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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: Final Report

Keywords

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

Rationale and background

Merck Sharp & Dohme B.V. 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 MK-8835-062; EUPAS31718) to investigate the association of ertugliflozin use with diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) using the Innovation in Medical Evidence Development and Surveillance System (IMEDS) framework. As requested in the Pharmacovigilance Risk Assessment Committee (PRAC) PASS Protocol Assessment Report dated 05 September 2019 (Section 11), two interim reports were delivered, summarizing preliminary results on the study population available at the time of report submission and to assess the availability of ertugliflozin exposure in the database to conduct the final analysis planned for MK-8835-062. The present report describes the final inferential analyses for MK-8835-062 conducted using data from IMEDS Distributed Database (IMEDS-DD), Optum Research Database, Centers for Medicare & Medicaid Services (CMS) Medicare Research Identifiable Files (RIFs), and CMS Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) RIFs.

Objectives of final report

The primary objectives of the study were:

- to assess the risk of DKA among new users of ertugliflozin relative to new users of sulfonylureas (SUs) or thiazolidinediones (TZDs); and

- to assess the risk of DKA among new users of ertugliflozin relative to new users of incretin-based drugs [i.e., dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs)].

The secondary objectives of the study were:

- to assess the risk of DKA among new users of ertugliflozin relative to new users of SUs or TZDs, separately in insulin users and non-insulin users at baseline; and
- to assess the risk of DKA among new users of ertugliflozin relative to new users of incretin-based drugs, separately in insulin users and non-insulin users at baseline.

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.

Participants

Three primary exposure cohorts of interest were defined as new users of: (1) ertugliflozin; (2) SU or 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 neuropathy, retinopathy, and amputation), prior anti-hyperglycemic agent (AHA) utilization, and health services utilization (number of unique medications, number of outpatient, inpatient, and emergency department visits).

Data sources: 1) the IMEDS Distributed Database (IMEDS-DD) from the Reagan-Udall Foundation for the Food and Drug Administration (FDA), 2) the Optum Research Database, 3) the CMS Medicare RIFs, and 4) the CMS Medicaid TAF RIFs.

Outcome

The study outcome was hospitalization for DKA, identified from principal discharge diagnosis of inpatient claims.

Statistical Methods

Time-to-event analyses were conducted separately for the two comparisons: new-use episodes of ertugliflozin (exposure) versus the new-use episodes of SU/TZD (comparator); and new-use episodes of ertugliflozin (exposure) versus new use episodes of incretin-based drugs (comparator). Cox proportional hazards models were used for risk estimation. Hazard ratios (HRs) and their 95% confidence intervals (CIs) before and after 1:1 propensity score-matching were reported (referent group: comparator drugs). Analyses were stratified by concomitant insulin use on the index date.

Results

Ertugliflozin versus SU/TZD: Among the 42,288 new users of ertugliflozin with 43,145 new-use episodes and 13,987 person-years at risk, 41 DKA events were observed (incidence rate: 2.93 per 1,000 person-years). In comparison, a total of 612 events were identified among the 835,324 new users of SU/TZD with 892,439 new-use episodes and 587,023 person-years at risk (incidence rate: 1.04 per 1,000 person-years). The HR after propensity score matching was 1.88 (95% CI 1.17-3.02) overall, 2.34 (95% CI 1.27-4.31) in the subgroup with no concomitant insulin use on the index date, and 1.17 (95% CI 0.54-2.52) in the subgroup with concomitant insulin use.

Ertugliflozin versus incretin-based drugs: Among the 41,407 new users of ertugliflozin with 42,249 new-use episodes and 13,399 person-years at risk, 37 DKA events were observed (incidence rate: 2.76 per 1,000 person-years). In comparison, a total of 613 events were identified among the 789,956 new users of incretin-based drugs with 842,438 new-use episodes and 479,913 person-years at risk (incidence rate: 1.28 per 1,000 person-years). The HR after propensity score matching was 2.40 (95% CI 1.40-4.11) overall, 2.84 (95% CI 1.42-5.66) in the subgroup with no concomitant insulin use on the index date, and 1.87 (95%CI 0.79-4.46) in the subgroup with concomitant insulin use.

Discussion

This study indicated a higher risk of DKA among new users of ertugliflozin compared with new users of SU/TZD or incretin-based drugs. The results were consistent with the findings from prior observational studies that compared DKA risk among users of SGLT2 inhibitors versus other AHAs.

Marketing Authorisation Holder(s)

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[1] Dr. Sengwee Toh, who has been the co-investigator of the project since July 2018, replaced Dr. Brown as the PI starting November 2021.

2 LIST OF ABBREVIATIONS

AHA	Anti-hyperglycemic agents
CPT	Current Procedural Terminology
CVD	Cardiovascular disease
CMS	Centers for Medicare & Medicaid Services
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase 4
EHR	Electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
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
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
MSD	Merck Sharp & Dohme, Corp.
NDC	National Drug Codes
PASS	Post-Authorization Safety Study
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

3 INVESTIGATORS

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Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD Associate Principal Scientist, Epidemiology Biostatistics and Research Decision Sciences Merck Sharp & Dohme LLC PPD
Other contacts	Not applicable
Vendor/Collaborator	Innovation in Medical Evidence and Development Surveillance

[2] Dr. Sengwee Toh, who has been the co-investigator of the project since July 2018, replaced Dr. Brown as the PI starting November 2021.

Investigators	Sengwee Toh, ScD[1] PPD [1] Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA [2] Formerly, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA [3] Reagan-Udall Foundation for the Food and Drug Administration, Washington DC, USA

4 OTHER RESPONSIBLE PARTIES

Not applicable.

5 MILESTONES OF MK-8835-062

Milestone	Planned date	Actual date
Start of data collection of MK-8835-062	1 July 2018	1 July 2018
End of data collection of MK-8835-062	31 March 2024	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	9 December 2022
Final report of study results	31 October 2024	

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 United States (US) on December 19, 2017 and in the European Union on March 21, 2018 for type 2 diabetes mellitus (T2DM) treatment to improve glycemic control in adults. As its marketing authorization holder, Merck Sharp & Dohme B.V. (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* (MK-8835-062; EUPAS31718) to investigate the association of ertugliflozin use with diabetic ketoacidosis (DKA) among patients with T2DM 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 anti-hyperglycemic agents (AHAs), among patients with T2DM 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 September 5, 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 to conduct the final analysis planned for MK-8835-062. The first interim report was submitted to the EMA on December 9, 2021. Findings of the first interim report 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 second interim report was submitted to the EMA on December 9, 2022. Findings from the second interim report indicated that the accrual trajectory of new users of ertugliflozin was unlikely to reach the target number needed to perform the final analyses, if data were limited to data sources included in the second interim analyses—IMEDS-DD, Optum Research Database, and Centers for Medicare & Medicaid Services (CMS) Medicare Research Identifiable Files (RIFs). To reach the target number needed to perform the final analyses, the CMS Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) RIFs, which contain data from Medicaid populations from multiple states in US, were to be included.

The present report describes the final analyses for MK-8835-062 conducted using data from IMEDS-DD, Optum Research Database, CMS Medicare RIFs, and CMS TAF RIFs.

7 OBJECTIVES OF THE STUDY

The primary objectives of the study were:

- to assess the risk of DKA among new users of ertugliflozin relative to new users of sulfonylureas (SUs) or thiazolidinediones (TZDs); and

- to assess the risk of DKA among new users of ertugliflozin relative to new users of incretin-based drugs [i.e., dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs)].

The secondary objectives of the study were:

- to assess the risk of DKA among new users of ertugliflozin relative to new users of SUs or TZDs, separately in insulin users and non-insulin users at baseline; and

- to assess the risk of DKA among new users of ertugliflozin relative to new users of incretin-based drugs, separately in insulin users and non-insulin users at baseline.

8 AMENDMENTS AND UPDATES

Not applicable.

9 RESEARCH METHODS

9.1 Study Design

A non-interventional cohort study using electronic healthcare data was conducted to compare the risk of DKA between new users of ertugliflozin and new users of other non-SGLT2 inhibitor AHAs among patients with T2DM. Eligible drug classes include SUs, TZDs, DPP-4 inhibitors, and GLP-1 RAs (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].

Propensity score matching was used for confounding adjustment, followed by Cox proportional hazards models for risk estimation. Propensity score matching is an effective confounding adjustment approach widely used in pharmacoepidemiology studies [Ref. 5.4: 00W5HN, 052V45, 052WSR]. The propensity score reduces large numbers of baseline variables by summarizing them into a single score. Compared with standard multivariable outcome regression modeling, this summary score approach makes risk adjustment and estimation feasible when the number of patients with health outcome of interest is low in relation to the number of covariates (a pattern commonly observed during early phase on newly marketed medical products). On average, matching eligible members on propensity score balances the exposed and comparator cohorts with respect to distributions of baseline characteristics. Matched members can then enter the risk estimation model with minimal further adjustment [Ref. 5.4: 00W5HN].

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, CMS Medicare RIFs, and CMS TAF RIFs. Health plan members enrolled with these insurers are predominately community-dwelling individuals and can be of all ages, commercially or publicly insured. All four data sources comprised data providers that had contributed or are currently contributing 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].

9.3 Participants

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

9.3.1 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.
- Six or more months of continuous enrollment (maximum allowable enrollment gap of 45 days) 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 Type II*, *Diabetes Mellitus*, *250.x2 Type II, Diabetes Mellitus* or ICD-10-CM *E11.x Type 2 Diabetes Mellitus*.

9.3.2 Exclusion Criteria

- 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 *O24.4x Gestational Diabetes Mellitus in Pregnancy.* Note: as a diagnosis of T1DM following T2DM may indicate that the T2DM diagnosis was incorrect, a sensitivity analysis was conducted using a "narrow T2DM population" definition by excluding patients with T1DM diagnosis any time during the study, before, on or post-index date.

- 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 index date and ongoing insulin use was 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 inpatient claims, 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*.

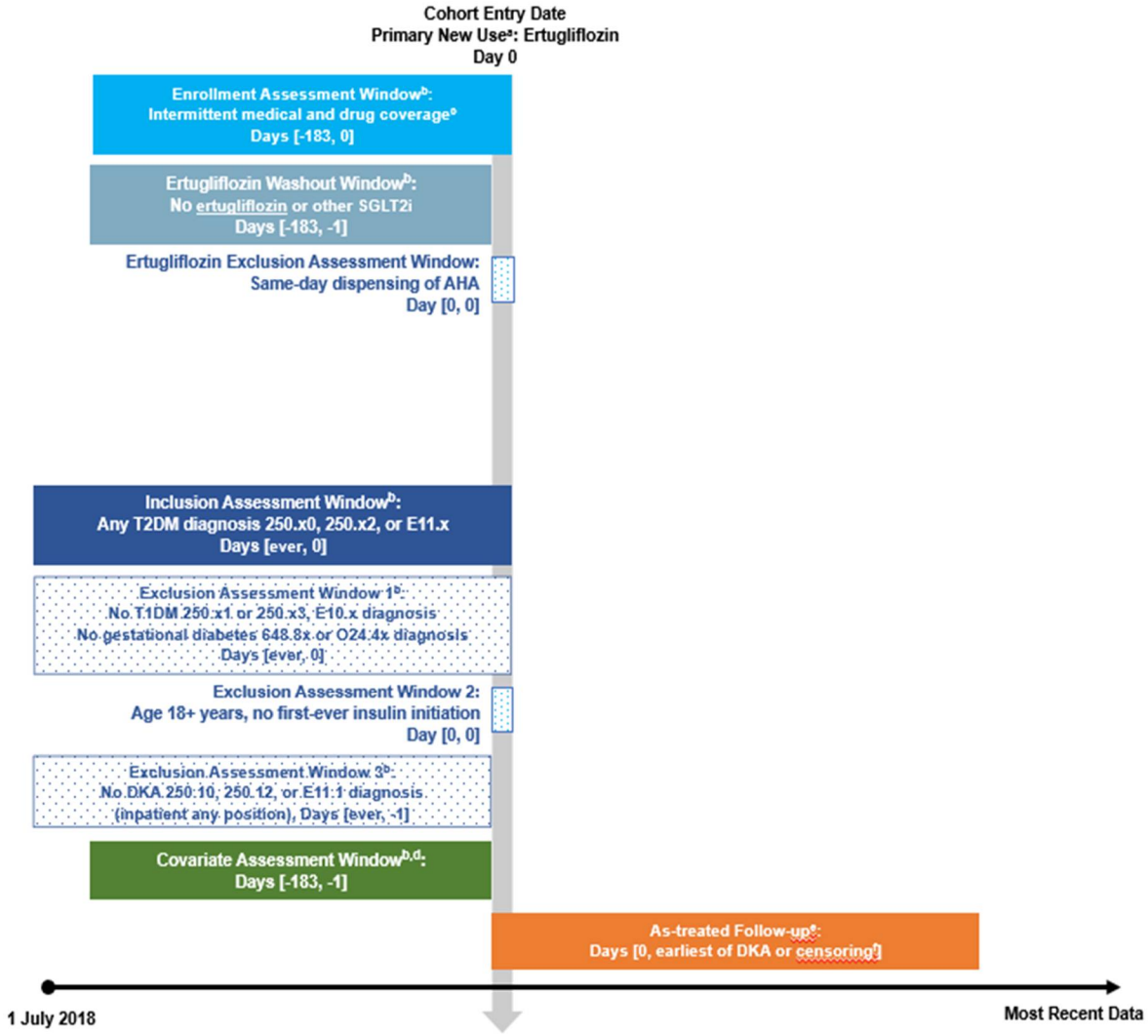
9.4 Variables

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 RAs). These exposure groups were identified via outpatient pharmacy claims.

A new user was defined as an individual 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 is considered the "primary new user" definition [Figure 1].

Figure 1 Design Schematic for Primary New Users: Ertugliflozin Example

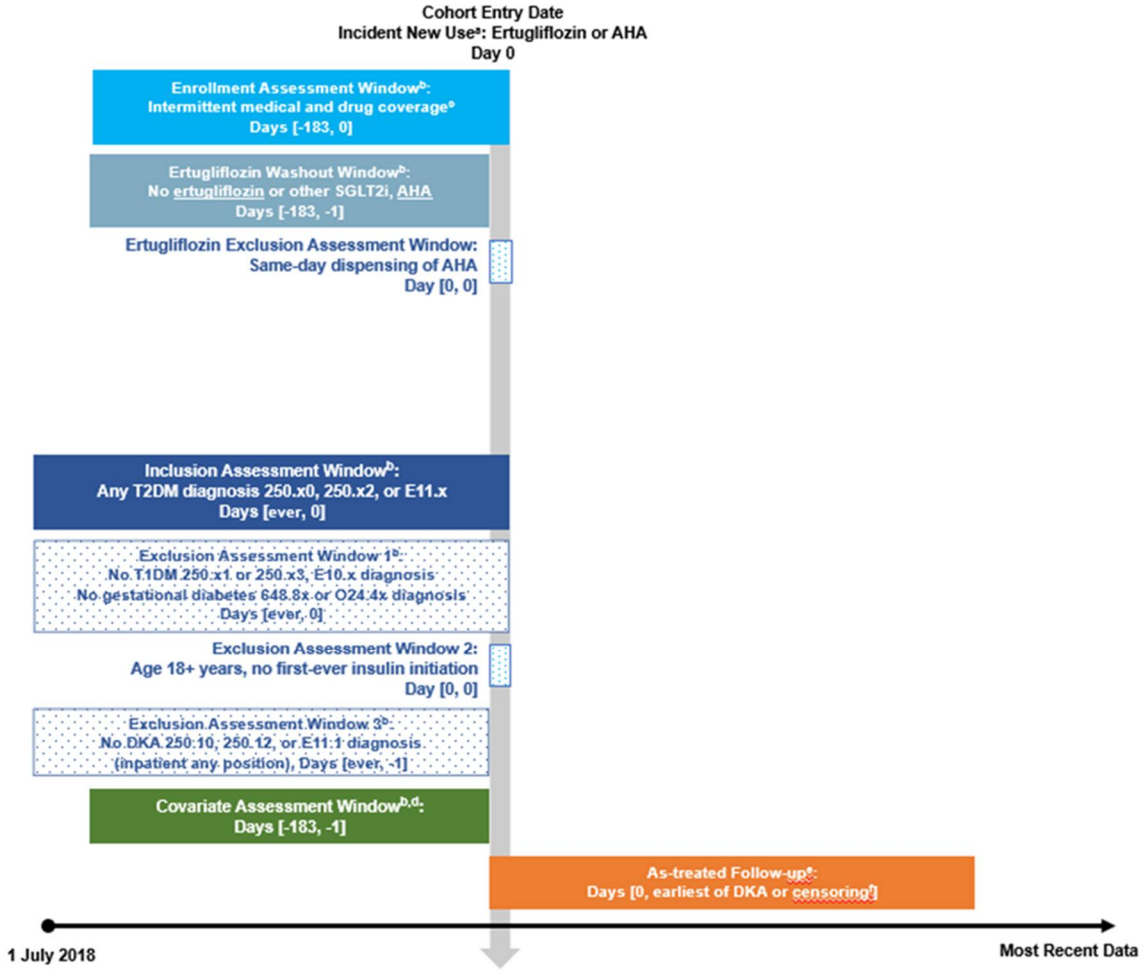


a. Index date (Day 0) is defined by date of the valid new use of ertugliflozin. Members are allowed to enter the analytic cohort multiple times.
b. Assessment window may start before query start date 1 July 2018.
c. Up to 45-day gaps in medical or prescription drug plan enrollment are allowed.
d. All covariates assessed in the 183-day window prior to the index date except the following which are assessed on the index date (Day 0) age, sex, calendar year, ongoing T2DM treatment, concomitant insulin use, and number of ongoing unique drug use by class.
e. Dispensings with days of supply gap up to 30 days are bridged. An extension of 30 days is appended after the last dispensing.
f. Censoring criteria include discontinuation of the index exposure, initiation of comparator AHA (if ertugliflozin new use), ertugliflozin (if AHA new use), other SGLT2i, first-ever insulin, disenrollment, end of data availability, recorded death.

AHA: antihyperglycemic agent; SGLT2i: sodium-glucose cotransporter 2 inhibitor; T2DM: type-2 diabetes mellitus; T1DM: type-1 diabetes mellitus

In a sensitivity analysis, we assessed the number of new users of ertugliflozin and comparators based on the "incident new user" definition, which required no prior use of any SGLT2 inhibitors (including ertugliflozin), a comparator AHA (i.e., SU/TZD when comparing ertugliflozin with SU/TZD; or DPP-4 inhibitors/GLP-1 RAs 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) is defined by date of the valid new use of ertugliflozin. Members are allowed to enter the analytic cohort multiple times.

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

c. Up to 45-day gaps in medical or prescription drug plan enrollment are allowed.

d. All covariates assessed in the 183-day window prior to the index date except the following which are assessed on the index date (Day 0) age, sex, calendar year, ongoing T2DM treatment, concomitant insulin use, and number of ongoing unique drug use by class.

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

f. Censoring criteria include discontinuation of the index exposure, initiation of comparator AHA (if ertugliflozin new use), ertugliflozin (if AHA new use), other SGLT2i, first-ever insulin, disenrollment, end of data availability, recorded death.

AHA: antihyperglycemic agent; SGLT2i: sodium-glucose cotransporter 2 inhibitor; T2DM: type-2 diabetes mellitus; T1DM: type-1 diabetes mellitus

A patient was allowed to contribute 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 (i.e., index exposure) during the study period; he/she could contribute follow- up time to both exposure groups or contribute follow-up time to the same exposure group more than once. Each time, 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. For example, if a TZD new user started on ertugliflozin right 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 based on the "primary new user" definition; however, the patient would not contribute ertugliflozin exposure time in the ertugliflozin-SU/TZD comparison based on the "incident new user" definition.

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. This 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 were 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, dispensing 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 calculations. For the last refill, the grace period was considered in 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 include ICD-10-CM *E11.1x Type 2 Diabetes Mellitus with Ketoacidosis*. The admission date was used as the diagnosis date.

A sensitivity analysis was conducted by using the hospitalization for DKA identified from all listed discharge diagnoses to capture as many DKA cases as possible, reflecting DKA cases in the real-world settings.

9.4.3 Covariates

We used propensity scores as an analytic strategy to reduce potential confounding due to imbalance in baseline covariates between two exposure groups in baseline covariates. The propensity score was the probability of a patient becoming an ertugliflozin versus comparator AHA new user, given a set of observed covariates [Ref. 5.4: 00W5HN, 052V45, 052WSR, 052X48].

This study included baseline demographics, use of AHAs, use of medications associated with DKA, comorbidity burden, pre-existing comorbidities, diabetic complications, lifestyle, and health services utilization as covariates in the propensity score estimation model. Two sets of propensity scores, one for the comparison of ertugliflozin versus SU/TZD and one for the

comparison of ertugliflozin versus incretin-based drugs, were generated. Ertugliflozin and comparator AHA new use cohorts were matched without replacement on propensity score by the nearest neighbor approach, using a caliper of 0.05 on the propensity score scale. Unless otherwise specified, all covariates listed in [Table 1] were evaluated within the 6 months prior to the index date, and medical conditions were assessed using medical encounter claims from any care setting.

Table 1 List of Covariates

Category	Covariates
Demographics	Age, sex, calendar year of cohort entry
Use of antihyperglycemic agents	Distribution of diabetes treatment by class (i.e., metformin, SU, TZD, alpha glucosidase or meglitinides, DPP-4 inhibitor, GLP-1 RA, SGLT2 inhibitor, and insulin)
Use of medications associated with DKA	Clozapine or olanzapine, lithium, terbutaline, oral corticosteroids, thiazides, pentamidine
Comorbidity burden	Combined comorbidity index [Ref. 5.4: 052TS6]
Pre-existing comorbidities	Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis), acute renal failure, cerebrovascular disease, myocardial infarction, stroke, coronary heart disease, heart failure, hypertension, hyperlipidemia, pancreatitis, hypovolemia, hypoxemia, 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, peripheral vascular disease, amputation
Lifestyle	Obesity surgery, alcohol use, tobacco use, cocaine abuse
Health services utilization	Number of unique pharmacological classes, dispensings, inpatient encounters, emergency department encounters, and ambulatory encounters
SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1 RA: glucagon-like peptide-1 receptor agonist; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.	

The approaches to handling concomitant AHAs in the analyses are summarized in [Table 2].

Table 2 Approaches to Handling Concomitant Use of Antihyperglycemic Agents

Timing and type of AHA Dispensing	Analysis Approach
If any AHA taken during the baseline period that was not eligible to be a study exposure	Included as covariate in propensity score estimation model
If any AHA taken during the baseline period that was eligible to be a study exposure	Included as covariate in propensity score estimation model when the "primary new user" definition as stated in [Sec. 9.4.1] is used.
If insulin was used at the index date	Conducted stratified analyses by insulin use at index date (Yes or No)
If non-ertugliflozin SGLT2 inhibitors were added during follow-up	Censored and ended follow-up
AHA: antihyperglycemic agent; SGLT2: sodium-glucose cotransporter-2	

Note that the numbers of unique AHA classes at the index date were not included as covariates in the propensity score estimation models because concomitant use of several AHAs was controlled for individually.

9.5 Data Sources and Measurement

This study employed the stepwise data expansion proposed in Interim Reports 1 and 2 and the final analysis was conducted using existing, electronic health insurance claims data from IMEDS DD and three additional sources—the Optum Research Database, the CMS Medicare Fee-for-Service RIFs, and the CMS Medicaid TAF RIFs. All four data sources comprised data providers that had contributed or are currently contributing to the US FDA's Sentinel System, a national electronic system for active surveillance of the safety of medical products 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 [Ref. 5.4: 052TMC, 052WPW]. The IMEDS-DD works with selected data partners from the Sentinel System, 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 largely comprises of current Sentinel data partners and is expected to be largely representative of the commercially insured population in US. At the time of this study, the IMEDS-DD had claims data available for research for over 125 million health plan

members who had overlapping medical and pharmacy insurance coverage. The average enrollment length was similar to other claims databases of members with medical and pharmacy coverage - about 39% of members had over three years of enrollment, and patients with chronic conditions such as diabetes and older members typically had longer than average enrollment periods within these databases.

This study included data from five national and regional health insurers of the IMEDS-DD in the US. All listed network partners had 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 a Sentinel 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.

Carelon Research, Inc (formerly known as HealthCore, Inc.), a wholly-owned subsidiary of Elevance Health, uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late phase research. The Carelon Research 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 Carelon Research Integrated Research Environment has the ability to link the claims data in the Carelon Research 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, Carelon Research 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 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 that 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 lives are available for research within this health system since 2007. Humana's geographic coverage for the IMEDS research population includes nearly every US state and is predominantly a Medicare population.

9.5.2 Optum Research Database

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 2022, data are available for approximately 12.0 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)

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) (also known as Traditional or Original Medicare) 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 the Medicare FFS enrollees with medical and pharmacy benefits. Hereafter, all specific references to CMS and Medicare data refer only to the FFS population.

9.5.4 Centers for Medicare & Medicaid Services (CMS) Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF RIFs)

Medicaid provides health insurance coverage to millions of eligible Americans, including low-income adults, children, pregnant individuals, elderly adults, and people with disabilities. States and U.S. territories administer these health insurance programs within broad federal guidelines that have changed over time, so benefits and eligibility requirements

vary by state and year. As a result, the populations may vary, based upon the criteria (namely income levels) required to be enrolled. The actual benefits may vary as well with some benefits being required and others being optional based upon the state. In May 2022, there were approximately 82 million enrolled in the Medicaid program.

9.5.5 Measurement

As with the prior analyses (feasibility assessment and the two interim analyses) 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 and CMS Medicaid TAF RIFs, at the IMEDS AC via the VRDC.

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, including one record per covered individual per unique enrollment span 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. 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 vary by data partners.

- *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, CMS Medicare RIFs, and CMS Medicaid TAF RIFs, six have death data and two have cause of death data [Ref. 5.4: 052X67]. Both death and cause of death data are lagged (by at least 2 years). Cause of death is coded as ICD-10-CM diagnosis codes.

Data contributing to the final analysis presented in this report 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 and Medicaid TAF RIFs on the VRDC. A universal package with pre-specified parameter values using Sentinel Routine Querying Tool version 12.0.1 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 strengths of the IMEDS network in scale and standardization of data, the potential for misclassification remained due to the use of diagnostic codes, drug claim codes, or procedure codes for identification of specific medical products or 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 was also a substantial underestimate of obesity, as this condition is often under-recorded in electronic health record (EHR) data or missing from insurance claims data. Further, analyses were limited to information obtained in the claims database of individual

data sources; therefore, care 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) 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, the duration of medical history available varied across patients. A detailed discussion is included in [Sec. 11.3].

9.7 Study Size Required to Conduct MK-8835-062

Study size required for MK-8835-062 was provided in Section 7.5 of the study protocol (Protocol MK-8835-062; 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 3]. 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 for DKA in ertugliflozin users relative to comparator AHA users, with targeted power of 80% and significance level of 0.05 in a two-sided test, a combined total of 66 DKA events from ertugliflozin and comparator AHA groups would be required. This could be achieved by having 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 patients with T2DM 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 patients with T2DM treated with comparator AHAs. As the literature evolved, these assumptions could change over time. In general, when DKA incidence rate in patients with T2DM treated with comparator AHAs increased, the required sample size to achieve the same power would be expected to decrease, holding constant the total number of DKA cases needed for any pre-specified HR. The study team reviewed more recent literature [Ref. 5.4: 05LSHQ, 05LSH3] during the final analysis and concluded that the above study size estimated during the earlier stage of the study remained valid.

Table 3 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 decision to include CMS Medicaid TAF RIFs was made based on Interim Report 2 which established that the required study sample size was not expected to be reached to perform the final analyses if data were limited to IMEDS-DD, Optum Research Database, and CMS Medicare RIFs.

9.8 Data Transformation

9.8.1 Data Management

As with the prior analyses (feasibility assessment and the first two interim analyses) 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 and CMS Medicaid TAF RIFs, at the IMEDS AC via the VRDC.

All incorporated datasets were applied the same data management, privacy protection methods, and quality assurance procedures as the Sentinel Distributed Database [Ref. 5.4: 052WPT, 052WWP, 052XV9]. 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 were 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] Quality Control.

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 were 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 remained behind each data source's local firewall, and the data partners maintained physical and operational control of their data. Query results were returned to the web portal in aggregate form. All communications between the web portal and the application used HTTP/SSL/TLS connections to securely transfer queries and results. In this study, queries against the CMS Medicare RIFs and CMS Medicaid TAF RIFs were conducted locally within the VRDC by the IMEDS AC.

As described in more detail in [Sec. 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. Data used in this study were anonymized and no personal identifiers were available to maintain patient confidentiality.

9.9 Statistical Methods

The study summarized the number of new-use episodes of ertugliflozin or a comparator AHA; baseline characteristics before each new-use episode; as-treated follow-up time ([Sec. 9.9.1]) based on duration of use and censoring criteria; incidence rate of DKA and 95% confidence intervals (CIs) by exposure before and after propensity score matching; and time-to-event analyses using Cox proportional hazards models before and after propensity score matching. The IMEDS AC separately combined data from the IMEDS-DD partner sites and Optum as one group, and data from CMS Medicare RIFs and CMS Medicaid TAF RIFs as another group.

9.9.1 Follow-up

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

- 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 first ever use of insulin
- 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.

9.9.2 Descriptive Analysis

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. Average follow-up time and incidence rates of DKA (per 1,000 person-years) along with 95% CIs, before and after propensity score matching were also summarized.

9.9.3 Comparative Analysis

9.9.3.1 Primary and Subgroup Analysis

The primary analysis compared the new-use episodes of ertugliflozin versus the new-use episodes of SU/TZD; and new-use episodes of ertugliflozin versus new-use episodes of incretin-based drugs for risk of DKA, based on "primary new user" definition specified in [Sec. 9.4.1].

Time-to-event analyses were conducted separately for the two comparisons. Cox proportional hazards models were used for risk estimation. Hazard ratios and their 95% CIs before and after propensity score matching were reported.

Subgroup analyses stratified by concomitant insulin use on the index date were conducted because insulin use is clinically considered to be associated with a longer history of diabetes or more advanced diabetes. Concomitant insulin use was defined as any insulin prescription claims whose duration plus a 30-day grace period included the index date.

9.9.3.2 Sensitivity Analyses

Sensitivity analyses with varying T2DM definition [Sec. 9.3.2], new user definitions [Sec. 9.4.1], DKA definition [Sec. 9.4.2], different approaches to define follow-up time [Sec. 9.9.1], and propensity score stratification [Sec. 9.9.3.3] were conducted to assess the robustness of study results. In addition, two ad hoc sensitivity analyses not initially pre-specified in the protocol were conducted: one was limited to a single cohort entry per patient only, and the other included variables related to COVID-19, an emerging risk factor for DKA [Ref. 5.4: 08CP54], in the propensity score estimation model. See the overview of comparative analyses in [Table 4].

Table 4 Overview of Comparative Analyses

Analysis	T2DMdefinition	DKA definition	New user definition	Follow-up approach	Subgroup analysis	Propensity score analysis type	Notes
Primary analysis	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Concomitant insulin use at baseline	1:1 matching	
Sensitivity analysis 1	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	Intent-to-treat approach	Not applicable	1:1 matching	
Sensitivity analysis 2	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 90-day grace period	Not applicable	1:1 matching	
Sensitivity analysis 3	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with no censoring at switching (overlapping period) or treatment augmentation	Not applicable	1:1 matching	
Sensitivity analysis 4	Primary T2DM definition	Principal discharge diagnosis	Incident new user definition	As-treated approach with 30-day grace period	Not applicable	1:1 matching	
Sensitivity analysis 5	Narrow T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Not applicable	1:1 matching	
Sensitivity analysis 6	Primary T2DM definition	Any discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Not applicable	1:1 matching	
Sensitivity analysis 7	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Not applicable	Stratification	
Sensitivity analysis 8	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Not applicable	1:1 matching	Analysis limits to single cohort entry per patient.

Analysis	T2DMdefinition	DKA definition	New user definition	Follow-up approach	Subgroup analysis	Propensity score analysis type	Notes
Sensitivity analysis 9	Primary T2DM definition	Principal discharge diagnosis	Primary new user definition	As-treated approach with 30-day grace period	Not applicable	1:1 matching	COVID-19 related variables were included in the propensity score estimation model.

9.9.3.3 Model Specifications for Propensity Score Estimation

Two sets of analyses were performed: one for the comparison of ertugliflozin versus SU/TZD and one for the comparison of ertugliflozin versus incretin-based drugs. Each of the primary and sensitivity analyses fit a logistic regression model to estimate the propensity score for new use of ertugliflozin (i.e., probability of newly initiating ertugliflozin versus SU/TZD; and probability of newly initiating ertugliflozin versus incretin-based drugs). Subgroup analyses used the propensity score estimated in the primary analysis and rematched new-use episodes within subgroup levels and within the matched new-use episodes of the primary analysis. All baseline covariates, including concomitant medication and AHA use, were considered in the propensity score estimation model as independent variables. Ertugliflozin and comparator AHA new-use episodes were matched 1:1 on propensity score by the nearest neighbor approach using a caliper width of 0.05 [Ref. 5.4: 05789N].

A patient was allowed to contribute to more than one exposure group at a different time points during the study period whenever he/she qualified as a new-use definition of that exposure category. To allow for the changing drug utilization patterns over time and minimize the impact of self-matching across exposure groups among patients who became eligible for both exposure groups at different time points, it was proposed in the study protocol to perform propensity score estimation and 1:1 propensity score matching sequentially, on a quarterly basis [Ref. 5.4: 05789G]. The repeating interval of propensity score estimation and subsequent adjustment were extended from quarter to the entire study period to retain sample size.

Covariate distributions by exposure were output before and after propensity score matching. Multiple propensity score matching diagnostics per analysis were applied: between exposure groups, absolute value of standardized difference was be used, with a difference < 0.1 indicating covariate balance [Ref. 5.4: 05789N]; within each data partner site, c statistics and propensity score histograms were examined [Ref. 5.4: 05789N].

As a sensitivity analysis, propensity score stratification into deciles was used to examine the robustness of study results using the entire data set for the analysis. Propensity score stratification is an alternative propensity score analysis method for confounding adjustment. Unlike propensity score matching, this method does not run the risk of losing patients when

no match can be found but strata without patients in both exposure groups would be dropped from the analysis.

9.9.4 Exploratory Analyses

As the "primary new user" definition allowed patients to be included in multiple exposure categories over time, it created non-mutually exclusive categories of patients, which could be more difficult to interpret. Separate exploratory analyses were conducted for each comparison to help address this concern and explore the potential impact to the validity of primary analysis results. In these analyses, the follow-up time for each defined new user was further divided into the following mutually exclusive categories, wherever applicable:

- Ertugliflozin exposure person-time excluding any time overlapping with comparator AHA group person-time;
- Comparator AHA exposure person-time excluding any time overlapping with ertugliflozin person-time;
- Multiple exposure person-time of ertugliflozin overlapping with a comparator AHA.

To create the 3 categories, exposure episodes were not censored upon initiation of the opposite drug. The number of DKA cases were reported in each category.

9.9.5 Missing Values

The study included the following 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 AHA 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.

9.9.6 Amendments to the Statistical Analytic Plan

The analytic models in this study assumed independent DKA risk for patients with multiple entries and no adjustment for within-subject correlation was applied.

The repeating interval of propensity score estimation and subsequent adjustment were extended from quarter to the entire study period to retain sample size.

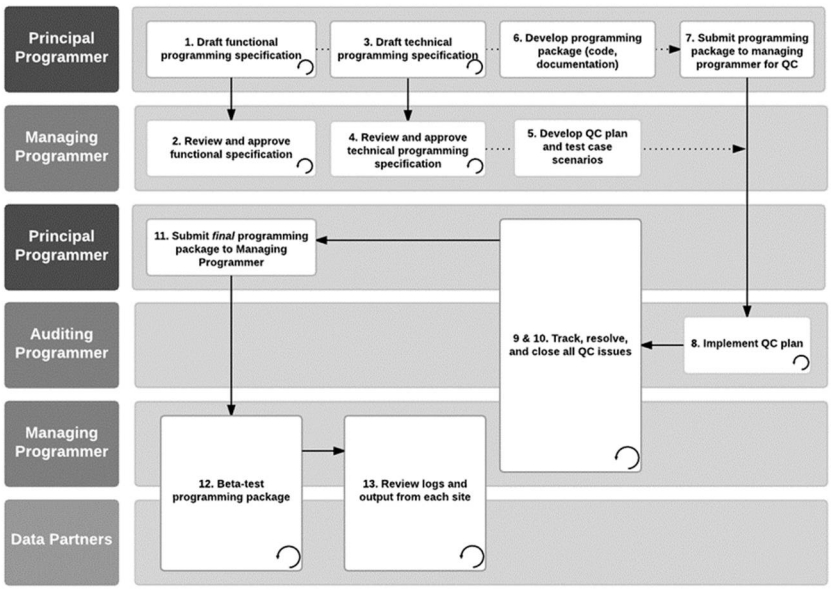
Two additional sensitivity analyses not initially pre-specified in the protocol were conducted: one was limited to a single cohort entry per patient only, and the other included variables related to COVID-19 in the propensity score estimation model.

9.10 Quality Control

As with prior analyses (feasibility assessment and the two interim analyses) 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 and CMS Medicaid TAF RIFs on the VRDC. All incorporated datasets were applied the same data management, privacy protection methods, and quality assurance procedures as the Sentinel Distributed Database [Ref. 5.4: 052WPT, 052WWP, 052XV9]. The quality assurance approach assessed consistency with the Sentinel Common Data Model, evaluated adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviewed 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.

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 final analyses used pre-existing databases – the IMEDS-DD, Optum Research Database, CMS Medicare RIFs, and CMS Medicaid TAF RIFs. Data were anonymized and no personal identifiers were available to maintain patient confidentiality (IMEDS IRB Protocol IRB2187, Optum IRB Review # 20221275, Carelon IRB Review # 1-1612020-1, HPHC IRB Review #1528711).

The final analyses were conducted in accordance with all legal and regulatory requirements. Additionally, the conduct of final analyses adhered to commonly accepted research practices, including those described in the 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

Main results from the analyses are provided in the following sections. Note that no events were observed in the primary analyses among new-use episodes of ertugliflozin in the data from the IMEDS-DD partner sites and Optum. Therefore, descriptive data on DKA cases and time-to-event analyses are presented only for new-use episodes of ertugliflozin, incretin-based drugs, and SU/TZD in the CMS Medicare RIFs and CMS Medicaid TAF RIFs.

10.2.1 New-Use Episodes of Ertugliflozin and SU/TZD in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

A total of 43,145 new-use episodes of ertugliflozin among 42,288 new users of ertugliflozin and 892,439 new-use episodes of SU/TZD among 835,324 new users of SU/TZD were identified between July 1, 2018 and December 31, 2021, based on the "primary new user" definition.

The baseline characteristics of primary new users of ertugliflozin and SU/TZD are shown in [Table 5]. Of the 43,145 ertugliflozin new-use episodes, the mean age was 53.0 years (SD=9.8 years). Ertugliflozin was initiated as monotherapy in 3,187 (7.4%) episodes. The most commonly utilized concomitant AHA class at the index date was metformin (78.3%), followed by SU (31.9%) and DPP-4 inhibitor (24.7%). The most common comorbidities included hypertension (53.3%) and hyperlipidemia (44.0%). Individuals with a history of cardiovascular disease (CVD) represented 16.8% 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.

Among the 892,439 SU or TZD new-use episodes, the mean age was 64.4 years (SD=10.4 years) and 29.0% initiated SU or TZD as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (61.2%), followed by DPP-4 inhibitors (11.2%) and insulin (9.3%). The most common comorbidities included hypertension (66.9%) and hyperlipidemia (55.3%), and 30.9% had a history of CVD.

Table 5 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones Before Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	43,145	100.0%	892,439	100.0%	N/A
Unique patients	42,288		835,324		N/A
Demographics[2] on the index date					
Age (years)	53.0	9.8	64.4	10.4	-1.128
Age					
18-44 years	8,967	20.8%	91,552	10.3%	0.294
45-64 years	31,463	72.9%	297,310	33.3%	0.865
65-74 years	1,990	4.6%	308,605	34.6%	-0.815
≥ 75 years	725	1.7%	194,972	21.8%	-0.659
Sex, female	23,117	54.7%	434,120	52.0%	0.054
Calendar year of initiation					
2018	3,525	8.2%	148,099	16.6%	-0.258
2019	20,235	46.9%	301,909	33.8%	0.269
2020	18,892	43.8%	290,553	32.6%	0.233
2021	493	1.1%	151,878	17.0%	-0.575
Number of unique AHA classes on the index date					
Mean/std	2.8	1.0	1.9	0.7	1.083
1	3,187	7.4%	258,377	29.0%	-0.583
2	14,282	33.1%	500,453	56.1%	-0.475
3	15,454	35.8%	117,519	13.2%	0.546
4	8,078	18.7%	15,038	1.7%	0.587
5+	2,144	5.0%	1,052	0.1%	0.312
Number of unique drug classes in the prior 6 months					
0	263	0.6%	49,263	5.5%	-0.288
1-5	7,196	16.7%	264,325	29.6%	-0.310
6-10	16,958	39.3%	342,337	38.4%	0.019
11-15	11,375	26.4%	164,005	18.4%	0.193
16+	7,353	17.0%	72,509	8.1%	0.271

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Use of AHA					
Prior 0-6 month AHA use					
Metformin	36,976	85.7%	546,289	61.2%	0.577
SU	16,983	39.4%	0	0.0%	NaN
TZD	3,814	8.8%	0	0.0%	NaN
Alpha glucosidase, meglitinides	783	1.8%	8,089	0.9%	0.078
DPP-4 inhibitor	12,754	29.6%	116,686	13.1%	0.411
GLP-1 receptor agonist	6,844	15.9%	45,881	5.1%	0.355
SGLT2 inhibitor	0	0.0%	3,564	0.4%	NaN
Insulin	12,696	29.4%	110,660	12.4%	0.428
Concomitant AHA use on the index date					
Metformin	33,781	78.3%	555,705	62.3%	0.356
SU	13,769	31.9%	786,897	88.2%	-1.403
TZD	2,968	6.9%	113,857	12.8%	-0.199
Alpha glucosidase, meglitinides	637	1.5%	6,421	0.7%	0.073
DPP-4 inhibitor	10,659	24.7%	100,079	11.2%	0.357
GLP-1 receptor agonist	5,863	13.6%	32,687	3.7%	0.359
SGLT2 inhibitor	43,145	100.0%	2,400	0.3%	27.234
Insulin	10,820	25.1%	82,820	9.3%	0.428
Concomitant insulin use on the index date or 29 days prior					
Insulin	11,620	26.9%	92,600	10.4%	0.435
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	422	1.0%	9,979	1.1%	-0.014
Lithium	169	0.4%	3,571	0.4%	-0.001
Terbutaline	0	0.0%	26	0.0%	NaN
Oral corticosteroids	4,303	10.0%	115,030	12.9%	-0.092
Thiazides	5,748	13.3%	115,442	12.9%	0.011
Pentamidine	0	0.0%	****	****	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	351	0.8%	8,367	0.9%	-0.013
Lithium	126	0.3%	2,814	0.3%	-0.004
Terbutaline	0	0.0%	16	0.0%	NaN
Oral corticosteroids	656	1.5%	33,700	3.8%	-0.141
Thiazides	4,693	10.9%	100,574	11.3%	-0.013

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Pentamidine	0	0.0%	****	****	NaN
Comorbidity burden					
Combined comorbidity index	1.0	1.5	1.7	2.5	-0.388
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	6,725	15.6%	199,875	22.4%	-0.174
Acute renal failure	605	1.4%	50,421	5.6%	-0.232
Cerebrovascular disease	1,325	3.1%	71,069	8.0%	-0.216
Myocardial infarction	752	1.7%	37,840	4.2%	-0.147
Stroke	1,094	2.5%	62,153	7.00%	-0.209
Coronary heart disease	3,707	8.6%	167,627	18.8%	-0.300
Heart failure	1,343	3.1%	75,273	8.4%	-0.230
Hypertension	22,976	53.3%	596,988	66.9%	-0.281
Hyperlipidemia	18,989	44.0%	493,327	55.3%	-0.227
Pancreatitis	278	0.6%	7,169	0.8%	-0.019
Hypovolemia	48	0.1%	4,013	0.4%	-0.064
Hypoxemia	846	2.0%	34,382	3.9%	-0.113
Thyroid disorders	4,681	10.8%	153,513	17.2%	-0.184
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	23,272	53.9%	404,082	45.3%	0.174
Neuropathy	7,010	16.2%	147,044	16.5%	-0.006
Retinopathy	4,261	9.9%	59,021	6.6%	0.119
Peripheral vascular disease	2,854	6.6%	103,452	11.6%	-0.174
Amputation	66	0.2%	2,473	0.3%	-0.027
Lifestyle					
Obesity	4,070	9.4%	115,419	12.9%	-0.111
Alcohol use	677	1.6%	18,634	2.1%	-0.039
Tobacco use	2,164	5.0%	51,734	5.8%	-0.035
Cocaine abuse	125	0.3%	3,089	0.3%	-0.010
Severe COVID-19 infection					
COVID-19 Algorithm 4 (i.e., inpatient diagnosis of COVID-19 along with ICU transfer or mechanical ventilation within 14 days prior to the index date)	*****	*****	620	0.1%	*****

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Health services utilization					
Number of generic medications	11.0	6.1	8.2	5.5	0.479
Number of unique pharmacological classes	10.6	5.6	7.9	5.1	0.492
Number of filled prescriptions	39.1	29.0	24.0	22.6	0.582
Number of inpatient encounters	0.1	0.4	0.2	0.6	-0.218
Number of non-acute institutional encounters	0.0	0.1	0.0	0.3	-0.179
Number of emergency department encounters	0.4	1.0	0.4	1.1	-0.012
Number of ambulatory encounters	9.6	11.1	10.0	13.3	-0.035
Number of other ambulatory encounters	6.9	18.5	5.9	16.6	0.055

[1] Value represents standard deviation 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 masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

[Table 6] shows the baseline characteristics of primary new-use episodes of ertugliflozin and SU/TZD after propensity score matching. All variables included in the logistic regression model to estimate the propensity scores had absolute values of standardized difference <0.1 after matching.

Table 6 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	42,907	100.0%	42,907	100.0%	N/A
Unique patients	42,054		42,577		N/A
Demographics[2] on the index date					
Age (years)	53.0	9.8	53.1	10.2	-0.006
Sex, female	22,980	54.6%	23,598	55.4%	-0.016
Calendar year of initiation					
2018	3,522	8.2%	3,335	7.8%	0.016
2019	20,101	46.8%	19,859	46.3%	0.011
2020	18,791	43.8%	19,261	44.9%	-0.022
2021	493	1.1%	452	1.1%	0.009
Use of AHA					
Prior 0-6 month AHA use					
Metformin	36,743	85.6%	37,422	87.2%	-0.046
Alpha glucosidase, meglitinides	763	1.8%	699	1.6%	0.012
DPP-4 inhibitor	12,591	29.3%	12,444	29.0%	0.008
GLP-1 receptor agonist	6,666	15.5%	6,156	14.3%	0.033
Insulin	12,503	29.1%	12,278	28.6%	0.012
Concomitant AHA use on the index date					
Metformin	33,567	78.2%	33,551	78.2%	0.001
Alpha glucosidase, meglitinides	620	1.4%	577	1.3%	0.009
DPP-4 inhibitor	10,536	24.6%	10,487	24.4%	0.003
GLP-1 receptor agonist	5,681	13.2%	5,118	11.9%	0.040
Concomitant insulin use on the index date or 29 days prior					
Insulin	11,432	26.6%	11,216	26.1%	0.011
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	420	1.0%	403	0.9%	0.004
Lithium	169	0.4%	183	0.4%	-0.005
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	4,279	10.0%	4,390	10.2%	-0.009
Thiazides	5,703	13.3%	5,820	13.6%	-0.008

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	350	0.8%	345	0.8%	0.001
Lithium	126	0.3%	142	0.3%	-0.007
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	654	1.5%	674	1.6%	-0.004
Thiazides	4,656	10.9%	4,711	11.0%	-0.004
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	0.9	1.5	1.0	1.5	-0.007
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	6,692	15.6%	6,686	15.6%	0.000
Acute renal failure	605	1.4%	587	1.4%	0.004
Cerebrovascular disease	1,312	3.1%	1,311	3.1%	0.000
Myocardial infarction	747	1.7%	720	1.7%	0.005
Stroke	1,083	2.5%	1,085	7.00%	-0.000
Coronary heart disease	3,663	8.5%	3,702	8.6%	-0.003
Heart Failure	1,335	3.1%	1,340	3.1%	-0.001
Hypertension	22,804	53.1%	23,028	53.7%	-0.010
Hyperlipidemia	18,800	43.8%	18,812	43.8%	-0.001
Pancreatitis	277	0.6%	233	0.5%	0.013
Hypovolemia	48	0.1%	53	0.1%	-0.003
Hypoxemia	837	2.0%	870	2.0%	-0.006
Thyroid disorders	4,632	10.8%	4,636	10.8%	-0.000
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	23,065	53.8%	23,130	53.9%	-0.003
Neuropathy	6,919	16.1%	6,775	15.8%	0.009
Retinopathy	4,198	9.8%	4,086	9.5%	0.009
Peripheral vascular disease	2,828	6.6%	2,857	6.7%	-0.003
Amputation	66	0.2%	66	0.2%	0.000

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Lifestyle					
Obesity	4,019	9.4%	3,967	9.2%	0.004
Alcohol use	675	1.6%	653	1.5%	0.004
Tobacco use	2,146	5.0%	2,096	4.9%	0.005
Cocaine abuse	125	0.3%	118	0.3%	0.003
Health services utilization					
Number of unique pharmacological classes	10.5	5.6	10.6	6.3	-0.016
Number of filled prescriptions	38.8	28.6	39.0	32.6	-0.004
Number of inpatient encounters	0.1	0.4	0.1	0.3	-0.002
Number of emergency department encounters	0.4	1.0	0.4	0.9	-0.003
Number of ambulatory encounters	9.6	11.1	9.6	12.5	-0.003

[1] Value represents standard deviation 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 masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis

10.2.2 New-Use Episodes of Ertugliflozin and SU/TZD in the data from IMEDS-DD partner sites and Optum

A total of 1,337 new-use episodes of ertugliflozin among 1,287 new users of ertugliflozin and 421,500 new-use episodes of SU/TZD among 387,414 new users of SU/TZD were identified between July 1, 2018 and June 30, 2023, based on the "primary new user" definition.

The baseline characteristics of primary new users of ertugliflozin and SU/TZD are shown in [Table 7].

Among the 1,337 ertugliflozin new-use episodes, the mean age was 57.7 years (SD=10.8 years) and 16.3% initiated ertugliflozin as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (60.5%), followed by DPP-4 inhibitors (24.2%) and SUs (22.5%). The most common comorbidities included hyperlipidemia (73.4%) and hypertension (70.2%), and 21.9% had a history of CVD.

Among the 421,500 SU or TZD new-use episodes, the mean age was 65.9 years (SD=10.7 years) and 30.4% initiated SU or TZD as monotherapy. The most commonly utilized

concomitant AHA class at the index date was metformin (60.6%), followed by DPP-4 inhibitors (9.0%) and insulin (8.1%). The most common comorbidities included hypertension (74.2%) and hyperlipidemia (67.3%), and 33.4% had a history of CVD.

Table 7 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New Users of Sulfonylureas/Thiazolidinediones Before Propensity Score Matching in the IMEDS-DD and Optum Databases from July 1, 2018 to June 30, 2023

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	1,337	100.0%	421,500	100.0%	N/A
Unique patients	1,287		387,414		N/A
Demographics[2] on the index date					
Age (years)	57.7	10.8	65.9	10.7	-0.766
Age					
18-44 years	168	12.6%	24,527	5.8%	0.235
45-64 years	855	63.9%	145,083	34.4%	0.618
65-74 years	230	17.2%	159,658	37.9%	-0.476
≥ 75 years	84	6.3%	92,232	21.9%	-0.460
Sex, female	569	44.2%	183,423	47.3%	-0.063
Calendar year of initiation					
2018	116	8.7%	39,393	9.3%	-0.023
2019	328	24.5%	81,568	19.4%	0.125
2020	391	29.2%	88,828	21.1%	0.189
2021	237	17.7%	92,866	22.0%	-0.108
2022	178	13.3%	81,890	19.4%	-0.166
2023	87	6.6%	36,955	8.8%	-0.086
Number of unique AHA classes on the index date					
Mean/std	2.5	1.0	1.8	0.7	0.722
1	218	16.3%	128,233	30.4%	-0.338
2	511	38.2%	235,863	56.0%	-0.361
3	426	31.9%	51,368	12.2%	0.489
4	148	11.1%	5,741	1.4%	0.410
5+	34	2.5%	295	0.1%	0.219
Number of unique drug classes in the prior 6 months					
0	19	1.4%	20,354	4.8%	-0.197
1-5	451	33.7%	145,970	34.6%	-0.019
6-10	552	41.3%	160,858	38.2%	0.064

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
11-15	227	17.0%	68,558	16.3%	0.019
16+	88	6.6%	25,760	6.1%	0.019
Use of AHA					
Prior 0-6 month AHA use					
Metformin	893	66.8%	252,661	59.9%	0.142
SU	385	28.8%	0	0.0%	NaN
TZD	108	8.1%	0	0.0%	NaN
Alpha glucosidase, meglitinides	25	1.9%	2,840	0.7%	0.107
DPP-4 inhibitor	266	19.9%	47,270	11.2%	0.241
GLP-1 receptor agonist	304	22.7%	34,026	8.1%	0.415
SGLT2 inhibitor	0	0.0%	182	0.0%	NaN
Insulin	247	18.5%	47,089	11.2%	0.207
Concomitant AHA use on the index date					
Metformin	809	60.5%	255,410	60.6%	-0.002
SU	301	22.5%	366,263	86.9%	-1.696
TZD	76	5.7%	59,862	14.2%	-0.288
Alpha glucosidase, meglitinides	16	1.2%	2,202	0.5%	0.073
DPP-4 inhibitor	324	24.2%	37,836	9.0%	0.419
GLP-1 receptor agonist	241	18.0%	23,812	5.6%	0.390
SGLT2 inhibitor	1,337	100.0%	108	0.0%	88.338
Insulin	184	13.8%	33,942	8.1%	0.184
Concomitant insulin use on the index date or 29 days prior					
Insulin	212	15.9%	38,462	9.1%	0.205
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	*****	*****	2,027	0.5%	*****
Lithium	*****	*****	834	0.2%	*****
Terbutaline	0	0.0%	14	0.0%	NaN
Oral corticosteroids	133	9.9%	55,846	13.2%	-0.103
Thiazides	146	10.9%	53,770	12.8%	-0.057
Pentamidine	0	0.0%	*****	*****	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	*****	*****	1,618	0.4%	*****
Lithium	*****	*****	656	0.2%	*****
Terbutaline	0	0.0%	*****	*****	NaN

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Oral corticosteroids	20	1.5%	14,665	3.5%	-0.128
Thiazides	119	8.9%	47,340	11.2%	-0.078
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	1.0	1.7	1.7	2.4	-0.364
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	181	13.5%	80,488	19.1%	-0.151
Acute renal failure	32	2.4%	22,265	5.3%	-0.151
Cerebrovascular disease	52	3.9%	31,923	7.6%	-0.159
Myocardial infarction	39	2.9%	20,390	4.8%	-0.100
Stroke	41	3.1%	28,368	6.7%	-0.170
Coronary heart disease	185	13.8%	80,969	19.2%	-0.145
Heart Failure	55	4.1%	38,016	9.0%	-0.199
Hypertension	939	70.2%	312,714	74.2%	-0.088
Hyperlipidemia	981	73.4%	283,573	67.3%	0.134
Pancreatitis	*****	*****	2,907	0.7%	*****
Hypovolemia	*****	*****	1,480	0.4%	*****
Hypoxemia	33	2.5%	20,895	5.0%	-0.132
Thyroid disorders	245	18.3%	72,913	17.3%	0.027
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	710	53.1%	209,273	49.6%	0.069
Neuropathy	261	19.5%	86,104	20.4%	-0.023
Retinopathy	85	6.4%	32,910	7.8%	-0.057
Peripheral vascular disease	108	8.1%	63,550	15.1%	-0.220
Amputation	*****	*****	1,044	0.2%	*****
Lifestyle					
Obesity	280	20.9%	74,298	17.6%	0.084
Alcohol use	*****	*****	8,068	1.9%	*****
Tobacco use	65	4.9%	25,929	6.2%	-0.057
Cocaine abuse	*****	*****	651	0.2%	*****

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Severe COVID-19 infection					
COVID-19 Algorithm 4 (i.e., inpatient diagnosis of COVID-19 along with ICU transfer or mechanical ventilation within 14 days prior to the index date)	0	0.0%	582	0.1%	NaN
Health services utilization					
Number of generic medications	8.1	5.0	7.6	5.0	0.102
Number of unique pharmacological classes	7.8	4.6	7.3	4.7	0.106
Number of filled prescriptions	23.9	18.1	19.7	16.8	0.241
Number of inpatient encounters	0.1	0.3	0.1	0.4	-0.169
Number of non-acute institutional encounters	0.0	0.2	0.0	0.2	-0.040
Number of emergency department encounters	0.3	0.9	0.5	1.4	-0.161
Number of ambulatory encounters	7.5	7.5	8.5	10.1	-0.114
Number of other ambulatory encounters	1.6	3.5	1.8	5.2	-0.040

[1] Value represents standard deviation 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 IMEDS and Optum data, values were masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

[Table 8] shows the baseline characteristics of primary new-use episodes of ertugliflozin and SU/TZD after propensity score matching. All variables included in the logistic regression model to estimate the propensity scores had absolute values of standardized difference <0.1 after matching.

Table 8 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones After Propensity Score Matching in the IMEDS-DD and Optum Databases from July 1, 2018 to June 30, 2023

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	1,335	100.0%	1,335	100.0%	N/A
Unique patients	1,285		1,334		N/A
Demographics					
Age (years)	57.7	10.8	57.3	12.2	0.034
Sex, female	569	44.3%	602	45.1%	-0.017
Calendar Year of Initiation					
2018	115	8.6%	113	8.5%	0.005
2019	328	24.6%	305	22.8%	0.041
2020	390	29.2%	405	30.3%	-0.025
2021	237	17.8%	242	18.1%	-0.010
2022	178	13.3%	183	13.7%	-0.011
2023	87	6.6%	87	6.6%	0.000
Use of AHA					
Prior 0-6 months AHA use					
Metformin	892	66.8%	910	68.2%	-0.029
Alpha glucosidase, meglitinides	25	1.9%	25	1.9%	0.000
DPP-4 inhibitor	266	19.9%	261	19.6%	0.009
GLP-1 receptor agonist	304	22.8%	295	22.1%	0.016
Insulin	247	18.5%	235	17.6%	0.023
Concomitant medication use on the index date					
Metformin	808	60.5%	829	62.1%	-0.032
Alpha glucosidase, meglitinides	16	1.2%	18	1.3%	-0.013
DPP-4 inhibitor	323	24.2%	313	23.4%	0.018
GLP-1 receptor agonist	241	18.1%	234	17.5%	0.014
Concomitant insulin use on the index date or 29 days prior					
Insulin	212	15.9%	194	14.5%	0.038
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	*****	*****	*****	*****	*****
Lithium	*****	*****	*****	*****	*****
Terbutaline	0	0.0%	0	0.0%	NaN

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Oral corticosteroids	133	10.0%	129	9.7%	0.010
Thiazides	146	10.9%	154	11.5%	-0.019
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	*****	*****	*****	*****	*****
Lithium	*****	*****	*****	*****	*****
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	20	1.5%	21	1.6%	-0.006
Thiazides	119	8.9%	132	9.9%	-0.033
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	1.0	1.7	1.0	1.8	-0.017
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	181	13.6%	176	13.2%	0.011
Acute renal failure	31	2.3%	32	2.4%	-0.005
Cerebrovascular disease	52	3.9%	36	2.7%	0.067
Myocardial infarction	39	2.9%	32	2.4%	0.033
Stroke	41	3.1%	25	1.9%	0.077
Coronary heart disease	185	13.9%	174	13.0%	0.024
Heart Failure	55	4.1%	51	3.8%	0.015
Hypertension	937	70.2%	952	71.3%	-0.025
Hyperlipidemia	979	73.3%	1,011	75.7%	-0.055
Pancreatitis	*****	*****	*****	*****	*****
Hypovolemia	*****	*****	*****	*****	*****
Hypoxemia	33	2.5%	34	2.5%	-0.005
Thyroid disorders	244	18.3%	241	18.1%	0.006
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	708	53.0%	739	55.4%	-0.047
Neuropathy	261	19.6%	267	20.0%	-0.011
Retinopathy	85	6.4%	72	5.4%	0.041
Peripheral vascular disease	108	8.1%	123	9.2%	-0.040
Amputation	*****	*****	*****	*****	*****

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Lifestyle					
Obesity	280	21.0%	294	22.0%	-0.026
Alcohol use	*****	*****	*****	*****	*****
Tobacco use	65	4.9%	62	4.6%	0.011
Cocaine abuse	*****	*****	*****	*****	*****
Health services utilization					
Number of unique pharmacological classes	7.8	4.6	8.0	5.1	-0.032
Number of filled prescriptions	23.9	18.1	24.2	22.2	-0.014
Number of inpatient encounters	0.1	0.3	0.1	0.3	-0.023
Number of emergency department encounters	0.3	0.9	0.3	0.8	0.032
Number of ambulatory encounters	7.5	7.5	7.7	9.0	-0.033

[1] Value represents standard deviation 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 IMEDS and Optum data, values were masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

10.2.3 New-Use Episodes of Ertugliflozin and Incretin-based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

A total of 42,249 new-use episodes of ertugliflozin among 41,407 new users of ertugliflozin and 842,438 new-use episodes of incretin-based drugs among 789,956 new users of incretin-based drugs were identified between July 1, 2018 and December 31, 2021, based on the "primary new user" definition.

The baseline characteristics of primary new users of ertugliflozin and incretin-based drugs are shown in [Table 9].

Among the 42,249 ertugliflozin new-use episodes, the mean age was 53.0 years (SD=9.8 years) and 7.5% initiated ertugliflozin as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (78.4%), followed by SU (34.2%) and insulin (24.6%). The most common comorbidities included hypertension (53.0%) and hyperlipidemia (44.0%), and 16.7% had a history of CVD.

Among the 842,438 new-use episodes of incretin-based drugs, the mean age was 64.0 years (SD=10.7 years) and 19.7% initiated an incretin-based drug as monotherapy. The most

commonly utilized concomitant AHA class at the index date was metformin (61.3%), followed by SU (29.7%) and insulin (21.6%). The most common comorbidities included hypertension (72.1%) and hyperlipidemia (60.7%), and 34.3% had a history of CVD.

Table 9 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs Before Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs Databases from July 1, 2018 to December 31, 2021

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	42,249	100.0%	842,438	100.0%	N/A
Unique patients	41,407		789,956		N/A
Demographics[2] on index date					
Age (years)	53.0	9.8	64.0	10.7	-1.071
Age					
18-44 years	8,709	20.6%	87,011	10.3%	0.287
45-64 years	30,941	73.2%	290,836	34.5%	0.843
65-74 years	1,909	4.5%	293,316	34.8%	-0.824
≥ 75 years	690	1.6%	171,275	20.3%	-0.627
Sex, female	22,614	54.6%	442,419	56.0%	-0.028
Calendar Year of Initiation					
2018	3,439	8.1%	128,175	15.2%	-0.222
2019	19,878	47.0%	278,575	33.1%	0.288
2020	18,474	43.7%	269,781	32.0%	0.243
2021	458	1.1%	165,907	19.7%	-0.640
Number of unique AHA classes on the index date					
Mean/std	2.8	1.0	2.2	0.8	0.667
1	3,187	7.5%	165,597	19.7%	-0.359
2	14,189	33.6%	397,418	47.2%	-0.280
3	15,207	36.0%	236,499	28.1%	0.170
4	7,709	18.2%	40,498	4.8%	0.430
5+	1,957	4.6%	2,426	0.3%	0.283
Number of unique drug classes in the prior 6 months					
0	288	0.7%	14,491	1.7%	-0.095
1-5	7,104	16.8%	163,904	19.5%	-0.069
6-10	16,604	39.3%	348,724	41.4%	-0.043
11-15	11,069	26.2%	210,111	24.9%	0.029
16+	7,184	17.0%	105,208	12.5%	0.128

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Use of AHA					
Prior 0-6 month AHA use					
Metformin	36,262	85.8%	548,806	65.1%	0.495
SU	17,111	40.5%	285,910	33.9%	0.136
TZD	3,858	9.1%	50,046	5.9%	0.121
Alpha glucosidase, meglitinides	772	1.8%	11,871	1.4%	0.033
DPP-4 inhibitor	12,299	29.1%	0	0.0%	NaN
GLP-1 receptor agonist	6,479	15.3%	0	0.0%	NaN
SGLT2 inhibitor	0	0.0%	6,228	0.7%	NaN
Insulin	12,217	28.9%	220,276	26.1%	0.062
Concomitant AHA use on the index date					
Metformin	33,109	78.4%	516,813	61.3%	0.377
SU	14,430	34.2%	250,561	29.7%	0.095
TZD	3,279	7.8%	42,610	5.1%	0.111
Alpha glucosidase, meglitinides	631	1.5%	9,451	1.1%	0.033
DPP-4 inhibitor	9,228	21.8%	475,431	56.4%	-0.758
GLP-1 receptor agonist	4,931	11.7%	368,297	43.7%	-0.767
SGLT2 inhibitor	42,249	100.0%	4,514	0.5%	19.268
Insulin	10,405	24.6%	182,282	21.6%	0.071
Concomitant insulin use on the index date or 29 days prior					
Insulin	11,177	26.5%	197,862	23.5%	0.069
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	418	1.0%	10,018	1.2%	-0.019
Lithium	169	0.4%	3,893	0.5%	-0.009
Terbutaline	0	0.0%	42	0.0%	NaN
Oral corticosteroids	4,190	9.9%	112,187	13.3%	-0.106
Thiazides	5,603	13.3%	127,333	15.1%	-0.053
Pentamidine	0	0.0%	*****	*****	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	348	0.8%	8,313	1.0%	-0.017
Lithium	127	0.3%	3,063	0.4%	-0.011
Terbutaline	0	0.0%	21	0.0%	NaN
Oral corticosteroids	654	1.5%	24,308	2.9%	-0.091
Thiazides	4,586	10.9%	104,387	12.4%	-0.048

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Pentamidine	0	0.0%	*****	*****	NaN
Comorbidity burden					
Combined comorbidity index	0.9	1.4	2	2.5	-0.498
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	6,568	15.5%	197,225	23.4%	-0.200
Acute renal failure	590	1.4%	52,821	6.3%	-0.256
Cerebrovascular disease	1,288	3.0%	71,796	8.5%	-0.236
Myocardial infarction	727	1.7%	38,581	4.6%	-0.164
Stroke	1,060	2.5%	62,514	7.00%	-0.228
Coronary heart disease	3,585	8.5%	174,825	20.8%	-0.353
Heart Failure	1,302	3.1%	81,532	9.7%	-0.272
Hypertension	22,408	53.0%	606,980	72.1%	-0.401
Hyperlipidemia	18,576	44.0%	511,573	60.7%	-0.340
Pancreatitis	290	0.7%	4,358	0.5%	0.022
Hypovolemia	44	0.1%	4,082	0.5%	-0.070
Hypoxemia	833	2.0%	35,711	4.2%	-0.131
Thyroid disorders	4,561	10.8%	170,117	20.2%	-0.262
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	22,691	53.7%	453,369	53.8%	-0.002
Neuropathy	6,812	16.1%	177,998	21.1%	-0.129
Retinopathy	4,193	9.9%	76,985	9.1%	0.027
Peripheral vascular disease	2,784	6.6%	115,596	13.7%	-0.238
Amputation	63	0.1%	2,781	0.3%	-0.037
Lifestyle					
Obesity	3,905	9.2%	153,942	18.3%	-0.264
Alcohol use	670	1.6%	14,832	1.8%	-0.014
Tobacco use	2,098	5.0%	49,060	5.8%	-0.038
Cocaine abuse	126	0.3%	2,642	0.3%	-0.003
Severe COVID-19 infection					
COVID-19 Algorithm 4 (i.e., inpatient diagnosis of COVID-19 along with ICU transfer or mechanical ventilation within 14 days prior to the index date)	*****	*****	284	0.0%	*****

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Health services utilization					
Number of generic medications	11.0	6.1	10.0	5.6	0.169
Number of unique pharmacological classes	10.5	5.6	9.6	5.2	0.170
Number of filled prescriptions	39.1	29.0	31.0	25.0	0.301
Number of inpatient encounters	0.1	0.4	0.2	0.6	-0.217
Number of non-acute institutional encounters	0.0	0.1	0.1	0.3	-0.191
Number of emergency department encounters	0.4	1.0	0.4	1.1	-0.015
Number of ambulatory encounters	9.6	11.0	11.7	14.0	-0.169
Number of other ambulatory encounters	6.8	18.5	6.9	18.4	-0.002

[1] Value represents standard deviation 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 masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

[Table 10] shows the baseline characteristics of primary new users of ertugliflozin and SU/TZD after propensity score matching. All variables included in the logistic regression model to estimate the propensity scores had absolute values of standardized difference <0.1 after matching.

Table 10 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs Databases from July 1, 2018 to December 31, 2021

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	42,247	100.0%	42,247	100.0%	N/A
Unique patients	41,405		41,997		N/A
Demographics[2] on the index date					
Age (years)	53.0	9.8	53.0	10.2	0.002
Sex, female	22,613	54.6%	22,942	54.6%	-0.000
Calendar Year of Initiation					
2018	3,439	8.1%	3,341	7.9%	0.009
2019	19,877	47.0%	19,858	47.0%	0.001
2020	18,473	43.7%	18,579	44.0%	-0.005
2021	458	1.1%	469	1.1%	-0.002
Use of AHA					
Prior 0-6 months AHA use					
Metformin	36,260	85.8%	36,265	85.8%	-0.000
SU	17,109	40.5%	17,218	40.8%	-0.005
TZD	3,856	9.1%	3,747	8.9%	0.009
Alpha glucosidase, meglitinides	770	1.8%	734	1.7%	0.006
Insulin	12,217	28.9%	12,190	28.9%	0.001
Concomitant AHA use on the index date					
Metformin	33,107	78.4%	33,123	78.4%	-0.001
SU	14,428	34.2%	14,423	34.1%	0.000
TZD	3,277	7.8%	3,213	7.6%	0.006
Alpha glucosidase, meglitinides	629	1.5%	589	1.4%	0.008
Concomitant insulin use on the index date or 29 days prior					
Insulin	11,177	26.5%	11,123	26.3%	0.003
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	418	1.0%	457	1.1%	-0.009
Lithium	169	0.4%	187	0.4%	-0.007
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	4,190	9.9%	4,184	9.9%	0.000
Thiazides	5,603	13.3%	5,580	13.2%	0.002

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	348	0.8%	382	0.9%	-0.009
Lithium	127	0.3%	133	0.3%	-0.003
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	654	1.5%	682	1.6%	-0.005
Thiazides	4,586	10.9%	4,550	10.8%	0.003
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	0.9	1.4	1	1.4	-0.008
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	6,568	15.5%	6,606	15.6%	-0.002
Acute renal failure	590	1.4%	582	1.4%	0.002
Cerebrovascular disease	1,287	3.0%	1,276	3.0%	0.002
Myocardial infarction	727	1.7%	722	1.7%	0.001
Stroke	1,059	2.5%	1,047	7.00%	0.002
Coronary heart disease	3,585	8.5%	3,583	8.5%	0.000
Heart Failure	1,302	3.1%	1,308	3.1%	-0.001
Hypertension	22,408	53.0%	22,395	53.0%	0.001
Hyperlipidemia	18,574	44.0%	18,588	44.0%	-0.001
Pancreatitis	290	0.7%	298	0.7%	-0.002
Hypovolemia	44	0.1%	47	0.1%	-0.002
Hypoxemia	833	2.0%	841	2.0%	-0.001
Thyroid disorders	4,560	10.8%	4,529	10.7%	0.002
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	22,689	53.7%	22,734	53.8%	-0.002
Neuropathy	6,811	16.1%	6,926	16.4%	-0.007
Retinopathy	4,193	9.9%	4,151	9.8%	0.003
Peripheral vascular disease	2,784	6.6%	2,815	6.7%	-0.003
Amputation	63	0.1%	58	0.1%	0.003

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Lifestyle					
Obesity	3,905	9.2%	3,939	9.3%	-0.003
Alcohol use	670	1.6%	658	1.6%	0.002
Tobacco use	2,097	5.0%	2,051	4.9%	0.005
Cocaine abuse	126	0.3%	111	0.3%	0.007
Health services utilization					
Number of unique pharmacological classes	10.5	5.6	10.6	6.0	-0.005
Number of filled prescriptions	39.1	29.0	39.1	31.7	-0.001
Number of inpatient encounters	0.1	0.4	0.1	0.3	-0.001
Number of emergency department encounters	0.4	1.0	0.4	0.9	-0.001
Number of ambulatory encounters	9.6	11.0	9.6	11.9	-0.004

[1] Value represents standard deviation 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 masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

10.2.4 New-Use Episodes of Ertugliflozin and Incretin-based Drugs in the data from IMEDS-DD partner sites and Optum

A total of 1,195 new-use episodes of ertugliflozin among 1,153 new users of ertugliflozin and 552,942 new-use episodes of incretin-based drugs among 505,095 new users of incretin-based drugs were identified between July 1, 2018 and June 30, 2023, based on the "primary new user" definition.

The baseline characteristics of primary new users of ertugliflozin and incretin-based drugs are shown in [Table 11].

Among the 1,195 ertugliflozin new-use episodes, the mean age was 58.0 years (SD=10.8 years) and 18.2% initiated ertugliflozin as monotherapy. The most commonly utilized concomitant AHA class at the index date was metformin (62.2%), followed by SU (23.5%) and GLP-1 RA (17.2%). The most common comorbidities included hyperlipidemia (73.7%) and hypertension (70.5%), and 22.3% had a history of CVD.

Among the 552,942 new-use episodes of incretin-based drugs, the mean age was 63.8 years (SD=10.9 years) and 24.9% initiated an incretin-based drug as monotherapy. The most

commonly utilized concomitant AHA class at the index date was metformin (57.7%), followed by SU (26.7%) and insulin (16.6%). The most common comorbidities included hypertension (77.3%) and hyperlipidemia (71.1%), and 33.6% had a history of CVD.

Table 11 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs Before Propensity Score Matching in the IMEDS-DD and Optum Databases from July 1, 2018 to June 30, 2023

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	1,195	100.0%	552,942	100.0%	N/A
Unique patients	1,153		505,095		N/A
Demographics[2] on the index date					
Age (years)	58.0	10.8	63.8	10.9	-0.539
Age					
18-44 years	139	11.6%	43,391	7.8%	0.128
45-64 years	765	64.0%	218,212	39.5%	0.507
65-74 years	214	17.9%	199,579	36.1%	-0.419
≥ 75 years	77	6.4%	91,760	16.6%	-0.322
Sex, female	510	44.2%	276,864	54.8%	-0.213
Calendar Year of Initiation					
2018	112	9.4%	34,797	6.3%	0.115
2019	297	24.9%	78,839	14.3%	0.270
2020	341	28.5%	89,590	16.2%	0.299
2021	212	17.7%	114,725	20.7%	-0.076
2022	155	13.0%	133,669	24.2%	-0.291
2023	78	6.6%	101,322	18.5%	-0.365
Number of unique antidiabetic drug classes on the index date					
Mean/std	2.4	1.0	2.1	0.8	0.363
1	218	18.2%	137,726	24.9%	-0.163
2	466	39.0%	263,385	47.6%	-0.175
3	366	30.6%	129,455	23.4%	0.163
4	118	9.9%	21,401	3.9%	0.239
5+	27	2.3%	975	0.2%	0.191
Number of unique drug classes in the prior 6 months					
0	19	1.6%	9,732	1.8%	-0.013
1-5	393	32.9%	136,973	24.8%	0.180
6-10	505	42.3%	230,320	41.7%	0.012

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
11-15	205	17.2%	122,428	22.1%	-0.126
16+	73	6.1%	53,489	9.7%	-0.133
Use of AHA					
Prior 0-6 months AHA use					
Metformin	806	67.4%	346,189	62.6%	0.102
SU	347	29.0%	169,011	30.6%	-0.033
TZD	98	8.2%	34,621	6.3%	0.075
Alpha glucosidase, meglitinides	21	1.8%	4,890	0.9%	0.077
DPP-4 inhibitor	238	19.9%	0	0.0%	NaN
GLP-1 receptor agonist	277	23.2%	0	0.0%	NaN
SGLT2 inhibitor	0	0.0%	291	0.1%	NaN
Insulin	231	19.3%	115,123	20.8%	-0.037
Concomitant AHA use on the index date					
Metformin	743	62.2%	318,878	57.7%	0.092
SU	281	23.5%	147,425	26.7%	-0.073
TZD	74	6.2%	29,335	5.3%	0.038
Alpha glucosidase, meglitinides	12	1.0%	3,719	0.7%	0.036
DPP-4 inhibitor	178	14.9%	193,521	35.0%	-0.478
GLP-1 receptor agonist	205	17.2%	360,117	65.1%	-1.116
SGLT2 inhibitor	1,195	100.0%	192	0.0%	75.880
Insulin	173	14.5%	91,901	16.6%	-0.059
Concomitant insulin use on the index date or 29 days prior					
Insulin	199	16.7%	100,922	18.3%	-0.042
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	*****	*****	3,004	0.5%	*****
Lithium	*****	*****	1,498	0.3%	*****
Terbutaline	0	0.0%	11	0.0%	NaN
Oral corticosteroids	113	9.5%	81,288	14.7%	-0.161
Thiazides	133	11.1%	83,787	15.2%	-0.119
Pentamidine	0	0.0%	*****	*****	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	*****	*****	2,354	0.4%	*****
Lithium	*****	*****	1,174	0.2%	*****
Terbutaline	0	0.0%	*****	*****	NaN

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Oral corticosteroids	17	1.4%	14,130	2.6%	-0.081
Thiazides	106	8.9%	69,558	12.6%	-0.120
Pentamidine	0	0.0%	*****	*****	NaN
Comorbidity burden					
Combined comorbidity index	0.9	1.7	1.7	2.3	-0.375
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	155	13.0%	104,613	18.9%	-0.163
Acute renal failure	26	2.2%	27,865	5.0%	-0.154
Cerebrovascular disease	46	3.8%	39,800	7.2%	-0.147
Myocardial infarction	35	2.9%	25,029	4.5%	-0.084
Stroke	36	3.0%	35,266	6.4%	-0.160
Coronary heart disease	168	14.1%	106,896	19.3%	-0.142
Heart Failure	47	3.9%	51,661	9.3%	-0.219
Hypertension	843	70.5%	427,289	77.3%	-0.154
Hyperlipidemia	881	73.7%	393,336	71.1%	0.058
Pancreatitis	*****	*****	2,189	0.4%	*****
Hypovolemia	*****	*****	1,806	0.3%	*****
Hypoxemia	27	2.3%	29,397	5.3%	-0.161
Thyroid disorders	220	18.4%	114,488	20.7%	-0.058
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	632	52.9%	291,575	52.7%	0.003
Neuropathy	232	19.4%	123,759	22.4%	-0.073
Retinopathy	77	6.4%	50,052	9.1%	-0.098
Peripheral vascular disease	97	8.1%	84,246	15.2%	-0.223
Amputation	*****	*****	1,424	0.3%	*****
Lifestyle					
Obesity	249	20.8%	146,381	26.5%	-0.133
Alcohol use	*****	*****	8,275	1.5%	*****
Tobacco use	58	4.9%	32,474	5.9%	-0.045
Cocaine abuse	*****	*****	696	0.1%	*****

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Severe COVID-19 infection					
COVID-19 Algorithm 4 (i.e., inpatient diagnosis of COVID-19 along with ICU transfer or mechanical ventilation within 14 days prior to the index date)	0	0.0%	331	0.1%	NaN
Health services utilization					
Number of generic medications	8.1	4.8	9.2	5.2	-0.214
Number of unique pharmacological classes	7.8	4.5	8.8	4.8	-0.214
Number of filled prescriptions	24.0	17.9	25.0	18.6	-0.053
Number of inpatient encounters	0.1	0.3	0.1	0.4	-0.132
Number of non-acute institutional encounters	0.0	0.2	0.0	0.2	-0.020
Number of emergency department encounters	0.3	1.0	0.5	1.4	-0.152
Number of ambulatory encounters	7.5	7.5	9.9	10.6	-0.262
Number of other ambulatory encounters	1.6	3.3	2.1	5.3	-0.127

[1] Value represents standard deviation 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 IMEDS and Optum data, values were masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

[Table 12] shows the baseline characteristics of primary new users of ertugliflozin and SU/TZD after propensity score matching. All variables included in the logistic regression model to estimate the propensity scores had standardized differences <0.1 after matching.

Table 12 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs After Propensity Score Matching in the IMEDS-DD and Optum Databases from July 1, 2018 to June 30, 2023

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	1,194	100.0%	1,194	100.0%	N/A
Unique patients	1,152		1,192		N/A
Demographics[2] on the index date					
Age (years)	58.0	10.8	58.0	11.9	-0.004
Sex, female	510	44.3%	546	45.8%	-0.031
Calendar Year of Initiation					
2018	111	9.3%	116	9.7%	-0.014
2019	297	24.9%	318	26.6%	-0.040
2020	341	28.6%	334	28.0%	0.013
2021	212	17.8%	209	17.5%	0.007
2022	155	13.0%	142	11.9%	0.033
2023	78	6.6%	75	6.3%	0.010
Use of AHA					
Prior 0-6 months AHA use					
Metformin	805	67.4%	818	68.5%	-0.023
SU	347	29.1%	376	31.5%	-0.053
TZD	98	8.2%	97	8.1%	0.003
Alpha glucosidase, meglitinides	21	1.8%	24	2.0%	-0.018
Insulin	231	19.3%	226	18.9%	0.011
Concomitant AHA use on the index date					
Metformin	742	62.1%	749	62.7%	-0.012
SU	281	23.5%	288	24.1%	-0.014
TZD	74	6.2%	77	6.4%	-0.010
Alpha glucosidase, meglitinides	12	1.0%	16	1.3%	-0.031
Concomitant insulin use on the index date or 29 days prior					
Insulin	199	16.7%	193	16.2%	0.014
Use of medications associated with DKA					
Baseline medication use					
Clozapine or olanzapine	*****	*****	*****	*****	*****
Lithium	*****	*****	0	0.0%	NaN
Terbutaline	0	0.0%	0	0.0%	NaN

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Oral corticosteroids	113	9.5%	124	10.4%	-0.031
Thiazides	133	11.1%	137	11.5%	-0.011
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	*****	*****	*****	*****	*****
Lithium	*****	*****	0	0.0%	NaN
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	17	1.4%	21	1.8%	-0.027
Thiazides	106	8.9%	112	9.4%	-0.017
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	0.9	1.7	0.9	1.7	0.012
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	155	13.0%	158	13.2%	-0.007
Acute renal failure	25	2.1%	28	2.3%	-0.017
Cerebrovascular disease	46	3.9%	42	3.5%	0.018
Myocardial infarction	35	2.9%	37	3.1%	-0.010
Stroke	36	3.0%	32	2.7%	0.020
Coronary heart disease	168	14.1%	166	13.9%	0.005
Heart Failure	47	3.9%	44	3.7%	0.013
Hypertension	842	70.5%	861	72.1%	-0.035
Hyperlipidemia	880	73.7%	864	72.4%	0.030
Pancreatitis	*****	*****	*****	*****	*****
Hypovolemia	*****	*****	*****	*****	*****
Hypoxemia	27	2.3%	36	3.0%	-0.047
Thyroid disorders	219	18.3%	218	18.3%	0.002
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	631	52.8%	602	50.4%	0.049
Neuropathy	232	19.4%	238	19.9%	-0.013
Retinopathy	77	6.4%	84	7.0%	-0.023
Peripheral vascular disease	97	8.1%	95	8.0%	0.006
Amputation	*****	*****	*****	*****	*****

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Lifestyle					
Obesity	249	20.9%	240	20.1%	0.019
Alcohol use	*****	*****	13	1.1%	*****
Tobacco use	58	4.9%	69	5.8%	-0.041
Cocaine abuse	*****	*****	*****	*****	*****
Health services utilization					
Number of unique pharmacological classes	7.8	4.6	7.9	4.7	-0.020
Number of filled prescriptions	24.0	17.9	24.0	19.7	-0.003
Number of inpatient encounters	0.1	0.3	0.1	0.3	-0.021
Number of emergency department encounters	0.3	1.0	0.3	1.3	-0.043
Number of ambulatory encounters	7.5	7.5	7.4	7.4	0.009

[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 IMEDS and Optum data, values were masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

10.2.5 Descriptive Data of the DKA Cases, Identified by Principal Discharge Diagnosis, among New-Use Episodes of Ertugliflozin, SU/TZD and Incretin-based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

In the ertugliflozin versus SU/TZD comparison pair in the CMS Medicare RIFs and CMS TAF RIFs, among the 42,288 new users of ertugliflozin, 41 experienced a DKA event (hospitalization with DKA as the primary discharge diagnosis), and among 835,324 new users of SU/TZD, 612 experienced a DKA event. The mean number of days between the index date and DKA event were 91.4 and 150.6 among new users of ertugliflozin and SU/TZD, respectively.

In the ertugliflozin versus incretin-based drugs comparison pair, among the 41,407 new users of ertugliflozin, 37 experienced a DKA event, and among 789,956 new users of incretin-based drugs, 613 experienced a DKA event. The mean number of days between the index date and DKA event were 85.4 and 158.0 among new users of ertugliflozin and incretin-based drugs, respectively.

Selected characteristics of new users with a DKA event in each exposure-comparator pair are provided in [Table 13].

Table 13 Descriptive Data of the Diabetic Ketoacidosis Cases, Identified by Principal Discharge Diagnosis, among New Users of Ertugliflozin, Sulfonylurea/Thiazolidinedione and Incretin-Based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Ertugliflozin versus SU/TZD		Ertugliflozin versus Incretin-based Drugs	
	Ertugliflozin	SU/TZD	Ertugliflozin	Incretin-based drugs
Total, N	41	612	37	613
Female, n (%)	25 (61.0%)	328 (53.6%)	25 (67.6%)	346 (56.4%)
Age (years), mean (std)	50.0 (10.1)	58.6 (12.8)	49.1 (10.2)	60.2 (12.6)
Concomitant Insulin Use, n (%)	14 (34.1%)	123 (20.1%)	12 (32.4%)	236 (38.5%)
Number of days between index date and DKA onset, mean (std)	91.4 (96.5)	150.6 (190.1)	85.4 (83.7)	158.0 (196.5)
Number of days between index date and DKA onset, range, n (%)				
0-30	16 (39.0%)	204 (33.3%)	13 (83.7%)	176 (28.7%)
31-60	*****	93 (15.2%)	*****	94 (15.3%)
61-90	*****	48 (7.9%)	*****	57 (9.3%)
91+	16 (39.0%)	267 (43.6%)	13 (35.1%)	286 (46.6%)

***** Due to small cell redaction rules, these cells are masked to prevent small cells (non-zero counts <11) or back-calculations

std: standard deviation; SU/TZD: Sulfonylurea/Thiazolidinedione; DKA: diabetic ketoacidosis

10.2.6 Descriptive Data of the DKA Cases, Identified by Any Discharge Diagnosis, among New-Use Episodes of Ertugliflozin, SU/TZD and Incretin-based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

In the ertugliflozin versus SU/TZD comparison pair in the CMS Medicare RIFs and CMS TAF RIFs, among the 42,288 new users of ertugliflozin, 90 experienced a DKA event (hospitalization with DKA as any of the listed discharge diagnoses), and among 835,324 new users of SU/TZD, 1,859 experienced a DKA event. The mean number of days between the index date and DKA event were 137.6 and 191.0 among new users of ertugliflozin and SU/TZD, respectively.

In the ertugliflozin versus incretin-based drugs comparison pair, among the 41,407 new users of ertugliflozin, 85 experienced a DKA event, and among 789,956 new users of incretin-based drugs, 1,827 experienced a DKA event. The mean number of days between the index date and DKA event were 117.9 and 179.6 among new users of ertugliflozin and incretin-based drugs, respectively.

Selected characteristics of new users with a DKA event in each exposure-comparator pair are provided in [Table 14].

Table 14 Descriptive Data of the Diabetic Ketoacidosis Cases, Identified by Any Discharge Diagnosis, among New Users of Ertugliflozin, Sulfonylurea/Thiazolidinedione and Incretin-Based Drugs in the CMS Medicare RIFs and the CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2022

	Ertugliflozin versus SU/TZD		Ertugliflozin versus Incretin-based Drugs	
	Ertugliflozin	SU/TZD	Ertugliflozin	Incretin-based drugs
Total, N	90	1,859	85	1,827
Female, n (%)	56 (62.2%)	969 (52.1%)	50 (58.8%)	1,002 (54.8%)
Age (years), mean (Std)	49.8 (11.0)	62.4 (12.0)	49.3 (11.6)	63.4 (12.4)
Concomitant Insulin Use, n (%)	45 (50.0%)	316 (17.0%)	39 (45.9%)	654 (35.8%)
Number of days between index date and DKA onset, mean (std)	137.6 (135.5)	191.0 (216.0)	117.9 (122.1)	179.6 (205.3)
Number of days between index date and DKA onset, range, n (%)				
0-30 31-60 61-90 91+	24 (26.7%) 11 (12.2%) 11 (12.2%) 44 (48.9%)	492 (26.4%) 226 (12.2%) 161 (8.7%) 980 (52.7%)	24 (28.2%) 12 (14.1%) 13 (15.3%) 36 (42.4%)	430 (23.5%) 290 (15.9%) 158 (8.7%) 949 (51.9%)

std: standard deviation; SU/TZD: Sulfonylurea/Thiazolidinedione; DKA: diabetic ketoacidosis

10.2.7 At-risk Times and Risk Estimates for DKA Events, Identified by Principal Discharge Diagnosis, among New-Use Episodes of Ertugliflozin and New-Use Episodes of SU/TZD-Primary and Subgroup Analysis in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

[Table 15] includes a summary of the at-risk times and risk estimates for DKA events (hospitalizations with DKA as the primary discharge diagnosis) among new users of ertugliflozin and new users of SU/TZD, overall and among the subgroups of users with and without concomitant insulin use on the index date. Among the 43,145 new-use episodes of ertugliflozin, 41 DKA events were observed (incidence rate: 2.93 per 1,000 person-years). In comparison, the 892,439 new-use episodes of SU/TZD were associated with 612 events (incidence rate: 1.04 per 1,000 person-years). New-use episodes of comparator AHAs served as the referent group in all Cox proportional hazards models. The HR prior to propensity score matching was 1.42 (95% CI 1.02-1.97). After propensity score matching, there were 42,907 new-use episodes each for ertugliflozin and SU/TZD. The matched ertugliflozin episodes accumulated approximately 14,000 person-years of at-risk time. The HR after propensity score matching was 1.88 (95% CI 1.17-3.02). In the subgroup with no concomitant insulin use on the index date, the effect size was higher than that in the subgroup with concomitant insulin use on the index date.

Table 15 Risk Estimates for Diabetic Ketoacidosis among New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones from Primary and Subgroup Analyses in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Primary Analysis							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	13,987.12	0.32	41	2.93	1.42 (1.02-1.97)	0.035
SU/TZD	892,439	587,022.64	0.66	612	1.04		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,907	13,911.67	0.32	41	2.95	1.88 (1.17-3.02)	0.009
SU/TZD	42,907	20,102.42	0.47	30	1.49		
No Concomitant Insulin Use (Days -29, 0)							
Site-adjusted Analysis[1]							
Ertugliflozin	31,525	10,213.52	0.32	27	2.64	1.49 (1.00-2.23)	0.05
SU/TZD	799,839	545,885.56	0.68	489	0.90		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	31,341	10,166.81	0.32	27	2.66	2.34 (1.27-4.31)	0.007
SU/TZD	31,341	15,696.50	0.50	17	1.08		
Concomitant Insulin Use (Days -29, 0)							
Site-adjusted Analysis[1]							
Ertugliflozin	11,620	3,773.60	0.32	14	3.71	0.80 (0.45-1.43)	0.457
SU/TZD	92,600	41,137.08	0.44	123	2.99		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	11,078	3,600.93	0.33	13	3.61	1.17 (0.54-2.52)	0.696
SU/TZD	11,078	4,207.33	0.38	13	3.09		

[1] All analyses implicitly adjusted for data sites, since risk-sets were created within the entire eligible population at each data site.

HR: hazard ratio; CI: confidence interval; SU/TZD: Sulfonylurea/Thiazolidinedione

10.2.8 At-risk Times and Risk Estimates for DKA Events, Identified by Principal Discharge Diagnosis, among New-Use Episodes of Ertugliflozin and New Users Incretin-based Drugs-Primary and Subgroup Analysis in the CMS Medicare RIFs and CMS Medicaid TAF RIFs

[Table 16] includes a summary of the at-risk times and risk estimates for DKA events (hospitalizations with DKA as the primary discharge diagnosis) among new users of ertugliflozin and new users of incretin-based drugs, overall and among the subgroups of users with and without concomitant insulin use on the index date. Among the 42,249 new-use episodes of ertugliflozin, 37 DKA events were observed (incidence rate: 2.76 per 1,000 person-years). In comparison, the 842,438 new-use episodes of incretin-based drugs were associated with 613 events (incidence rate: 1.28 per 1,000 person-years). New-use episodes of comparator AHAs served as the referent group in all cox-proportional hazards models. The HR prior to propensity score matching was 1.47 (95% CI 1.04-2.08). After propensity score matching, there were 42,247 new-use episodes each for ertugliflozin and incretin-based drugs. The matched ertugliflozin episodes accrued 13,398 person-years of at-risk time. The hazard ratio after propensity score matching was 2.40 (95% CI 1.40-4.11). In the subgroup with no concomitant insulin use on the index date, the effect size was higher than that in the subgroup with concomitant insulin use on the index date.

Table 16 Risk Estimates for Diabetic Ketoacidosis among New-Use Episodes of Ertugliflozin and New Users Incretin-Based Drugs from Primary and Subgroup Analyses in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Primary Analysis							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	13,398.67	115.83	37	2.76	1.47 (1.04-2.08)	0.031
Incretins	842,438	479,913.00	208.07	613	1.28		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,247	13,398.66	115.84	37	2.76	2.40 (1.40-4.11)	0.001
Incretins	42,247	19,749.69	170.75	21	1.06		
No Concomitant Insulin Use (Days -29, 0)							
Site-adjusted Analysis[1]							
Ertugliflozin	31,072	10,526.60	123.74	25	2.37	1.72 (1.12-2.64)	0.013
Incretins	644,576	389,000.97	220.43	377	0.97		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	30,869	10,455.21	123.71	25	2.39	2.84 (1.42-5.66)	0.003
Incretins	30,869	15,359.36	181.74	12	0.78		
Concomitant Insulin Use (Days -29, 0)							
Site-adjusted Analysis[1]							
Ertugliflozin	11,177	2,872.07	93.86	12	4.18	1.22 (0.67-2.21)	0.519
Incretins	197,862	90,912.03	167.82	236	2.60		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	10,923	2,805.19	93.80	12	4.28	1.87 (0.79-4.46)	0.156
Incretins	10,923	4,187.04	140.01	*****	*****		

[1] All analyses implicitly adjusted for data sites, since risk-sets were created within the entire eligible population at each data site.

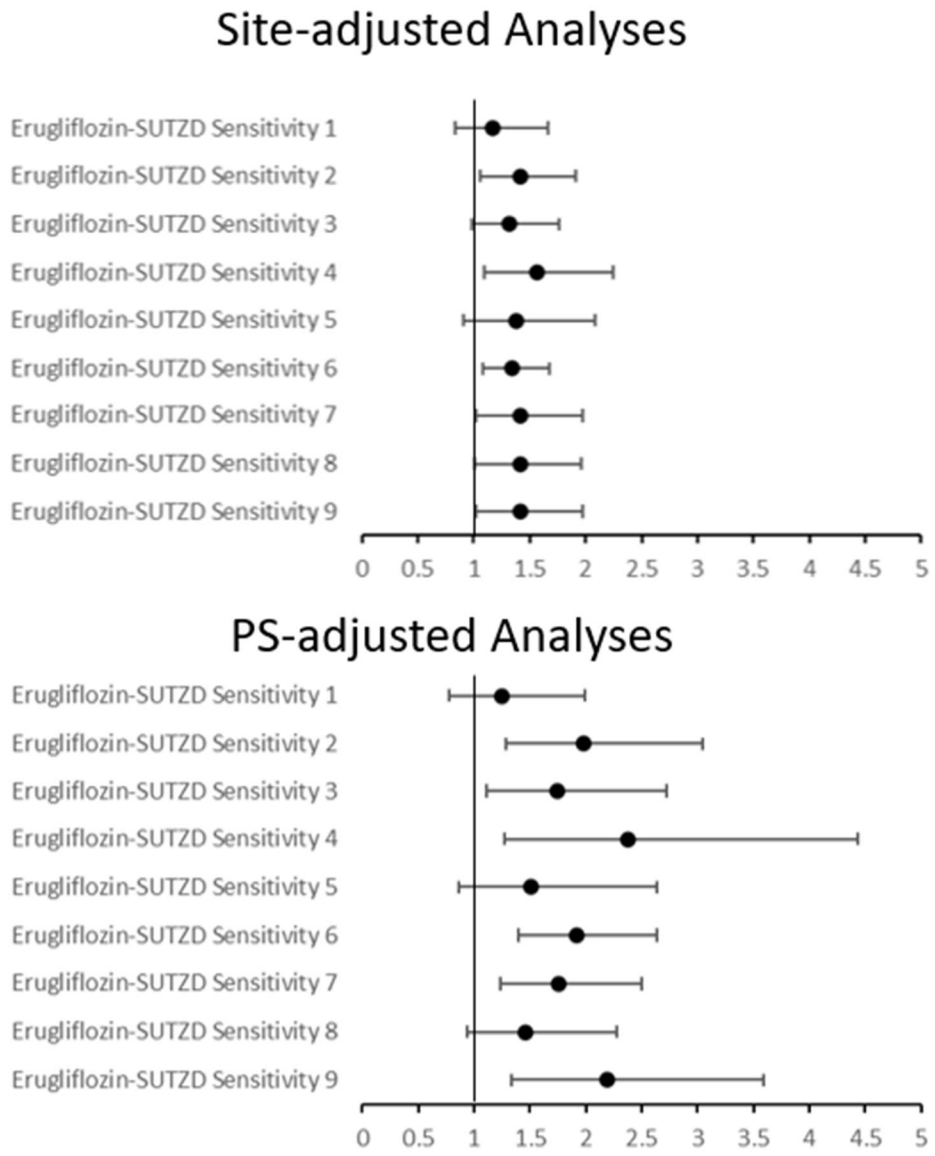
***** Due to small cell redaction rules for CMS data, these cells are masked to prevent small cells (non-zero counts <11) or back-calculations

HR: hazard ratio; CI: confidence interval; SU/TZD: Sulfonylurea/Thiazolidinedione

10.3 Results from Sensitivity Analyses

[Figure 4] shows the results from the site-adjusted and propensity score-adjusted sensitivity analyses comparing new-use episodes of ertugliflozin versus new-use episodes of SU/TZD. After propensity score adjustment, HRs ranged from 1.25 (sensitivity analysis 1-intent-to-treat approach) to 2.37 (sensitivity analysis 4-incident new user definition). The 95% CIs for HRs from all models except sensitivity analyses 1, 5 (narrow T2DM definition), and 8 (single cohort entry per patient) excluded the null.

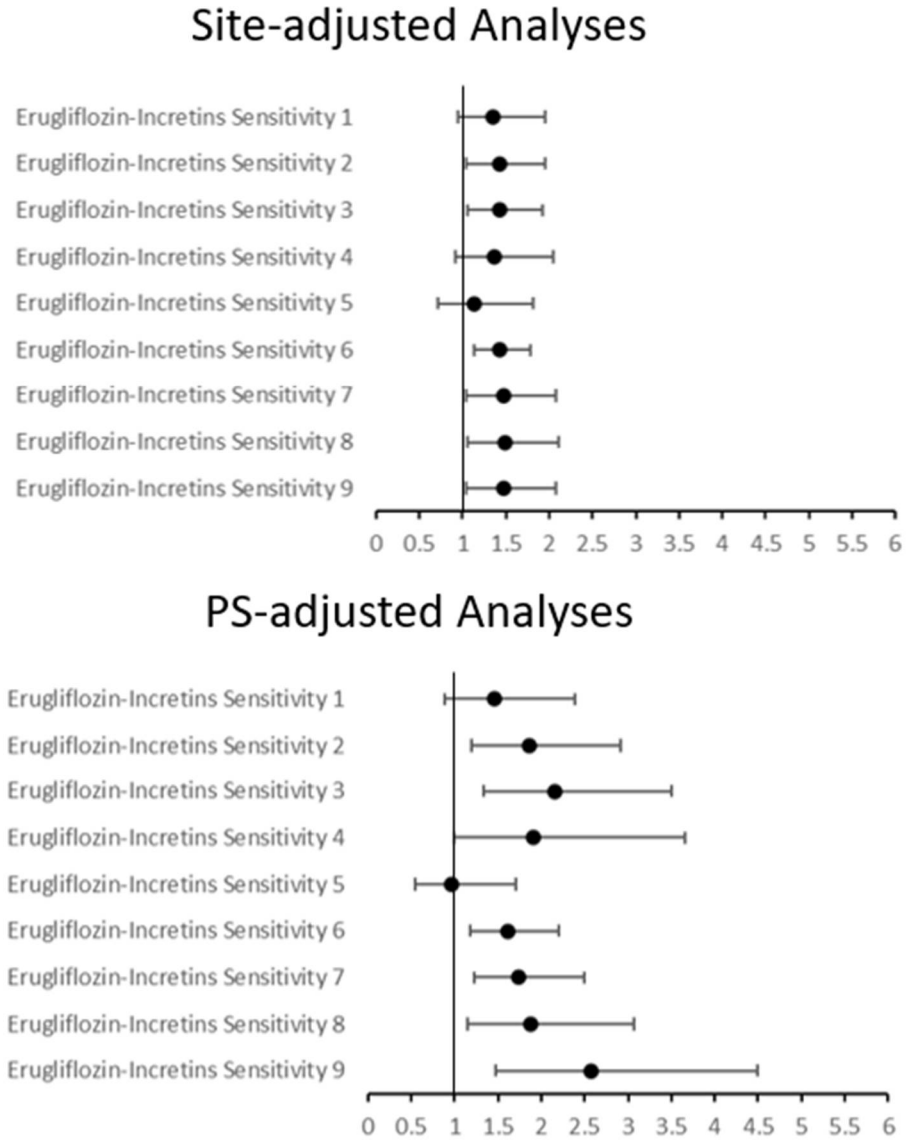
Figure 4 Hazard Ratios from Site-Adjusted and Propensity Score (PS)-Adjusted Sensitivity Analyses Comparing New-Use Episodes of Ertugliflozin versus New-Use Episodes of SU/TZD in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021



Site-adjusted analyses implicitly adjusted for data sites, since risk-sets were created within the entire eligible population at each data site; sensitivity analysis 1: intent-to-treat approach; sensitivity analysis 2: as-treated approach with 90-day grace period; sensitivity analysis 3: as-treated approach with no censoring at switching or treatment augmentation; sensitivity analysis 4: incident new user definition; sensitivity analysis 5: narrow definition of type 2 diabetes mellitus; sensitivity analysis 6: outcome defined as discharge diagnosis of diabetes ketoacidosis in any position; sensitivity analysis 7: propensity score stratification; sensitivity analysis 8: single cohort entry per individual; and sensitivity analysis 9: COVID-19 related variables included in the propensity score estimation models

[Figure 5] shows the results from the site-adjusted and propensity score-adjusted sensitivity analyses comparing new-use episodes of ertugliflozin versus new-use episodes of incretin-based drugs. After propensity score adjustment, HRs ranged from 0.96 (sensitivity analysis 5-discharge diagnosis of DKA in any position as the outcome) to 2.58 (sensitivity analysis 9-propensity score estimation models controlling for COVID-19-related variables). The 95% CIs for HRs from all models except sensitivity analyses 1, 4, and 5 excluded the null.

Figure 5 Hazard Ratios from Site-Adjusted and Propensity Score (PS)-Adjusted Sensitivity Analyses Comparing New-Use Episodes of Ertugliflozin versus New-Use Episodes of Incretin-Based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021



Site-adjusted analyses implicitly adjusted for data sites, since risk-sets were created within the entire eligible population at each data site; sensitivity analysis 1: intent-to-treat approach; sensitivity analysis 2: as-treated approach with 90-day grace period; sensitivity analysis 3: as-treated approach with no censoring at switching or treatment augmentation; sensitivity analysis 4: incident new user definition; sensitivity analysis 5: narrow definition of type 2 diabetes mellitus; sensitivity analysis 6: outcome defined as discharge diagnosis of diabetes ketoacidosis in any position; sensitivity analysis 7: propensity score stratification; sensitivity analysis 8: single cohort entry per individual; and sensitivity analysis 9: COVID-19 related variables included in the propensity score estimation models

At-risk times and risk estimates from all sensitivity analyses are provided in [Annex Table 1].

10.4 Results from Exploratory Analyses

In the propensity score matched cohorts, overlapping person-time of ertugliflozin with a comparator AHA was observed in 7.5% of all ertugliflozin and SU/TZD new-use episodes in the ertugliflozin versus SU/TZD comparison, and 10.8% of all ertugliflozin and incretin-based drugs new-use episodes in the ertugliflozin versus incretin-based drugs comparison. Very few events were observed during the overlap. Details are provided in [Annex Table 2].

11 DISCUSSION

11.1 Key Results

In this large population-based cohort study of patients with T2DM, the risk of hospitalization with a primary discharge diagnosis of DKA was higher among new users of ertugliflozin compared with new users of SU/TZD or incretin-based drugs. In both comparisons, the HRs were higher among new users with no concomitant insulin use than those with concomitant insulin use. In general, the findings were robust across stratified and sensitivity analyses.

The effect estimates from this study are consistent with the findings from prior observational studies that compared DKA risk among users of SGLT2 inhibitors versus other AHAs [Ref. 5.4: 04QDG5, 05LSHQ, 08LJ0X, 052V37, 052X49, 08LJ28, 07WYS2, 08LJ22, 05LSH3, 05LSHP, 08LJML, 0864HV] and meta-analyses of data from randomized controlled trials [Ref. 5.4: 05HF4J, 08LJMF, 08LJQG, 08LJ0S] (see [Annex Table 3]). Recent PASS studies (EUPAS13413; EUPAS23705) have also reported an increased risk of DKA among new users of SGLT2 inhibitors compared with the new users of several non-SGLT2 inhibitor AHAs.

Previous studies have shown heterogeneity in the magnitudes of risk of DKA among individual SGLT2 inhibitors. A population-based cohort study of over 350,000 adults with T2DM from 7 Canadian provinces reported a 3-fold increase in the risk of DKA among users of SGLT2 inhibitors compared to users of DPP-4 inhibitors [Ref. 5.4: 05LSH3] HR, 2.85, 95%, CI, 1.99-4.08. In specific SGLT2 inhibitor analyses, canagliflozin and dapagliflozin were associated with the highest (HR 3.58; 95% CI 2.13-6.03) and lowest (HR 1.86; 95% CI 1.11-3.10) risks, respectively. In another large cohort of privately insured individuals from the US, the HR ranged from 1.49 for canagliflozin to 2.16 for dapagliflozin when compared to DPP-4 inhibitors. The HR ranged from 1.19 for empagliflozin to 1.73 for canagliflozin in comparison with SUs [Ref. 5.4: 08LJ0X].

The HRs for DKA associated with the use of ertugliflozin were higher among the subgroups with no-concomitant insulin use than those with concomitant insulin use. However, it should be noted that the subgroup analyses stratified by concomitant insulin use were limited by fewer events and person-years at risk. A similar finding has been reported previously among users of SGLT2 inhibitors compared to users of DPP-4 inhibitors [Ref. 5.4: 05LSH3]. Though patients with concomitant insulin use in general have more frequent diabetes-related comorbidities and greater background risk of DKA (as shown in [Annex Table 4],

[Annex Table 5], [Annex Table 6], [Annex Table 7]), with the exogenous supply of insulin, the increased risk of DKA among users of SGLT2 inhibitors was mitigated. This mitigation is likely due to the beneficial effect of insulin on suppressing ketogenesis [Ref. 5.4: 08M3K9].

The effect sizes from the current study are generally comparable or lower than ones reported in the referenced studies. Importantly, the incremental absolute risk of DKA associated with ertugliflozin in the current study was 0.26 per 1,000 episodes when compared with SU/TZD, and 0.38 per 1,000 episodes when compared with incretin-based drugs. Thus, the increase in absolute risk associated with ertugliflozin was relatively low. Nevertheless, the findings from this study reinforce the concern that DKA could be an adverse event of SGLT2 inhibitors.

In the unmatched cohorts, it was noted that new users of ertugliflozin were generally younger and less obese, had fewer diabetes-related comorbidities, and less concomitant use of medications associated with DKA than new users of comparator drugs. For DKA cases, there was slightly higher proportion of females in the new users of ertugliflozin. Similar findings have been reported in other PASS study (EUPAS13413) and prior observational studies [Ref. 5.4: 08LJ28, 07WYS2] that investigated the association between SGLT2 inhibitors and DKA.

The analytic models in this study assumed independent DKA risk for patients with multiple entries and no adjustment for within-subject correlation was applied. An examination of frequencies of cohort re-entries and times between successive entries revealed that assuming independent DKA risk was unlikely to substantially bias the effects [Annex Table 8]. This is further supported by similar findings in the sensitivity analyses that restricted cohort entry to once per patient, albeit the 95% CI for the ertugliflozin-SU/TZD comparison in this analysis crossed the null. In the exploratory analysis regarding the overlapping person-time of ertugliflozin with comparator drugs, it was noted that 10.8% or fewer episodes had overlapping person-time, and very few events occurred during the overlap [Annex Table 2], which should have minimum impact on the results.

11.2 Strengths

A key strength of this study is the precision of the estimates, attributed to the large sample size. There were over 40,000 episodes of ertugliflozin in both propensity score matched comparisons. The accrued person-years at risk for the ertugliflozin groups were 13,911 in the ertugliflozin versus SU/TZD comparison and 13,398 in the ertugliflozin versus incretin-based drugs comparison—both being substantially higher than the minimum threshold of 8,819 person-years at risk estimated in the a priori power calculations. A validated algorithm was used for defining the outcome. The new user active comparator cohort increased overlap of measured characteristics between the groups and reduced the potential for unmeasured confounding. Additionally, due to the broad range of potential confounders included in the propensity score models, the risk of major residual confounding was mitigated.

11.3 Limitations

Several limitations should be considered.

First, due to logistical reasons, it was not feasible to aggregate data across the commercially and publicly insured populations to generate combined estimates from the time-to-event analyses. Aggregation across the two insurance groups would have further improved the generalizability of the findings. However, given the limited numbers of ertugliflozin exposures and events in the commercially insured population, incorporating these data is unlikely to alter the conclusions of this study. Moreover, the publicly insured population includes a higher proportion of medically indigent and elderly individuals than the commercially insured. Given their increased susceptibility to DKA, the publicly insured population is crucial for studying the risk of DKA among ertugliflozin users [Ref. 5.4: 08M2N5].

Second, the repeating interval of propensity score estimation and subsequent adjustment were extended from quarter to the entire study period to retain sample size, which prevented the execution of sequential propensity score matching that allows for changing drug utilization patterns over time. However, since about 90% of all ertugliflozin episodes began in 2019 or 2020, significant changes in utilization patterns are not anticipated within this short time frame.

Third, despite the strengths of 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. Nevertheless, these misclassifications and errors are expected to be non-differentially distributed across the exposed and comparator groups.

Fourth, 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 or not itemized under coverage. Race/ethnicity, clinical details such as laboratory results (e.g., HbA1c), and lifestyles are often missing or incomplete.

Fifth, 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. Although this could result in drug exposure misclassification, systematic differences in this misclassification among the exposed and comparator groups were not anticipated.

11.4 Interpretation

In this large population-based cohort study of patients with T2DM, the risk of hospitalization with a primary discharge diagnosis of DKA was higher among new users of ertugliflozin compared with new users of SU/TZD or incretin-based drugs. In general, the findings were robust across stratified and sensitivity analyses and consistent with the findings from prior studies that investigated the association between SGLT2 inhibitors and DKA.

11.5 Generalizability

The data for the time-to-event analyses were derived from a diverse population with large sample size. The study results are likely generalizable to populations with similar characteristics, both within and outside the US.

12 CONCLUSION

This large population-based cohort study of patients with T2DM showed a higher risk of DKA among new users of ertugliflozin compared with SU/TZD or incretin-based drugs. The findings are consistent with prior studies. It is important for physicians and patients to remain vigilant regarding the possibility of DKA as an adverse reaction associated with ertugliflozin.

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ANNEX LIST

Annex Table 1 Risk Estimates for Diabetic Ketoacidosis among New-Use Episodes of Ertugliflozin, Sulfonylureas/Thiazolidinediones, and Incretin-Based Drugs from Sensitivity Analyses in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Ertugliflozin versus SU/TZD comparison							
Sensitivity Analysis 1: Intent to Treat Approach							
Site-adjusted Analysis[1]							
Ertugliflozin	42,288	10,937.83	0.26	35	3.20	1.17 (0.83-1.66)	0.372
SU/TZD	835,324	503,691.54	0.60	648	1.29		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,018	10,878.72	0.26	34	3.13	1.25 (0.78-1.99)	0.353
SU/TZD	42,018	16,176.09	0.38	38	2.35		
Sensitivity Analysis 2: 90-day Grace Period							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	16,990.33	0.39	50	2.94	1.42 (1.0-1.91)	0.019
SU/TZD	892,439	741,681.40	0.83	803	1.08		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,907	16,907.54	0.39	50	2.96	1.98 (1.29-3.04)	0.002
SU/TZD	42,907	25,450.45	0.59	36	1.41		
Sensitivity Analysis 3: No Censoring on Switching or Treatment Augmentation							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	21,436.70	0.50	53	2.47	1.32 (0.98-1.76)	0.067
SU/TZD	892,439	589,625.17	0.66	619	1.05		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,907	21,312.93	0.50	53	2.49	1.74 (1.11-2.72)	0.015
SU/TZD	42,907	20,744.55	0.48	30	1.45		
Sensitivity Analysis 4: Incident New User							
Site-adjusted Analysis[1]							
Ertugliflozin	24,297	11,016.40	0.45	33	3.00	1.56 (1.09-2.24)	0.016
SU/TZD	888,875	586,359.50	0.66	611	1.04		

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	24,292	11,014.25	0.45	33	3.00	2.37 (1.27-4.43)	0.007
SU/TZD	24,292	11,175.06	0.46	14	1.25		
Sensitivity Analysis 5: Narrow Definition of T2DM							
Site-adjusted Analysis[1]							
Ertugliflozin	42,246	13,628.08	0.32	26	1.91	1.38 (0.9-2.08)	0.125
SU/TZD	868,429	571,285.89	0.66	418	0.73		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,019	13,564.67	0.32	26	1.92	1.51 (0.86-2.63)	0.149
SU/TZD	42,019	19,772.11	0.47	24	1.21		
Sensitivity Analysis 6: Discharge Diagnosis of DKA in Any Position							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	13,974.90	0.32	90	6.44	1.34 (1.08-1.67)	0.009
SU/TZD	892,439	586,775.06	0.66	1,859	3.17		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,907	13,900.24	0.32	89	6.40	1.92 (1.39-2.64)	<0.001
SU/TZD	42,907	20,099.15	0.47	65	3.23		
Sensitivity Analysis 7: Propensity Score Stratification							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	13,987.12	0.32	41	2.93	1.42 (1.02-1.97)	0.035
SU/TZD	892,439	587,022.64	0.66	612	1.04		
Propensity Score Adjusted Stratified Analysis; Percentiles= 10							
Ertugliflozin	43,145	13,987.12	0.32	41	2.93	1.76 (1.24-2.50)	0.002
SU/TZD	892,439	559,524.55	0.63	600	1.07		
Sensitivity Analysis 8: Single Cohort Entry per Individual							
Site-adjusted Analysis[1]							
Ertugliflozin	42,288	13,798.57	0.33	41	2.97	1.41 (1.01-1.96)	0.041
SU/TZD	835,324	563,629.06	0.67	589	1.05		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,018	13,710.38	0.33	41	2.99	1.46 (0.94-2.28)	0.094
SU/TZD	42,018	19,881.02	0.47	38	1.91		

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Sensitivity Analysis 9: COVID-19 Related Variables in the Propensity Score Models							
Site-adjusted Analysis[1]							
Ertugliflozin	43,145	13,987.12	0.32	41	2.93	1.42 (1.02-1.97)	0.035
SU/TZD	892,439	587,022.64	0.66	612	1.04		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,908	13,905.68	0.32	41	2.95	2.19 (1.34-3.59)	0.002
SU/TZD	42,908	20,249.57	0.47	26	1.28		
Ertugliflozin versus Incretin-based Drugs Comparison							
Sensitivity Analysis 1: Intent to Treat Approach							
Site-adjusted Analysis[1]							
Ertugliflozin	41,407	10,375.64	0.25	33	3.18	1.35 (0.94-1.95)	0.105
Incretins	789,956	390,309.72	0.49	566	1.45		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	41,404	10,375.60	0.25	33	3.18	1.45 (0.89-2.39)	0.138
Incretins	41,404	14,356.40	0.35	30	2.09		
Sensitivity Analysis 2: 90-day Grace Period							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	16,372.38	0.39	44	2.69	1.43 (1.04-1.96)	0.027
Incretins	842,438	617,700.03	0.73	809	1.31		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,247	16,372.36	0.39	44	2.69	1.86 (1.19-2.92)	0.007
Incretins	42,247	24,997.58	0.59	34	1.36		
Sensitivity Analysis 3: No Censoring on Switching or Treatment Augmentation							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	20,984.49	0.50	53	2.53	1.43 (1.06-1.92)	0.019
Incretins	842,438	483,600.65	0.57	623	1.29		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,247	20,982.72	0.50	53	2.53	2.16 (1.33-3.50)	0.002
Incretins	42,247	20,463.46	0.48	24	1.17		

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Sensitivity Analysis 4: Incident New User							
Site-adjusted Analysis[1]							
Ertugliflozin	24,775	10,803.80	0.44	26	2.41	1.36 (0.91-2.05)	0.136
Incretins	836,210	478,831.64	0.57	608	1.27		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	24,775	10,803.80	0.44	26	2.41	1.91 (1.00-3.65)	0.051
Incretins	24,775	11,421.76	0.46	14	1.23		
Sensitivity Analysis 5: Narrow Definition of T2DM							
Site-adjusted Analysis[1]							
Ertugliflozin	41,381	13,126.42	0.32	20	1.52	1.13 (0.71-1.81)	0.596
Incretins	814,400	463,185.70	0.57	421	0.91		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	41,379	13,126.41	0.32	20	1.52	0.96 (0.54-1.70)	0.886
Incretins	41,379	19,120.04	0.46	29	1.52		
Sensitivity Analysis 6: Discharge Diagnosis of DKA in Any Position							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	13,390.86	0.32	85	6.35	1.42 (1.13-1.79)	0.002
Incretins	842,438	479,649.30	0.57	1,827	3.81		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,247	13,390.84	0.32	85	6.35	1.61 (1.18-2.20)	0.003
Incretins	42,247	19,736.19	0.47	75	3.80		
Sensitivity Analysis 7: Propensity Score Stratification							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	13,398.67	0.32	37	2.76	1.47 (1.04-2.08)	0.031
Incretins	842,438	479,913.00	0.57	613	1.28		
Propensity Score Adjusted Stratified Analysis; Percentiles= 10							
Ertugliflozin	42,249	13,398.66	0.32	37	2.76	1.74 (1.22-2.49)	0.002
Incretins	842,438	464,853.07	0.55	603	1.30		
Sensitivity Analysis 8: Single Cohort Entry per Individual							
Site-adjusted Analysis[1]							
Ertugliflozin	41,407	13,214.90	0.32	37	2.80	1.49 (1.05-2.11)	0.026
Incretins	789,956	460,682.84	0.58	584	1.27		

	Number of Episodes	Person-Years at Risk	Average Person-Years at Risk	Events	Incidence Rate per 1,000 Person-Years	HR (95% CI)	Wald P-value
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	41,404	13,214.86	0.32	37	2.80	1.87 (1.14-3.07)	0.014
Incretins	41,404	19,328.70	0.47	27	1.40		
Sensitivity Analysis 9: COVID-19 Related Variables in the Propensity Score Models							
Site-adjusted Analysis[1]							
Ertugliflozin	42,249	13,398.67	0.32	37	2.76	1.47 (1.04-2.08)	0.031
Incretins	842,438	479,913.00	0.57	613	1.28		
Fixed Ratio 1:1 Propensity Score Matched							
Ertugliflozin	42,247	13,398.66	0.32	37	2.76	2.58 (1.48-4.50)	<0.001
Incretins	42,247	19,695.70	0.47	19	0.96		

[1] All analyses implicitly adjusted for data sites, since risk-sets were created within the entire eligible population at each data site.

HR: hazard ratio; SU/TZD: sulfonylureas/thiazolidinediones: T2DM: type 2 diabetes mellitus; DKA: diabetic ketoacidosis

Annex Table 2 Follow-up Time and Number of Diabetic Ketoacidosis Events for New-Use Episodes of Ertugliflozin, Sulfonylureas/Thiazolidinediones, and Incretin-Based Drugs (Exploratory Analyses of Primary Analysis only) in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

Follow-up Time Category	New Users	New Episodes	New Episodes with an Event	Years at Risk	Average Years at Risk per Episode
Ertugliflozin versus SU/TZD Comparison					
Before Propensity Score Matching					
Ertugliflozin only	42,288	43,145	47	20,618.96	0.48
Overlapping ertugliflozin and SU/TZD	5,328	5,380	*****	2,059.64	0.38
SU/TZD only	835,324	892,439	614	590,968.55	0.66
After Propensity Score Matching					
Ertugliflozin only	42,054	42,907	47	20,494.12	0.48
Overlapping ertugliflozin and SU/TZD	5,240	6,470	*****	2,513.98	0.39
SU/TZD	42,577	42,907	30	20,598.50	0.48
Ertugliflozin versus incretin-based drugs Comparison					
Before Propensity Score Matching					
Ertugliflozin	41,407	42,249	50	20,638.31	0.49
Overlapping ertugliflozin and incretin-based drugs	7,713	7,813	****	3,025.74	0.39
Incretin-based drugs	789,956	842,438	617	484,391.93	0.57
After Propensity Score Matching					
Ertugliflozin	41,405	42,247	50	20,636.54	0.49
Overlapping ertugliflozin and incretin-based drugs	7,612	9,090	*****	3,536.52	0.39
Incretin-based drugs	41,997	42,247	23	20,232.32	0.48

To create the 3 categories, exposure episodes were not censored upon initiation of the comparator drug.

**** Due to small cell redaction rules for CMS data, values were masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

SU/TZD: sulfonylureas/thiazolidinediones

Annex Table 3 Summary of Prior Observational Studies and Meta-Analyses of Randomized Controlled Trials Comparing Risk of Diabetic Ketoacidosis among Users of Sodium-glucose Cotransporter 2 Inhibitors versus Other Antihyperglycemic Agents or Placebo

	Comparison Groups	HR (95% CI)
Observational Studies		
PMID: 28448895 Wang et al	SGLT2is versus non-SGLT2i AHAs	1.13 (0.43-3.00)
PMID: 31456304 Wang et al	SGLT2is versus SUs	**1.43 (1.01-2.01)**
PMID: 35147696 Dawwas et al	SGLT2is versus SUs	**1.56 (1.30-1.87)**
PMID: 28591538 Fralick et al	SGLT2is versus DPP4is	**2.2 (1.4–3.6)**
PMID: 29569427 Kim et al	SGLT2is versus DPP4is	0.96 (0.58-1.57)
PMID: 33236515 Han et al	SGLT2is versus DPP4is	0.96 (0.63-1.46)
PMID: 31467044 Pasternak et al	SGLT2is versus DPP4is	**2.14 (1.17 to 4.09)**
PMID: 33336894 Fralick et al	SGLT2is versus DPP4is	**1.84 [1.26-2.70]**
PMID: 32716707 Douros et al	SGLT2is versus DPP4is	**2.85 (1.99–4.08)**
PMID: 31456304 Wang et al	SGLT2is versus DPP4is	**1.04 (0.80-1.34)**
PMID: 35147696 Dawwas et al	SGLT2is versus DPP4is	**1.63 (1.36-1.96)**
PMID: 30429124 Ueda et al	SGLT2is versus GLP1RAs	**2.14 (1.01 -4.52)**
PMID: 34570599 Patrono et al	SGLT2is versus GLP1RAs	**1.61 (1.39, 1.86)**
PMID: 31456304 Wang et al	SGLT2is versus GLP1RAs	1.05 (0.78-1.42)
PMID: 33495295 Patorno et al	SGLT2is versus GLP1RAs	**1.46 (1.02, 2.07)**
PMID: 32716707 Douros et al	Canagliflozin versus DPP4is	**3.58 (2.13–6.03)**
PMID: 32716707 Douros et al	Empagliflozin versus DPP4is	**2.52 (1.23–5.14)**
PMID: 35147696 Dawwas et al	Canagliflozin versus DPP4is	**1.49 (1.19-1.87)**
PMID: 32716707 Douros et al	Dapagliflozin versus DPP4is	**1.86 (1.11–3.10)**
PMID: 35147696 Dawwas et al	Dapagliflozin versus DPP4is	**2.16 (1.13-4.10)**
PMID: 34729891 Patrono et al	Empagliflozin versus DPP4is	**1.71 (1.08-2.71)**
PMID: 35147696 Dawwas et al	Empagliflozin versus DPP4is	**1.69 (1.19-2.40)**
PMID: 35147696 Dawwas et al	Canagliflozin versus SUs	**1.73 (1.38-2.18)**
PMID: 35147696 Dawwas et al	Dapagliflozin versus SUs	**1.64 (0.96-2.80)**
PMID: 35147696 Dawwas et al	Empagliflozin versus SUs	**1.19 (0.85-1.68)**
Meta Analyses of Randomized Controlled Trials		
PMID: 30424892 Zelniker et al	SGLT2is versus placebo	**2.20 (1.25-3.87)**

	Comparison Groups	HR (95% CI)
PMID: 32364674 Liu et al	SGLT2is versus placebo or active controls	**2.13 (1.38-3.27)***
PMID: 33887983 Qiu et al	SGLT2is versus placebo	**2.57 (1.53-4.31)****
PMID: 34116926 Colacci et al	SGLT2is versus placebo or active controls	**2.46 (1.16-5.21)**

*Peto odds ratio

**pooled risk ratio

HR: hazard ratio; SGLT2i: sodium-glucose Cotransporter 2 inhibitors; AHA: antihyperglycemic agent; SU: sulfonylurea; DPP4i: dipeptidyl peptidase 4 inhibitor; GLP1 RA: Glucagon-like peptide-1 receptor agonist

Annex Table 4 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021 (Episodes with No Concomitant Insulin Use)

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	31,341	100%	31,341	100%	
Unique patients	30,727		31,125		
Demographics[2] on the index date					
Age (years)	53.0	10.0	53.0	10.4	0.002
Sex, female	16,452	53.5%	16,845	54.1%	-0.012
Calendar year of initiation					
2018	2,463	7.9%	2,267	7.2%	0.024
2019	14,566	46.5%	14,593	46.6%	-0.002
2020	13,919	44.4%	14,110	45.0%	-0.012
2021	393	1.3%	371	1.2%	0.006
Use of AHA					
Prior 0-6 month AHA use					
Metformin	27,381	87.4%	27,767	88.6%	-0.038
Alpha glucosidase, meglitinides	551	1.8%	462	1.5%	0.023
DPP-4 inhibitor	9,565	30.5%	9,187	29.3%	0.026
GLP-1 receptor agonist	3,700	11.8%	3,370	10.8%	0.033
Insulin	1,065	3.4%	1,053	3.4%	0.002
Concomitant AHA use on the index date					
Metformin	25,139	80.2%	25,048	79.9%	0.007
Alpha glucosidase, meglitinides	461	1.5%	398	1.3%	0.017
DPP-4 inhibitor	8,133	26.0%	7,829	25.0%	0.022
GLP-1 receptor agonist	3,212	10.2%	2,836	9.0%	0.041
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	304	1.0%	289	0.9%	0.005
Lithium	121	0.4%	138	0.4%	-0.008
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	3,077	9.8%	3,255	10.4%	-0.019

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Thiazides	3,841	12.3%	4,062	13.0%	-0.021
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	249	0.8%	249	0.8%	0.000
Lithium	90	0.3%	105	0.3%	-0.009
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	460	1.5%	509	1.6%	-0.013
Thiazides	3,155	10.1%	3,283	10.5%	-0.013
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	0.8	1.4	0.8	1.4	-0.004
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	4,316	13.8%	4,269	13.6%	0.004
Acute renal failure	315	1.0%	307	1.0%	0.003
Cerebrovascular disease	861	2.7%	837	2.7%	0.005
Myocardial infarction	461	1.5%	462	1.5%	-0.000
Stroke	696	2.2%	680	2.2%	0.003
Coronary heart disease	2,379	7.6%	2,437	7.8%	-0.007
Heart Failure	764	2.4%	826	2.6%	-0.013
Hypertension	16,114	51.4%	16,385	52.3%	-0.017
Hyperlipidemia	13,696	43.7%	13,743	43.8%	-0.003
Pancreatitis	162	0.5%	135	0.4%	0.013
Hypovolemia	25	0.1%	25	0.1%	0.000
Hypoxemia	519	1.7%	553	1.8%	-0.008
Thyroid disorders	3,324	10.6%	3,362	10.7%	-0.004
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	14,877	47.5%	15,085	48.1%	-0.013
Neuropathy	4,041	12.9%	3,820	12.2%	0.021
Retinopathy	2,250	7.2%	2,226	7.1%	0.003
Peripheral vascular disease	1,740	5.6%	1,653	5.3%	0.012

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Amputation	24	0.1%	24	0.1%	0.000
Lifestyle					
Obesity	2,616	8.3%	2,685	8.6%	-0.008
Alcohol use	468	1.5%	458	1.5%	0.003
Tobacco use	1,468	4.7%	1,477	4.7%	-0.001
Cocaine abuse	76	0.2%	73	0.2%	0.002
Health services utilization					
Number of unique pharmacological classes	9.8	5.3	9.9	6.1	-0.017
Number of filled prescriptions	35.0	26.5	35.2	30.8	-0.008
Number of inpatient encounters	0.1	0.3	0.1	0.3	-0.008
Number of emergency department encounters	0.3	1.0	0.3	0.8	-0.002
Number of ambulatory encounters	8.9	10.5	9.1	12.1	-0.021

[1] Value represents standard deviation 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 masked in order to prevent displaying small cells (non-zero counts <11) or back-calculations.

NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis

Annex Table 5 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Sulfonylureas/Thiazolidinediones After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021 (Episodes with Concomitant Insulin Use)

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	11,078	100%	11,078	100%	
Unique patients	10,944		11,002		
Demographics[2] on the index date					
Age (years)	53.1	9.3	53.4	9.8	-0.031
Sex, female	6,299	57.6%	6,487	59.0%	-0.029
Calendar year of initiation					
2018	953	8.6%	1,010	9.1%	-0.018
2019	5,348	48.3%	5,054	45.6%	0.053
2020	4,679	42.2%	4,933	44.5%	-0.046
2021	98	0.9%	81	0.7%	0.017
Use of AHA					
Prior 0-6 month AHA use					
Metformin	9,122	82.3%	9,283	83.8%	-0.039
Alpha glucosidase, meglitinides	201	1.8%	229	2.1%	-0.018
DPP-4 inhibitor	2,914	26.3%	3,177	28.7%	-0.053
GLP-1 receptor agonist	2,893	26.1%	2,739	24.7%	0.032
Insulin	11,078	100.0%	11,077	100.0%	0.013
Concomitant AHA use on the index date					
Metformin	8,186	73.9%	8,133	73.4%	0.011
Alpha glucosidase, meglitinides	150	1.4%	174	1.6%	-0.018
DPP-4 inhibitor	2,304	20.8%	2,591	23.4%	-0.062
GLP-1 receptor agonist	2,407	21.7%	2,245	20.3%	0.036
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	108	1.0%	110	1.0%	-0.002
Lithium	44	0.4%	44	0.4%	0.000
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	1,138	10.3%	1,078	9.7%	0.018

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Thiazides	1,786	16.1%	1,699	15.3%	0.022
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	95	0.9%	94	0.8%	0.001
Lithium	34	0.3%	36	0.3%	-0.003
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	183	1.7%	155	1.4%	0.021
Thiazides	1,439	13.0%	1,374	12.4%	0.018
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	1.3	1.5	1.3	1.6	-0.038
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	2,226	20.1%	2,339	21.1%	-0.025
Acute renal failure	249	2.2%	273	2.5%	-0.014
Cerebrovascular disease	425	3.8%	459	4.1%	-0.016
Myocardial infarction	274	2.5%	251	2.3%	0.014
Stroke	364	3.3%	392	3.5%	-0.014
Coronary heart disease	1,233	11.1%	1,238	11.2%	-0.001
Heart Failure	542	4.9%	499	4.5%	0.018
Hypertension	6,437	58.1%	6,426	58.0%	0.002
Hyperlipidemia	4,914	44.4%	4,921	44.4%	-0.001
Pancreatitis	109	1.0%	97	0.9%	0.011
Hypovolemia	20	0.2%	26	0.2%	-0.012
Hypoxemia	297	2.7%	298	2.7%	-0.001
Thyroid disorders	1,262	11.4%	1,236	11.2%	0.007
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	7,889	71.2%	7,805	70.5%	0.017
Neuropathy	2,772	25.0%	2,886	26.1%	-0.024
Retinopathy	1,901	17.2%	1,810	16.3%	0.022
Peripheral vascular disease	1,034	9.3%	1,175	10.6%	-0.042

	Ertugliflozin		SU/TZD		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Amputation	36	0.3%	41	0.4%	-0.008
Lifestyle					
Obesity	1,342	12.1%	1,247	11.3%	0.027
Alcohol use	187	1.7%	180	1.6%	0.005
Tobacco use	638	5.8%	593	5.4%	0.018
Cocaine abuse	44	0.4%	42	0.4%	0.003
Health services utilization					
Number of unique pharmacological classes	12.5	5.8	12.7	6.3	-0.036
Number of filled prescriptions	49.5	31.2	49.8	35.1	-0.010
Number of inpatient encounters	0.1	0.4	0.1	0.4	-0.005
Number of emergency department encounters	0.5	1.1	0.5	1.0	-0.026
Number of ambulatory encounters	11.5	12.2	11.2	13.4	0.024

[1] Value represents standard deviation 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.

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NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis

Annex Table 6 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs Databases from July 1, 2018 to December 31, 2021 (Episodes with No Concomitant Insulin Use)

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	30,869	100%	30,869	100%	
Unique patients	30,253		30,693		
Demographics[2] on the index date					
Age (years)	53.0	10.0	53.0	10.4	0.005
Sex, female	16,183	53.5%	16,506	53.8%	-0.006
Calendar Year of Initiation					
2018	2,410	7.8%	2,419	7.8%	-0.001
2019	14,412	46.7%	14,487	46.9%	-0.005
2020	13,681	44.3%	13,585	44.0%	0.006
2021	366	1.2%	378	1.2%	-0.004
Use of AHA					
Prior 0-6 months AHA use					
Metformin	27,014	87.5%	26,991	87.4%	0.002
SU	13,382	43.4%	13,631	44.2%	-0.016
TZD	2,841	9.2%	2,814	9.1%	0.003
Alpha glucosidase, meglitinides	554	1.8%	523	1.7%	0.008
Insulin	1,034	3.3%	1,056	3.4%	-0.004
Concomitant AHA use on the index date					
Metformin	24,809	80.4%	24,812	80.4%	-0.000
SU	11,500	37.3%	11,649	37.7%	-0.010
TZD	2,451	7.9%	2,440	7.9%	0.001
Alpha glucosidase, meglitinides	468	1.5%	432	1.4%	0.010
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	304	1.0%	328	1.1%	-0.008
Lithium	124	0.4%	130	0.4%	-0.003
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	3,000	9.7%	3,105	10.1%	-0.011

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Thiazides	3,776	12.2%	3,930	12.7%	-0.015
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	250	0.8%	279	0.9%	-0.010
Lithium	92	0.3%	93	0.3%	-0.001
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	461	1.5%	504	1.6%	-0.011
Thiazides	3,112	10.1%	3,242	10.5%	-0.014
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	0.8	1.4	0.8	1.4	-0.006
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	4,244	13.7%	4,264	13.8%	-0.002
Acute renal failure	301	1.0%	334	1.1%	-0.011
Cerebrovascular disease	844	2.7%	839	2.7%	0.001
Myocardial infarction	447	1.4%	463	1.5%	-0.004
Stroke	681	2.2%	673	2.2%	0.002
Coronary heart disease	2,325	7.5%	2,363	7.7%	-0.005
Heart Failure	736	2.4%	771	2.5%	-0.007
Hypertension	15,851	51.3%	15,888	51.5%	-0.002
Hyperlipidemia	13,497	43.7%	13,613	44.1%	-0.008
Pancreatitis	171	0.6%	190	0.6%	-0.008
Hypovolemia	24	0.1%	30	0.1%	-0.007
Hypoxemia	516	1.7%	546	1.8%	-0.007
Thyroid disorders	3,256	10.5%	3,327	10.8%	-0.007
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	14,632	47.4%	14,576	47.2%	0.004
Neuropathy	3,970	12.9%	3,939	12.8%	0.003
Retinopathy	2,246	7.3%	2,263	7.3%	-0.002
Peripheral vascular disease	1,726	5.6%	1,648	5.3%	0.011

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Amputation	26	0.1%	15	0.0%	0.014
Lifestyle					
Obesity	2,532	8.2%	2,596	8.4%	-0.008
Alcohol use	465	1.5%	451	1.5%	0.004
Tobacco use	1,416	4.6%	1,462	4.7%	-0.007
Cocaine abuse	79	0.3%	73	0.2%	0.004
Health services utilization					
Number of unique pharmacological classes	9.8	5.3	9.9	5.8	-0.019
Number of filled prescriptions	35.2	26.8	35.6	29.7	-0.012
Number of inpatient encounters	0.1	0.3	0.1	0.3	-0.009
Number of emergency department encounters	0.3	1.0	0.3	0.8	-0.005
Number of ambulatory encounters	8.9	10.4	9.1	11.4	-0.019

[1] Value represents standard deviation 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.

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NaN: Not a number; AHA: antihyperglycemic agent; std: standard deviation; SU: sulfonylurea; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; DKA: diabetic ketoacidosis.

Annex Table 7 Aggregated Baseline Characteristics of New-Use Episodes of Ertugliflozin and New-Use Episodes of Incretin-Based Drugs After Propensity Score Matching in the CMS Medicare RIFs and CMS Medicaid TAF RIFs Databases from July 1, 2018 to December 31, 2021 (Episodes with Concomitant Insulin Use)

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Episodes	10,923	100%	10,923	100%	
Unique patients	10,788		10,879		
Demographics[2] on the index date					
Age (years)	53.1	9.3	53.1	9.7	-0.007
Sex, female	6,214	57.6%	6,187	56.9%	0.015
Calendar Year of Initiation					
2018	941	8.6%	833	7.6%	0.036
2019	5,285	48.4%	5,168	47.3%	0.021
2020	4,609	42.2%	4,833	44.2%	-0.041
2021	88	0.8%	89	0.8%	-0.001
Use of AHA					
Prior 0-6 months AHA use					
Metformin	8,928	81.7%	8,957	82.0%	-0.007
SU	3,551	32.5%	3,426	31.4%	0.025
TZD	978	9.0%	901	8.2%	0.025
Alpha glucosidase, meglitinides	204	1.9%	204	1.9%	0.000
Insulin	10,923	100.0%	10,922	100.0%	0.014
Concomitant AHA use on the index date					
Metformin	8,006	73.3%	7,986	73.1%	0.004
SU	2,785	25.5%	2,631	24.1%	0.033
TZD	792	7.3%	750	6.9%	0.015
Alpha glucosidase, meglitinides	152	1.4%	151	1.4%	0.001
Use of medications associated with DKA					
Prior 0-6 months medication use					
Clozapine or olanzapine	107	1.0%	123	1.1%	-0.014
Lithium	42	0.4%	54	0.5%	-0.017
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	1,131	10.4%	1,031	9.4%	0.031

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Thiazides	1,748	16.0%	1,594	14.6%	0.039
Pentamidine	0	0.0%	0	0.0%	NaN
Concomitant medication use on the index date					
Clozapine or olanzapine	93	0.9%	97	0.9%	-0.004
Lithium	32	0.3%	37	0.3%	-0.008
Terbutaline	0	0.0%	0	0.0%	NaN
Oral corticosteroids	188	1.7%	171	1.6%	0.012
Thiazides	1,417	13.0%	1,265	11.6%	0.042
Pentamidine	0	0.0%	0	0.0%	NaN
Comorbidity burden					
Combined comorbidity index	1.3	1.5	1.3	1.6	-0.019
Pre-existing comorbidities					
Acute illness (i.e., serious infection, surgery, trauma, acute febrile illness, or sepsis)	2,223	20.4%	2,249	20.6%	-0.006
Acute renal failure	264	2.4%	229	2.1%	0.022
Cerebrovascular disease	415	3.8%	417	3.8%	-0.001
Myocardial infarction	276	2.5%	253	2.3%	0.014
Stroke	355	3.3%	358	3.3%	-0.002
Coronary heart disease	1,210	11.1%	1,176	10.8%	0.010
Heart Failure	544	5.0%	512	4.7%	0.014
Hypertension	6,300	57.7%	6,261	57.3%	0.007
Hyperlipidemia	4,891	44.8%	4,792	43.9%	0.018
Pancreatitis	119	1.1%	103	0.9%	0.015
Hypovolemia	17	0.2%	14	0.1%	0.007
Hypoxemia	294	2.7%	280	2.6%	0.008
Thyroid disorders	1,252	11.5%	1,161	10.6%	0.027
Diabetic complications					
Moderate to severe renal insufficiency (i.e. stage 3-5 chronic kidney disease or end stage renal disease) or diabetic nephropathy	7,769	71.1%	7,898	72.3%	-0.026
Neuropathy	2,750	25.2%	2,910	26.6%	-0.033
Retinopathy	1,895	17.3%	1,839	16.8%	0.014
Peripheral vascular disease	1,014	9.3%	1,136	10.4%	-0.038

	Ertugliflozin		Incretin-based drugs		Standardized Difference
	N/mean	%/std[1]	N/mean	%/std[1]	
Amputation	28	0.3%	42	0.4%	-0.023
Lifestyle					
Obesity	1,324	12.1%	1,286	11.8%	0.011
Alcohol use	195	1.8%	193	1.8%	0.001
Tobacco use	654	6.0%	560	5.1%	0.038
Cocaine abuse	42	0.4%	33	0.3%	0.014
Health services utilization					
Number of unique pharmacological classes	12.6	5.9	12.5	6.1	0.023
Number of filled prescriptions	50.0	32.1	49.3	34.4	0.020
Number of inpatient encounters	0.1	0.4	0.1	0.4	0.015
Number of emergency department encounters	0.5	1.1	0.5	1.0	0.008
Number of ambulatory encounters	11.5	12.2	11.2	13.0	0.030

[1] Value represents standard deviation where no % follows.

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Annex Table 8 Time to Cohort Re-Entry among New-Use Episodes of Ertugliflozin, Sulfonylureas/Thiazolidinediones, and Incretin-Based Drugs in the CMS Medicare RIFs and CMS Medicaid TAF RIFs from July 1, 2018 to December 31, 2021

	Number of New-use episodes	Mean	Std	Min	Q1	Median	Q3	Max
Ertugliflozin versus SU/TZD Primary Analysis								
Before Propensity Score Matching								
Ertugliflozin to Ertugliflozin	767	399.71	136.23	213	294	371.7	478	839
SU/TZD to SU/TZD	56,840	509.09	201.91	186	349	469.8	639	1,278
Ertugliflozin to SU/TZD	2,790	228.02	183.82	1	77	190.1	345	1,230
SU/TZD to Ertugliflozin	6,028	231.04	204.28	1	57	177.2	361	1,216
After Propensity Score Matching								
Ertugliflozin to Ertugliflozin	827	403.31	135.50	213	297	377.7	484	839
SU/TZD to SU/TZD	316	431.24	148.51	213	312	407.3	534	842
Ertugliflozin to SU/TZD	863	212.46	174.03	1	71	175.5	317	796
SU/TZD to Ertugliflozin	1,001	210.36	188.21	1	51	161.0	327	856
Ertugliflozin versus Incretin-based Drugs Primary Analysis								
Before Propensity Score Matching								
Ertugliflozin to Ertugliflozin	715	397.51	132.08	213	293	371.7	480	839
Incretins to Incretins	52,095	511.99	207.23	188	349	467.6	643	1,278
Ertugliflozin to Incretins	4,835	203.04	179.97	1	55	158.5	312	1,135
Incretins to Ertugliflozin	7,163	221.35	200.29	1	57	169.9	338	1,181
After Propensity Score Matching								
Ertugliflozin to Ertugliflozin	815	404.99	135.74	213	296	379.4	492	839
Incretins to Incretins	242	422.27	138.01	210	303	407.6	519	876
Ertugliflozin to Incretins	991	199.72	180.73	1	54	145.5	309	853
Incretins to Ertugliflozin	1,210	208.24	186.00	1	59	155.0	314	863

Min: Minimum; Q1: first quartile; Q3: third quartile; Max: maximum; SU/TZD: sulfonylureas/thiazolidinediones