IRB/IEC review. Data used in this study were anonymized and no personal identifiers were available to maintain patient confidentiality.

9.9 Statistical methods

9.9.1 Main statistical methods

The present interim analyses remained descriptive. In addition to the number of new users of ertugliflozin or a comparator AHA, this study summarizes the number of new use episodes (defined in the following section) of ertugliflozin or a comparator AHA, baseline characteristics before each new use episode, and as-treated follow-up time based on duration of use (9.4.1. Exposure) and censoring.

9.9.1.1 Follow-up

Follow-up for each new use of a given exposure was as treated and began on the index date until the earliest of hospitalized DKA or any of the following censoring criteria met:

- Discontinuation of the index exposure, defined as last refill date plus days of supply on the last refill plus 30 days
- Initiation of the opposite exposure (i.e., ertugliflozin new users starting a SU/TZD; ertugliflozin new users starting an incretin-based drugs; or vice versa)

- Initiation of other SGLT2 inhibitor(s)
- Initiation of insulin, defined as no insulin use any time before the date of this initiation
- Disenrollment from either medical or prescription drug insurance plan
- End of data availability
- Recorded death

A patient could contribute follow-up time to more than one exposure group or to the same exposure group more than once, as long as he/she qualified as a new user of that exposure category during the course of the study period. Each time, the period from the initiation of a study exposure (i.e., index exposure) to the end of follow-up of the index exposure was defined as one "new use episode". The total person-years for a given study exposure was the sum of total follow-up time contributed by all qualified new use episodes.

9.9.1.2 Baseline characteristics

Patient characteristics, comorbidities, and health services utilization at the level of new use episodes were summarized in descriptive statistics. Continuous variables were reported as means and standard deviations (SDs), and categorical variables were summarized as number and proportion of the total study population in each cohort.

9.9.2 Missing values

The study included three continuous variables in the general characteristic assessment: age, Charlson-Elixhauser combined comorbidity score [Ref. 5.4: 052TS6], AHA utilization, and health services utilization metrics. All were expected to be non-missing/recorded, given that cohort members were required to have age information available in order to meet eligibility requirement and that both comorbidity score and the count of health services have their respective numeric lower boundaries (for example, zero or no non-antihyperglycemic use).

The study dichotomized all categorical variables in the general characteristic assessment. The Sentinel Common Data Model [Ref. 5.4: 052TNG, 052Y0K] allows the assignment to "unknown" value for these exception variables but no missing value. Absence of any diagnosis, procedure, or drug code required in the condition or drug utilization algorithms was considered that no condition or drug utilization was present.

9.9.3 Sensitivity analyses

None.

9.9.4 Amendments to the statistical analysis plan

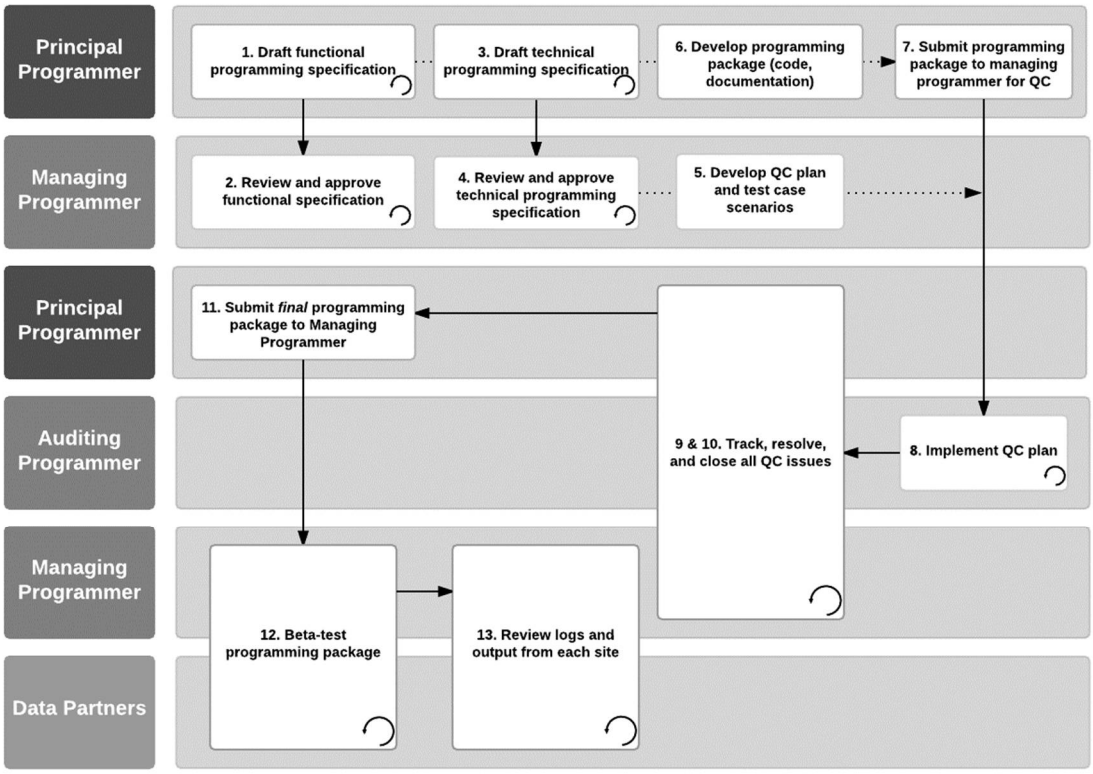
None.

9.10 Quality control

As with prior analyses (feasibility assessment and the first interim analysis) conducted within the IMEDS framework, data management was performed locally, which means for this study: at the individual IMEDS-DD partner sites, Optum, and specifically for CMS Medicare RIFs on the VRDC. All incorporated datasets were applied the same data management, privacy protection methods, and quality assurance procedures with the Sentinel Distributed Database [Ref. 5.4: 052WPT, 052WWP, 052XV9]. The quality assurance approach assesses consistency with the Sentinel Common Data Model, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across data partners. Full quality assurance process and details on the Sentinel data curation approach are documented on the Sentinel website [Ref. 5.4: 052XV9, 052XSG]. The data curation approach is consistent with guidance set forth by the US FDA in its current recommendations for data quality assurance, specifically – "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC)", published in May 2013 [Ref. 5.4: 052W62]. This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data.

In addition to quality assurance of data elements, the IMEDS AC adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check custom SAS programs and deliverables. Figure 3 illustrates the standard operating procedures (SOPs) for SAS programming quality assurance and quality control in the Sentinel System. Besides, after the identification of the error in the Interim Report 1, a corrective and preventive action has been developed to minimize such errors in the future.

Figure 3. Standard Operating Procedure for SAS Programming Quality Assurance and Quality Control in the Sentinel System



10 RESULTS

10.1 Participants

10.1.1 Protection of Human Subjects

The preliminary analyses used pre-existing databases – the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs. Data were anonymized and no personal identifiers were available to maintain patient confidentiality. This work was determined to be exempt from IRB review (IMEDS IRB Protocol IRB2187, HPHC IRB Review #1077644).

The preliminary analyses were conducted in accordance with all legal and regulatory requirements. Additionally, the conduct of feasibility assessment was adhered to commonly accepted research practices, including those described in European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of

Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets [Ref. 5.4: 052W62].

10.2 Main results

10.2.1 New use episodes of ertugliflozin

A total of 2,196 new users and 2,235 new use episodes of ertugliflozin were identified between 1 July 2018 and 31 December 2021, based on the "primary new user" definition. Of these, 1,239 new users and 1,251 new use episodes of ertugliflozin were identified from the CMS Medicare RIFs alone. There were 1,369 new users of ertugliflozin meeting the criteria for "incident new users" definition relevant to SU/TZD, defined as not having used any SGLT2 inhibitors (including ertugliflozin) nor SU or TZD during the 6 months prior to the index date. A total of 1,070 new users of ertugliflozin met the criteria for "incident new users" definition relevant to DPP-4 inhibitors/GLP-1 receptor agonists, defined as not having used any SGLT2 inhibitors (including ertugliflozin) nor any incretin-based drugs during the 6 months prior to the index date.

The baseline characteristics of primary new users of ertugliflozin are shown in Table 3. Of the 2,235 ertugliflozin new use episodes, the mean age was 62.9 years (SD=10.7 years). Three hundred and thirty-nine (15.2%) episodes initiated ertugliflozin as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (61.7%), followed by DPP-4 inhibitors (31.5%) and SU (26.4%). The most common comorbidities included hypertension (77.4%) and hyperlipidemia (75.6%). Individuals with a history of cardiovascular disease (CVD) represented 29.4% of ertugliflozin new use episodes, categorized based on ICD-10-CM diagnoses for myocardial infarction, coronary heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, or stroke.

Table 3. Baseline Characteristics of Primary New Users of Ertugliflozin identified in the IMEDS Distributed Database, Optum Research Database, and CMS Medicare Research Identifiable Files between 1 July 2018 and 31 December 2021

	Ertugliflozin	
	N/Mean	**%/SD[1]**
Number of episodes	2,235	100.0%
Number of patients	2,196	
Demographics[2] on the index date		
Age, in years	62.9	10.7
18-44	194	8.7%
45-64	929	41.6%
65-74	802	35.9%
≥75	310	13.9%
Sex, female	1,011	46.0%
Calendar year of initiation		
2018	253	11.3%

	Ertugliflozin	
	N/Mean	**%/SD[1]**
2019	871	39.0%
2020	918	41.1%
2021	193	8.6%
Antihyperglycemic management on the index date		
Monotherapy	339	15.2%
Dual therapy	810	36.2%
Triple therapy or more	1,086	48.6%
Concomitant antihyperglycemic agent use on the index date		
Metformin	1,379	61.7%
DPP-4 inhibitor	704	31.5%
SU	590	26.4%
GLP-1 agonist	352	15.7%
Insulin	319	14.3%
TZD	143	6.4%
Others (alpha-glucosidase inhibitor, meglitinide)	39	1.7%
Use of medications associated with DKA on the index date		
Clozapine/olanzapine	20	0.9%
Lithium	11*	0.5%
Terbutaline	0	0.0%
Oral corticosteroid	38	1.7%
Thiazide	225	10.1%
Pentamidine	0	0.0%
Comorbidity burden		
Charlson-Elixhauser combined comorbidity score	1.3	1.9
Comorbidity/pre-existing conditions		
Acute illness (i.e., serious infection, trauma, acute febrile illness, or sepsis)	353	15.8%
Any surgical procedures	1,882	84.2%
Surgery, inpatient only	52	2.3%
Acute renal failure	42	1.9%
Cardiovascular disease	658	29.4%
Cerebrovascular disease	136	6.1%
Coronary heart disease	424	19.0%
Heart failure	120	5.4%
Myocardial infarction	77	3.4%
Peripheral vascular disease	232	10.4%
Stroke	115	5.1%
Hypertension	1,730	77.4%
Hyperlipidemia	1,690	75.6%
Hypoglycemia	28	1.3%

	Ertugliflozin	
	N/Mean	**%/SD[1]**
Hypovolemia	10*	0.4%
Hypoxemia	41	1.8%
Obesity	462	20.7%
Pancreatitis	16*	0.7%
Thyroid disorders	481	21.5%
Diabetic complications		
Moderate-to-severe renal insufficiency	194	8.7%
Nephropathy	301	13.5%
Neuropathy	485	21.7%
Retinopathy	172	7.7%
Amputation	12*	0.5%
Health Services Utilization		
Number of unique drug classes	9.1	4.7
Number of unique generic medications	9.4	5.0
Number of dispensings	29.0	20.6
Number of inpatient encounters	0.1	0.3
Number of non-acute institutional encounters	0.0	0.2
Number of emergency department encounters	0.3	1.1
Number of ambulatory encounters	9.5	8.7
Number of other ambulatory encounters	2.3	5.2

[1] Value represents standard deviation (SD) where no % follows.
[2] For categorical variables, numbers of episodes and percentages of episodes based on the total numbers of episodes were calculated, except for sex, for which numbers of unique patients and percentages of unique patients based on the total numbers of unique patients were calculated.
** Due to small cell redaction rules for CMS data, values were replaced with an addition up to 10 in order to prevent small cells (non-zero counts <11) or back-calculations.*
T2DM: type 2 diabetes mellitus. T1DM: type 1 diabetes mellitus. SGLT2: sodium-glucose cotransporter-2. SU: sulfonylurea. TZD: thiazolidinedione. DPP-4: dipeptidyl peptidase-4. GLP-1: glucagon-like peptide-1.

10.2.2 New use episodes of SU/TZD

A total of 668,154 new users and 702,727 new use episodes of SU or TZD were identified between 1 July 2018 and 31 December 2021, based on the "primary new user" definition. There were 667,939 new users of SU or TZD meeting the criteria for "incident new users" definition relevant to SU/TZD, defined as not having used any SGLT2 inhibitors (including ertugliflozin) nor SU or TZD during the 6 months prior to the index date.

The baseline characteristics of primary new users of SU or TZD are shown in Table 4. Among the 702,727 SU or TZD new use episodes, mean age was 68.7 years (SD=10.5 years), and 33.5% initiated SU or TZD as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (59.8%), followed by DPP-4 inhibitors (10.9%) and

insulin (6.9%). The most common comorbidities included hypertension (77.4%), hyperlipidemia (68.6%), and 36.7% had a history of CVD.

Table 4. Baseline Characteristics of Primary New Users of Sulfonylurea or Thiazolidinedione (SU/TZD) in the IMEDS Distributed Database, Optum Research Database, and CMS Medicare Research Identifiable Files between 1 July 2018 and 31 December 2021

	SU/TZD	
	N/Mean	**%/SD[1]**
Number of episodes	702,727	100.0%
Number of patients	668,154	
Demographics[2] on the index date		
Age, in years	68.7	10.5
18-44	27,390	3.9%
45-64	164,250	23.4%
65-74	317,055	45.1%
≥75	194,032	27.6%
Sex, female	330,032	49.4%
Calendar year of initiation		
2018	126,610	18.0%
2019	255,013	36.3%
2020	248,802	35.4%
2021	72,302	10.3%
Antihyperglycemic management on the index date		
Monotherapy	235,229	33.5%
Dual therapy	380,302	54.1%
Triple therapy or more	87,195	12.4%
Concomitant antihyperglycemic agent use on the index date		
Metformin	420,366	59.8%
DPP-4 inhibitor	76,481	10.9%
SU	615,488	87.6%
GLP-1 agonist	27,398	3.9%
Insulin	48,732	6.9%
TZD	92,407	13.1%
Others (alpha-glucosidase inhibitor, meglitinide)	4,894	0.7%

	SU/TZD	
	N/Mean	**%/SD[1]**
Use of medications associated with DKA on the index date		
Clozapine/olanzapine	4,954	0.7%
Lithium	1,687	0.2%
Terbutaline	19*	0.0%
Oral corticosteroid	28,829	4.1%
Thiazide	81,679	11.6%
Pentamidine	10*	0.0%
Comorbidity burden		
Charlson-Elixhauser combined comorbidity score	2.0	2.7
Comorbidity/pre-existing conditions		
Acute illness (i.e., serious infection, trauma, acute febrile illness, or sepsis)	143,918	20.5%
Any surgical procedures	571,665	81.3%
Surgery, inpatient only	40,799	5.8%
Acute renal failure	42,931	6.1%
Cardiovascular disease	257,811	36.7%
Cerebrovascular disease	64,773	9.2%
Coronary heart disease	160,081	22.8%
Heart failure	70,137	10.0%
Myocardial infarction	37,307	5.3%
Peripheral vascular disease	101,402	14.4%
Stroke	57,102	8.1%
Hypertension	544,054	77.4%
Hyperlipidemia	482,144	68.6%
Hypoglycemia	9,920	1.4%
Hypovolemia	3,257	0.5%
Hypoxemia	31,520	4.5%
Obesity	115,466	16.4%
Pancreatitis	5,147	0.7%
Thyroid disorders	141,383	20.1%
Diabetic complications		
Moderate-to-severe renal insufficiency	129,717	18.5%
Nephropathy	172,247	24.5%
Neuropathy	138,769	19.7%
Retinopathy	50,692	7.2%
Amputation	1,680	0.2%

	SU/TZD	
	N/Mean	**%/SD[1]**
Health Services Utilization		
Number of unique drug classes	7.8	4.7
Number of unique generic medications	8.1	5.0
Number of dispensings	22.3	19.0
Number of inpatient encounters	0.2	0.5
Number of non-acute institutional encounters	0.0	0.3
Number of emergency department encounters	0.4	1.1
Number of ambulatory encounters	10.0	12.2
Number of other ambulatory encounters	3.2	8.1

[1] Value represents standard deviation (SD) where no % follows.
[2] For categorical variables, numbers of episodes and percentages of episodes based on the total numbers of episodes were calculated, except for sex, for which numbers of unique patients and percentages of unique patients based on the total numbers of unique patients were calculated.
** Due to small cell redaction rules for CMS data, values were replaced with an addition up to 10 in order to prevent small cells (non-zero counts <11) or back-calculations.*
T2DM: type 2 diabetes mellitus. T1DM: type 1 diabetes mellitus. SGLT2: sodium-glucose cotransporter-2. SU: sulfonylurea. TZD: thiazolidinedione. DPP-4: dipeptidyl peptidase-4. GLP-1: glucagon-like peptide-1.

10.2.3 New use episodes of incretin-based drugs

A total of 622,290 new users and 659,103 new use episodes of incretin-based drug were identified between 1 July 2018 and 31 December 2021, based on the "primary new user" definition. There were 621,981 new users of incretin-based drug meeting the criteria for "incident new users" definition relevant to incretin-based drug, defined as not having used any SGLT2 inhibitors (including ertugliflozin) nor incretin-based drug during the 6 months prior to the index date.

The baseline characteristics of primary new users of incretin-based drugs are presented in Table 5. Among the 659,103 new use episodes of incretin-based drug, mean age was 67.5 years (SD=10.9 years), and 23.6% initiated incretin-based drug as monotherapy. The most concomitantly utilized AHA class at the index date was metformin (59.3%), followed by SU (31.8%) and insulin (15.0%). The most common comorbidities included hypertension (80.8%), hyperlipidemia (73.0%), and 38.4% had a history of CVD.

Table 5. Baseline Characteristics of Primary New Users of Incretin-Based Drugs in the IMEDS Distributed Database, Optum Research Database, and CMS Medicare Research Identifiable Files between 1 July 2018 and 31 December 2021

	Incretin-Based Drugs	
	N/Mean	**%/SD[1]**
Number of episodes	659,103	100.0%
Number of patients	622,290	
Demographics[2] on the index date		
Age, in years	67.5	10.9
18-44	33,553	5.1%
45-64	178,260	27.0%
65-74	282,433	42.9%
≥75	164,857	25.0%
Sex, female	331,429	53.3%
Calendar year of initiation		
2018	109,339	16.6%
2019	236,872	35.9%
2020	224,884	34.1%
2021	88,008	13.4%
Antihyperglycemic management on the index date		
Monotherapy	155,461	23.6%
Dual therapy	310,608	47.1%
Triple therapy or more	192,687	29.3%
Concomitant antihyperglycemic agent use on the index date		
Metformin	391,082	59.3%
DPP-4 inhibitor	383,952	58.3%
SU	209,824	31.8%
GLP-1 agonist	275,730	41.8%
Insulin	99,114	15.0%
TZD	37,041	5.6%
Others (alpha-glucosidase inhibitor, meglitinide)	7,255	1.1%
Use of medications associated with DKA on the index date		
Clozapine/olanzapine	4,637	0.7%
Lithium	1,807	0.3%
Terbutaline	13*	0.0%
Oral corticosteroid	19,228	2.9%
Thiazide	80,975	12.3%
Pentamidine	0	0.0%

	Incretin-Based Drugs	
	N/Mean	**%/SD[1]**
Comorbidity burden		
Charlson-Elixhauser combined comorbidity score	2.1	2.6
Comorbidity/pre-existing conditions		
Acute illness (i.e., serious infection, trauma, acute febrile illness, or sepsis)	138,062	20.9%
Any surgical procedures	557,020	84.5%
Surgery, inpatient only	37,625	5.7%
Acute renal failure	43,317	6.6%
Cardiovascular disease	253,247	38.4%
Cerebrovascular disease	62,064	9.4%
Coronary heart disease	157,452	23.9%
Heart failure	71,487	10.8%
Myocardial infarction	35,691	5.4%
Peripheral vascular disease	103,660	15.7%
Stroke	54,384	8.3%
Hypertension	532,397	80.8%
Hyperlipidemia	481,176	73.0%
Hypoglycemia	16,401	2.5%
Hypovolemia	3,196	0.5%
Hypoxemia	30,829	4.7%
Obesity	145,252	22.0%
Pancreatitis	3,191	0.5%
Thyroid disorders	150,969	22.9%
Diabetic complications		
Moderate-to-severe renal insufficiency	134,971	20.5%
Nephropathy	178,591	27.1%
Neuropathy	151,733	23.0%
Retinopathy	59,468	9.0%
Amputation	1,803	0.3%
Health Services Utilization		
Number of unique drug classes	9.0	4.7
Number of unique generic medications	9.4	5.1
Number of dispensings	26.8	20.4
Number of inpatient encounters	0.2	0.5

	Incretin-Based Drugs	
	N/Mean	**%/SD[1]**
Number of non-acute institutional encounters	0.1	0.3
Number of emergency department encounters	0.4	1.1
Number of ambulatory encounters	11.0	12.2
Number of other ambulatory encounters	3.5	8.8

[1] Value represents standard deviation (SD) where no % follows.
[2] For categorical variables, numbers of episodes and percentages of episodes based on the total numbers of episodes were calculated, except for sex, for which numbers of unique patients and percentages of unique patients based on the total numbers of unique patients were calculated.
** Due to small cell redaction rules for CMS data, values were replaced with an addition up to 10 in order to prevent small cells (non-zero counts <11) or back-calculations.*
T2DM: type 2 diabetes mellitus. T1DM: type 1 diabetes mellitus. SGLT2: sodium-glucose cotransporter-2. SU: sulfonylurea. TZD: thiazolidinedione. DPP-4: dipeptidyl peptidase-4. GLP-1: glucagon-like peptide-1.

10.2.4 Person-time accumulation to date

Follow-up started from the index date between 1 July 2018 and 31 December 2021 through the earliest occurrence of the outcome or any censoring event (as described in 9.9.1.1 Follow-up) and was estimated per exposure-comparator pair as planned for comparison in the primary analysis of MK8835-062 (Table 6). Among new users of ertugliflozin or SU/TZD: from 704,962 primary new use episodes, a total of 464,160 person-years accrued, resulting in an average of 0.66 person-year per new use episode; from 703,900 incident new use episodes, a total of 463,949 person-years accrued, resulting in an average of 0.66 person-year per new use episode.

Among new users of ertugliflozin or incretin-based drugs: from 661,124 primary new use episodes, a total of 360,257 person-years accrued, resulting in an average of 0.54 person-year per new use episode; from 659,852 incident new use episodes, a total of 360,036 person-years accrued, resulting in an average of 0.55 person-year per new use episode.

In summary, the average follow-up for a new use episode of ertugliflozin and comparator ranged from 0.54 to 0.66 person-year, depending on the new user type (primary/incident) and comparator.

Table 6. Summary of At-Risk Time in the IMEDS Distributed Database, Optum Research Database, and CMS Medicare Research Identifiable Files in this Study

New user definition	Exposure	New Users	New Use Episodes	Person-Years at Risk	
				Total	Average per Episode
Primary	Ertugliflozin or SU/TZD	670,350	704,962	464,160	0.66
	Ertugliflozin or incretin-based drugs	624,278	661,124	360,257	0.54
Incident	Ertugliflozin or SU/TZD	669,308	703,900	463,949	0.66
	Ertugliflozin or incretin-based drugs	623,051	659,852	360,036	0.55

10.2.5 Evaluation of the stepwise data addition approach

The present interim analyses implemented the stepwise data addition proposed in Interim Report 1. With the combination of the refreshed IMEDS-DD and the newly included Optum Research Database and CMS Medicare RIFs, the number of ertugliflozin new users increased to 2,196 primary new users and 1,369 incident new users.

Despite significant growth in sample size, the required study sample size is not expected to be reached to perform the final analyses. Therefore, we seek to continue the stepwise data addition and proceed with further data expansion by adding a multi-state Medicaid database – specifically, the CMS Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) RIFs – as proposed in response to Interim Report 1 comments. The results will be directly incorporated in the Final Report.

Like the CMS Medicare RIFs, the CMS TAF RIFs represent the publicly (or government-) insured population. Specifically, these files include administrative data and claims of the Medicaid and Children's Health Insurance Program (CHIP) from 49 states and jurisdictions in the US. Medicaid and CHIP are joint federal and state programs that provide free or low-cost health coverage to millions of Americans, including low-income individuals, families and children, pregnant women, the elderly, and people with disabilities. The federal government provides a portion of the funding and sets guidelines for the programs, whereas each state government regulates its own coverages and costs. As of July 2022, there were 89 million members enrolled in Medicaid and CHIP [Ref. 5.4: 085XNR]. As with all existing data sources in the present analyses, the CMS TAF RIFs is now a contributing dataset to the US FDA's Sentinel Distributed Database and will share the same data management, privacy protection methods, and quality assurance procedures with the Sentinel Distributed Database once it is incorporated as a data source for this study. For non-Sentinel purposes (such as IMEDS), access to the CMS TAF RIFs with relevant data years to this study only recently became available for application approaching the end of 2021 and would not have been granted in time for the present analyses.

From publicly available data summaries [Ref. 5.4: 085XGH, 085XGL], for the period 2018 through 2020, there were 47,742 and 713,574 outpatient pharmacy claims for ertugliflozin in the Medicare FFS and Medicaid populations, respectively. Based on findings from the present analyses, we are able to roughly estimate the sample size gain after adding the CMS TAF RIFs to the final analysis. Assuming ertugliflozin users in Medicaid share the same ratio of total outpatient pharmacy claims to new use episodes and the same average follow-up time with the FFS ertugliflozin users in Medicare, we project to observe 18,699 primary new use episodes of ertugliflozin accumulating 10,097 to 12,341 person-years in the Medicaid population. It is important to note that this calculation also depends on comparable data completeness and quality between the CMS T-MSIS TAF and Medicare RIFs. Any violation of the assumptions and conditions may lead to smaller sample size increase than projected.

Provided that the above projection is accurate, then together with the continuous accrual of ertugliflozin users in existing data sources, we anticipate reaching the required sample size in the final study after including the CMS TAF RIFs as another additional data source.

11 DISCUSSION

11.1 Key results

From the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs together, a total of 2,196 primary new users of ertugliflozin were identified between 1 July 2018 and 31 December 2021, compared to 668,154 primary new users of SU or TZD and 622,290 primary new users of incretin-based drug identified during the same period. Significant sample size gain was observed after including the Optum Research Database and CMS Medicare RIFs as additional data sources. Specifically for ertugliflozin, new users from the Medicare FFS population accounted for more than half of this exposure cohort. Adding the CMS Medicare RIFs in particular allowed greater capture of T2DM patients in the real-world setting and enhanced generalizability of study results. As demonstrated in Interim Report 1, the successful implementation of the stepwise data addition relied on the unique advantage of the IMEDS framework: like Sentinel Distributed Database. Once a dataset is converted into the Sentinel Common Data Model [Ref. 5.4: 052TNG, 052Y0K], the dataset is compatible with the Sentinel routine analytic tools to permit rapid queries. The Optum Research Database and CMS Medicare RIFs are no exception. The Sentinel Common Data Model, when in use with the Sentinel routine analytic tools, eliminates heterogeneity in data format and analytic programming which is commonly seen in the common protocol approach [Ref. 5.4: 07WYRJ]. Standardization of both data and programming preserves transparency for study design and analytic execution, and it enables reproducibility as a unique advantage of a distributed data network [Ref. 5.4: 07WYRJ].

Despite the expected increase in mean age (from 56.4 to 62.9 years) as a result of including the Medicare FFS population, the demographic and clinical characteristics of the ertugliflozin new users remained comparable with those reported in observational studies of other SGLT2 inhibitors, especially with the subset of studies that also included data from the Medicare FFS or other older adult-dominant populations. The reference studies include EMPagliflozin compaRative effectIveness and SafEty (EMPRISE; EUPAS20677)

[Ref. 5.4: 05LSHM, 07WZGS, 0864HV]; Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D) [Ref. 5.4: 07WZM0]; Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL; CVD-REAL Nordic) [Ref. 5.4: 07WXVY, 07WZK0, 07WYLZ]; Diabetic Ketoacidosis in Patients with Type 2 Diabetes Treated with Sodium Glucose Co-Transporter 2 Inhibitors versus Other Antihyperglycemic Agents: An Observational Study of Four US Administrative Claims Databases (EUPAS23705) [Ref. 5.4: 05LSHQ]; and two Canadian Network for Observational Drug Effect Studies (CNODES) studies assessing the association of SGLT2 inhibitor exposure and various outcomes [Ref. 5.4: 07WYNH, 05LSH3]. Of note, most of these large-scale observational studies adopted a multi-database approach in the analysis which resembles the IMEDS framework used here.

Despite considerable growth in sample size, the required study sample size is not expected to be reached to perform the final analyses. Therefore, we seek to continue the stepwise data addition and proceed with more data expansion by adding the CMS TAF RIFs. Based on publicly available data summaries and findings from the present analyses, the projected number of ertugliflozin new users from Medicaid, together with data refresh(es) of all existing data sources, will likely offer sufficient sample size to power the final analysis, provided all data assumptions and conditions are met. Similar to the Medicare FFS beneficiaries included in the present analyses, the Medicaid beneficiaries represent another publicly insured population in US that may be different from individuals who are commercially insured, e.g., those captured in the IMEDS-DD and Optum Research Database. Generalizability of the final study results is expected to be further extended after inclusion of the Medicaid data. As with the Optum Research Database and CMS Medicare RIFs, the CMS TAF RIFs are an active contributing data source to the Sentinel Distributed Database.

11.2 Limitations

Several limitations should be considered in the context of the preliminary analyses.

First, despite the strengths of the IMEDS framework and the claims databases incorporated, there was the potential for misclassification due to the use of diagnostic, drug, or procedure codes for identification of specific medical conditions. Data input errors could also be present in the databases, which is an inherent limitation in almost all database studies.

Second, the preliminary analyses were limited to information captured in the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs. As with any other non-interventional database studies using health insurance administrative claims, patient medical history and treatment exposure in this study were captured by health services utilization. These types of data are collected and maintained for billing or record-keeping purposes. Most of the time, only services during medical encounters are recorded, excluding those not covered by health plans (e.g., over-the-counter medications and free drug

samples) or not itemized under coverage (e.g., bundled payment for inpatient encounters). Race/ethnicity, clinical details (e.g., hemoglobin A1c [HbA1c] laboratory results), and death are often missing or incomplete. There is also a substantial underestimation of obesity or lifestyle measures, such as alcohol use, as they are often under-recorded in the EHR or missing from health insurance administrative and claims data.

Third, drug exposure was inferred from outpatient pharmacy claims in this study, and days of supply information on these claims was used to determine study drug exposure and baseline or concomitant utilization. These outpatient pharmacy claims do not necessarily mean that patient consumed the drug and are a surrogate measure of actual drug exposure. This could result in drug exposure misclassification.

Fourth, as with all distributed data networks, the IMEDS framework does not guarantee data uniqueness at the patient level across data sources. During the study period, a patient may contribute data to multiple data partners. However, given that the same health service utilization is not commonly covered by multiple health plans, repeated observation of the same patient-time in the datasets is minimized.

Fifth, the potential sample size gain after adding the CMS TAF RIFs was estimated in this report without using any publicly available number and follow-up information of ertugliflozin users in the Medicaid population. The actual sample size increase may be smaller than the projection provided in Section 10.2.5.

11.3 Interpretation

The present preliminary analyses of MK8835-062 were conducted using the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs. Such setup of distributed data network in the IMEDS framework resembles the multi-database design commonly adopted in recently published observational safety studies of SGLT2 inhibitors such as EMRPISE, OBSERVE-4D, and CVD-REAL. The IMEDS framework employs the Sentinel Common Data Model for standardization of demographic and clinical data elements from various network partners [Ref. 5.4: 052TNG, 052Y0K]. By doing so, the IMEDS framework enables rapid queries across the included databases, thanks to compatibility and use of the analytic tools established and actively maintained by the Sentinel System.

Successful implementation of the stepwise data addition has resulted in a significant sample size increase since the first interim analysis. Nonetheless, the required study sample size is not expected to be reached to perform the final analyses if data are limited to the current data sources. Using the same approach adopted in the present analyses, we propose to continue data expansion by adding the CMS TAF RIFs to the final analyses. The number of person-years of exposure to ertugliflozin across all data sources will be provided in the final report.

After initial data expansion, the baseline characteristics of the identified ertugliflozin new users remained largely similar to the real-world SGLT2 inhibitor user profiles reported by recent publications [Ref. 5.4: 05LSHM, 05LSHQ, 07WZM0] [Ref. 5.4: 07WZGS, 04SDMH, 07WXVY, 07WZK0, 07WYNH, 05LSH3].

11.4 Generalisability

The study results are generalizable to both the commercially and publicly insured populations from which the study population was derived as well as other populations with similar characteristics. Inclusion of additional data sources, such as the multi-state Medicaid data provided through the CMS TAF RIFs, will further improve the precision of the effect estimates. It will also improve the generalizability with real-world T2DM patients who receive treatment, including those with low income and Medicaid coverage in US.

12 CONCLUSION

After initial implementation of the stepwise data addition proposed in Interim Report 1, 2,196 T2DM patients were identified who met the inclusion and exclusion criteria pre-specified in the study protocol and newly started ertugliflozin between 1 July 2018 and the most recent data available from the IMEDS-DD, Optum Research Database, and CMS Medicare RIFs. The demographic and clinical characteristics of these ertugliflozin new users remained comparable with those reported in observational studies of other SGLT2 inhibitors, such as EMPRISE [Ref. 5.4: 05LSHM, 07WZGS, 0864HV], OBSERVE-4D [Ref. 5.4: 07WZM0], and CVD-REAL [Ref. 5.4: 07WXVY, 07WZK0], [Ref. 5.4: 07WYLZ]. We also identified 668,154 new users of SU/TZD and 622,290 new users of incretin-based drugs during the same study period.

Findings from the current phase of the study indicate that the accrual trajectory of new users of ertugliflozin is unlikely to reach the target number needed to perform the final analyses, if data are limited to data sources included in the present preliminary analyses. To reach the target number needed to perform the final analyses, we will add the CMS TAF RIFs, which contain data from Medicaid populations from multiple states in US.

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ANNEXES

Annex 1 List of Stand-Alone Documents

Not Applicable

Annex 2 Study Protocol

(05BK7R)

Annex 3 Additional Information

Not Applicable