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APPLICATION NUMBER:

209803Orig1s000
209805Orig1s000
209806Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	NDA 209803, NDA 209805, and NDA 209806
Priority or Standard	Standard
Submit Date(s)	December 19, 2016
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Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Established Name	**NDA 209803:** Ertugliflozin **NDA 209805:** Ertugliflozin and Sitagliptin Fixed Combination Drug Product (FCDP) **NDA 209806:** Ertugliflozin and Metformin FCDP
(Proposed) Trade Name	STEGLATRO STEGLUJAN SEGLUROMET
Applicant	Merck Sharpe and Dohme Corp.
Formulation(s)	Ertugliflozin 5 mg and 15 mg tablet Ertugliflozin/Sitagliptin FCDP: (b) (4) 5 mg/100 mg, and 15 mg/100 mg tablets Ertugliflozin/Metformin FCDP: 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg tablets
Dosing Regimen	Taken once daily in the morning (STEGLATRO and STEGLUJAN) and Taken twice daily with meals (SEGLUROMET)
Proposed Indication(s)	**NDA 209803:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) **NDA 209805:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both ertugliflozin and sitagliptin is appropriate **NDA 209806:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4)

Intended Population(s)	Patients with T2D
Recommended Indication(s)	**NDA 209803:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) **NDA 209805:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both ertugliflozin and sitagliptin is appropriate **NDA 209806:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
Recommendation on Regulatory Action	Approval (pending labeling negotiations)

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Glossary

4-MSU	4-Month Safety Update
AACE	American Association of Clinical Endocrinologists
AC	Advisory Committee
ACE	American College of Endocrinology
ACEI	Angiotensin Converting Enzyme Inhibitor
ACP	American College of Physicians
ADA	American Diabetes Association
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	Antihyperglycemic Agent
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
ASaT	All Subjects As Treated
AST	Aspartate Aminotransferase
AUC	Area-Under-the-Curve
B-CELL	Beta-Cell
BE	Bioequivalence
BID	Twice Daily (‘Bis in Die’)
BILI	Bilirubin
BL	Baseline
BMD	Bone Mineral Density
BMI	Body Mass Index
BPCA	Best Pharmaceuticals for Children Act
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
BW	Body Weight
Ca	Calcium
CAC	Clinical Adjudication Committee
CANVAS	Canagliflozin Cardiovascular Assessment Study
CANVAS-R	Study of the Effects of Canagliflozin on Renal Endpoints
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CEC	Clinical Events Committee
CFR	Code of Federal Regulations

CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CL/F	Clearance/Fraction
cLDA	Constrained Longitudinal Data Analysis
C_{MAX}	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Controls
CMQ	Custom MedDRA Query
CO2	Total Carbon Dioxide (Bicarbonate)
CrCl	Creatinine Clearance
CREAT	Creatinine
CRF	Case Report Form
CRP	C-Reactive Protein
CRRT	Continuous Renal Replacement Therapy
CRT	Clinical Review Template
CSR	Clinical Study Report
CT	Computerized Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
CVMA	Cardiovascular Meta-Analysis
CVOT	Cardiovascular Outcomes Trial
CYP3A4/5	Cytochrome P450 3A4/5
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complication Trial
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DMF	Drug Master File
DPP-4	Dipeptidyl Peptidase-4
Dx	Diagnosis
DXA	Dual-Energy X-Ray Absorptiometry
EASD	European Association for the Study of Diabetes
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ER	Emergency Room
ERTU	Ertugliflozin
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESRD	End Stage Renal Disease
EU	European Union
FAERS	FDA Adverse Event Reporting System

FAS	Full Analysis Set
FBG	Fasting Blood Glucose
FCDP	Fixed Combination Drug Product
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDCA	Food Drug and Cosmetic Act
FEV	Forced Expiratory Volume
FPG	Fasting Plasma Glucose
G6PD	Glucose-6-Phosphate Dehydrogenase
GAD	Glutamic Acid Decarboxylase
GCP	Good Clinical Practice
GI	Gastrointestinal
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLIM	Glimepiride
GLP-1	Glucagon-Like Peptide-1
GM	Geometric Mean
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HCl	Hydrochloride
HCO_3	Bicarbonate
HCT	Hematocrit
HDL-C	High-Density Lipoprotein Cholesterol
Hgb	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
hOAT-3	Human Organic Anion Transporter-3
Hx	History
ICH	International Conference on Harmonization
ICRC	Internal Case Review Committee
IM	Intramuscular
IND	Investigational New Drug
INF	Infinity
INR	International Normalized Ratio
IP	Investigational Product
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
IU	International Unit
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System

IWRS	Integrated Web Response System
JDRF	Juvenile Diabetes Research Foundation
K	Potassium
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
LLN	Lower Limit of Normal
LPGA	L-pyroglutamic acid
Lymph	Lymphocyte
MACE	Major Adverse Cardiovascular Events
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification in Diet and Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	Multiple Endocrine Neoplasia Syndrome Type 2
MET	Metformin
Mg	Magnesium
MHDECODE	Medical History Decode
MI	Myocardial Infarction
MMTT	Mixed Meal Tolerance Test
MRHD	Maximum Recommended Human Dose
MTC	Medullary Thyroid Carcinoma
NA	Sodium
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trial
NDA	New Drug Application
NGSP	National Glycohemoglobin Standardization Program
NME	New Molecular entity
NOEL	No-Observed-Effects-Level
NOAEL	No-Observed-Adverse-Effect-Level
NR	Not Reported
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PDLC	Predefined Limits of Change
PE	Pulmonary Embolism
PeRC	Pediatric Review Committee
Phos	Phosphate
PIND	Pre-Investigational New Drug

PK	Pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PLT	Platelet
PMR	Postmarketing Requirement
PO	Oral ('Per Os')
PPG	Postprandial Glucose
PRDECOD	Procedure Decode
PRDURDD	Procedure Duration
PREA	Pediatric Research Equity Act
PreNDA	Pre-New Drug Application
PRRELSAE	Procedure Related to Serious Adverse Event
PRRESULT	Procedure Result
PT	Preferred Term
PTH	Parathyroid Hormone
QD	Once Daily ('Quaque Die')
QTcF	Fridericia Corrected QT
REMS	Risk Evaluation and Mitigation Strategy
RTB	Return to Baseline
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVOR	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCr	Serum Creatinine
SD	Standard Deviation
SGLT1	Sodium-Glucose Cotransporter 1
SGLT2	Sodium-Glucose Cotransporter 2
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
SITA	Sitagliptin
SMQ	System MedDRA Query
SOC	System Organ Class
SS	Steady-State
$T_{1/2}$	Elimination Half-Life
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TBILI	Total Bilirubin
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TG	Triglycerides
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides
TIA	Transient Ischemic Attack

TID	Trice daily
T_{MAX}	Time to Maximum Concentration
Total-C	Total Cholesterol
TQT	Thorough QT
TSH	Thyroid-Stimulating Hormone
TZD	Thiazolidinedione
UA	Uric Acid
UGE	Urine Glucose Excretion
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
VAI	Voluntary Action Indicated
WBC	White Blood Cell
WK	Week
XR	Extended-release
YR	Year

1 Executive Summary

1.1. Product Introduction

STEGLATRO (ertugliflozin) is new molecular entity submitted for marketing approval by the Merck Sharpe and Dohme Corp. (referred to as the Applicant throughout the remainder of this review) as a New Drug Application (NDA 209803) in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FDCA)[1] and Section 314 of Title 21 Code of Federal Regulations (CFR) 314.50.[2]

Ertugliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. During clinical development, ertugliflozin administration to subjects with type 2 diabetes mellitus (T2D) was associated with dose-dependent increases in urinary glucose and urinary volume, and lower hemoglobin A1c (HbA1c) concentrations.

The proposed indication for STEGLATRO is as an adjunct to diet and exercise to improve glycemic control in adults with T2D. STEGLATRO is intended for once daily oral administration, and will be available as film-coated tablets containing 5 mg or 15 mg of ertugliflozin.

The Applicant also has submitted two new fixed combination drug products (FCDPs), STEGLUJAN (ertugliflozin/sitagliptin) under NDA 209805, pursuant to Section 505(b)(1); and SEGLUROMET (ertugliflozin/metformin) under NDA 209806, pursuant to Section 505(b)(2) of the FDCA. NDA 209806 relies, in part, for approval on the Food and Drug Administration's (FDA) finding of safety and effectiveness for the listed drug, GLUCOPHAGE (metformin hydrochloride; NDA 020357, Bristol Myers Squibb).

The DPP-4 inhibitor component of STEGLUJAN (i.e., sitagliptin) is an approved antihyperglycemic agent with the indication 'as an adjunct to diet and exercise to improve glycemic control in adults with T2D'. Sitagliptin is a competitive dipeptidyl peptidase-4 (DPP-4) inhibitor that slows the inactivation of the incretin hormones, thereby increasing their concentrations in the blood, and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with T2D.[3]

The proposed indication for STEGLUJAN is as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both ertugliflozin and sitagliptin is appropriate. STEGLUJAN is intended for once daily oral administration, and will be available as film-coated tablets in the following dosage forms: (b) (4) ertugliflozin 5 mg/sitagliptin 100 mg; and ertugliflozin 15 mg/sitagliptin

100 mg.

SEGLUROMET consists of ertugliflozin and metformin, a biguanide. Metformin is approved with the indication 'as an adjunct to diet and exercise to improve glycemic control in adults and children with T2D'. Metformin improves glucose tolerance, decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity.

The proposed indication for SEGLUROMET is an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4)
SEGLUROMET is intended for twice daily oral administration with meals, and will be available as film-coated tablets in the following formulations: ertugliflozin 2.5 mg/metformin 500 mg; ertugliflozin 2.5 mg/metformin 1000 mg; ertugliflozin 7.5 mg/metformin 500 mg; and ertugliflozin 7.5 mg/metformin 1000 mg.

All three ertugliflozin products are not indicated for the treatment of type 1 diabetes mellitus (T1D) or diabetic ketoacidosis (DKA), and should not be used in patients with moderate or severe renal impairment.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I believe that the Applicant has provided substantial evidence of effectiveness to support approval of these products in adult patients with T2D and an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2.

To support the proposed indication for NDA 209803 (ertugliflozin), the Applicant has provided clinical data from seven multicenter, randomized, double-blind, placebo- or active comparator-controlled, clinical trials involving 4,863 subjects with T2D. Six of these trials evaluated the effects of ertugliflozin (5 and 15 mg) as monotherapy and in combination with metformin (≥1500 mg/day) and/or sitagliptin (100 mg). In a dedicated moderate renal impairment trial (P001/1016), ertugliflozin also was studied in combination with other antihyperglycemic medications, including insulin and a sulfonylurea, in T2D subjects with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2). The Applicant intends to include all seven efficacy trials in Section 14 of product labeling.

Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to week 26), both ertugliflozin 5 mg and 15 mg once daily resulted in modest, but statistically significant (all $p<0.001$) reductions in HbA1c concentrations compared to the placebo or active comparator in five of these trials (P003/1022, P005/1019, P006/1015, P007/1017, and P017/1047). For Trial P002/1013, a 52-week active-comparator trial, only the ertugliflozin 15 mg treatment arm was determined to be noninferior to the glimepiride arm (mean daily dose 3 mg).

For the moderate renal impairment trial (P001/1016), the HbA1c changes from baseline to Week 26 were not significantly different between the once daily placebo and ertugliflozin 5 mg or 15 mg treatment arms. Therefore, I do not recommend the use of ertugliflozin-containing products for patients with moderate to severe renal impairment.

To support marketing approval of NDA 209805 (ertugliflozin/sitagliptin FCDP), the Applicant is relying on three of the above seven trials, which randomized 1,985 T2D subjects. In these trials, the efficacy of ertugliflozin (5 and 15 mg) was evaluated in a factorial study in which ertugliflozin and/or sitagliptin were administered as add-on combination therapy with metformin (Trial P005/1019), as add-on combination therapy with metformin plus sitagliptin (Trial P006/1015), and as initial combination therapy with sitagliptin (Trial P017/1047). For the factorial trial, ertugliflozin 5 mg or 15 mg used in combination with sitagliptin 100 mg provided statistically significant improvements in HbA1c concentrations compared to the individual components at Week 26. The other two trials provided supportive evidence of added efficacy with combination therapy.

For NDA 209806 (ertugliflozin/metformin FCDP), the Applicant is relying on four of the above trials (P002/1013, P005/1019, P006/1015, P007/1017), which randomized 3,643 subjects with T2D. In these trials, the efficacy of ertugliflozin (5 and 15 mg) was evaluated as add-on combination therapy with maximally tolerated doses of background metformin therapy (≥1500 mg/day). These trials provide evidence of an added benefit from combination therapy of ertugliflozin as add-on to metformin, with or without sitagliptin. The labeled indication of this FCDP will need to reflect the supporting clinical trial data (i.e., 'as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) .

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2D) is a condition of chronic impaired glucose homeostasis that leads to chronic hyperglycemia and increases the risk for vascular complications (both microvascular and macrovascular).[4,5] Therapies for T2D have focused on improving glycemic control as assessed by change in HbA1c. While there are multiple drug products approved both as individual drugs and as FCDPs, many patients are unable to achieve the desired glucose targets. Thus, additional therapeutic options are needed to facilitate individualization of therapy.

To support marketing approval of ertugliflozin (NDA 209803), an SGLT2 inhibitor, the Applicant has conducted seven Phase 3 clinical trials that evaluated the efficacy and safety of ertugliflozin 5 mg and 15 mg once daily doses as monotherapy, and as add-on to metformin and/or sitagliptin, and other antihyperglycemic agents (Trial P001/1016). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to Week 26), the ertugliflozin 5 mg and 15 mg once daily doses resulted in modest, but statistically significant (all $p<0.001$) reductions in HbA1c concentrations compared to the placebo in five of these trials (P003/1022, P005/1019, P006/1015, P007/1017, and P017/1047). The improvement in glycemic control for both ertugliflozin doses is considered clinically meaningful (i.e., all placebo-subtracted reductions in HBA1c ≥ -0.48%).[6] Additionally, the ertugliflozin 15 mg dose was noninferior to glimepiride (mean dose 3 mg/day) at Week 52 in Trial P002/1013), with reductions in HbA1c for both the 5 mg and 15 mg ertugliflozin doses maintained throughout the 52-week treatment period.

For NDA 209805 (ertugliflozin/sitagliptin FCDP), the two active pharmaceutical ingredients (an SGLT2 inhibitor plus a DPP-4 inhibitor) are combined at fixed dosages (i.e., ertugliflozin 5 mg or 15 mg with sitagliptin (b) (4) 100 mg), which allows for dosing of both via four different tablet formulations. The contribution of both antihyperglycemic components to the claimed effect has been demonstrated at the doses studied in a factorial trial (P005/1019), with additional support from two Phase 3 clinical trials (P006/1015 and P017/1047). These three trials also were submitted to support NDA 209803. The results of the factorial trial provide evidence that the combination of recommended doses of ertugliflozin and sitagliptin, added to maximum tolerated background metformin (≥1500 mg/day), is statistically superior to either of the individual components in reducing HbA1c at Week 26. The other two trials demonstrated superiority over placebo with ertugliflozin as add-on combination therapy with metformin plus sitagliptin and as initial combination therapy with sitagliptin.

For NDA 209806 (ertugliflozin/metformin FCDP), ertugliflozin plus a biguanide (metformin) are combined at fixed dosages (i.e., ertugliflozin 2.5 mg or 7.5 mg with metformin 500 mg or 1000 mg) in four different tablet formulations. Four of the seven Phase 3 trials (P002/1013,

P005/1019, P006/1015, P007/1017) submitted to NDA 209803 also were used to support the claimed effect of this FCDP. For the two placebo-controlled trials (P006/1015 and P007/1017), ertugliflozin 5 mg or 15 mg once daily as add-on combination therapy with metformin (≥1500 mg/day), with and without sitagliptin (100 mg/day), provided statistically significant reductions in HbA1c at Week 26 compared to placebo.

(b) (4) (b) (4) the Applicant's dedicated moderate renal impairment trial (P001/1016) failed to show superiority over placebo for either the ertugliflozin 5 mg or 15 mg daily dose as add-on therapy to background antihyperglycemic therapy, (b) (4)

The most common adverse reactions, reported in ≥2% of subjects and more frequently in ertugliflozin-treated subjects included female and male genital mycotic infections, urinary tract infections, headache, vaginal symptoms, increased urination, nasopharyngitis, back pain, weight decreased, and thirst. Additionally, the occurrence of documented hypoglycemia (i.e., blood glucose <70 mg/dL) was reported in 4.1% (21/515) of placebo-treated subjects compared with 5.2% (27/519) and 4.9% (25/510) of subjects in the ertugliflozin 5 mg and 15 mg arms, respectively. The incidence of severe hypoglycemia (i.e., the subject required the assistance of another person to recover, lost consciousness, or experienced a seizure) was relatively low and similar between treatment arms (i.e., 1%, 0.4% and 0.4%, respectively). The numbers of hypoglycemic events, particularly severe events, were limited in the clinical trials in which ertugliflozin was used as add-on/combination therapy with sitagliptin and/or metformin. However, for the ertugliflozin plus sitagliptin factorial trial (P005/1019), hypoglycemia was observed in 9% (22/244) of subjects in the ertugliflozin 15 mg/sitagliptin 100 mg arm compared to ≤5.6% in all other treatment arms (sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin 15 mg, and ertugliflozin 5 mg/sitagliptin 100 mg). The safety profile of ertugliflozin and the ertugliflozin FCDPs are reflective of what would be expected of SGLT2 inhibitors as monotherapy and in combination with a DPP-4 inhibitor or biguanide.

One safety finding identified across the ertugliflozin clinical program was a numeric imbalance in the number of subjects who experienced lower limb amputations in at-risk subjects (e.g., preexisting cardiovascular (CV), cerebrovascular and/or peripheral arterial disease), that favored the non-ertugliflozin comparator arm. These events were reported in 11 (0.2%) ertugliflozin-treated subjects compared to one subject (0.1%) randomized to the comparator arm. Associated serious adverse events (cellulitis, diabetic vascular disorders, diabetic foot infections, gangrene, osteomyelitis, peripheral arterial occlusive disease, and peripheral ischemia) often preceded surgery. Although the event rate is relatively low, another SGLT2 inhibitor carries a Boxed Warning for the risk of lower limb amputations in patients with established CV disease.

In summary, the totality of the clinical trial data suggests that ertugliflozin and each of the components of the ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs contribute to improving glycemic control at the doses evaluated in the pivotal Phase 3 clinical trials. However,

there is some concern regarding the potential for an increased risk of lower limb amputations in at-risk patient populations. Additionally, efficacy has not been established in patients with moderate renal impairment, while potential use in this special population may be associated with an increased risk for adverse outcomes. I believe that the overall benefit-risk for T2D patients is favorable, and that the identified safety concerns can be addressed through labeling and routine pharmacovigilance. Thus, I would recommend approval of this NME (NDA 209803) and the respective FCDPs (NDAs 209805 and 209806) with an amended indication for the ertugliflozin/metformin FCDP, and the recommendation that all three ertugliflozin-containing products not be used in patients with moderate renal impairment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2D) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular (e.g., myocardial infarction, stroke) complications.[4,5] The Center for Disease Control (CDC) estimates that there are nearly 30 million patients with T2D in the United States.[7]	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk for morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial (DCCT),[8-14] the United Kingdom Prospective Diabetes (UKPD) study,[5,15-18] and the Kumamoto Study,[19] improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., reduced microvascular complications). • There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class), approved to improve glycemic control in patients with T2D. Many of these medications are also approved as fixed combination drug products (FCDPs). • There are different safety concerns for each class. Metformin is often considered first-line therapy with the choice of subsequent therapies individualized by prescribers based on the patient.[20,21] • While all approved antihyperglycemic medications have been shown to improve glycemic control, data on the ability of individual agents to	Despite the many available treatment options, many patients continue to have difficulty with achieving the desired degree of glycemic control. Further, T2D is a progressive disorder and patients typically need additional agents added as the course of the disease progresses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	improve clinical outcomes is generally limited or not available.	
Benefit	• Seven Phase 3 trials, that met the criteria for adequate and well-controlled studies (21 CFR 314.126),[22] were submitted to support marketing approval of ertugliflozin, and the ertugliflozin/sitagliptin and ertugliflozin/ metformin FCDPs. The results from six of the seven Phase 3 clinical trials demonstrated that administration of ertugliflozin 5 mg or 15 mg once daily as monotherapy or as add-on to sitagliptin and/or metformin results in greater HbA1c reductions compared to adding placebo or the individual components at the doses evaluated in these trials. Secondary efficacy endpoints for these trials (e.g., proportions of subjects with HbA1c concentrations <7%, and reductions in fasting plasma glucose, body weight, and systolic blood pressure) were supportive and consistent with the effects observed with other SGLT2 inhibitors.	The totality of Phase 3 clinical trial data provides evidence to support the efficacy of ertugliflozin for the proposed indication, 'as adjunct to diet and exercise to improve glycemic control in adults with T2D'. Further, in accordance with 21 CFR Section 300.50,[23] one of these trials (P005/1019) was a full factorial trial that showed that each component of the ertugliflozin/sitagliptin FCDP makes a contribution to the claimed effects of this product. Two additional trials provided supportive evidence that combination therapy has added benefit on glycemic control over the individual components at the doses used in these trials. Four of the seven trials also were used to support efficacy of the ertugliflozin/metformin FCDP. Since these trials were designed as add-on to background metformin therapy, benefit of this product would be most relevant to the population of T2D patients with inadequate glycemic control despite maximum tolerated treatment with metformin (≥1500 mg/day) or in patients already receiving ertugliflozin plus metformin as combination therapy, as these patient populations were evaluated in the pivotal Phase 3 clinical trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The risks associated with ertugliflozin and the ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs are consistent with what is expected with other SGLT2 inhibitors (e.g., female and male genital mycotic infections, urinary tract infections, and increased urination), and with what would be anticipated from combining the two individual products of each FCDP. The WARNINGS AND PRECAUTIONS section of proposed product labeling will include additional adverse reactions included in class labeling for other SGLT2 inhibitors (e.g., hypotension, ketoacidosis, acute kidney injury and impairment of renal function, urosepsis and pyelonephritis, and hypoglycemia). • The main safety issue identified in these Applications was a numeric imbalance in the number of ertugliflozin-treated subjects who experienced lower limb amputations (i.e., 11/3409 subjects vs. 1/1450 subjects in the comparator arm), of which one individual underwent two separate amputations, and a second had both a revascularization procedure and an amputation. All cases had preexisting risk factors, and precipitating medical events (e.g., limb infection, peripheral artery disease, and gangrene) were common. Since this safety concern is already included as a Boxed Warning for one other SGLT2 inhibitor, it will be important that product labeling adequately inform prescribers and patients of this risk, and that routine monitoring for associated signs and symptoms be recommended. • Although hypoglycemia is a risk with any antihyperglycemic medication, the occurrence of hypoglycemic events when ertugliflozin was administered as monotherapy was relatively low (2.6%), with higher rates observed in combination with sitagliptin and/or metformin. Events of	The clinical risks associated with use of the ertugliflozin and ertugliflozin plus sitagliptin or metformin are what would be expected with the use of SGLT2 inhibitors or combination therapy with these drugs, respectively. However, a numeric imbalance in the number of cases of lower limb amputations was observed in subjects randomized to the ertugliflozin treatment arms. Preexisting risks and precipitating medical conditions were reported in the identified cases. This potential safety signal can be addressed with appropriate labeling and continued pharmacovigilance. Based on the totality of the safety data submitted, and the observed adverse event findings, no new safety signals were identified. The risks associated with the use of ertugliflozin as monotherapy or in combination with sitagliptin or metformin are anticipated, monitorable, and similar to those observed in other SGLT2 inhibitor clinical programs, including combination therapy with a DPP-4 inhibitor and/or metformin.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	severe hypoglycemia (i.e., requiring assistance, lost consciousness, or experienced a seizure regardless of blood glucose) were limited. • [redacted] (b) (4) based on the results of the Applicant's dedicated moderate renal impairment trial (P001/1016), efficacy at this level of renal function has not been established. Further, across the clinical program, use of ertugliflozin in individuals with this level of renal function was associated with numerically higher incidences of adverse outcomes, including deaths, serious adverse events (SAEs), and discontinuations due to AEs. Therefore, the use of ertugliflozin-containing products in patients with an eGFR <60 mL/min/1.73 m^2 is not recommended. • The risk of ketoacidosis, a potentially fatal condition, has recently been added to the WARNINGS AND PRECAUTIONS sections of approved SGLT2 inhibitor products.[24-26] Across the ertugliflozin clinical program, ketoacidosis was identified in three of 3,409 (0.1%) ertugliflozin-treated subjects, with no events occurring in the non-ertugliflozin treatment arm. These cases were each associated with intercurrent illness (infection/sepsis, gastroenteritis). As with SGLT2 inhibitor class labeling, the proposed product labeling includes information on ketoacidosis in the WARNINGS AND PRECAUTIONS section. Based on the existing data, this should be adequate.	
Risk Management	• No risk evaluation and mitigation strategy is recommended for this product.	The adverse reactions and safety profile of ertugliflozin and the ertugliflozin FCDPs can be adequately labeled to communicate the above safety concerns.

1.4. Patient Experience Data

Not applicable. Patient experience data (e.g., experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition) were not submitted nor reviewed as part of the three NDAs that are the subject of this review.

2 Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1D; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2D; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia).[27] According to the 2017 National Diabetes Statistics Report, diabetes affects an estimated 30.3 million people within the United States (U.S.),[7] of which T2D accounts for 90-95% of all diagnosed cases.[4,7] As of 2013, diabetes also is the most expensive medical condition to diagnose and treat in the U.S., accounting for $101.4 billion in healthcare spending.[28]

Patients with T1D may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2D can be asymptomatic. As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. For patients with T2D, the presence of microvascular and macrovascular disease are independently associated with a 10-year risk of death, major adverse cardiovascular events (MACE: nonfatal myocardial infarction, nonfatal stroke, or CV death) and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness), while coexistence of both micro- and macrovascular disease is associated with a 2.0-, 2.9- and 6.3-fold greater risk of these complications, respectively.[29] Diabetes remains a leading cause of kidney failure, adult-onset blindness, and non-traumatic lower limb amputations in the U.S.[4] Additionally, people with diabetes are twice as likely to have cardiovascular disease (CVD) or stroke as nondiabetic individuals—and at an earlier age.[4] Diabetes was the seventh leading cause of death in 2015,[7] and CVD remains a major cause of death among diabetics. Based on the results of the Diabetes Control and Complication Trial (DCCT),[8-14] the United Kingdom Prospective Diabetes Study (UKPDS),[5,15-18] and the Kumamoto Study,[19] improved glycemic

control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

2.2. Analysis of Current Treatment Options

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and one or more of the drug products presented in Table 1 (a more detailed listing of available products, including FCDPs, and associated safety concerns is presented in Table 42, Appendix 13.2). The 2015 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement advocates the use of a patient-centered approach for the management of T2D, which includes the assessment of glycemic efficacy, hypoglycemia risk, impact on weight, adverse effects, costs, and patient preference.[20] The 2017 clinical practice guidelines issued by the U.S. Department of Veterans Affairs/U.S. Department of Defense also support individualized treatment plans based on many of these same factors.[30] In the ADA/EASD report, they recommend initiating antihyperglycemic therapy for the management of T2D with metformin as monotherapy. Should a single agent alone fail to achieve/maintain the HbA1c target over three months, the next step would be to add a second agent (e.g., GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, thiazolidinedione, basal insulin, or sulfonylurea), with addition of a third agent should dual antihyperglycemic therapy fail to achieve the desired HbA1c target over the subsequent three-month period.[20] Similar recommendations also have been published in the ADA's Standards of Medical Care in Diabetes–2017,[21] and suggested by the American College of Physicians (ACP),[31,32] and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE).[33] Several studies have also reported advantages from adding a third noninsulin agent to a two-drug combination that is not yet or no longer achieving the glycemic target,[20,34,35] as well as triple therapy with both oral and injectable antihyperglycemic agents.[36-38] Intensive treatment with triple oral antihyperglycemic therapy in newly diagnosed T2D patients also has been shown to have a durable antihyperglycemic effect (i.e., maintenance of β-cell function and glycemic control for ≥6 years).[39] Additionally, two FCDPs that contain an SGLT2 inhibitor plus a DPP-4 inhibitor (i.e., empagliflozin/linagliptin[40,41] and dapagliflozin/saxagliptin[42]) were approved primarily based on Phase 3 trials which demonstrated improved glycemic control as add-on therapy in combination with metformin.

Despite the number of drugs approved for the treatment of T2D (i.e., 12 antihyperglycemic pharmacologic classes), a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an antihyperglycemic drug. Several published reports suggest that approximately half of U.S. adults with diabetes do not meet the recommended glycemic goals.[43-45] Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations (please refer to Table 42).[21,31,33] For example, thiazolidinediones may be associated with increased bone fracture risk in postmenopausal women or elderly men, edema,

and weight gain and are not recommended for use in many patients with congestive heart failure, while DPP-4 inhibitors carry a class warning for a risk of heart failure and severe/disabling arthralgia. Metformin and SGLT2 inhibitors are contraindicated in patients with severe renal dysfunction. Additionally, SGLT2 inhibitors may be associated with genital mycotic infections and urinary tract infections (including urosepsis and pyelonephritis), as well as volume depletion/orthostatic hypotension and acute kidney injury. Use of insulin and insulin analogues, meglitinides and sulfonylureas may be associated with hypoglycemia and weight gain. Amylin mimetics, alpha-glucosidase inhibitors, biguanides, bile acid sequestrants, and GLP-1 receptor agonists may cause intolerable gastrointestinal side effects, and pancreatitis and allergic reactions have been reported with DPP-4 inhibitors and GLP-1 receptor agonists. Additionally, metabolic acidosis (e.g., lactic acidosis, and ketoacidosis) has occurred with the use of metformin and SGLT2 inhibitors, and the thiazolidinedione, rosiglitazone, has been linked with a possible risk of bladder cancer. Antihyperglycemic products administered by inhalation or injection require training, and patients may be reluctant to self-inject (e.g., aversion to needles). More recently, the FDA issued a Drug Safety Communication confirming an increased risk of leg and foot amputations with one other SGLT2 inhibitor (i.e., canagliflozin).[46,47]

Diabetes disease progression and nonadherence to the prescribed antihyperglycemic regimen influence the potential to achieve/maintain adequate glycemic control. Progressive β-cell dysfunction in patients with T2D may lead to secondary treatment failures over time, such that approximately half of these patients require more than one antihyperglycemic agent within three years following diagnosis.[48] Nonadherence to oral antihyperglycemic agents has been reported in 7%-64% of patients with T2D,[49,50] and has been associated with poor glycemic control,[51,52] diabetes-related hospitalizations[53,54] and increased mortality.[53] For patients requiring combination antihyperglycemic therapy, adherence may improve with a reduction in pill burden through the use of FCDPs.[55-57]

For these reasons, and because T2D is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there remains a need for new antihyperglycemic treatment options, as well as the use of combination therapy. In the NDAs included in this review, the Applicant has provided results from seven Phase 3 clinical trials intended to determine whether ertugliflozin as monotherapy or in combination with sitagliptin or with metformin would improve glycemic response compared to placebo or active comparators. Additional supportive safety and efficacy data are also included.

Table 1: Approved Therapeutic Options for the Management of Type 2 Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products*
Alpha-Glucosidase Inhibitors	Acarbose; Meglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide
Insulins and Insulin Analogues	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Pre-mixed insulins (various)
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapafliflozin; Empagliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

Source: Drugs@FDA: FDA Approved Drug Products, available at: http://www.accessdata.fda.gov/scripts/cder/daf/.[58]
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium-glucose cotransporter 2.
*Insulin plus non-insulin FCDPs (e.g., insulin degludec/liraglutide and insulin glargine/lixisenatide) and non-insulin FCDPs are presented in Appendix 13.2, Table 42.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Steglatro (ertugliflozin)

Steglatro is a new molecular entity that inhibits sodium-glucose cotransporter 2 (SGLT2).[59] This product is selective for SGLT2, with approximately a 2000-fold *in vitro* selectivity for human SGLT2 over SGLT1.[60] The sodium-dependent glucose transport protein is expressed in the proximal renal tubules, and is responsible for the majority of the reabsorption of filtered

glucose from the tubular lumen. By inhibiting SGLT2, ertugliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. In patients with T2D, ertugliflozin administration is associated with dose-dependent increases in urinary glucose and urinary volume, lower HbA1c and fasting plasma glucose concentrations, and reductions in body weight and systolic blood pressure (SBP).

The Applicant states that ertugliflozin "improves glycemic control via a mechanism independent of insulin and pancreatic β-cell function and its durability is not dependent on β-cell function" and "represents a potentially effective and durable therapy across the typical disease progression of T2D." Further, since the extent of urinary glucose excretion (UGE) is dependent on ambient blood glucose levels (i.e., UGE decreases as blood glucose concentrations decrease), (b) (4).

Ertugliflozin or ertugliflozin containing products are currently not marketed in any country. Approved SGLT2 inhibitors include canagliflozin (approved in 2013),[61] dapagliflozin (approved in 2014),[62] and empagliflozin (approved in 2014).[63]

STEGLATRO is formulated as ertugliflozin 5 mg and 15 mg film-coated tablets.

The Applicant has proposed a recommended starting dose of Steglatro 5 mg once daily, taken in the morning, with or without food. The dose may be increased to 15 mg once daily in those tolerating the 5 mg dose but needing additional glycemic control. The Applicant (b) (4) (b) (4) (b) (4) contraindicates its use in those with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.

Based on the results of the Applicant's dedicated moderate renal impairment trial (P001/1016; please refer to Section 6) which did not show improved glycemic control compared to placebo, as well as numerically higher rates of adverse clinical outcomes (i.e., deaths, SAEs, and discontinuations due to AEs) reported for subjects in this trial and across the ertugliflozin clinical program (see Sections 8 and 10), this reviewer would not recommend the use of ertugliflozin in patients with an eGFR <60 mL/min/1.73 m^2. This recommendation also applies to the FCDPs discussed below.

STEGLUJAN (ertugliflozin/sitagliptin)

Steglujan is a FCDP that contains ertugliflozin plus sitagliptin. Although this product is not marketed within or outside of the U.S., one of the individual active moieties, sitagliptin (JANUVIA; NDA 21995), was approved by the Food and Drug Administration (FDA) in 2006 at the proposed doses to be used for this FCDP.[64] There is extensive experience worldwide with this DPP-4 inhibitor.

Sitagliptin belongs to the class of antihyperglycemic agents known as dipeptidyl peptidase-4

(DPP-4) inhibitors, and is administered orally once daily. This product is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[65] Other approved DPP-4 inhibitors include alogliptin (NESINA, approved in 2013),[66] linagliptin (TRADJENTA, approved in 2011),[67] and saxagliptin (ONGLYZA, approved in 2006).[68] Additionally, other SGLT2 inhibitor/DPP-4 inhibitor combination products have been approved, and include empagliflozin/linagliptin (GLYXAMBI, approved in 2015),[69] and dapagliflozin/saxagliptin (QTERN, approved in 2017).[70]

In patients with T2D, DPP-4 enzyme activity is inhibited for a 24-hour period following oral administration of sitagliptin. Inhibition of DPP-4 slows inactivation of incretin hormones (e.g., glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]), resulting in a two- to three-fold increase in incretin blood concentrations. Subsequently, glucagon concentrations decrease and glucose-dependent insulin secretion from pancreatic beta cells increases. These pharmacodynamics changes are associated with lower HbA1c and fasting glucose concentrations, and reduced glucose excursion following an oral glucose load or meal.[65,71]

The Applicant notes that the pathogenesis of T2D involves multiple metabolic defects, and therefore, combination therapy with antihyperglycemic agents that have different mechanisms of action may achieve greater reductions in HbA1c and enable patients to achieve target glycemic goals. They also claim that their ertugliflozin/sitagliptin FCDP could result in improved glycemic control (b) (4)

The proposed formulations for STEGLUJAN include: (ertugliflozin/sitagliptin) (b) (4) 5 mg/100 mg, and 15 mg/100 mg film-coated tablets.

This product will be dosed once daily, with or without food, and the recommended starting dose is ertugliflozin 5 mg/sitagliptin 100 mg, which may be increased to 15 mg/100 mg once daily in those tolerating the current dose, but need additional glycemic control. (b) (4) (b) (4) (b) (4) (b) (4) it is contraindicated in patients with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m^2), end-stage renal disease or dialysis. As noted above, I do not recommend the use of ertugliflozin products in patients with an eGFR <60 mL/min/1.73 m^2.

SEGLUROMET (ertugliflozin/metformin)

SEGLUROMET is a FCDP that contains ertugliflozin plus metformin. This FCDP is not approved in any country. However, metformin is approved in the U.S., Europe and other countries, and there is extensive experience worldwide with this antihyperglycemic agent. For this 505(b)(2) Application, the Applicant intends to use GLUCOPHAGE (metformin hydrochloride; NDA 020357; approved in 1995) as the listed drug product. This product belongs to the pharmacologic class

known as biguanides, and is approved as an adjunct to diet and exercise to improve glycemic control in adults and children with T2D.[72] Additionally, other SGLT2 inhibitor/metformin FCDPs are approved in the U.S., and include: canagliflozin/metformin (INVOKAMET, approved August 8, 2014,[73] and INVOKAMET XR, approved September 20, 2016[74]); dapagliflozin/metformin (XIGDUO XR, approved October 29, 2014[75]); and empagliflozin/metformin (SYNJARDY, approved August 26, 2015,[76] and SYNJARDY XR, approved December 9, 2016[77]).

Metformin improves glucose tolerance, lowering both basal and postprandial plasma glucose. Additionally, metformin decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not typically produce hypoglycemia in patients with T2D or in healthy subjects except in unusual circumstances and is not associated with hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.[72]

The Applicant's rationale for the development of this FCDP was similar to that proposed for the STEGLUJAN clinical program.

The following dosage strengths are proposed for this FCDP: (ertugliflozin/metformin) 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg film-coated tablets.

SEGLUROMET is dosed twice daily with meals. The initial dose should be individualized based on the patient's current regimen, with a maximum recommended dose of ertugliflozin 7.5 mg /metformin 1000 mg twice daily. The Applicant proposes to contraindicate the use of this product for patients with an eGFR <30 mL/min/1.73 m2, (b) (4) As noted above, I do not recommend the use of ertugliflozin products in patients with an eGFR <60 mL/min/1.73 m^2.

3.2. Summary of Presubmission/Submission Regulatory Activity

The relevant regulatory history for ertugliflozin and the FCDPs is presented in Table 2 below.

Table 2: Summary of Relevant Presubmission/Submission Regulatory History

Date	Event/Description	Summary of Relevant Agency Interactions
NDA 209803/ IND 106447 (Ertugliflozin)		
September 28, 2012	Initial Investigational New Drug Application	—
December 17, 2012	End of Phase 2 Meeting	• The Applicant was encouraged to study at least two doses in your Phase 3 clinical program.

Date	Event/Description	Summary of Relevant Agency Interactions
		• The FCDPs would need to be submitted under separate INDs. • For Trial P001/1016, the Agency recommended that enrollment of ≥50% of the population have an eGFR <45 mL/min/1.73 m^2; and that subjects with moderate renal impairment be enrolled into the Phase 2/3 clinical development program.
July 21, 2013	Transfer of Sponsorship from Pfizer to Merck	—
August 26, 2013	Final Agreed Initial Pediatric Study Plan	• The Applicant proposed to request a waiver for children under age 10, and a deferral for children between the ages of 10-17 years, (b) (4) (b) (4)
September 10, 2013	FDA Type C Written Response	• The Applicant proposed to evaluate the ertugliflozin 5 mg and 15 mg doses in their clinical development program. • The Agency informed the Applicant that a decision whether the proposed dedicated moderate renal impairment study and pooled data analysis of subjects with Stage 3 CKD from the Phase 3 studies will be adequate to support registration of ertugliflozin for subjects with an eGFR of (b) (4) would be a review issue at the time of NDA submission, and depend on the efficacy and safety findings in this patient population.
September 6, 2016	Pre-NDA Meeting	• The Applicant informed FDA regarding surreptitious metformin use in Trial P001/1016, and potential confounding of the primary efficacy analysis. • In the 4 MSU, the Applicant proposed to provide the following exposure data: 3128 subjects with exposures ≥25 weeks; 2670 subjects with exposures ≥50 weeks; and 786 subjects with ≥76 weeks. • The Applicant was informed that for the ertugliflozin/metformin FCDP, all of the supporting Phase 3 clinical

Date	Event/Description	Summary of Relevant Agency Interactions
		trials (P007/1017, P002/1013, P005/1019, and P006/1015) were designed as add-on to background metformin, and therefore may need to be reflected in the labeled indication (e.g., as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients already being treated with both ertugliflozin and metformin). • Amputations and revascularization procedures were to be designated as adverse events of special interest (AESI). • The Agency reiterated that estimations of the treatment effect should be based on the intent-to-treat (de facto) estimand, which considers the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy, including use of glycemic rescue therapy, bariatric surgery, or bone mineral density rescue therapy.
NDA 209805/ IND 122330 (Ertugliflozin/Sitagliptin FCDP)		
June 12, 2014	PIND Meeting Written Response (Phase 1 and 3 clinical development plan)	• The Applicant was cautioned regarding the risk with institution of clinical trials for a FCDP prior to approval of all the component drugs.
July 30, 2014	Initial Investigational New Drug Application	—
August 20, 2015	Final Agreed Initial Pediatric Study Plan	• The Applicant proposed to request a waiver for all pediatric populations.
June 8, 2015	FDA Type C Written Response (revised clinical pharmacology and biopharmaceutics plan)	• FDA recommended that the BE studies be conducted on the highest and lowest strengths of the FCDP (i.e., ertugliflozin 15 mg/sitagliptin 100 mg and ertugliflozin 5 mg/sitagliptin (b) (4) mg, respectively).
October 20, 2016	FDA Proprietary Name Request Conditionally Acceptable	• FDA concluded that the proposed name, STEGLUJAN would be

Date	Event/Description	Summary of Relevant Agency Interactions
		conditionally acceptable.
NDA 209806/ IND 122329 (Ertugliflozin/Metformin FCDP)		
July 3, 2014	PIND Meeting Written Response	• Phase 1 and 3 clinical development plan: The Applicant was cautioned regarding the risk with institution of clinical trials for a FCDP prior to approval of all the component drugs. • The Applicant was informed that all of Phase 3 trials intended to support the ertugliflozin/ metformin FCDP evaluate the superiority of ertugliflozin as add-on to background metformin therapy and not in treatment-naïve patients, which may affect the wording of an eventual indication, and need to be reflected in product labeling.
August 13, 2014	Initial Investigational New Drug Application	—
August 20, 2015	Final Agreed Initial Pediatric Study Plan	• The Applicant proposed to request a waiver for children under age 10, and a deferral for children between the ages of 10-17 years.
June 8, 2015	FDA Type C Written Response (Revised clinical pharmacology and biopharmaceutics plan)	• The Agency recommended that the BE studies be conducted on the highest and lowest strengths of the FCDP (i.e., ertugliflozin 7.5 mg/metformin 1000 mg and ertugliflozin 2.5 mg/metformin 500 mg, respectively).
November 16, 2016	FDA Proprietary Name Request Conditionally Acceptable	• FDA concluded that the proposed name, SEGLUROMET would be conditionally acceptable.

Source: Adapted from the Applicant's Regulatory History document, available at: \\cdsesub1\evsprod\nda209803\0000\m1\us\regulatory-history.pdf
Abbreviations: 4-MSU, Four Month Safety Update; AESI, adverse events of special interest; BE, bioequivalence; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FCDP, fixed combination drug product; FDA, Food and Drug Administration; IND, Investigational New Drug; NDA, New Drug Application; PIND, pre-Investigational New Drug; and T2D, type 2 diabetes mellitus.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable – ertugliflozin and the ertugliflozin FCDPs are not marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Dr. Cynthia Kleppinger, from the Office of Scientific Investigations (OSI), was asked to inspect five domestic and five foreign clinical sites (accounting for four [i.e., P001/1016, P003/1022, P006/1015, and P007/1017] of the seven supporting Phase 3 clinical trials, 10 clinical investigators, and 171 enrolled subjects), the contract research organization (i.e., Covance), and the co-sponsor (i.e., Pfizer). The clinical site inspections primarily focused on review of informed consent documents (ICDs), institutional review board (IRB)/ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, curricula vitae and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, and subject source documents (e.g., medical history records, drug accountability, concomitant medication records, and AE reports). The source records also were compared to the Applicant's data line listings.

Regulatory violations were noted for the co-sponsor and for one of the clinical investigators (Dr. Gilbert Martinez). The classification for the co-sponsor was Voluntary Action Indicated (VAI) because the study monitors did not always ensure the completion of protocol training prior to research involvement by study staff (i.e., clinical investigators, sub-investigators, and study coordinators), as required by the monitoring plan. Dr. Kleppinger felt that the regulatory violations reported were unlikely to impact the primary efficacy and safety analyses. The classification for Dr. Martinez also was VAI, and a Form FDA-483 was issued for 'an investigation that was not conducted in accordance with the investigational plan'. This involved two protocol deviations (i.e., 2 subjects enrolled prior to the required 8-week dose stabilization period of metformin and sitagliptin, and enrollment of an additional subject who did not meet the inclusion criteria for the wash-off/titration/dose-stabilization period). Dr. Kleppinger felt that these deviations would not significantly impact the primary efficacy and safety analyses, and that the "reliability of data from the involved study site was acceptable for use in support of the indication for this Application." It is noted that all classifications are considered preliminary until the final communication letter is sent to the inspected entity.

Based on the inspections of the clinical sites, the co-sponsor and the contract research organization, Dr. Kleppinger felt that the inspectional findings support the validity of data as

reported by the Applicant under these NDAs. For more detailed information, please refer to her review (dated August 18, 2017, filed under NDA 209803, 209805, and 209806).

4.2. **Product Quality**

Dr. Suong Tran is the Product Quality Application Technical Lead for all three Applications. The Active Pharmaceutical Ingredients (API) review was completed by Erika Englund, drug product review by Elise Luong, the manufacturing process and microbiology review by Chaoying Ma (NDA 209803) and Hong Yang (NDA 209806), the manufacturing facilities review by Allison Aldridge (NDA 209803) and Michael Klapal (NDA 209806), and the biopharmaceutics review by Hansong Chen (NDA 209803) and Kalpan Paudel (NDA 209806). During the review cycle, major deficiencies were observed during inspection of one of the manufacturing facilities (b) (4) of sitagliptin phosphate monohydrate for NDA 209805. However, following a repeat inspection of this site on (b) (4) the facility compliance status was changed to Compliant. The reviewers from the Office of Product Quality (OPQ) recommended approval for all three Applications, and there are no significant quality issues pending at this time. Please refer to the respective reviews for detailed information related to product quality.

Since ertugliflozin is unstable, it was developed as a co-crystal with L-pyroglutamic acid (LPGA) to improve its physical and chemical properties (e.g., stability). (b) (4) All specified impurities were evaluated for mutagenicity and none were found to be positive.

The drug product for NDA 209803 is an immediate-release oral 5 mg (6.477 mg ertugliflozin-LPGA) and a 15 mg (19.431 ertugliflozin-LPGA) film-coated tablet, which differs in tablet weight and size. For NDA 209805, the drug product is an immediate-release oral film-coated tablet, consisting of the following fixed ratio ertugliflozin/sitagliptin combinations: (b) (4) 5 mg/100 mg, (b) (4) and 15 mg/100 mg. The drug product for NDA 209806 is an immediate release oral film-coated tablet, consisting of the following fixed ratio combinations of ertugliflozin/metformin hydrochloride (HCl): 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/(b) (4) mg, and 7.5 mg/1000 mg.

For all three products, there were no novel or human/animal-derived excipients, the ertugliflozin-related degradants were determined not to be mutagenic, and the regulatory drug product specifications were considered adequate. The shelf-life of each product is 24 months at room temperature.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer for all three NDAs was Dr. Jessica Hawes. Please refer to her reviews (dated August 17 and 31, 2017) for detailed discussion of the nonclinical findings.

Dr. Hawes noted that ertugliflozin is selective for SGLT2 in humans, and that off-target effects (i.e., adverse drug-related nonclinical findings on bone or the gastrointestinal system by SGLT1 inhibition) observed in rats and dogs are not likely to occur at clinical exposures of 15 mg/day, and may be related to species differences in relative receptor binding affinities. Based on the area-under-the-curve from time 0 to 24 hours at steady state [$AUC_{0\text{-}24,ss}$], the Applicant claims that the highest proposed ertugliflozin dose (15 mg daily) represents a clinical exposure that is approximately 12-fold lower than the exposure at the no observed adverse effect level (NOAEL) in the rat 6-month toxicology study (the most sensitive species). Additionally, the O-glucuronide metabolites of ertugliflozin (i.e., M5a and M5c) do not appear to have significant SGLT2 or SGLT1 inhibitory activity at the proposed human doses, and have been sufficiently qualified in the Applicant's nonclinical program. At clinically relevant doses, ertugliflozin and its glucuronide metabolites also do not meaningfully inhibit or induce major drug metabolizing isoenzymes and transporting proteins (e.g., cytochrome P450 isoenzymes, organic anion transporting polypeptides, and diphosphate-glucuronsyltransferase), and therefore significant drug interactions with concomitant medications that are substrates for these proteins are not anticipated.

Dr. Hawes stated that the primary drug-related nonclinical effects involved the renal system. Although these SGLT2 inhibitor-related AEs (e.g., glucosuria and osmotic diuresis) were considered monitorable, treatable, and reversible at the proposed human doses, irreversible renal findings were observed in juvenile rats during renal development (corresponding to the 2nd and 3rd trimesters of pregnancy in humans) following ertugliflozin exposures that were 17-fold higher than the anticipated clinical exposure. No additional concerns for drug-related fetal developmental effects or reproductive fertility were observed at clinically relevant exposures.

In the Applicant's two-year carcinogenicity studies (CD-1 mice and Sprague-Dawley rats), there were no ertugliflozin-related neoplastic findings in mice at doses up to 50 times the human exposure of 15 mg/day; however, an increased incidence of benign and combined benign and malignant adrenal medullary pheochromocytoma occurred in male rats at approximately 18 times the anticipated human exposure. Dr. Hawes noted that this may be an off-target SGLT1 inhibitory effect (e.g., altered calcium homeostasis in a species sensitive to these changes), of

which the relevance to humans is unclear. Ertugliflozin was not mutagenic or clastogenic (i.e., microbial reverse mutation, in vitro cytogenetic, and *in vivo* rat micronucleus assays).

Dr. Hawes felt that the existing nonclinical data support approval of NDA 209803, and that no additional nonclinical studies would be recommended.

For the ertugliflozin/sitagliptin FCDP and the ertugliflozin/metformin FCDP, Dr. Hawes felt that coadministration of ertugliflozin plus either sitagliptin or metformin in the respective 13-week repeat-dose toxicity studies in rats was generally tolerated, safety margins were sufficient, and no synergistic toxicities were observed. Combination genetic toxicology and carcinogenicity studies for these FCDPs were not conducted or required. For both FCDPs the nonclinical data were considered sufficient to support clinical dosing and market approval.

4.5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers were Drs. Suryanarayana Sista (NDA 209803) and Lei He (NDA 209805 and NDA 209806). Please refer to the respective reviews (dated August 18, 2017, August 7, 2017) for detailed discussion of the clinical pharmacology findings.

In total, the Applicant conducted 38 clinical studies including 29 clinical pharmacology and biopharmaceutic studies, two Phase 2 studies, and seven Phase 3 studies to support the efficacy and safety of ertugliflozin and the two FCDPs. Additionally, Trial P023/1037 (the dedicated BE bridging study) demonstrated that the to-be-marketed formulation and the formulation used in the Phase 3 clinical trials were bioequivalent.

Based on dose-response model-predicted responses of HbA1c, fasting plasma glucose, body weight, and 24-hour urine glucose excretion (UGE_{0-24}) data from their Phase 2 studies (P016/1006, a 12-week dose-ranging study, and P042/1004, a 4-week study) the Applicant believes that the ertugliflozin 5 mg and 15 mg doses achieve >80% and >90% of the maximum response, respectively for these endpoints. Dr. Sista felt that from a clinical pharmacology perspective the proposed dosing regimen (i.e., ertugliflozin 5 mg once daily, followed by an increase to 15 mg once daily if additional glycemic control is needed), was acceptable, and that dosing was not altered by intrinsic and extrinsic factors. However, ertugliflozin is not recommended in patients with severe hepatic impairment (i.e., there is no clinical experience in subjects with Child-Pugh class C hepatic impairment) or in individuals with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2).

Dr. He was the reviewer for the two ertugliflozin FCDPs. For the ertugliflozin/sitagliptin FCDP, she felt that the PK/PD data provided by the Applicant indicate that each strength of the FCDP is bioequivalent to the individual components (as used in the Phase 3 clinical trials). Further,

there was no clinically meaningful drug-drug interactions between ertugliflozin and sitagliptin, as systemic exposures of both components of the FCDP were similar to the individual components administered as separate doses. To support the ertugliflozin/metformin FCDP, the Applicant submitted six clinical pharmacology studies (two BE, one PK interaction, one food effect, and two PK/PD studies). The Applicant's pivotal PK/PD trial (P035/1051) showed similar steady-state (SS) PK and PD when ertugliflozin was administered as a single or split dose (intended to provide a bridge between a QD and BID dosing regimens).

Based on these reviews, the Office of Clinical Pharmacology felt that the results of the submitted studies supported approval of all three NDAs.

4.5.1. Mechanism of Action/Pharmacodynamics

***Ertugliflozin*:**
By inhibiting SGLT2 (the transporter in the proximal tubules responsible for approximately 90% of the reabsorption of glucose filtered through the glomerulus), ertugliflozin increases renal glucose excretion and improves glycemic control. The amount of glucose removed is dependent on the blood glucose concentration and the glomerular filtration rate. Ertugliflozin increases the amount of glucose excreted in the urine in both healthy subjects and T2D patients following oral administration, and 5 and 15 mg doses in T2D patients result in excretion of approximately 70 grams/day of glucose in the urine. This urinary glucose excretion is associated with increases in urinary volume.

Please refer to Sections 8.4.8 and 8.4.9 for discussion regarding the pharmacodynamic effects of ertugliflozin on the cardiac conduction system.

Ertugliflozin/Sitagliptin FCDP:
The proposed FCDP includes sitagliptin, a competitive DPP-4 inhibitor that slows inactivation of the incretin hormones which play a role in glucose-dependent insulin and glucagon secretion.[65,71,78] The net result of the presence of incretin hormones is improved glycemic control. Sitagliptin administration in patients with T2D results in inhibition of DPP-4 activity for approximately 24 hours. Following an oral glucose load or meal, there is a two- to three-fold increase in circulating levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and increased glucose-dependent insulin secretion, which are associated with a rise in insulin concentrations, a decrease in glucagon concentrations, lower fasting glucose concentrations, and reduced glucose excursion.[65,71,78]

Ertugliflozin/Metformin FCDP:
This FCDP includes metformin, a biguanide that improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic

glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Additionally, metformin does not typically produce hypoglycemia in patients with T2D or in healthy subjects except in unusual circumstances, and does not cause hyperinsulinemia. Insulin secretion remains generally remains unchanged, while fasting insulin levels and day-long plasma insulin response may decrease.[79] Patients with T2D also may have increased hepatic glucose output, which can potentially be decreased by approximately 75% in metformin users.[80]

The sitagliptin and metformin components of the proposed ertugliflozin FCDPs are intended to provide complementary modes of action with ertugliflozin.

4.5.2. **Pharmacokinetics**

Ertugliflozin:

Following single oral ertugliflozin doses of 5 mg and 15 mg in a fasted state, peak plasma concentrations (Tmax) are achieved in approximately one hour, and the absolute bioavailability is approximately 100%. Administration of ertugliflozin with a high fat/high caloric meal decreases the maximum plasma concentration (C_{max}) by approximately 29%, and appears to affect the rate (prolongs the T_{max} by 1 hour), but not the extent of absorption (i.e., no effect on the area-under-the-curve [AUC_{inf}]). Ertugliflozin is approximately 94% protein bound in the plasma, and the mean elimination half-life ($t_{1/2}$) is approximately 16.6 hours, with 41% of a dose eliminated in the feces and 50% in the urine. Compared to subjects with normal renal function, subjects with mild, moderate or severe renal impairment had approximately a 1.6 to 1.7-fold increase in the AUC.

Ertugliflozin/Sitagliptin FCDP:

The absolute bioavailabilty of sitagliptin monotherapy is approximately 87%.[65] Following administration of the FCDP with a high fat meal, the ertugliflozin Cmax was decreased by 29%, without meaningful effects on the ertugliflozin AUC_{inf}. No meaningful effect was seen on the sitagliptin AUC_{inf} and C_{max}. Sitagliptin is approximately 38% bound to plasma proteins, and the mean elimination $t_{1/2}$ is approximately 12.4 hours. Approximately 13% of a dose is eliminated in the feces and 87% in the urine.[65]

Ertugliflozin/Metformin FCDP:

The bioavailability of metformin following oral administration is approximately 50-60%.[79] The absorption of ertugliflozin and metformin following administration of the FCDP with a high-fat meal is comparable to what is reported for the individual tablets, with reductions in the C_{max} of both, without meaningful effects on the AUC_{inf}. Metformin is negligibly bound to plasma proteins, and the mean elimination $t_{1/2}$ is approximately 6.2 hours in the plasma and 17.6 hours in the blood, with 90% of the absorbed drug eliminated renally within 24 hours.[79]

4.6. Devices and Companion Diagnostic Issues

Not applicable. The three NDAs that are the subject of this review do not involve a companion device or diagnostic product.

4.7. Consumer Study Reviews

Not applicable. The Applications did not involve label comprehension, patient self-selection, or other human factors studies.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

To support the efficacy and safety of ertugliflozin (NDA 209803) for the proposed indication, the Applicant has submitted data from seven Phase 3 clinical trials (Table 3). Additionally, Trials P005/1019, P006/1015, and P017/1047 were used to support the proposed ertugliflozin/sitagliptin FCDP (NDA 209805); while Trials P002/1013, P005/1019, P006/1015, and P007/1017 were used to support the proposed ertugliflozin/metformin FCDP (NDA 209806).

Table 3: Listing of Phase 3 Clinical Trials Relevant to this NDA

Trial Identifier (Abbreviated Title)	Trial Design	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Patients Randomized	Study Population	No. of Centers and Countries
Phase 3 Efficacy and Safety Trial							
P001/1016 (Moderate Renal Impairment Study) **NCT01986855** *Trial Initiation Date: 03-Dec-2013* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel-group, placebo-controlled	• Ertu 5 mg PO QD • Ertu 15 mg PO QD • Placebo PO QD *Glycemic Rescue:* Adjust/add AHA	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • BW • SBP • FPG • % Subjects with HbA1c <7%	Phase A: 26 wks Phase B: 26 wks	• Placebo: 154 • Ertu 5 mg: 158 • Ertu 15 mg: 155 (1:1:1 allocation)	• ≥25 years old • T2D • HbA1c 7-10.5% • eGFR of ≥30 to <60 mL/min/1.73m^2 *Background Therapy:* • Diet/exercise alone +/- non-Met AHA	**171 Sites,** **13 Countries,** **5 Regions:** Asia Europe North America South Africa South America
P002/1013* (Ertu vs. Glim as Add-on to Met Study) **NCT01999218** *Trial Initiation Date: 17-Dec-2013* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel-group, active-controlled	• Ertu 5 mg PO QD • Ertu 15 mg PO QD • Glim 1 to 6 or 8 mg PO QD *Glycemic Rescue:* Sita	BL to Wk 52 Change: *Primary* • HbA1c *Secondary* • BW • SBP	Phase A: 52 wks Phase B: 52 wks	• Glim: 437 • Ertu 5 mg: 448 • Ertu 15 mg: 441 (1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 7-9% • eGFR of ≥55 mL/min/1.73m^2 *Background Therapy:* • Met ≥1500 mg x ≥8wks	**232 Sites** **16 Countries** **5 Regions:** Asia Europe North America South Africa South America
P003/1022[†] (Monotherapy Study) **NCT01958671** *Trial Initiation Date: 18-Oct-2013* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel-group study (placebo-controlled followed by active-controlled)	• Ertu 5 mg PO QD • Ertu 15 mg PO QD • Placebo PO QD *Glycemic Rescue:* Met	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • BW • SBP • FPG • % Subjects with HbA1c <7%	Phase A: 26 wks (placebo-controlled) Phase B: 26 wks (active-controlled)	• Placebo: 153 *(Met, Phase B)*[‡] • Ertu 5 mg: 156 • Ertu 15 mg: 152 (1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 7-10.5% • eGFR of ≥55 mL/min/1.73m^2 *Background Therapy:* • Diet and exercise (Phase A) • Met (Phase B)	**81 Sites** **7 Countries** **5 Regions:** Asia Europe North America South Africa South America

Trial Identifier (Abbreviated Title)	Trial Design	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Patients Randomized	Study Population	No. of Centers and Countries
P005/1019 ¶* (Ertu + Sita Factorial Study) **NCT02099110** *Trial Initiation Date: 29-Apr-2014* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel-group, active-controlled, factorial	• Ertu 5 mg + Sita 100 mg PO QD • Ertu 15 mg + Sita 100 mg PO QD • Ertu 5 mg PO QD • Ertu 15 mg PO QD • Sita 100 mg PO QD *Glycemic Rescue:* Glim or Insulin glargine	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • BW • FPG • SBP • % Subjects with HbA1c <7% • β-cell responsivity static component	Phase A: 26 wks Phase B: 26 wks	• Sita 100 mg: 247 • Ertu 5 mg: 250 • Ertu 15 mg: 248 • Ertu 5 mg + Sita 100 mg: 243 • Ertu 15 mg + Sita 100 mg: 245 (1:1:1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 7.5-11% • eGFR of ≥60 mL/min/1.73m² *Background Therapy:* • Met ≥1500 mg x ≥8wks	**242 Sites** **21 Countries** **5 Regions:** Asia Australia/New Zealand Europe North America South/Central America
P006/1015¶*† (Add-on to Met and Sita Study) **NCT02036515** *Trial Initiation Date: 07-Apr-2014* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel group, placebo-controlled	• Ertu 5 mg PO QD • Ertu 15 mg PO QD • Placebo PO QD *Glycemic Rescue:* Glim or Insulin glargine	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • BW • SBP • FPG • % Subjects with HbA1c <7%	Phase A: 26 wks Phase B: 26 wks	• Placebo: 153 • Ertu 5 mg: 156 • Ertu 15 mg: 154 (1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 7-10.5% • eGFR of ≥60 mL/min/1.73m² *Background Therapy:* • Met ≥1500 mg + Sita 100 mg x ≥8wks	**104 Sites** **12 Countries** **4 Regions:** Asia Europe North America South America
P007/1017*† (Placebo-controlled Add-on to Met Study) **NCT02033889** *Trial Initiation Date: 10-Jan-2014* *Trial Completion Date: Ongoing*	Multicenter, randomized, double-blind, parallel group, placebo-controlled	• Ertu 5 mg PO QD • Ertu 15 mg PO QD • Placebo PO QD *Glycemic Rescue:* Glim (+ basal insulin prn)	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • FPG • BW • % Subjects with HbA1c <7% • SBP • BMD (Wks 26, 52, and 104)	Phase A: 26 wks Phase B: 78 wks	• Placebo: 209 *(Glim, Phase B)‡* • Ertu 5 mg: 207 • Ertu 15 mg: 205 (1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 7-10.5% • eGFR of ≥55 mL/min/1.73m² • 44% post-menopausal (≥3 yr) women *Background Therapy:* • Met ≥1500 mg x ≥8wks	**103 Sites** **14 Countries** **6 Regions:** Asia Australia/New Zealand Europe North America South Africa South America

Trial Identifier (Abbreviated Title)	Trial Design	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Patients Randomized	Study Population	No. of Centers and Countries
P017/1047 (Ertu + Sita Initial Combination Study) **NCT02226003** *Trial Initiation Date: 25-Sep-2014* *Trial Completion Date: 23-Feb-2016*	Multicenter, randomized, double-blind, parallel group, placebo-controlled	• Ertu 5 mg + Sita 100 mg PO QD • Ertu 15 mg + Sita 100 mg PO QD • Placebo PO QD *Glycemic Rescue:* Glim	BL to Wk 26 Change: *Primary* • HbA1c *Secondary* • FPG • % Subjects with HbA1c <7% • BW • SBP	Single Phase: 26 wks	• Placebo: 97 • Ertu 5 mg + Sita 100 mg: 98 • Ertu 15 mg + Sita 100 mg: 96 (1:1:1 allocation)	• ≥18 years old • T2D • HbA1c 8-10.5% • eGFR of ≥60 mL/min/1.73m^2 *Background Therapy:* • Diet and exercise	**96 Sites** **10 Countries** **2 Regions:** Asia Europe North America

Source: Adapted from the Applicants Tabular Listing of All Clinical Studies, available at: \\cdsesub1\evsprod\nda209803\0000\m5\52-tab-list\tabular-listing.pdf.
Abbreviations: +/-, plus or minus; β-cell, beta cell; BID, twice daily; BL, baseline; BW, body weight; eGFR, estimated glomerular filtration rate; Ertu, ertugliflozin; FPG, fasting plasma glucose; Glim, glimepiride; HbA1c, hemoglobin A1c (glycosylated hemoglobin); Met, metformin; NCT, National Clinical Trial; OL, open-label; PO, orally; PPG, postprandial glucose; prn, as needed; QD, daily; SBP, sitting systolic blood pressure; Sita, sitagliptin; T2D, type 2 diabetes mellitus; wks, weeks; QD, daily; vs., versus; and yr, year.
¶ Trials used to support safety and efficacy for NDA 209805 (Ertugliflozin/Sitagliptin FCDP).
*Trials used to support safety and efficacy for NDA 209806 (Ertugliflozin/Metformin FCDP).
†Trials used in the Placebo Pool (i.e., short-term placebo-controlled safety pool).
‡Placebo-treated subjects who did not receive glycemic rescue therapy in Phase A received blinded metformin in Phase B for Trial P003/1022, and in Trial P007/1017, blinded glimepiride during Phase B.

5.2. Review Strategy

This review will focus primarily on the efficacy and safety findings (i.e., the prespecified primary and secondary endpoints) from the seven Phase 3 clinical trials (Table 3) that the Applicant intends to include in Section 14 (CLINICAL STUDIES) of proposed product labeling. For a detailed discussion of the statistical analyses of these trials, please refer to the Statistical Reviews (dated August 25, 2017 [N209803]; and August 28, 2017 [NDA 209806]) of Dr. Alexander Cambon, the primary statistical reviewer for all three Applications. The review strategy for the safety findings is presented in Section 8.1 (Safety Review Approach).

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Phase 3 Trials

6.1.1. Study Designs

The seven Phase 3 trials used to support efficacy of ertugliflozin were all multicenter, randomized, double-blinded, controlled trials, and met regulatory standards for adequate and well-controlled studies (21 CFR 314.126).[22] These studies included five placebo-controlled trials and two active-controlled trials. The respective trial designs are presented in Appendix 13.3.

The placebo-controlled trials evaluated ertugliflozin 5 mg and 15 mg as monotherapy (P003/1022; Figure 5), coadministered with sitagliptin (P017/1047; Figure 10), as add-on to metformin (P007/1017; Figure 6), as add-on to metformin plus sitagliptin (P006/1015; Figure 7), and as add-on to standard antihyperglycemic medications in subjects with Stage 3 chronic kidney disease (P0001/1016, dedicated moderate renal impairment trial; Figure 11). The active-controlled trials compared these same ertugliflozin doses to glimepiride (Trial P002/1013;Figure 8), and as add-on to metformin when coadministered with sitagliptin in a factorial trial (P005/1019; Figure 9). All trials included a 2-week placebo run-in period prior to randomization. Six of the seven trials were ongoing (i.e., 26-week treatment periods [Phase A] for the evaluation of efficacy were completed; 26-78 week long-term safety extensions [Phase B] were ongoing at the time of NDA submission).

6.1.2. Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria for the Phase 3 trials are presented in Table 4. Generally, these trials enrolled relatively healthy adult subjects with T2D. Although higher risk subjects are currently being enrolled in the Applicant's dedicated cardiovascular outcomes trial (CVOT, Trial P004/1021), data from this trial were not evaluated in order to maintain the blinding of treatment allocations and data integrity.

Table 4: Summary of Key Inclusion and Exclusion Criteria by Phase 3 Trial

Trials	P001	P002	P003	P005	P006	P007	P017
INCLUSION CRITERIA							
Age ≥18 yrs	X	X	X	X	X	X	X
T2D men/women (ADA criteria)[81]	X	X	X	X	X	X	X
HbA1c 7-9%		X					
HbA1c 7-10.5%	X		X		X	X	
HbA1c 7.5-11%				X			
HbA1c 8-10.5%							X
Background metformin ≥1500 mg/d for ≥8 wks		X		X		X	
Background metformin ≥1500 mg/d/sitagliptin100 mg/d for ≥8 wks					X		
Adherence ≥80% for 2-wk placebo run-in	X	X	X	X	X	X	X
eGFR ≥30 to <60 mL/min/1.73 m^2	X						
BMI ≥18 kg/m^2	X	X	X	X	X	X	X
EXCLUSION CRITERIA							
T1D, Hx of DKA, Secondary DM	X	X	X	X	X	X	X
Hx of hypersensitivity/intolerance to study meds	X	X	X	X	X	X	X
Prespecified antihyperglycemic agents							
Other non-protocol antihyperglycemic agents		X	X	X	X	X	X
Rosiglitazone or SGLT2 inhibitors	X						
Prespecified renal/urologic Dx*	X						
Medications/surgery affecting BW¶	X	X	X	X	X	X	X
Prespecified medical conditions†	X	X	X	X	X	X	X
BMD T-score <-2.5 or protocol prespecified bone/joint-related Dx¶						X	
Pregnant/breastfeeding	X	X	X	X	X	X	X
Excessive alcohol consumption‡	X	X	X	X	X	X	X
SBP >160 mmHg and/or DPB >90 mmHg	X	X	X	X	X	X	X
Abnormal clinical labs							
eGFR <55 mL/min/1.73 m^2		X	X			X	
eGFR <60 mL/min/1.73 m^2				X	X		X
SCr ≥1.3 mg/dL males/≥1.2 mg/dL females		X	X	X	X	X	
Fasting blood glucose >260-300 mg/dL	X	X	X	X	X	X	X
Fasting blood glucose <120-130				X	X		X
Fasting TG >600 mg/dL	X	X	X	X	X	X	X
ALT or AST >2x ULN	X	X	X	X	X	X	X
TBILI >1.5x ULN			X			X	
TSH outside of normal reference limits	X	X	X	X	X	X	X
Hemoglobin <10 g/dL	X						
Hemoglobin <12 g/dL males/<11 g/dL females		X	X	X	X		X

Source: Adapted from the Applicants' Clinical Study Reports for Trials P001/1016, P002/1013, P003/1022; P005/1019, P006/1015, P007/1017, and P017/1047, available at:
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p001v01\p001v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p003v01\p003v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p005v01\p005v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p006v01\p006v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01.pdf
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p017\p017.pdf
Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; BMI, body mass index; BW, body weight; d, day; DKA, diabetic ketoacidosis; Dx, diagnosis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Hx, history; meds, medications; SBP, systolic blood pressure; SCr, serum creatinine; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TBILI, total bilirubin; TG, triglycerides; TSH, thyroid-stimulating hormone; wk, week; and yr, years.
*Proteinuria >3000 mg/day with albuminuria and edema; rapidly progressive glomerulonephritis; lupus nephritis; renal or systemic vasculitis; renal artery stenosis with renovascular hypertension or ischemic nephropathy; familial renal glucosuria; obstructive uropathy or indwelling urinary catheter.
¶Bariatric surgery, or weight-loss programs or mediations that may affect body weight.
†Generally included: myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischemic attack (TIA), NYHA functional class III-IV heart failure (within 3 months), malignancy (≤5 years), human immunodeficiency virus, blood dyscrasia/hemolysis/unstable red blood cells/hematological disorder, active liver disease, malabsorption condition, recent surgery (<4-6 wks); hyperthyroidism; clinically significant ECG findings; other severe acute or chronic medical/psychiatric condition or laboratory abnormality that would make subject participation inappropriate; requires ≥14 days of systemic corticosteroids or ≥7 days of nonsteroidal anti-inflammatory drugs; and/or unstable doses of antihyperlipidemic, antihypertensives or thyroid hormone replacement therapy.
‡Usually included binge drinking, >2 drinks/day, or >14 drinks/week.
ΠSubjects history of osteoporosis (BMD T-score <-2.5), rheumatoid arthritis, illness that could affect BMD, bilateral hip prosthesis, fewer than 3 vertebrae evaluable for dual-energy x-ray absorptiometry (DXA), hyperparathyroidism, atraumatic vertebral fracture or high or low impact fracture of the hip or wrist, use of bisphosphonates or other medications that may affect bone metabolism

Overall, I thought that the trial designs, including the inclusion/exclusion criteria, patient populations, exposures, and treatment durations, were adequate and consistent with other antihyperglycemic Phase 3 clinical development programs submitted to the Division.

6.1.3. **Study Treatments**

Depending on the respective Phase 3 trial, investigational product (IP) was administered once daily in the morning and provided by the Applicant as follows:

- ***P001/1013:*** Ertugliflozin 5 mg and 10 mg tablets, and matching placebo
- ***P002/1013:*** Ertugliflozin 5 mg and 10 mg tablets, glimepiride 1 mg and 2 mg tablets (or capsules), and matching placebo
- ***P003/1022:*** Ertugliflozin 5 mg and 10 mg tablets, and matching placebo
- ***P005/1019:*** Ertugliflozin 5 mg and 10 mg tablets, sitagliptin 100 mg tablets and matching placebo
- ***P006/1015:*** Ertugliflozin 5 mg and 10 mg tablets, and matching placebo
- ***P007/1017:*** Ertugliflozin 5 mg and 10 mg tablets, and matching placebo

- ***P017/1047:*** Ertugliflozin 5 mg and 10 mg tablets, sitagliptin 100 mg tablets, and matching placebo

(*Note: For all Phase 3 clinical trials, the ertugliflozin 15 mg dose was administered as a 5 mg plus a 10 mg tablet*)

Rationale for Dose Selection:

Based on the Applicant's dose-response modeling from their Phase 2 data, they felt that the ertugliflozin 5 mg and 15 mg doses should achieve >80% and >90% of the maximum PD response (e.g., changes in HbA1c, FPG, body weight, and UGE_{0-24}), respectively (see Section 4.5). Further, they claim that a maximum proposed ertugliflozin dose of 15 mg daily would have adequate safety margins based on their nonclinical data (see Section 4.4).

The dose of sitagliptin was selected based on the approved dose. The Applicant claims that a sitagliptin dose of 100 mg daily has been shown to provide effective improvements across glycemic endpoints and to be well tolerated. For trials that require metformin as background therapy, stable doses of ≥1500 mg for at least eight weeks have been considered acceptable.

Blinding and Treatment Assignments:

Study medications were typically provided by the Applicant using a double-blind/masking technique (e.g., matching placebo was provided in identical packaging as active treatment). Subjects, investigators, personnel or designees (Covance and Parexel) of the Applicant, remained blinded throughout the Phase A double-blind treatment period, while personnel (e.g., Covance and Parexel) involved in the conduct of the trial, subjects, and trial site staff also remained blinded until completion of Phase B.

Subjects were randomized into each study arm using 1:1 treatment allocations. Additionally, randomization was stratified by eGFR group, medical history of CVD, and insulin use for Trial P001/1013; participation in a mixed meal tolerance test (MMTT, yes/no) for Trial P005/1019; use of sulfonylurea at screening (yes/no) for Trial P006/1015; postmenopausal status in females for Trial P007/1017; and antihyperglycemic wash-off status (yes/no) for Trial P017/1047. Randomization was performed centrally using an interactive voice response system/integrated web response system (IVRS/IWRS), with subjects being assigned randomly using a computer-generated randomization.

Generally, the blinding and randomization methods used by the Applicant in the respective Phase 3 trials were acceptable.

Dose Modifications of Study Medications:

Except for Trial P002/1013, where glimepiride doses could be up- or down-titrated (doses could range from 1 mg/day up to 6 or 8 mg/day, depending on local approved labeling), dose titration of blinded study medication was not permitted at any time during the study. Additionally, open-label metformin doses remained unchanged during the double-blind treatment period.

6.1.4. Administrative Structure of the Ertugliflozin Development Program

Merck and Pfizer co-developed the ertugliflozin Phase 3 clinical development program, with Merck-managed trials conducted with their designee, Covance, and those managed by Pfizer conducted with Parexel. Additionally, five independent adjudication committees, blinded to randomization codes, evaluated potential fracture, pancreatitis, CV, hepatic, and renal events, and a blinded Internal Case Review Committee (ICRC) assessed potential cases of ketoacidosis.

6.1.5. Protocol Procedures and Schedule

All Phase 3 trials included a 2-week placebo run-in period, with scheduled study visits at baseline and Weeks 6, 12, 18, and 26 (Phase A). Depending on the trial, additional visits (Phase B) were scheduled at 4- to 13-week intervals until study completion (see Appendix 13.3). Adverse event monitoring and assessments of vital signs, clinical laboratory parameters and adherence to IP were usually performed at these study visits.

Dietary Restrictions/Instructions:

Subjects usually received counseling on dietary and life-style modifications (in accordance with local medical standards of care for subjects with T2D) by a dietician or qualified healthcare professional at screening, and were asked to follow the recommendations throughout the trial. Additional follow-up at subsequent visits may have been performed by other study personnel responsible for the evaluation of the subject. Investigational sites also reinforced diet and exercise counseling prior to repeat central laboratory measurements used for confirmation of abnormal FPG values that met glycemic thresholds for rescue therapy (see Table 5).

Concurrent Medications:

Three of the seven trials required the use of background metformin therapy, while a fourth included both sitagliptin plus metformin (Table 3: Listing of Phase 3 Clinical Trials Relevant to this NDA). For Trial P001/1016, stable doses of non-metformin antihyperglycemic medications

were permitted. Medications commonly used by diabetic patients or recommended as standard of medical care were typically allowed. However, stable dosing regimens of antihypertensives, antihyperlipidemics, hormonal contraceptives, and thyroid hormone replacement therapy were required prior to randomization. Use of medications that could affect body weight was not allowed for any of the trials (Table 4), and the use of herbal supplements and natural products was discouraged.

Adherence to Study Treatment:

The investigator was required to maintain an accountability record of study medications, and subjects were asked to bring in any used or unused bottles at each visit. Adherence to IP was assessed through subject interview and tablet counts. Subjects who were <80% compliant with the treatment regimen during the 2-week placebo run-in phase were ineligible to participate in the trial. During the remainder of the trial, the importance of adherence to study medications was reinforced for all subjects who were <80% compliant following randomization.

Rescue Medication:

Subjects with inadequate glycemic control during Phase A, the double-blind treatment period, were eligible to receive open-label rescue medication based on the criteria presented in Table 5. These criteria are consistent with the 2008 Diabetes Guidance.[6] Subjects who met any of the criteria were required to complete a rescue visit, and subsequently prescribed open-label antihyperglycemic rescue medication in accordance with local approved labeling/standard of care (see Table 3: Listing of Phase 3 Clinical Trials Relevant to this NDA for study-specific rescue therapy). Subjects were asked to continue with the planned study visits and continued to receive blinded study medication. In Phase B, subjects were eligible to receive open-label rescue therapy in addition to their study medication based on HbA1c or FPG criteria. These subjects also were required to complete a rescue visit, and continue with their scheduled follow-up visits.

In correspondence with the Applicant (dated December 28, 2015, July 29, 2016, and September 30, 2016), the Agency reiterated that the primary efficacy analysis should use all HbA1c data from all subjects randomized, regardless of treatment adherence and rescue status.

Table 5: Criteria for Initiation of Antihyperglycemic Rescue Therapy

Study Visits	Rescue Laboratory Criteria (Central Lab)*
Phase A (double-blind treatment period)	
Week 6	FPG >270 mg/dL
After Week 6 to Week 12	FPG >240 mg/dL
Weeks 12-26	FPG >200 mg/dL
Phase B (long-term safety extension period)¶	
After Week 26	FPG >200 mg/dL or HbA1c >8%

Source: Adapted from the Applicants' Clinical Study Reports for Trials P001/1016, P002/1013, P003/1022; P005/1019, P006/1015, P007/1017, and P017/1047, labeled as Table 9-4, page 149/2401; Table 9-6, page 95 of 2209; Table 3, page 84 of 3191; Table 9-5, page 110 of 2273; Table 9-5, page 87 of 1074; Table 3, page 98 of 3124; and Table 9-5, page 90 of 1028, respectively, available at:
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Abbreviations: FPG, fasting plasma glucose, and HbA1c, hemoglobin A1c.
*Note: To meet the FPG criteria, a repeat/confirmatory measurement was performed within 3-7 days of notification from the central laboratory.
¶For Trial P002/1013, Phase B began after Week 52.

Subject Withdrawal/Discontinuation:

Subjects were discontinued from study medication for the following reasons:

- Withdrawal of informed consent
- Protocol-defined hyperglycemia criteria
- Protocol-defined recurrent hypoglycemia episodes
- Protocol-defined abnormal liver function
- Protocol-defined abnormal renal function tests
- Bariatric surgery
- Requirement of prohibited medications
- Pregnancy
- Unblinding of investigator or subject
- Any medical condition/circumstance which, in the opinion of the investigator, indicates that continued participation would not be in the best interest of the subject

If the subject withdrew consent from participating in the trial, no further evaluations were performed, and no additional data collected. Subjects prematurely discontinuing the trial for reasons other than withdrawn consent were asked to attend a discontinuation visit and a post-treatment follow-up visit/phone call (i.e., 14 days after the last exposure to IP), and to be contacted periodically (e.g., per the scheduled study visits) by phone for collection of important health status information.

6.1.6. **Study Endpoints**

Primary Efficacy Endpoint:

- Mean change from baseline in HbA1c (%) at Week 26 (or Week 52 for Trial P002/1013)

The primary efficacy endpoint for all seven Phase 3 trials was the change from baseline (randomization) in HbA1c (%). HbA1c is considered an appropriate efficacy endpoint, and a positive result would indicate a clinically meaningful benefit for the following reasons:

- HbA1c is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months.[82]
- The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5%.[83,84]
- HbA1c has excellent reliability, predicts some of the diabetes-specific complications, and provides a basis for treatment decisions in patients with T2D.[85-87]
- Lowering HbA1c reduces microvascular complications[8,15,16,87] and may lower the risk of macrovascular complications[5,10] in patients with T1D and T2D.

For these reasons, the FDA draft guidance entitled *Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* states, "for purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control."[6] Scheduled measurements of HbA1c used for eligibility criteria, efficacy analyses, and need for glycemic rescue, were performed at a Central Laboratory.

Secondary Efficacy Endpoints:

In addition to the primary efficacy endpoint, the Applicant also evaluated other glycemic endpoints, as well as non-glycemic and pharmacodynamic endpoints. The secondary endpoints (b) (4) of ertugliflozin and the ertugliflozin FCDPs are:

- Proportion of subjects with an HbA1c <7%
- Mean change from baseline to Week 26 (or Week 52; Trial P002/1013) in:
  - FPG (mg/dL)
  - 2-hour PPG (mg/dL)
  - Body weight (kg)
  - Sitting SBP (mmHg)
  - Sitting DBP (mmHg)

The glycemic endpoints (HbA1c <7%, FPG, and 2-hour PPG) are considered supportive measures of efficacy in Phase 3 trials.[6] The analyses of these endpoints also were based on measurements performed by a Central Laboratory. To control for Type I error due to multiple testing, the above secondary efficacy endpoints (i.e., proportion of subjects with an HbA1c <7%, FPG, 2-hour PPG, body weight, sitting SBP, and sitting DBP) were included in the Applicant's prespecified testing sequence.

Other Relevant Endpoints:

- The proportion of subjects who required glycemic rescue
- Time to glycemic rescue
- Change from baseline in β-cell responsivity static component (Φs; reflective of the second-phase insulin secretory response[88,89])
- Safety: Adverse events (AEs), and clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings

6.1.7. Statistical Analysis Plan

The Applicant performed their efficacy analyses using the Full Analysis Set (FAS), which consisted of all randomized subjects who received ≥1 dose of IP and had at least one endpoint measurement (i.e., baseline or post-randomization). For the analyses of the primary endpoint (i.e., mean change in HbA1c from baseline to Week 26 [or 52 for Trial P002/1013]) and continuous secondary endpoints, as well as for the efficacy analyses using a pool of placebo-controlled trials, they used a constrained, longitudinal data analysis (cLDA) model.[90] This model assumes a common mean across treatment arms at baseline (i.e., due to randomization), and a different mean for each treatment at each post-baseline time point. Treatment, time, treatment-time interactions, and additional protocol-specified covariates were used in the model. For Trial P002/1013 (i.e., the ertugliflozin vs. glimepiride noninferiority trial), the Applicant used a HbA1c noninferiority margin of 0.3%, which is consistent with other active comparator noninferiority Phase 3 trials submitted to the Division.[6]

For the analysis of the proportions of subjects with HbA1c <7% (i.e., a binary endpoint based on subjects meeting or not meeting this glycemic target using the observed or cLDA imputed HbA1c value), the Applicant used a logistic regression model to estimate the odds ratio for comparison of treatment arms. The regression model included terms for treatment, baseline HbA1c, and other protocol-specified covariates.

The prespecified study-wise type I error rate related to the primary and secondary efficacy endpoints was controlled at the two-sided 0.05 level by using a hierarchical closed testing procedure (i.e., statistical testing proceeded to each subsequent endpoint only if the two-sided p-value was <0.05 for all previous endpoint analyses). Please refer to the Statistical Review (NDA 209803) by Dr. Cambon for a detailed listing of the hierarchical testing order of the primary and secondary endpoints of each trial.

The Applicant also performed several sensitivity analyses (e.g., cLDA that included data after glycemic rescue therapy, Tipping point and Jump-to-Reference) for the primary efficacy endpoint to evaluate the effects of missing data (i.e., due to early discontinuation of IP and censoring following glycemic rescue therapy). The Tipping point analysis was used to assess how large the difference between the non-missing and the missing data would need to be to alter the conclusion of the analysis.[91] The Jump-to-Reference approach assumes that missing data in the ertugliflozin treatment arm follow the same distribution as in the comparator arm.[92]

In his statistical review, Dr. Cambon noted that the Applicant's data analysis set excluded measurements obtained after discontinuation of IP for both the primary and sensitivity analyses, and that the cLDA analysis treated HbA1c measurements obtained after initiation of glycemic rescue therapy as missing data. He expressed concern with the exclusion of these data by the Applicant for their efficacy analyses, as these results may not reflect the actual efficacy findings should all of the subjects who participated in the trial and all of the data following rescue therapy have been included in the analyses. He felt that the preferred analysis population should include all randomized subjects who have a baseline measurement and were exposed to IP, and that the analysis set should include all measurements, regardless of whether subjects received rescue therapy or discontinued IP. Therefore, he reanalyzed the primary and key secondary efficacy endpoints using all available data, including HbA1c data measurements collected after rescue or discontinuation. Based on the existing data, he recommended an analysis of covariance (ANCOVA) return to baseline (RTB) statistical approach for the efficacy analyses, which assumes that the subjects with missing data return to their baseline measurement. Further, to evaluate the robustness of the Applicant's conclusions, he performed additional sensitivity and subgroup (i.e., sex, race, age, geographic region) analyses. For a more detailed discussion of the Statistical Analysis Plan (SAP) and the statistical approach used by Dr. Cambon, please refer to his Statistical Review (NDA 209803, dated August 25, 2017).

Protocol Amendments

Review of relevant changes in the conduct of the respective Phase 3 trials and planned analyses did not reveal notable protocol amendments that would alter the final review and interpretation of the efficacy data for the submitted NDAs.

Data Quality and Integrity: Sponsor's Assurance

The Applicant states that their clinical trials are subject to quality control and quality assurance oversight (e.g., on-site monitoring inclusive of source data verification, medical monitoring of clinical trial data and resultant databases, and quality reviews of regulatory submission documents), including independent audits in accordance with their Standard Operating Procedures. The study sites were monitored to assess compliance with the clinical protocol and general principles of Good Clinical Practice (GCP), and the clinical data were verified against the source documentation and reviewed for accuracy, completeness, and consistency. Potential issues of fraud, misconduct, and/or serious GCP non-compliance were further investigated.

6.1.8. Study Results

Compliance with Good Clinical Practices

The Applicant states that all studies in the ertugliflozin clinical development program were conducted in accordance with GCP and the Declaration of Helsinki. Further, they claim that their Phase 3 development program was planned, conducted, and analyzed in accordance with the US and European Union (EU) regulatory guidance documents that were in effect at the time the trials were initiated.

Financial Disclosure

The Applicant submitted a Form FDA 3454 for the covered trials. They note that the following clinical investigators/subinvestigators had reportable financial interests/arrangements to disclose: (b) (6), who participated in Trials P005/ (b) (6) and P006/ (b) (6) (i.e., held shares of Pfizer stock valued at $250,000.00); and (b) (6), who participated in a Phase 2 trial, P016/ (b) (6) (received $36,857.55 in payments by Pfizer for consulting and speaking fees). Based on a review of the clinsite.xpt and dm.xpt datasets, and the Center for Drug Evaluation and Research (CDER) Clinical Inspection Site Selection Tool (v2.4.15), it appears that Dr. (b) (6) enrolled (b) (6) subjects (n=(b) (6) in P005/ (b) (6); and n (b) (6) in P006/ (b) (6)). Therefore, I do not feel that the participation of the two investigators in question would alter the integrity of the Phase 3 data or efficacy findings.

Subject Disposition

In total, the seven trials randomized and treated 4859 adult T2D subjects (i.e., 1450 subjects to placebo or comparator, 1716 subjects to ertugliflozin 5 mg, and 1697 subjects to ertugliflozin 15 mg) who had inadequate glycemic control (baseline HbA1c was between 7% to 11%). The cumulative study disposition of subjects at the time of the 4-MSU submission is presented in Table 6. Approximately 59% of randomized subjects have completed the respective trials, with approximately 27% still receiving IP. Reasons for discontinuations from these trials were similar between non-ertugliflozin and ertugliflozin treatment arms, with withdrawal of consent by the subject and lost to follow-up, reported for at least 2% of subjects in any treatment arm (380 subjects total). Of these subjects, SAEs were reported in 6.9% (9/130), 5.4% (6/112)), and 5.1% (7/138) of non-ertugliflozin-, ertugliflozin 5 mg- and ertugliflozin 15 mg-treated subjects, respectively. These data are limited and inadequate to ascertain the presence of treatment-related trends.

Table 6: Cumulative Trial Disposition (Randomized Population)*

	Non-Ertugliflozin	Ertugliflozin 5 mg	Ertugliflozin 15 mg
NUMBER OF SUBJECTS ENROLLED, N=12066			
NUMBER OF SUBJECT RANDOMIZED, N=4864			
NUMBER OF SUBJECT RANDOMIZED AND TREATED, N=4859			
Number of Subjects Randomized and Treated	**1450**	**1716**	**1693**
Completed, n (%)	791 (54.6)	1,067 (62.2)	1,030 (60.7)
Ongoing	441 (30.4)	446 (26.0)	437 (25.7)
Discontinued	218 (15.0)	203 (11.8)	231 (13.6)
Withdrew consent	89 (6.1)	67 (3.9)	89 (5.2)
Lost to follow-up	41 (2.8)	45 (2.6)	49(2.9)
Adverse event	21 (1.4)	18 (1.0)	26 (1.5)
Hyperglycemia	15 (1.0)	20 (1.2)	22 (1.3)
Nonadherence to IP	6 (0.4)	9 (0.5)	8 (0.5)
Protocol violation	4 (0.3)	9 (0.5)	8 (0.5)
Subject relocated	6 (0.4)	4 (0.2)	8 (0.5)
Death	9 (0.6)	11 (0.6)	6 (0.4)
Study terminated by Applicant	13 (0.9)	9 (0.5)	5 (0.3)
Screen failure	0	0	5 (0.3)
Physician decision	6 (0.4)	7 (0.4)	4 (0.2)
Excluded medication	4 (0.3)	2 (0.1)	1 (0.1)
Lack of efficacy	2 (0.1)	2 (0.1)	0
Hypoglycemia	1 (0.1)	0	0
Pregnancy	1 (0.1)	0	0

Source: Adapted from the Applicant's 4-MSU report, labeled as Table 2.7.4:5, page 23-24 of 486, available at: \\cdsesub1\evsprod\nda209803\0014\m2\27-clin-sum\summary-clin-safety.pdf and confirmed with the sur-iss adsl.xpt and dsplus.xpt datasets.

Protocol Violations/Deviations

A protocol deviation was defined as any change, divergence, or departure from the study design or procedures defined in an approved protocol; and a major protocol deviation was defined as any protocol deviation which may significantly/adversely impact the completeness, accuracy, and/or reliability of the trial data or that may significantly/adversely affect a subject's rights, safety, or well-being. Across the Phase 3 clinical program, major protocol deviations were reported in approximately 24% to 48% of subjects (i.e., 23.6% in Trial P005/1019; 26.0% in Trial P003/1022; 28.2% in Trial P017/1047; 29.4% in Trial P006/1015; 31.2% in Trial P002/1013; 32.9% in Trial P007/1017; and 48.4% in Trial P001/1016).The most common deviations for these trials included 'subjects did not give appropriate informed consent', 'failure to conduct major/significant evaluations', and 'eligibility criteria not met'. A review of the major deviations did not reveal any obvious/important trends or treatment differences across trial arms.

In their post hoc analyses of Study P001/1016 (the dedicated moderate renal impairment trial), the Applicant noted that metformin may have been used in violation of the protocol (i.e., metformin was a protocol-prohibited medication). Approximately 17% of subjects included in the Week 26 HbA1c analysis may have been exposed to metformin, based on the finding of at least one positive assay result. The Applicant felt that this may have confounded the primary efficacy findings, resulting in a failed trial. (b) (4)

(b) (4)

(b) (4)

it appears the metformin exposures were similar across all treatment arms (FAS), with positive assay results identified in approximately 16.9% (26/154), 15% (24/158), and 18% (28/155) of subjects in the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms. Further, the use of other non-metformin antihyperglycemic medications was allowed, and both the FDA (as of April 8, 2016)[93] and the European Medicines Agency (EMA; as of October 13, 2016)[94] currently accept the use of metformin in patients with moderate renal impairment (eGFR between 30-59 mL/min/1.73 m^2). Across the ertugliflozin Phase 3 clinical program, there also appeared to be numerically more subjects in the ertugliflozin treatment arms who experienced adverse outcomes (deaths, SAEs, withdrawals due to AEs) at this level of renal function (please refer to Sections 8.4 and 10.1 [Table 41]).

Demographics and Clinical Characteristics

A total of 4859 were randomized and treated into the seven Phase 3 trial, of 1450 subjects received placebo or active comparator, 1716 subjects received ertugliflozin 5 mg, and 1693 subjects received ertugliflozin 15 mg. Relevant demographics and baseline clinical characteristics of the all treated subject populations for these trials are presented in Table 7. Additionally, demographics/clinical characteristics by treatment group (i.e., non-ertugliflozin,

ertugliflozin 5 mg and ertugliflozin 15 mg) and by individual treatment arm are presented in Table 14 and in the Statistical Review (NDA 209803, dated August 25, 2017) of Dr. Cambon, respectively.

Generally, the trial populations were predominantly White, and relatively young, with limited numbers of individuals over 75 years of age. The trials were conducted worldwide, with approximately 33% of randomized subjects residing in the North American region. The average body mass index (BMI) was >30 kg/m^2, and the mean baseline HbA1c concentrations were >8%. The mean durations of diabetes ranged from five to 14 years. Excluding Trial P001/1016, most subjects had normal renal function or mild renal impairment.

Table 7: Demographics, Clinical Characteristics and Concomitant Medications (Phase 3 Trials)

Trials*	P001/1016 (N=467)	P002/1013 (N=1325)	P003/1022 (N=461)	P005/1019 (N=1232)	P006/1015 (N=462)	P007/1017 (N=621)	P017/1047 (N=291)
DEMOGRAPHICS							
Age, mean ± SD — yr	67.3 ± 8.6	58.2 ± 9.6	56.4 ± 11.0	55.1 ± 10.1	59.1 ± 9.0	56.6 ± 8.8	55.6 ± 10.0
<65 yr — no. (%)	162 (34.7)	140 (74.6)	341 (74.0)	1033 (83.8)	324 (70.1)	524 (84.4)	233 (80.1)
≥65 yr — no. (%)	305 (65.3)	336 (25.4)	120 (26.0)	199 (16.2)	138 (29.9)	97 (15.6)	58 (19.9)
≥75 yr — no. (%)	101 (21.6)	50 (3.8)	15 (3.3)	28 (2.3)	13 (2.8)	4 (0.6)	8 (2.7)
Female sex — no. (%)	236 (50.5)	683 (51.5)	200 (43.4)	568 (46.1)	199 (43.1)	333 (53.6)	124 (42.6)
Race — no. (%)							
White	380 (81.4)	966 (72.9)	386 (83.7)	989 (80.3)	337 (72.9)	411 (66.2)	263 (90.4)
Black/African American	19 (4.1)	61 (4.6)	29 (6.3)	46 (3.7)	9 (1.9)	64 (10.3)	13 (4.5)
Asian	45 (9.6)	239 (18.0)	39 (8.5)	131 (10.6)	94 (20.3)	100 (16.1)	0
Other	23 (4.9)	59 (4.5)	7 (1.5)	22 (1.8)	22 (4.8)	46 (7.4)	3 (1.0)
Ethnicity (Hispanic/Latino) — no. (%)							
Hispanic/Latino	87 (18.6)	273 (20.60	103 (22.3)	425 (34.5)	72 (15.6)	113 (18.2)	105 (36.1)
Not Hispanic/Latino	379 (81.2)	1051 (79.3)	358 (77.7)	807 (65.5)	389 (84.2)	507 (81.6)	186 (63.9)
Not Reported/Unknown	1 (0.2)	1 (0.1)	0	0	1 (0.2)	1 (0.2)	0
Region — no. (%)							
North America	134 (28.7)	383 (28.9)	308 (66.8)	375 (30.4)	93 (20.1)	169 (27.2)	143 (49.1)
Europe	186 (39.8)	597 (45.1)	118 (25.6)	510 (41.4)	209 (45.2)	224 (36.1)	148 (50.9)
Latin America	54 (11.6)	133 (10.0)	9 (2.0)	210 (17.0)	33 (7.1)	21 (3.4)	0
Asia	80 (17.1)	174 (13.1)	6 (1.3)	116 (9.4)	127 (27.5)	85 (13.7)	0
South Africa	13 (2.8)	38 (2.9)	20 (4.3)	0	0	111 (17.9)	0
Australia/New Zealand	0	0	0	21 (1.7)	0	11 (1.8)	0
CLINICAL CHARACTERISTICS							
BMI, mg/m^2 — mean ± SD	32.5 ± 6.1	31.4 ± 6.1	33 ± 6.7	31.9 ± 6.3	30.8 ± 6.0	30.9 ± 4.7	32.2 ± 6.1
Duration of T2D, mean ± SD — yr	14.2 ± 8.5	7.5 ± 5.7	5.0 ± 5.1	6.9 ± 5.4	9.5 ± 5.7	8.0 ± 6.0	6.3 ± 6.1
Glycemic Status							
HbA1c % — mean ± SD	8.2 ± 0.9	7.8 ± 0.6	8.2 ± 1.0	8.6 ± 1.0	8.0 ± 0.9	8.1 ± 0.9	8.9 ± 0.9
<8% — no. (%)	217 (46.5)	847 (63.9)	224 (48.6)	363 (29.5)	249 (53.9)	304 (49.0)	32 (11.0)
8 to <9% — no. (%)	147 (31.5)	431 (32.5)	145 (31.5)	458 (37.2)	134 (29.0)	194 (31.2)	113 (11.0)
≥9% — no. (%)	93 (19.9)	46 (3.5)	90 (19.5)	390 (31.7)	76 (16.5)	115 (18.5)	145 (49.8)
Unknown	10 (2.1)	1 (0.1)	2 (0.4)	21 (1.7)	3 (0.6)	8 (1.3)	1 (0.3)
FPG, mg/dL — mean ± SD	158.5 ± 53.6	161 ± 34.8	180.1 ± 47.4	180.4 ± 47.8	169.7 ± 38.2	168.4 ± 43.8	197.8 ± 47.0
eGFR, mL/min/1.73m^2 — mean ± SD	46.6 ± 8.8	87.2 ± 18.5	87.7 ± 18.6	92.4 ± 20.0	87.9 ± 16.9	90.5 ± 19.3	90.7 ± 19.0
<30	12 (2.6)	1 (0.1)	0	0	0	0	0
30 to <60 — no. (%)	428 (91.6)	54 (4.1)	17 (3.7)	27 (2.2)	8 (1.7)	24 (3.9)	4 (1.4)

Trials*	P001/1016 (N=467)	P002/1013 (N=1325)	P003/1022 (N=461)	P005/1019 (N=1232)	P006/1015 (N=462)	P007/1017 (N=621)	P017/1047 (N=291)
30 to <45	159 (34.0)	4 (0.3)	0	2 (0.2)	0	1 (0.2)	0
45 to <60	308 (66.0)	50 (3.8)	17 (3.7)	25 (2.0)	8 (1.7)	23 (3.7)	4 (1.4)
60 to <90 — no. (%)	27 (5.8)	713 (53.8)	251 (54.4)	588 (47.7)	257 (55.6)	290 (46.7)	155 (53.3)
≥90 — no. (%)	0	557 (42.0)	193 (41.9)	616 (50.0)	197 (42.6)	307 (49.4)	131 (45.0)
Unknown	0	0	0	1 (0.1)	0	0	1 (0.3)
CONCOMITANT MEDICATIONS							
Antihypertensives	439 (94.0)	906 (68.4)	249 (54.0)	729 (59.2)	322 (69.7)	423 (68.1)	139 (47.8)
ACEIs/ARBs	398 (85.2)	799 (60.3)	223 (48.4)	658 (53.4)	288 (62.3)	375 (60.4)	120 (41.2)
Antihyperlipidemic medications	362 (77.5)	693 (52.3)	245 (53.1)	535 (43.4)	286 (61.9)	349 (56.2)	93 (32.0)
Statins	318 (68.1)	610 (46.0)	225 (48.8)	468 (38.0)	257 (55.6)	314 (50.6)	79 (27.1)
Diuretics	260 (55.7)	360 (27.2)	96 (20.8)	253 (20.5)	113 (24.5)	205 (33.0)	57 (19.6)
Loop diuretics	112 (24.0)	28 (2.1)	12 (2.6)	14 (1.1)	13 (2.8)	12 (1.9)	5 (1.7)

Source: Adapted from the Applicants' Clinical Study Reports from:
Trial P001/1016, labeled as Tables 10-8-9, pages 204-209 of 2401, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01.pdf
Trial P002/1013, labeled as Tables 10-5-7, pages 152-159 of 2209, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01.pdf
Trial P003/1022, labeled as Tables 16-18, pages 134-139 of 3191, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p003v01\p003v01.pdf
Trial P005/1019, labeled as Tables 10-6-8, pages 168-176 of 2273, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p005v01\p005v01.pdf
Trial P006/1015, labeled as Tables, pages of, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p006v01\p006v01.pdf
Trial P007/1017, labeled as Tables, pages of, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01.pdf
Trial P017/1047, labeled as Tables, pages of, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p017\p017.pdf
Applicant's Summary of Clinical Efficacy, labeled as Table 80, pages 217-224 of 375, available at: \\cdsesub1\evsprod\nda209803\0000\m2\27-clin-sum\summary-clin-efficacy-t2dm.pdf
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; no., number; SD, standard deviation; T2D, type 2 diabetes mellitus; and yr, years.
*All subjects randomized who received ≥1 dose of investigational product.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Adherence to Study Treatment:

Adherence to oral antihyperglycemic therapy has been reported to range from 36-93% in patients remaining on treatment for six to 24 months.[49] Additionally, prospective electronic monitoring studies have documented that patients took 67-85% of their oral antihyperglycemic doses as prescribed.[49] Although there is no universally accepted definition for what constitutes adequate adherence, a compliance rate of approximately 80% is reasonable.[53,54,95]

For purposes of identifying patients that were not adherent to study treatment, the Applicant chose to use a threshold of 75% (i.e., patients who reported use of 75% or more of IP were considered adherent; patients who reported use of <75% of IP were considered nonadherent).

In the ertugliflozin clinical development program, the incidence of nonadherence to IP during the double-blind treatment period (Phase A) across the Phase 3 trials ranged from 0 to 2.1%. Rates for the individual studies were reported as follows:

- **Trial P003/1022:** No subjects (0/461)
- **Trial P005/1019:** 1% (12/1232) of subjects
- **Trial P007/1017:** 1% (6/621) of subjects
- **Trial P001/1016:** 1.5% (7/467) of subjects
- **Trial P006/1015:** 1.9% (9/462) of subjects
- **Trial P002/1013:** 2% (27/1325) of subjects
- **Trial P017/1047:** 2.1% (6/291) of subjects

No trends were observed between treatment arms. Further, it is unlikely that these relatively low rates of nonadherence would affect the interpretation of the primary and key secondary efficacy findings.

Concomitant Medications:

Concomitant medications typically used as standard of care with T2D are presented in Table 7 above. Across the Phase 3 trials, antihypertensive (48-94% of subjects) and antihyperlipidemic medications (32-78% of subjects) were commonly used by subjects. Use of these medications was allowed in the respective protocols, similar to other antihyperglycemic development programs. However, subjects were to have been on stable doses of these medications before and during the trials.

Rescue Medication Use:

Glycemic rescue criteria were prespecified as described above (Section 6.1.5 and Table 3: Listing of Phase 3 Clinical Trials Relevant to this NDA). However as previously stated, the Applicant did not account for the data from subjects who received antihyperglycemic rescue therapy or discontinued the use of study medication prior to completion of the double-blind treatment period (Phase A) in their primary efficacy analyses. This could result in the evaluation of only those subjects who achieved a therapeutic response or tolerated therapy. In his Statistical Review, Dr. Cambon noted that rescue medication was used before the final HbA1c efficacy assessment by 0% up to 31.3% of subjects in a given treatment arm, with the highest rates typically reported in the placebo treatment arm. In his reanalysis of the primary and key secondary efficacy endpoints, these missing data are accounted for using an ANCOVA return to baseline (RTB) approach. Please refer to his reviews for further discussion.

Efficacy Results – Primary Endpoint

The results of the Applicant's primary and a key secondary efficacy analysis for Trial P001/1016 (i.e., change in HbA1c from baseline to Week 26 performed using the FAS and a cLDA approach that excluded glycemic rescue) are presented in Table 8 below. In this trial the between group differences (i.e., ertugliflozin 5 mg vs. placebo and ertugliflozin 15 mg vs. placebo) were not statistically significant. As prespecified in the SAP, formal hypothesis testing within the ordered testing procedure was stopped at this step (i.e., secondary hypotheses were not to be tested). Additionally, in a secondary analysis of this endpoint in the subset of subjects with a baseline eGFR of 45 to <60 mL/min/1.73 m^2, the placebo-subtracted differences were again nonsignificant. Based on these data, I would not recommend the use of ertugliflozin in patients with moderate renal impairment (i.e., eGFR 30 to <60 mL/min/1.73 m^2). Please refer to Section 8.4 regarding the safety findings in subjects with renal impairment.

Table 8: HbA1c Change from Baseline (FAS, Excluding Rescue Approach) Trial P001/1016

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons Difference in LS Means (95% CI) vs. Placebo†	p-Value
Change from Baseline in HbA1C (%) at Week 26: cLDA				
Placebo	154	-0.26 (-0.41, -0.11)		
Ertugliflozin 5 mg	158	-0.29 (-0.44, -0.14)	-0.03 (-0.23, 0.18)	0.807
Ertugliflozin 15 mg	155	-0.41 (-0.56, -0.27)	-0.15 (-0 35, 0.06)	0.155
Change from Baseline in HbA1C (%) at Week 26: eGFR ≥45 to <60 mL/min/1.73m² Stratum: cLDA				
Placebo	99	-0.28 (-0.47, -0.08)		
Ertugliflozin 5 mg	105	-0.31 (-0.49, -0.13)	-0.03 (-0.28, 0.23)	0.828
Ertugliflozin 15 mg	97	-0.37 (-0.56, -0.18)	-0.09 (-0 35, 0.17)	0.496

N is the number of subjects in the analysis population. n is the number of subjects with the event of interest.

† cLDA model is fitted with fixed effects for treatment, time, interaction of time by treatment. Additionally, for analyses in the overall population, the model contained terms for eGFR stratum (<45 or ≥45 mL/min/1.73m²) and baseline treatment with insulin stratum (yes/no), and for analyses in each eGFR stratum, the model contained a term for baseline treatment with insulin stratum.

§ Logistic regression model fitted with terms for treatment, baseline A1C and baseline treatment with insulin stratum (yes/no). Missing data were imputed using the cLDA model.

Source: Adapted from the Applicant's Clinical Study Report P001V01, page 16 of 2401, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p001v01\p001v01.pdf

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and LS, least squares.

The Applicant's primary efficacy analyses for the six remaining trials (performed using the FAS and a cLDA approach) that they intend to include in product labeling, and the reanalysis of these data by the Agency, are presented in Table 9. Additionally, key secondary analyses that included HbA1c changes from baseline (Trials P002/1013 and P005/1019) are also presented. For product labeling, Dr. Cambon recommends the use of the intent-to-treat (ITT) estimands (i.e., based on all available data, regardless of rescue or discontinuation) and an ANCOVA RTB

statistical approach for handling missing data. This section of the review will primarily focus on the RTB results that the Agency considers acceptable for product labeling.

Table 9: HbA1c Change from Baseline Analyses (Phase 3 Trials)

Analysis	Comparator	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Trial P003/1022 (Placebo-Controlled Monotherapy Trial)			
Applicant's cLDA Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
HbA1c (%)	N=153	N=156	N=151
Baseline (mean)	8.1 ± 0.92	8.2 ± 0.88	8.4 ± 1.12
Change from baseline to week 26 (LS mean[†])	0.20 ± 0.089	-0.79 ± 0.081	-0.96 ± 0.082
Difference from placebo (LS mean[†], 95% CI)		-0.99 (-1.22, -0.76)	-1.16 (-1.39, -0.93)
P-Value		P<0.001	P<0.001
FDA's RTB Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
Change from baseline to week 26	-0.17	-0.75	-0.84
Difference from placebo (LS mean, 95% CI)		-0.58 (-0.80, -0.36)	-0.67 (-0.89, -0.44)
P-Value		P<0.001	P<0.001
Trial P007/1017 (Placebo-Controlled Trial in Combination with Metformin)			
Applicant's cLDA Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
HbA1c (%)	N=209	N=207	N=205
Baseline (mean)	8.2 ± 0.90	8.1 ± 0.89	8.1 ± 0.93
Change from baseline to week 26 (LS mean[†])	-0.03 ± 0.065	-0.73 ± 0.062	-0.91 ± 0.063
Difference from placebo (LS mean[†], 95% CI)		-0.70 (-0.87, -0.53)	-0.88 (-1.05, -0.71)
P-value		P<0.001	P<0.001
FDA's RTB Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
Change from baseline to week 26	-0.17	-0.72	-0.86
Difference from placebo (LS mean, 95% CI)		-0.55 (-0.71, -0.39)	-0.69 (-0.86, -0.53)
P-Value		P<0.001	P<0.001
Trial P002/1013 (Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on to Metformin)			
Applicant's cLDA Analysis	**Glimepiride***	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
HbA1c (%)	N=437	N=448	N=440
Baseline (mean)	7.8 ± 0.60	7.8 ± 0.60	7.8 ± 0.60
Change from baseline to week 52 (LS mean[†])	-0.74 ± 0.045	-0.56 ± 0.045	-0.64 ± 0.045
Difference from glimepiride (LS mean[†], 95% CI)		0.18 (0.06, 0.30)[¶]	0.10 (-0.02, 0.22)[‡]
FDA's RTB Analysis	**Glimepiride***	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
Change from baseline to week 52	-0.63	-0.46[¶]	-0.53
Difference from glimepiride (LS mean, 95% CI)-0.89 to -0.44)		0.17 (0.04, 0.30)	0.10[‡] (-0.02, 0.23)[‡]
Trial P006/1015 (Add-on Trial in Combination with Metformin and Sitagliptin)			
Applicant's cLDA Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
HbA1c (%)	N=153	N=156	N=153
Baseline (mean)	8.0 ± 0.93	8.1 ± 0.86	8.0 ± 0.83

Analysis	Comparator	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Change from baseline to week 26 (LS mean†)	-0.09 ± 0.070	-0.78 ± 0.067	-0.86 ± 0.068
Difference from placebo (LS mean†, 95% CI)		-0.69 (-0.87, -0.50)	-0.76 (-0.95, -0.58)
P-Value		P<0.001	P<0.001
FDA's RTB Analysis	**Placebo**	**Ertugliflozin 5 mg**	**Ertugliflozin 15 mg**
Change from baseline to week 26	-0.21	-0.69	-0.79
Difference from placebo (LS mean, 95% CI)		-0.48 (-0.66, -0.30)	-0.58 (-0.76, -0.40)
P-Value		P<0.001	P<0.001
Trial P017/1047 (Initial Combination Therapy of Ertugliflozin and Sitagliptin)			
Applicant's cLDA Analysis	**Placebo**	**Ertu 5 mg + Sita 100 mg**	**Ertu 15 mg + Sita 100 mg**
HbA1c (%)	N=96	N=98	N=96
Baseline (mean)	8.9 ± 0.86	8.9 ± 0.87	9.0 ± 0.87
Change from baseline to week 26 (LS mean†)	-0.44 ± 0.127	-1.60 ± 0.110	-1.68 ± 0.112
Difference from placebo (LS mean†, 95% CI)		-1.16 (-1.49, -0.84)	-1.24 (-1.57, -0.91)
P-Value		P<0.001	P<0.001
FDA's RTB Analysis	**Placebo**	**Ertu 5 mg + Sita 100 mg**	**Ertu 15 mg + Sita 100 mg**
Change from baseline to week 26	-0.58	-1.56	-1.52
Difference from placebo (LS mean, 95% CI)		-0.97 (-1.28, -0.66)	-0..94 (-1.26, -0.62)
P-Value		P<0.001	P<0.001

Trial P005/1019 (Factorial Trial with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin)					
Applicant's cLDA Analysis	**Sita 100 mg**	**Ertu 5 mg**	**Ertu 15 mg**	**Ertu 5 mg + Sita 100 mg**	**Ertu 15 mg + Sita 100 mg**
HbA1c (%)	N=247	N=250	N=248	N=243	N=244
Baseline (mean)	8.5 ± 1.03	8.6 ± 1.05	8.6 ± 1.01	8.6 ± 0.99	8 6 ± 0.97
Change from baseline to week 26 (LS mean†)	-1.05 ± 0.062	-1.02 ± 0.061	-1.08 ± 0.062	-1.49 ± 0.062	-1.52 ± 0.062
Difference (LS mean†, 95% CI) from:					
Sita 100 mg				-0.43 (-0.60, -0.27)¶	-0.47 (-0.63, -0.30)
P-value				P<0.001	P<0.001
Ertu 5 mg				-0.46 (-0.63, -0.30)¶	
P-value				P<0.001	
Ertu 15 mg					-0.49 (-0.66, -0.33)
P-value					P<0.001
FDA's RTB Analysis	**Sita 100 mg**	**Ertu 5 mg**	**Ertu 15 mg**	**Ertu 5 mg + Sita 100 mg**	**Ertu 15 mg + Sita 100 mg**
Change from baseline to week 26	-1.02	-1.04	-1.01	-1.40	-1.39
Difference (LS mean, 95% CI) from:					
Sita 100 mg				-0.37 (-0.55, -0.19)¶	-0.37 (-0.55, -0.19)
P-value				P<0.001	P<0.001
Ertu 5 mg				-0.36 (-0.54, -0.18)¶	
P-value				P<0.001	
Ertu 15 mg					-0.38 (-0.56, -0.21)
P-value					P<0.001

Source: Adapted from Dr. Alexander Cambon's Statistical Review (dated August 25, 2017), labeled as Tables 14, pages 31-32; and from the Applicant's proposed product labeling, available at: \\cdsesub1\evsprod\nda209803\0000\m1\us\01-annotated-uspi-mk8835-t-original.pdf and from the Applicant's Summary of Clinical Efficacy, labeled as Table 15, page 99-100 of 143, available at: \\cdsesub1\evsprod\nda209803\0000\m2\27-clin-sum\summary-clin-efficacy-t2dm.pdf

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; Ertu, ertugliflozin; HbA1c, hemoglobin A1c; LS, least squares; RTB, return to baseline; and Sita, sitagliptin.

N includes all randomized, treated patients who had at least one measurement of the outcome variable.
†Least squares means adjusted for treatment, time, prior antihyperglycemic medication, baseline eGFR and the interaction of time by treatment.
‡Non-inferiority is declared, as the upper bound of the 2-sided 95% CI for the mean difference is less than 0.3%.
*The median daily dose of glimepiride was 3.0 mg/day (mean ± SD, 3.0 ± 1.5 mg/day); approximately 43.7% received a maximum dose of ≥5 mg/day for >7 days and 58.4% received maximum dose of ≥4 mg/day for >7 days.
¶This comparison was a key secondary analysis.

Based on his reanalysis of the efficacy data (Table 9), Dr. Cambon concluded the following for the primary endpoints:

- Superiority of ertugliflozin 15 mg and ertugliflozin 5 mg compared to placebo was demonstrated for the primary endpoint (HbA1c change from baseline to Week 26) for the four placebo-controlled trials: P003/1022, P007/1017, P006/1015, and P017/1047.
- Noninferiority (prespecified noninferiority margin 0.3%) was achieved at Week 52 for the primary endpoint in the active-control trial (P002/1013) for the ertugliflozin 15 mg arm vs. glimepiride.
- Superiority was demonstrated at Week 26 for the primary endpoint in the full factorial trial (P005/1019) for the ertugliflozin 15 mg plus sitagliptin 100 mg arm vs. sitagliptin 100 mg and vs. ertugliflozin 15 mg.

I concur with Dr. Cambon's analyses and assessments. In four of the six trials, statistically significant reductions in HbA1c were reported in the respective ertugliflozin treatment arms, regardless of exclusion (Applicant's analyses) or inclusion (Agency reanalysis) of HbA1c data collected after glycemic rescue/discontinuation. The comparator-subtracted HbA1c reductions from baseline were less with the Agency's reanalysis, but these changes would still be considered clinically meaningful. For the factorial trial (P005/1019), both ertugliflozin/sitagliptin treatment arms (i.e., 5 mg/100 mg and 15 mg/100 mg) resulted in statistically significant reductions in HbA1c concentrations compared to the individual components. For the sixth trial (P003/1013), noninferiority with glimepiride was only achieved for the ertugliflozin 15 mg treatment arm. In this trial, the mean/median glimepiride daily dose was 3.0 mg, and approximately 58% of subjects took a maximum dose of ≥4 mg/day. Although the average daily dose of glimepiride in this trial is somewhat low (i.e., less than half of the maximum approved dose of 8 mg/day in the U.S.), I think it is adequate when considering regional differences in the maximum recommended dose (i.e., 6 mg/day vs. 8 mg/day), as well as the observed HbA1c change from baseline at Week 52 (i.e., -0.74% as add-on therapy to metformin) and incidence of documented hypoglycemic events (i.e., 27% [119/437] of subjects) reported in the glimepiride arm.

Data Quality and Integrity – Reviewers' Assessment

In his review, Dr. Cambon noted that across the seven Phase 3 trials, missing data ranged from 5-23%, with few retrieved dropouts. Further, his concerns regarding the Applicant treating observations following glycemic rescue as missing data and excluding data following treatment discontinuation remained statistical issues during the review cycle. However, he felt that the collective evidence from his review supports approval. Additionally, as noted in Section 4.1 above, Dr. Kleppinger from OSI felt that the inspectional findings support the validity of the data for the three NDAs. Many of the safety analyses performed by the Applicant also were confirmed with the submitted datasets in my review. Based on these assessments, I concur that the data quality was acceptable.

Efficacy Results – Secondary and other relevant endpoints

Reanalysis of key secondary efficacy endpoints performed by the Applicant using the RTB approach (as requested by the Agency on June 16, 2017) are presented in Table 10 (Note: changes in HbA1c from baseline that were key secondary endpoints for the ertugliflozin 5 mg treatment arm are depicted in Table 9). Based on these analyses, several of the secondary endpoints (e.g., proportion of subjects with HbA1c <7%, and change from baseline in fasting plasma glucose, body weight, and SBP) that were statistically significant (in accordance with the prespecified hierarchical testing procedure) could be considered for product labeling. Product labeling for other approved SGLT2 inhibitors includes similar information.

Table 10: Applicant's Reanalysis (RTB) of Key Secondary Endpoints (Change from Baseline)

Endpoint	Comparison	N	Baseline (Mean ± SD)	Change from BL (LS Mean ± SE)*	LS Mean Difference*	LCL	UCL	P-value
Trial P003/1022 (Placebo-Controlled Monotherapy Trial)								
FPG (mg/dL)	PBO	150	180.2 ± 45.8	-11.6 ± 3.1				
	Ertu 5 mg	151	180.9 ± 48.6	-31.0 ± 2.9	-19.4	-27.6	-11.2	<0.001
	Ertu 15 mg	149	179.1 ± 48.2	-36.4 ± 3.0	-24.8	-33.2	-16.4	<0.001
Body Weight (kg)	PBO	153	94.2 ± 25.2	-1.0 ± 0.3				
	Ertu 5 mg	156	94.0 ± 25.4	-3.0 ± 0.3	-2.0	-2.8	-1.2	<0.001
	Ertu 15 mg	152	90.6 ± 18.3	-3.1 ± 0.3	-2.1	-2.9	-1.3	<0.001
PPG (mg/dL)	PBO	150	256.2 ± 76.9	2.8 ± 5.5				
	Ertu 5 mg	145	260.3 ± 76.1	-52.9 ± 5.4	-55.7	-70.9	-40.5	<0.001
	Ertu 15 mg	141	262.9 ± 78.2	-51.0 ± 5.4	-53.8	-68.8	-38.8	<0.001
HbA1c <7%—n (%)	**PBO**: 25.9 (16.9) vs. **Ertu 5 mg**: 46.7 (30.1) vs. **Ertu 15 mg**: 58.6 (38.8)							
Trial P007/1017 (Placebo-Controlled Trial in Combination with Metformin)								
FPG (mg/dL)	PBO	202	169.1 ± 41.7	-8.7 ± 2.9				
	Ertu 5 mg	199	168.1 ± 45.5	-30.3 ± 2.9	-21.7	-27.8	-15.5	<0.001
	Ertu 15 mg	201	167.9 ± 44.4	-40.9 ± 2.9	-32.3	-38.5	-26.0	<0.001
Body Weight (kg)	PBO	209	84.5 ± 17.1	-1.4 ± 0.3				
	Ertu 5 mg	207	84.9 ± 17.2	-3.2 ± 0.3	-1.8	-2.4	-1.2	<0.001
	Ertu 15 mg	205	85.3 ± 16.5	-3.0 ± 0.3	-1.7	-2.2	-1.1	<0.001

Endpoint	Comparison	N	Baseline (Mean ± SD)	Change from BL (LS Mean ± SE)*	LS Mean Difference*	LCL	UCL	P-value
SBP (mmHg)¶	PBO	201	129.3 ± 15.4	-1.8 ± 1.1				
	Ertu 5 mg	201	130.5 ± 13.8	-5.1 ± 1.0	-3.3	-5.6	-1.1	0.004
	Ertu 15 mg	197	130.2 ± 11.9	-5.7 ± 1.1	-3.8	-6.1	-1.5	0.001
DBP (mmHg)¶	PBO	201	77.5 ± 7.6	-0.3 ± 0.6				
	Ertu 5 mg	201	78.5 ± 8.3	-1.3 ± 0.6	-1.5	-2.9	-0.1	0.033
	Ertu 15 mg	197	78.1 ± 7.5	-1.6 ± 0.7	-1.9	-3.3	-0.4	0.010
HbA1c <7%—n (%)	**PBO**: 38.2 (18.4) vs. **Ertu 5 mg**: 74.3 (36.3) vs. **Ertu 15 mg**: 87.0 (43.3)							
Trial P002/1013 (Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on to Metformin)								
Body Weight (kg)	Glim	437	86.8 ± 20.7	0.6 ± 0.2				
	Ertu 5 mg	448	88.0 ± 18.9	-2.6 ± 0.2	-3.2	-3.7	-2.7	<0.001
	Ertu 15 mg	440	85.6 ± 19.1	-3.0 ± 0.2	-3.6	-4.1	-3.1	<0.001
HbA1c <7%—n (%)	**Glim**: 208.3 (47.7) vs. **Ertu 5 mg**: 176.6 (39.5) vs. **Ertu 15 mg**: 185.6 (42.2)							
Trial P006/1015 (Add-on Trial in Combination with Metformin and Sitagliptin)								
FPG (mg/dL)	PBO	152	169.6 ± 37.8	-6.5 ± 2.8				
	Ertu 5 mg	156	167.7 ± 37.7	-25.7 ± 2.8	-19.2	-26.8	-11.6	<0.001
	Ertu 15 mg	152	171.7 ± 39.1	-32.1 ± 2.8	-25.6	-33.2	-18.0	<0.001
Body Weight (kg)	PBO	153	86.5 ± 20.8	-1.0 ± 0.2				
	Ertu 5 mg	156	87.6 ± 18.6	-3.0 ± 0.2	-1.9	-2.6	-1.3	<0.001
	Ertu 15 mg	153	86.6 ± 19.5	-2.8 ± 0.2	-1.8	-2.4	-1.2	<0.001
SBP (mmHg)¶	PBO	153	130.2 ± 13.3	-0.2 ± 0.9				
	Ertu 5 mg	156	132.1 ± 12.5	-3.8 ± 0.9	-3.7	-6.1	-1.2	0.003
	Ertu 15 mg	153	131.6 ± 13.2	-4.5 ± 0.9	-4.3	-6.7	-1.9	<0.001
HbA1c <7%—n (%)	**PBO**: 30.6 (20.2) vs. **Ertu 5 mg**: 53.6 (34.6) vs. **Ertu 15 mg**: 64.3 (42.3)							
Trial P017/1047 (Initial Combination Therapy of Ertugliflozin and Sitagliptin)								
FPG (mg/dL)	PBO	96	207.5 ± 44.9	-11.8 ± 4.5				
	Ertu 5 mg + Sita 100 mg	98	198.0 ± 47.7	-47.1 ± 4.1	-35.4	-47.3	-23.4	<0.001
	Ertu 15 mg + Sita 100 mg	96	187.7 ± 46.7	-50.8 ± 4.3	-39.1	-51.4	-26.8	<0.001
PPG (mg/dL)	PBO	88	287.3 ± 74.0	-11.5 ± 6.8				
	Ertu 5 mg + Sita 100 mg	93	281.3 ± 86.6	-78.0 ± 6.4	-66.5	-84.9	-48.1	<0.001
	Ertu 15 mg + Sita 100 mg	95	281.6 ± 76.7	-81.8 ± 6.4	-70.3	-88.6	-52.1	<0.001
Body Weight (kg)	PBO	97	95.0 ± 20.5	-0.6 ± 0.4				
	Ertu 5 mg + Sita 100 mg	98	90.8 ± 20.7	-2.7 ± 0.3	-2.2	-3.1	-1.2	<0.001
	Ertu 15 mg + Sita 100 mg	96	91.3 ± 22.5	-2.8 ± 0.3	-2.3	-3.3	-1.3	<0.001
SBP (mmHg)¶	PBO	97	127.4 ± 14.1	1.6 ± 1.2				
	Ertu 5 mg + Sita 100 mg	98	130.7 ± 12.7	-2.4 ± 1.1	-4.0	-7.2	-0.8	0.015
	Ertu 15 mg + Sita 100 mg	96	129.2 ± 12.2	-3.5 ± 1.1	-5.2	-8.4	-1.9	0.002
HbA1c <7%—n (%)	**PBO**: 8.9 (9.3) vs. **Ertu 5 mg + Sita 100 mg**: 36.4 (37.1) vs. **Ertu 15 mg + Sita 100 mg**: 31.6 (32.9)							
Trial P005/1019 (Factorial Trial with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin)								
FPG (mg/dL)	Sita 100 mg	246	177.4 ± 46.6	-24.3 ± 2.3				
	Ertu 5 mg	250	184.1 ± 52.2	-34.0 ± 2.2				
	Ertu 15 mg	247	179.5 ± 45.7	-34.6 ± 2.3				
	Ertu 5 mg + Sita 100 mg	240	183.8 ± 44.3	-41.1 ± 2.3				
	vs. Sita 100 mg				-16.8	-23.2	-10.4	<0.001
	vs. Ertu 5 mg				-7.0	-13.3	-0.7	0.029
	Ertu 15 mg + Sita 100 mg	241	177.2 ± 49.4	-44.3 ± 2.3				
	vs. Sita 100 mg				-20.0	-26.4	-13.6	<0.001
	vs. Ertu 15 mg				-9.8	-16.1	-3.4	0.003

Endpoint	Comparison	N	Baseline (Mean ± SD)	Change from BL (LS Mean ± SE)*	LS Mean Difference*	LCL	UCL	P-value
Body Weight (kg)	Sita 100 mg	247	89.8 ± 23.5	-0.4 ± 0.2				
	Ertu 5 mg	250	88.6 ± 22.2	-2.6 ± 0.2				
	Ertu 15 mg	248	88.0 ± 20.3	-3.4 ± 0.2				
	Ertu 5 mg + Sita 100 mg	243	89.5 ± 20.9	-2.4 ± 0.2				
	vs. Sita 100 mg				-1.9	-2.6	-1.3	<0.001
	Ertu 15 mg + Sita 100 mg	244	87.5 ± 20.5	-2.7 ± 0.2				
	vs. Sita 100 mg				-2.3	-3.0	-1.6	<0.001
SBP (mmHg)¶	Sita 100 mg	247	128.4 ± 12.2	-0.5 ± 0.7				
	Ertu 5 mg	250	129.7 ± 12.5	-4.0 ± 0.7				
	Ertu 15 mg	248	128.9 ± 12.5	-3.6 ± 0.7				
	Ertu 5 mg + Sita 100 mg	243	130.2 ± 12.6	-2.8 ± 0.7				
	vs. Sita 100 mg				-2.3	-4.3	-0.4	0.019
	Ertu 15 mg + Sita 100 mg	244	129.1 ± 13.3	-3.4 ± 0.7				
	vs. Sita 100 mg				-2.9	-4.8	-1.0	0.003
HbA1c <7%—n (%)	**Sita 100 mg**: 93.1 (38.5) vs. **Ertu 5 mg**: 71.6 (29.3) vs. **Ertu 15 mg**: 83.2 (33.7) vs. **Ertu 5 mg + Sita 100 mg**: 126.3 (53.3) vs. **Ertu 15 mg + Sita 100 mg**: 122.6 (50.9)							

Source: Adapted from the Applicant's Supplemental Efficacy Analyses submitted on July 21, 2017 for Trials:
P003V01, available at: \\cdsesub1\evsprod\nda209803\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p003v01\p003v01-tables.pdf
P007V01, available at: \\cdsesub1\evsprod\nda209803\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01-tables.pdf
P002V01, available at: \\cdsesub1\evsprod\nda209803\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01-tables.pdf
P006V01, available at: \\cdsesub1\evsprod\nda209803\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p006v01\p006v01-tables.pdf
P017, available at: \\cdsesub1\evsprod\nda209803\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p017\p017-tables.pdf
P005V01, available at: \\cdsesub1\evsprod\nda209803\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p005v01\p005v01-tables.pdf
and Dr. Alexander Cambon's Statistical Review (dated August 25, 2017), labeled as Tables 14, pages 31-32; and from the Applicant's proposed product labeling, available at: \\cdsesub1\evsprod\nda209803\0000\m1\us\01-annotated-uspi-mk8835-t-original.pdf
Abbreviations: BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; Ertu, ertugliflozin; FPG, fasting plasma glucose; Glim, glimepiride; HbA1c, hemoglobin A1c; LCL, lower confidence limit; LS, least squares; PBO, placebo; PPG, postprandial glucose; RTB, return to baseline; SBP, systolic blood pressure; Sita, sitagliptin; vs, versus; and UCL, upper confidence limit.
*Based on ANCOVA model using imputed values for missing data based on the Return to Baseline approach, with fixed effects for treatment, prior antihyperglycemic medication (yes, no), baseline eGFR (continuous) and baseline value (i.e., FPG, body weight, PPG, SBP, or DBP).
¶Blood pressure measurements (SBP and DBP) were assessed in the sitting position.

Generally, other glycemic endpoints (e.g., proportion of subjects who required glycemic rescue and time to glycemic rescue) were supportive. However, these endpoints should be considered as exploratory as they were not included in the hierarchical testing procedure (i.e., did not control for Type I error). For the only trial (P005/1019) in which the change from baseline in β-cell responsivity static component was a key secondary endpoint included in the prespecified testing sequence, differences between treatment arms were not statistically significant.

Dose/Dose Response

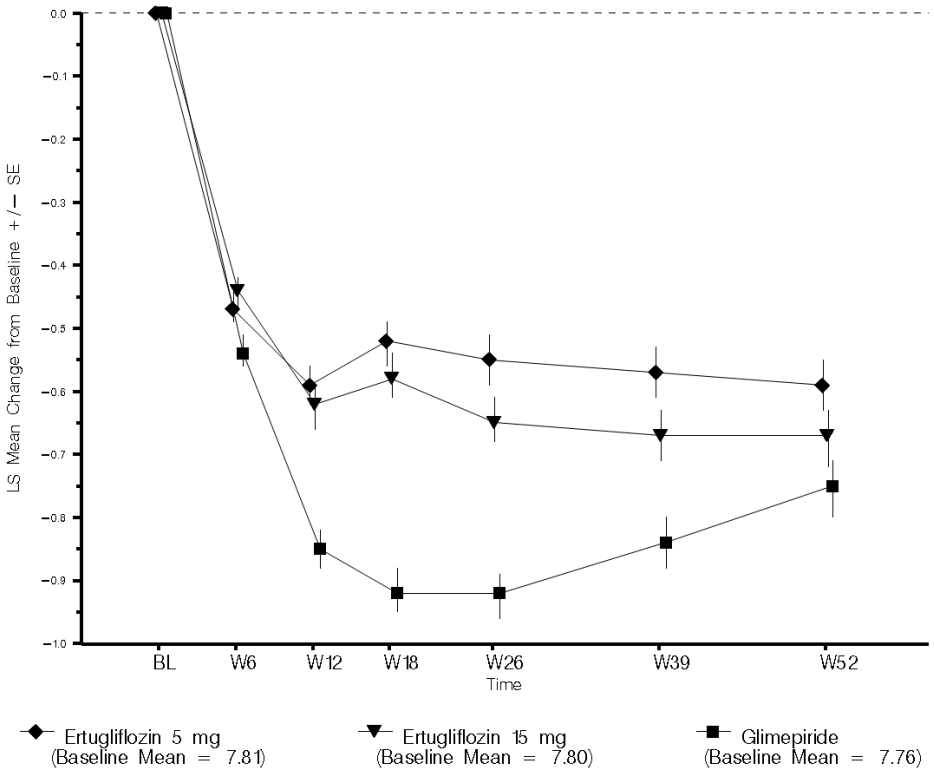
The Phase 3 trials were not powered or designed to detect between-dose differences. Please

refer to Sections 4.4, 4.5, 7.1.4 for discussion of assessments of dose and dose-response in the ertugliflozin clinical development program.

Durability of Response

For six of the seven trials, the primary endpoint was assessed at 26 weeks (i.e., at the end of the double-blind treatment period [Phase A]). These trials allowed subjects to participate in a 26- to 78-week site- and subject-blind long-term treatment period (Phase B). Since these trials were ongoing at the time of NDA submission, the long-term efficacy and safety data were not available. One of the trials (Trial P002/1013, ertugliflozin vs. glimepiride) did have longer term efficacy data, as the primary endpoint was assessed at 52-weeks. In this trial, the ertugliflozin 15 mg arm was noninferior to glimepiride (i.e., noninferior margin <0.3 HbA1c percentage units) at Week 52 (Figure 1). However, both the ertugliflozin 5 mg (-0.59%; 95% CI -0.68% to -0.51%) and 15 mg (-0.67%; 95% CI, -0.76% to -0.59%) treatment arms resulted in reductions in HbA1c concentrations that appeared stable throughout the 52-week treatment period.

Figure 1: LS Mean Change in HbA1c from Baseline to Week 52 (cLDA)*



Source: Reproduced from the Applicant's P002v01 Clinical Study Report, labeled as Figure 14.2.11.1.1.1, page 982 of 2209, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01.pdf
Abbreviations: BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; HbA1c, hemoglobin A1c; SE, standard error; and W, week.
*Data after rescue is included.

Persistence of Effect

Not applicable. Ertugliflozin, sitagliptin and metformin have relatively short half-lives (i.e., 16.6, 12.4, and 6.2 hours, respectively). Therefore, following treatment discontinuation, persistence of the antihyperglycemic effects of these study medications would not be expected.

Additional Analyses Conducted on the Individual Trial

Dr. Cambon requested additional analyses from the Applicant and conducted several sensitivity analyses of the primary efficacy endpoint (data not shown). Please refer to his Statistical Review for detailed discussion of the sensitivity analyses performed to support the findings of the primary efficacy analysis.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Findings for the primary endpoint for six of the seven Phase 3 trials are presented in Table 9. The Applicant also performed an integrated analysis of the primary efficacy endpoint (across three placebo-controlled Phase 3 trials (P003/1022, P007/1017, and P006/1015) using the FAS and excluding subjects following glycemic rescue. As would be expected, statistically significant HbA1c reductions from baseline to Week 26 also were observed in both ertugliflozin treatment arms compared to placebo in the Applicant's pooled analysis (Table 11). The Applicant acknowledges that this pooled analysis was exploratory, and therefore no formal hypotheses were tested or adjustments made for multiplicity.

Table 11: Pooled Analysis of Mean Change in HbA1c from Baseline to Week 26 – Placebo-Controlled Trials (P003/1022, P007/1017, and P006/1015)

	Baseline		Week 26		Change from baseline at Week 26*		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)†
Placebo	512	8.11 (0.91)	359	7.77 (1.03)	515	-0.15 (0.93)	0.00 (-0.08, 0.08)
Ertugliflozin 5 mg	515	8.09 (0.88)	462	7.28 (0.80)	519	-0.77 (0.87)	-0.76 (-0.84, -0.68)
Ertugliflozin 15 mg	504	8.16 (0.97)	448	7.21 (0.85)	509	-0.95 (0.92)	-0.91 (-0.99, -0.83)
Pairwise comparison					Difference in LS Means (95% CI)†		
Ertugliflozin 5 mg versus Placebo					-0.76 (-0.87, -0.65)		
Ertugliflozin 15 mg versus Placebo					-0.91 (-1.02, -0.80)		
Conditional Pooled SD of Change from Baseline= 0.85							

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the full analysis set (i.e., randomized subjects who took at least 1 dose of study medication and had at least one measurement at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

† Based on cLDA model with fixed effects for treatment, time, trial, baseline eGFR and the interaction of time by treatment. Time is treated as a categorical variable.

Source: Adapted from the Applicant's Summary of Clinical Efficacy, labeled as Table 22, page 122 of 143, available at: \\cdsesub1\evsprod\nda209803\0000\m2\27-clin-sum\summary-clin-efficacy-t2dm.pdf

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; LS, least squares; SD, standard deviation.

* Excludes HbA1c data after glycemic rescue or discontinuation.

7.1.2. Secondary and Other Endpoints

Please refer to Table 10 and Dr. Cambon's review for evaluation of secondary endpoints for each of the seven Phase 3 trials. In their pooled analyses of the three placebo-controlled trials, secondary endpoints (proportions of subjects with HbA1c concentrations <7%, and reductions in body weight) also were supportive (data not shown).

7.1.3. **Subpopulations**

To increase statistical power, Dr. Cambon also performed subgroup analyses (based on the following intrinsic factors: sex, race, age, and geographic region) of a pool of four Phase 3 trials (i.e., P003/1022, P005/1019, P006/1015, and P007/1017). These analyses included study and treatment as factors in the model, and baseline eGFR and HbA1c as covariates. He determined that there was no evidence of significant differences (i.e., estimated treatment differences and associated CIs) between any of the subgroups. Please refer to his review for detailed information.

Additionally, the Applicant was requested (September 13, 2017) to conduct additional subgroup analyses for Trials P005/1019 (factorial trial) and P002/1013 (noninferiority trial) individually, and Trials P003/1022, P006/1015, P007/1017, and P005/1019 combined using the FAS (including rescue approach) and the RTB missing data approach. The pooled subgroup analyses (dated September 16, 2017) yielded similar results to those conducted by Dr. Cambon (data not shown). The analyses of the individual trials (i.e., Trials P005/1019 and P002/1013) also did not show significant differences between any subgroups.

7.1.4. **Dose and Dose-Response**

In the Applicant's dose-response model, based on the data from one of their Phase 2 trial (P016/1006) and four of the seven Phase 3 trials (P001/1016, P007/1017, P005/1019, and P003/1022), the difference in predicted between-dose HbA1c reduction from baseline to Week 26 was <0.1% greater in the ertugliflozin 15 mg arm (-7.13%; 95% CI, -0.841 to -0.565%) compared to the 5 mg arm (-0.625%; 95% CI, -0.783% to -0.482%). However, with the ertugliflozin 15 mg arm the Applicant also reported that they observed numerically higher proportions of subjects with HbA1c <7% in trials that included ertugliflozin-only treatment arms (Trials P003/1022, P007/1017, P002/1013, P006/1015) and numerically greater reductions in FPG concentrations in all seven trials. The clinical relevance of these nominal changes is uncertain, but it does suggest that the 15 mg dose of ertugliflozin offers a benefit for some patients above what would be seen with the 5 mg dose.

For the ertugliflozin FCDPs, the Applicant only submitted data to support ertugliflozin 5 mg and 15 mg in combination with sitagliptin 100 mg daily, and/or added to background metformin therapy (≥1500 mg/day). Therefore, assessments of dose and dose response with the non-ertugliflozin components of the proposed ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs were not performed.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Since HbA1c reflects mean glycemic control over two to three months, efficacy is typically assessed after at least 24 to 26 weeks of antihyperglycemic therapy. All seven Phase 3 clinical trials included a 26- to 52-week double-blind treatment period. Please refer to Section 6.1.8 above for discussion related to the duration and durability of glycemic efficacy related to Trial P002/1013.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

A second SGLT2 inhibitor, empagliflozin, is currently approved to reduce the risk of CV death in adult patients with T2D and established CV disease. The completion of the Applicant's ongoing CVOT (Trial P004/1021) will provide useful information to assess whether the potential for CV benefit in at-risk patients with T2D may be a class or product-specific effect. This trial also includes three 18-week sub-studies that evaluate the efficacy of ertugliflozin in subjects receiving background insulin with or without metformin, background sulfonylurea monotherapy, and background metformin plus a sulfonylurea. Since these antihyperglycemic agents are commonly used as combination therapy for patients with T2D, the findings from these sub-studies may help to determine the potential benefit and risks associated with ertugliflozin used in combination with these medications. Additionally, Trial P007/1017, of which 44% of the enrolled population is postmenopausal, includes long-term (Week 104) assessments of BMD and bone biomarkers. The results of this ongoing trial will provide important safety information on the effects of ertugliflozin on bone that may be relevant when considering the use of this product in special populations (e.g., pediatric patients and individuals at risk for fractures).

7.2.2. Other Relevant Benefits

As discussed in more detail in Section 1.4 above, T2D affects more than 30 million people in the U.S.,[7] and is a progressive and serious, life-threatening condition. Further, a significant number of patients with T2D do not achieve adequate glycemic control despite the availability of numerous therapeutic options (Table 42), and nonadherence or intolerance to the prescribed treatment regimen is common. Therefore, an oral, once-daily antihyperglycemic agent, as well as FCDPs that include two pharmacologic antihyperglycemic drug classes with different mechanisms of action and a relatively low risk of hypoglycemia (i.e., SGLT2 inhibitor plus DDP-4 inhibitor, or SGLT2 inhibitor plus metformin) could be of benefit to patients and may improve

adherence to prescribed therapy.

7.3. Integrated Assessment of Effectiveness

To support marketing approval of NDA 209803 (ertugliflozin), the Applicant has provided clinical data from seven multicenter, randomized, double-blind, placebo- or active comparator-controlled, clinical trials involving 4863 subjects with T2D. Six of these trials evaluated the effects of ertugliflozin (5 and 15 mg) as monotherapy and in combination with metformin (≥1500 mg/day) and/or a sitagliptin (100 mg). In a dedicated moderate renal impairment trial, ertugliflozin also was studied in combination with other antihyperglycemic medications, including insulin and a sulfonylurea, in subjects with T2D with moderate renal impairment (eGFR 45 to <60 mL/min/1.73 m^2). The Applicant intends to include all seven efficacy trials in Section 14 of product labeling.

Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to Week 26), both ertugliflozin 5 mg and 15 mg once daily resulted in modest, but statistically significant (all $p<0.001$) reductions in HbA1c concentrations compared to placebo in five of these trials (P003/1022, P005/1019, P006/1015, P007/1017, and P017/1047). For Trial P002/1013, a 52-week active-comparator trial, only the ertugliflozin 15 mg treatment arm was noninferior to the glimepiride arm (mean daily dose 3 mg). Additionally, for the moderate renal impairment trial (P001/1016), the HbA1c reductions from baseline to Week 26 were not significantly different between once daily placebo and ertugliflozin 5 mg or 15 mg. Therefore, ertugliflozin-containing products should not be recommended for patients with moderate to severe renal impairment.

To support marketing approval of NDA 209805 (ertugliflozin/sitagliptin FCDP), the Applicant is relying on three of the above seven trials, which randomized 1,985 subjects with T2D. In these trials, the efficacy of ertugliflozin (5 and 15 mg) was evaluated in a factorial study in which ertugliflozin and/or sitagliptin were administered as add-on combination therapy with metformin (Trial P005/1019), as add-on combination therapy with metformin plus sitagliptin (Trial P006/1015), and as initial combination therapy with sitagliptin (Trial P017/1047). For the factorial trial, ertugliflozin 5 mg or 15 mg used in combination with sitagliptin 100 mg provided statistically significant improvement in HbA1c compared to the individual components at Week 26. The other two trials also provided supportive evidence of added efficacy with combination therapy.

For NDA 209806 (ertugliflozin/metformin FCDP), the Applicant is relying on four of the above trials, which randomized 3,643 subjects with T2D. In these trials, the efficacy of ertugliflozin (5 and 15 mg) was evaluated only as add-on combination therapy with background metformin (Trials P007/1017 and P002/1013, P006/1015, P007/1017), and a factorial trial was not conducted/submitted. Although these trials provide evidence of an added benefit from

combination therapy of ertugliflozin plus metformin, the labeled indication of this FCDP will need to reflect the supporting clinical trial data (i.e., 'as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are (b) (4)

Based on the totality of these data, and in accordance with 21 CFR 314.126(a)(b),[22] I believe that the Applicant has provided substantial evidence of effectiveness to support approval of NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin/sitagliptin FCDP), and NDA 209806 (ertugliflozin/metformin FCDP), with an amended patient population (for all three products), and an amended indication for the ertugliflozin/metformin product.

8 Review of Safety

8.1. Safety Review Approach

The safety evaluation for this Application was primarily based on the integrated safety data from the 26-week treatment periods (Phase A) of three Phase 3 placebo-controlled trials (i.e., P003/1022, P006/1015, and P007/1017; referred to as the Placebo Pool), and the long-term safety data (i.e., Phases A and B) from all seven Phase 3 trials (referred to as the Broad Pool). The Broad Pool also included the additional four trials (i.e., P001/1016, P002/1013, P005/1019, and P017/1047). Descriptions of the trial designs and populations are provided in Table 3: Listing of Phase 3 Clinical Trials Relevant to this NDA. Since six of the seven trials were ongoing at the time of this NDA submission, key safety data from the Four-Month Safety Update (4-MSU) also were reviewed, and will be presented for the Broad Pool, unless specified otherwise.

The safety evaluation plan for this Application included routine assessments, as well as a focus on potential risks associated with DPP-4 inhibitors, metformin, and SGLT2 inhibitors (i.e., adverse events of special interest [AESI]). The Applicant considered the following events as potential or established SGLT2 class-related AEs: osmotic diuresis, volume depletion, changes in renal function, genital infection, urinary tract infection, ketoacidosis, amputation/peripheral revascularization, bone safety/fracture, and changes in lipids. Other relevant safety events of interest included: hypoglycemia, pancreatitis, hepatic events, hypersensitivity, malignancy, and venous thromboembolic events. The Applicant established five independent adjudication committees to evaluate bone fractures, pancreatitis, hepatic events, renal events, and CV events (including deaths), as well as an internal case review committee to adjudicate potential cases of ketoacidosis. Additionally, clinical study reports and analysis datasets were reviewed for safety. Selected AEs and laboratory abnormalities were crosschecked with those provided with the NDA documents.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database was comprised of all subjects randomized and treated (i.e., took at least one dose of IP). A summary of the size of the safety population and duration of exposure to IP is presented in Table 12. Overall, 4,859 subjects were randomized and treated, of which 1,716 received ertugliflozin 5 mg, 1,693 ertugliflozin 15 mg and 1,450 non-ertugliflozin therapy. The mean and median durations of treatment exposure were similar across arms, with approximately 66% of ertugliflozin-treated subjects receiving IP for at least one year.

For the ertugliflozin/metformin FCDP, the Applicant's primary safety pool included 1,083 subjects who were exposed to IP during the Phase A (i.e., 26-week) treatment periods of two placebo-controlled trials in which ertugliflozin was added to background metformin with or without sitagliptin (i.e., Trials P007/1017 and P006/1015, respectively). The mean duration of exposure to the ertugliflozin plus metformin combinations in these trials was 176 days.

Since the trial designs were different for the three Phase 3 trials used to support the ertugliflozin/sitagliptin FCDP (Trials P005/1019, P006/1015, and P017/1047), the Applicant did not pool the safety data from these trials. Exposure data for Phase A treatment periods of the individual studies are presented in Table 13. In these trials, subjects were exposed to ertugliflozin plus sitagliptin combination therapy for a mean duration of approximately 173 days.

Table 12: Integrated Safety Populations, Size and Duration of Exposure (Placebo, 4-MSU and Ertu/Met Pools)

	Non-ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Phase 3 Trials — no. (%)				
P001/1016	154 (10.6)	158 (9.2)	155 (9.2)	313 (9.2)
P002/1013*	437 (30.1)	448 (26.1)	440 (26.0)	888 (26.0)
P003/1022†	153 (10.6)	156 (9.1)	152 (9.0)	308 (9.0)
P005/1019¶*	247 (17.0)	493 (28.7)	492 (29.1)	985 (28.9)
P006/1015¶*†	153 (10.6)	156 (9.1)	153 (9.0)	309 (9.1)
P007/1017*†	209 (14.4)	207 (12.1)	205 (12.1)	412 (12.1)
P017/1047¶	97 (6.7)	98 (5.7)	96 (5.7)	194 (5.7)
4-MSU Broad Pool Treatment Exposure				
Mean (range) — days	396.0 (1, 768)	391.5 (1, 758)	391.0 (1, 754)	391.2 (1, 758)
Median (IQR) — days	365.0 (354.0, 546.0)	365.0 (357.0, 516.0)	365.0 (357.0, 527.0)	365.0 (357.0, 523.0)
≥364 Days — no. (%)	929 (64.1)	1124 (65.5)	1122 (66.3)	2246 (65.9)
	Placebo (n=515)	**Ertugliflozin 5 mg (n=519)**	**Ertugliflozin 15 mg (n=510)**	**All Ertugliflozin (n=1029)**
Placebo Pool Treatment Exposure				
Mean (range) — days	170.2 (1, 245)	174.8 (1, 239)	172.6 (1, 238)	173.7 (1, 239)
	Placebo (n=362)	**Ertugliflozin 5 mg (n=363)**	**Ertugliflozin 15 mg (n=358)**	**All Ertugliflozin (n=721)**
Ertugliflozin/Metformin FCDP Pool Treatment Exposure				
Mean (range) — days	174..4 (1, 245)	177.7 (2, 239)	174.2 (1, 238)	176.0 (1, 239)

Source: Derived from the iss-broad and sur-iss adsl.xpt and explus.xpt datasets, available at:
Application 209803 - Sequence 0000 - 5.3.5.3 [[Study ID]] - [[Study Title]] - iss-broad - Integrated Summary of Safety - Broad
Application 209803 - Sequence 0014 - 5.3.5.3 [[Study ID]] - [[Study Title]] - sur - Integrated Summary of Safety - SUR
Application 209803 - Sequence 0000 - 5.3.5.3 [[Study ID]] - [[Study Title]] - iss - Integrated Summary of Safety

Abbreviations: 4-MSU, Four-Month Safety Update; Ertu, ertugliflozin, FCDP, fixed combination drug product; IQR, 25th and 75th interquartile range; Met, metformin; and no., number.

† Trials used in the Placebo Pool (i.e., short-term placebo-controlled safety pool).

¶ Trials used to support safety and efficacy for NDA 209805 (Ertugliflozin/Sitagliptin FCDP).

* Trials used to support safety and efficacy for NDA 209806 (Ertugliflozin/Metformin FCDP).

Table 13: Ertugliflozin/Sitagliptin FDCP Safety Population, Size and Duration of Exposure (Trials P005/1019, P006/1015, and P017/1047)

	Duration of Exposure		
	N	Mean Duration (Days)	Range (Days)
Study P005/1019 Ertugliflozin + Sitagliptin Factorial Study			
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	172.5	1-203
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	170.9	1-241
Ertugliflozin 5 mg	250	173.7	1-199
Ertugliflozin 15 mg	248	172.1	1-217
Sitagliptin 100 mg	247	171.8	1-220
Study P006/1015 Add-on to Metformin and Sitagliptin Study			
Ertugliflozin 5 mg	156	172.7	2-196
Ertugliflozin 15 mg	153	174.0	1-210
Placebo	153	172.9	7-215
Study P017/1047 Ertugliflozin + Sitagliptin Initial Combination Study			
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	173.1	1-204
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	172.7	5-201
Placebo	97	157.8	1-210

Source: Adapted from the Applicant's Ertugliflozin/Sitagliptin Fixed-Dose Combination Summary of Clinical Safety, labeled as Table 4, page 46 of 184, available at: \\cdsesub1\evsprod\nda209805\0000\m2\27-clin-sum\summary-clin-safety-a.pdf

8.2.2. Relevant characteristics of the safety population:

For the safety population, the baseline demographic and clinical characteristics were similar across the treatment arms (Table 14). There were similar distributions of males and females, and approximately 33% of the population was from the U.S. The mean baseline HbA1c was approximately 8.2%, and average duration of diabetes was 7.9 years. The majority of subjects in all treatment arms were <65 years of age; were mostly white; had a BMI above 30 kg/m^2, and an eGFR ≥60 mL/min/1.73m^2. The safety population included relatively limited numbers of subjects who were ≥75 years of age, and non-White participants represented only 21.4% of randomized/treated subjects.

Table 14: Demographics and Clinical Characteristics (Broad Pool)*

	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (N=3409)
DEMOGRAPHICS				
Age, mean ± SD — yr	57.8± 10.3	57.9 ± 10.2	57.8 ± 10.2	57.9 ± 10.2
<65 yr — no. (%)	1072 (73.9)	1267 (78.3)	1266 (74.8)	2533 (74.3)
≥65 yr — no. (%)	378 (26.1)	449 (26.2)	427 (25.2)	876(25.7)
≥75 yr — no. (%)	67 (4.6)	75 (4.4)	77 (4.5)	152 (4.5)
Female sex — no. (%)	663 (45.7)	831 (48.4)	849 (50.1)	1680 (49.3)
Race — no. (%)				
White	1113 (76.8)	1336 (77.9)	1283 (75.8)	2619 (76.8)
Asian	190 (13.1)	218 (12.7)	240 (14.2)	458 (13.4)
Black/African American	75 (5.2)	78 (4.5)	88 (5.2)	166 (4.9)
Other	72 (5.0)	84 (4.9)	82 (4.8)	166 (4.9)
Region — no. (%)				
Europe	594 (41.0)	704 (41.0)	694 (41.0)	1398 (41.0)
North America	481 (33.2)	577 (33.6)	547 (32.3)	1124 (33.0)
Asia	176 (12.1)	192 (11.2)	220 (13.0)	412 (12.1)
South America	127 (8.8)	165 (9.6)	168 (9.9)	333 (9.8)
South Africa	60 (4.1)	65 (3.8)	57 (3.4)	122 (3.6)
Australia/New Zealand	12 (0.8)	13 (0.8)	7 (0.4)	20 (0.6)
Country — no. (%)				
United States of America	396 (27.3)	492 (28.7)	451 (26.6)	943 (27.7)
Romania	108 (7.4)	114 (6.6)	114 (6.7)	228 (6.7)
Russia	74 (5.1)	95 (5.5)	97 (5.7)	192 (5.6)
Canada	85 (5.9)	85 (5.0)	96 (5.7)	181 (5.3)
Poland	56 (3.9)	85 (5.0)	80 (4.7)	165 (4.8)
Hungary	94 (6.5)	87 (5.1)	78 (4.6)	165 (4.8)
Slovakia	66 (4.6)	82 (4.8)	80 (4.7)	162 (4.8)
Argentina	44 (3.0)	73 (4.3)	72 (4.3)	145 (4.3)
Czech Republic	59 (4.1)	68 (4.0)	76 (4.5)	144 (4.2)
Mexico	62 (4.3)	58 (3.4)	70 (4.1)	128 (3.8)
Philippines	36 (2.5)	55 (3.2)	68 (4.0)	123 (3.6)
South Africa	60 (4.1)	65 (3.8)	57 (3.4)	122 (3.6)
Republic of Korea	52 (3.6)	42 (2.4)	51 (3.0)	93 (2.7)
Israel	41 (2.8)	37 (2.2)	55 (3.2)	92 (2.7)
Ukraine	32 (2.2)	40 (2.3)	49 (2.9)	89 (2.6)
United Kingdom	45 (3.1)	42 (2.4)	33 (1.9)	75 (2.2)
Bulgaria	30 (2.1)	29 (1.7)	33 (1.9)	62 (1.8)
Malaysia	14 (1.0)	26 (1.5)	16 (0.9)	42 (1.2)
Chile	7 (0.5)	19 (1.1)	14 (0.8)	33 (1.0)
Taiwan	19 (1.3)	16 (0.9)	15 (0.9)	31 (0.9)
Italy	5 (0.3)	14 (0.8)	15 (0.9)	29 (0.9)
Colombia	14 (1.0)	15 (0.9)	12 (0.7)	27 (0.8)
Finland	9 (0.6)	12 (0.7)	13 (0.8)	25 (0.7)
Hong Kong	12 (0.8)	12 (0.7)	12 (0.7)	24 (0.7)
Lithuania	6 (0.4)	13 (0.8)	9 (0.5)	22 (0.6)

	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (N=3409)
Croatia	3 (0.2)	9 (0.5)	8 (0.5)	17 (0.5)
Serbia	3 (0.2)	10 (0.6)	3 (0.2)	13 (0.4)
New Zealand	8 (0.6)	7 (0.4)	6 (0.4)	13 (0.4)
Estonia	4 (0.3)	4 (0.2)	6 (0.4)	10 (0.3)
Thailand	2 (0.1)	4 (0.2)	3 (0.2)	7 (0.2)
Australia	4 (0.3)	6 (0.3)	1 (0.1)	7 (0.2)
CLINICAL CHARACTERISTICS				
BMI, mg/m^2 — mean ± SD	31.6 ± 6.3	31.9 ± 6.1	31.5 ± 5.8	31.7 ± 6.0
<30 mg/m^2 — no. (%)	637 (43.9)	717 (41.8	750 (44.3)	1467 (43.0)
≥30 mg/m^2 — no. (%)	813 (56.1)	999 (58.2)	943 (55.7)	1942 (57.0)
Duration of T2D, mean ± SD — yr	7.8 ± 6.3	7.9 ± 6.5	8.0 ± 6.3	8.0 ± 6.4
<3 yr — no. (%)	338 (23.3)	430 (25.1)	393 (23.2)	823 (24.1)
≥3 to ≤10 yr — no. (%)	705 (48.6)	766 (44.6)	799 (47.2)	1565 (45.9)
>10 yr — no. (%)	407 (28.1)	520 (30.3)	501 (29.6)	1021 (30.0)
Glycemic Status				
HbA1c% — mean ± SD[¶]	8.1 ± 0.9	8.2 ± 0.9	8.2 ± 0.9	8.2 ± 0.9
<8% — no. (%)[†]	705 (48.6)	766 (44.6)	764 (45.1)	1530 (44.9)
8 to <9% — no. (%)	478 (33.0)	584 (34.0)	562 (33.2)	1146 (33.6)
≥9% — no. (%)	256 (17.7)	345 (20.1)	353 (20.9)	698 (20.5)
FPG, mg/dL — mean ± SD	169.6 ± 44.5	173.2 ± 46.1	171.2 ± 44.5	172.2 ± 45.3
eGFR, mL/min/1.73m^2 — mean ± SD[‡]	84.7 ± 22.6	85.6 ± 22.0	85.6 ± 22.2	85.6 ± 22.1
<30 mL/min/1.73m^2 — no. (%)	7 (0.5)	1 (0.1)	5 (0.3)	6 (0.2)
≥30 to <60 mL/min/1.73m^2 — no. (%)	182 (12.6)	195 (11.4)	185 (10.9)	380 (11.1)
≥60 to <90 mL/min/1.73m^2 — no. (%)	681 (47.0)	820 (47.8)	781 (46.1)	1601 (47.0)
>90 mL/min/1.73m^2 — no. (%)	579 (39.9)	699 (40.7)	722 (42.6)	1421 (41.7)
Not reported	1 (0.1)	1 (0.1)	0	1 (<0.1)

Source: Derived from the iss-broad and sur-iss adsl.xpt and explus.xpt datasets, available at:
Application 209803 - Sequence 0000 - 5.3.5.3 [[Study ID]] - [[Study Title]] - iss-broad - Integrated Summary of Safety - Broad
Application 209803 - Sequence 0014 - 5.3.5.3 [[Study ID]] - [[Study Title]] - sur - Integrated Summary of Safety - SUR
Abbreviations: BMI, body mass index; C-peptide, connecting peptide; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; no., number; PPG, postprandial glucose; SD, standard deviation; T2D, type 2 diabetes mellitus; US, United States; and yr, years.
* All subjects randomized who received ≥1 dose of investigational product.
[¶] Non-Ertugliflozin (n=1439); Ertugliflozin 5 mg (n=1695); Ertugliflozin 15 mg (n=1679); and All Ertugliflozin (n=3374).
[†] Non-Ertugliflozin (n=1437); Ertugliflozin 5 mg (n=1697); Ertugliflozin 15 mg (n=1681); and All Ertugliflozin (n=3378).
[‡] Non-Ertugliflozin (n=1449); Ertugliflozin 5 mg (n=1715); Ertugliflozin 15 mg (n=1693); and All Ertugliflozin (n=3408).

8.2.3. **Adequacy of the safety database:**

In their Type C meeting request (dated October 20, 2015), the Applicant stated that the long-term safety extension periods (i.e., Phase B) would be ongoing for six of the seven Phase 3 clinical trials used to support efficacy and safety; and proposed to provide extended safety analyses of SAEs and exposure data for these trials. In the Type C Meeting Written Responses (dated December 28, 2015), the Applicant was informed that full safety data for these ongoing Phase 3 trials (i.e., not only SAEs) would be expected at the time of NDA submission for the safety database required for NDA review and product registration. In response, the Applicant proposed the following exposure estimates (excluding the safety data from the CVOT, Trial P004/1021): 3489 subjects randomized to ertugliflozin; with 3000 exposures of ≥26 week duration, 2090 exposures ≥52 weeks; and 170 exposures ≥78 weeks. The following exposures were provided in the Application: 3409 subjects were randomized to ertugliflozin, of which 3128 were exposed for ≥25 week, 2575 for ≥50 weeks, and 371 for ≥78 weeks. Based on these data, and the submission of additional safety data in the 4-MSU (Table 12), I feel the safety database is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

Safety was evaluated based on the following: treatment-emergent adverse events (TEAEs), clinical laboratory assessments, changes in vital signs, ECGs findings, and physical examinations. The quality of the overall submission was adequate. The frequency of safety assessments for the short-term (i.e., Phase A 26-week placebo-controlled) and long-term (i.e., Phase B safety extension) treatment periods (e.g., approximately every 6-13 weeks) were adequate to evaluate safety for these Applications. Additionally, many of the key safety findings reported in these Applications were reproduced and confirmed using the Placebo Pool (Integrated Summary of Safety [iss]) and Broad Pools (Integrated Summary of Safety-Broad [iss-broad] and 4MSU-ISS [sur-iss]) integrated datasets. Based on these analyses, there were no obvious issues related to data quality. Please refer to Sections 4.1, and 6.1.8 for additional discussion related to data quality.

8.3.2. **Categorization of Adverse Events**

The integrated analyses were conducted primarily using the data from subjects randomized and treated (i.e., all subjects who received ≥1 dose of double-blind study medication). Safety analyses were performed by the Applicant on all data regardless of rescue (unless specified otherwise) for the blinded treatment periods. Adverse events were classified by System Organ Class (SOC) and/or Preferred Term (PT), and coded based on Medical Dictionary for Regulatory Activities (MedDRA) versions 19.0.

The Applicant used the following definitions in their safety analyses. An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs occurring from Day 1 of IP administration up to 14 days after the last dose, and included results from laboratory and ECG evaluations performed up to two days after the last dose of IP. Worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of IP, also was considered to be an AE. The occurrence of AEs was identified based on information volunteered by the subject or by general questioning and examination of subjects at each visit. The AE information obtained and documented in the electronic case report form (eCRF) included: the event, onset and resolution dates, intensity (mild, moderate, and severe), action taken, treatment required, outcome, and the Investigator's opinion regarding the relationship to study treatment.

A serious AE (SAE) was defined as any untoward medical occurrence that:

- Resulted in death
- Was life-threatening (defined as an event in which the subject was at risk of death at the time of the event)
- Required inpatient hospitalization or caused prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was an important medical event

The definitions, coding and cutoff dates for inclusion of TEAEs after discontinuing investigational product were acceptable. Also, the verbatim terms (i.e., AE CRF text and the iss, iss-broad, and sur-iss analysis datasets) provided by the investigators and the MedDRA PTs for which these AEs were coded were screened for correctness, and the coding of these data appeared appropriate.

The Applicant also created Custom MedDRA Queries (CMQs) for identifying AESI (i.e., 'Special Safety Topics') from lists of prespecified PTs (i.e., Version 19.0 MedDRA terms) or Standardized MedDRA Queries (SMQs). These AESI were primarily related to safety findings in the ertugliflozin nonclinical and clinical programs, and known safety signals/theoretical concerns (e.g., related to mechanisms of action) associated with other SGLT2 inhibitors, DPP-4 inhibitors and metformin. For the integrated safety assessment AESI included: accidents and injuries (to identify potential cases where volume depletion may have been a precipitating factor); acute renal failure/changes in renal function); amputations (reported in the procedures datasets); bone safety/fractures; changes in lipids; genital mycotic infections (including complicated genital infections); hepatic events; hypoglycemia; increased urination; ketoacidosis; malignancy;

osmotic diuresis; pancreatitis; peripheral revascularization; potential hypersensitivity; thirst; urinary tract infections (including complicated urinary tract infections); venous embolic and thrombotic events; and volume depletion.

For completeness, my safety evaluation also included the use of MedDRA Adverse Event Diagnosis Service (MAED) SMQs, as well as 'broad' CMQs that were derived using existing SMQs and PTs for AESI from other DPP-4 inhibitor, metformin and SGLT2 inhibitor clinical programs, including new/evolving safety issues identified for these products. These CMQs and associated PTs (which also included the Applicant's list of PTs for respective CMQs) are presented in Appendix 13.4. Assessments for AESIs will be described in more detail in the relevant sections. Additionally, since obvious trends suggestive of a dose-response were often not apparent, tabular summaries for many of the safety analyses are sorted and presented by the prevalence of events in the combined ertugliflozin treatment arms (i.e., 5 mg plus 15 mg dose groups).

8.3.3. **Routine Clinical Tests**

Blood and urine samples were obtained at baseline and typically at scheduled visits during and at the end of the treatment/early termination for evaluation of standard safety laboratory panels (chemistry, hematology, and urinalysis). Blood specimens for evaluation of lipid and glycemic parameters were collected under fasted conditions. The laboratory data were evaluated based on changes from baseline and marked abnormalities (Predefined Limits of Change [PDLC]). A listing of the PDLCs by relevant laboratory parameter, and the numbers/proportions (%) of subjects with these abnormalities, is discussed in more detail in Section 8.4.6. The clinical laboratory panels and the frequency of safety assessments were adequate, based on the patient population studied, the proposed indication, and the known toxicity profiles of ertugliflozin and other SGLT2 inhibitors, sitagliptin and other DPP-4 inhibitors, and metformin.

Vital signs (including orthostatic changes in blood pressure and pulse rate), typically assessed at scheduled clinic visits, were evaluated based on changes from baseline. The normality or abnormality of scheduled ECG findings (transferred to a central vendor for reading/interpretation) was summarized in frequency tables.

8.4. **Safety Results**

A summary of the AEs reported in the integrated Placebo Pool and Broad Pool safety populations of this Application is presented in Table 15. Overall, approximately 50% and more than 60% of subjects in all treatment arms for the Placebo and the Broad Safety Pools experienced at least one AE, respectively. The proportion of subjects experiencing at least one AE was similar between treatment arms. Subjects experiencing at least one SAE or

discontinuing study due to SAEs were also similar across treatment arms in both the Placebo and Broad Pools. Although there were no deaths reported during the 26-week blinded treatment period in the Placebo Pool, more deaths occurred in ertugliflozin-treated subjects compared to subjects in the non-ertugliflozin treatment arms in the Broad Pool (0.5% vs. 0.2%, respectively). A review of AEs, SAEs, and discontinuations due to AEs or SAEs did not reveal any apparent trends for these events among the ertugliflozin treatment arms in the Placebo Pool. In the Broad Pool, although the numbers were limited, higher proportions of subjects discontinued IP due to AEs more commonly associated with SGLT2 inhibitors; such as 'glomerular filtration rate decreased', 'balanoposthitis', 'vulvovaginal mycotic infection', 'urinary tract infection', 'acute kidney injury', 'pollakiuria', 'vulvovaginal candidiasis', 'vulvovaginal pruritus', 'dizziness', 'weight decreased', and 'polyuria'. Additionally, SAEs of 'acute kidney injury'/'glomerular filtration rate decreased' (n=4), 'acute myocardial infarction' (n=2), and 'pyelonephritis'/'pyelonephritis acute' (n=2) resulted in treatment discontinuation in the combined ertugliflozin treatment arms only. These safety findings are discussed further in Section 8.4.3 below.

Although the proportions increased slightly, similar proportions of AEs, SAEs, discontinuations due to AEs or SAEs, and fatal AEs were observed in the 4-MSU Safety Pool (data not shown). In the updated report, four additional AEs leading to death occurred in the non-ertugliflozin arm (i.e., accumulated total of 7/1450 subjects [0.48%]), while none were reported for the two ertugliflozin arms (accumulated total deaths at the time of the 4-MSU was 18/3409 [0.5%]).

Table 15: Summary of Adverse Events (Placebo and Broad Pools)

	Placebo Pool				Broad Pool			
	Placebo (n=515)	Ertu 5 mg (n=519)	Ertu 15 mg (n=510)	ALL Ertu (n=1029)	Non-Ertu (n=1450)	Ertu 5 mg (n=1716)	Ertu 15 mg (n=1693)	ALL Ertu (n=3409)
Event — no. (%)								
≥1 AE	263 (51.1)	236 (45.5)	257 (50.4)	493 (47.9)	940 (64.8)	1074 (62.6)	1049 (62.0)	2123 (62.3)
D/C due to AE	9 (1.7)	12 (2.3)	7 (1.4)	19 (1.8)	60 (4.1)	70 (4.1)	74 (4.4)	144 (4.2)
≥1 SAE	15 (2.9)	17 (3.3)	12 (2.4)	29 (2.8)	80 (5.5)	110 (6.4)	98 (5.8)	208 (6.1)
D/C due to SAE	2 (0.4)	1 (0.2)	0	1 (0.1)	10 (0.7)	17 (1.0)	15 (0.9)	32 (0.9)
AE leading to Death	0	0	0	0	3 (0.2)	10 (0.6)	8 (0.5)	18 (0.5)

Source: Derived from the adsl.xpt, aeplus.xpt and aerpt.xpt datasets, and adapted from the Applicants' Summary of Clinical Safety, labeled as Tables 20 and 21, page 68-69 of 372, available at:
\\cdsesub1\evsprod\nda209803\0000\m2\27-clin-sum\summary-clin-safety.pdf
Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Application 209803 - Sequence 0014 - Analysis Dataset Legacy -
Abbreviations: AE, adverse event; D/C, discontinuation; Ertu, ertugliflozin; no., number; and SAE, serious adverse event.

8.4.1. Deaths

At the time of the 4-MSU, there were a total of 25 fatal AEs, 18 (0.53%) in the ertugliflozin treatment arms and 7 (0.48%) in the non-ertugliflozin arm (Table 16). The median days of exposures to IP were 227 in the combined ertugliflozin arms and 490 in the non-ertugliflozin arm, with a sudden death reported following 25 days of exposure to ertugliflozin 5 mg. All other deaths occurred following at least 111 days of exposure. No obvious treatment differences or dose-response effects were observed; however, the number of events were limited. Cardiovascular deaths ('acute myocardial infarction'/'myocardial infarction', 'sudden death'/'cardiac death', 'cardiac death', 'cardiogenic death') were the most common causes of death, with similar proportions of these events occurring between ertugliflozin and non-ertugliflozin treatment arms (10 [0.29%] vs. 4 [0.28%]). Increased age, preexisting CV disease, other comorbidities, and multiple CV risk factors were often present. Additionally, more ertugliflozin-treated subjects with impaired renal function (baseline eGFR <60 mL/min/1.73 m^2) had fatal events (i.e., 2.3% [9/387] vs. 1.6% [3/190]).

Inclusion of all fatal AEs reported during the post-randomization period resulted in 20/3409 (0.59%) and 10/1450 (0.69%) deaths in the ertugliflozin and non-ertugliflozin treatment arms, respectively. There were no deaths during the 26-week (Phase A) treatment periods of Trials P005/1019, P006/1015 or P017/1047, used to support the safety and efficacy of the ertugliflozin/sitagliptin FCDP. Also, no deaths occurred in subjects in the 26-week Ertugliflozin/Metformin Pool.

Table 16: Subjects with Fatal Adverse Events (4-MSU)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total Fatal AEs — no. (%)	**7 (0.48)**	**10 (0.58)**	**8 (0.47)**	**18 (0.53)**
Mean Exposure (range) — days	449 (166-710)	239 (25-407)	252 (111-455)	245 (25-455)
Median Exposure (IQR) — days	490 (232-658)	217 (179-366)	239 (181-304)	227 (179-318)
Acute myocardial infarction	0	1 (0.06)	3 (0.18)	4 (0.12)
Sudden death	2 (0.14)	3 (0.17)	1 (0.06)	4 (0.12)
Sudden cardiac death	0	1 (0.06)	0	1 (0.03)
Cardiac death	0	1 (0.06)	0	1 (0.03)
Haemorrhagic stroke	0	0	1 (0.06)	1 (0.03)
Ischaemic stroke	0	0	1 (0.06)	1 (0.03)
Multiple organ dysfunction syndrome	0	1 (0.06)	0	1 (0.03)
Septic shock	0	0	1 (0.06)	1 (0.03)
Pneumonia	0	1 (0.06)	0	1 (0.03)
Chronic obstructive pulmonary disease	0	1 (0.06)	0	1 (0.03)
Depression	0	1 (0.06)	0	1 (0.03)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Plasma cell myeloma	0	0	1 (0.06)	1 (0.03)
Myocardial infarction	1 (0.07)	0	0	0
Cardiogenic shock	1 (0.07)	0	0	0
Injury	1 (0.07)	0	0	0
Hepatic cancer	1 (0.07)	0	0	0
Death	1 (0.07)	0	0	0

Source: Derived from the iss-broad and sur-iss adsl.xpt and explus.xpt datasets, available at:
Application 209803 - Sequence 0014 - 5.3.5.3 [[Study ID]] - [[Study Title]] - sur - Integrated Summary of Safety - SUR
Abbreviations: 4-MSU, Four-Month Safety Update; IQR, 25th and 75th interquartile range; and no., number.

All clinical narratives associated with death were reviewed. As mentioned above, Subject 0101207 died suddenly following only 25 days of exposure to ertugliflozin compared to all other deaths, which occurred following almost four months of exposure to IP. This case was reviewed further to evaluate whether this death could potentially be treatment related. A brief narrative summary for the case is provided as follows:

Ertugliflozin 5 mg arm:

Subject 0101207: a 70-year-old white female who participated in Trial P001/1016 (i.e., the dedicated moderate renal impairment trial) was reported to have experienced a sudden death on Study Day 25. The subject had a medical history that included T2D (18 years), chronic kidney disease (baseline eGFR of 47 mL/min/1.73 m^2), hyperlipidemia, hypertension, obesity (baseline BMI 49.1 kg/m^2), edema, sleep apnea syndrome, and past smoking history. Relevant prior and concomitant medications included insulin glargine, glimepiride, simvastatin, budesonide plus formoterol, hydrochlorothiazide plus losartan, furosemide, and metoclopramide. On Day 1, the subject's blood pressure ranged from 152-160/79-86 mmHg, and her labs were significant for a total cholesterol (Total-C) of 313 mg/dL, low-density lipoprotein-cholesterol (LDL-C) of 206 mg/dL, and an HbA1c of 10.3%. The baseline electrocardiogram was reported as abnormal ('other T wave change'). On Day 25, the subject called the investigator and reported new onset asthmatic symptoms for which beclomethasone dipropionate and albuterol inhalers were being prescribed by a local healthcare provider. She also commented that her blood glucose concentrations were high in the morning, but specific values were not reported. The investigator informed the subject to continue study medication and increase her current dose of insulin glargine from 30 to 40 units/day. While leaving the healthcare facility (local primary care provider's office) with her husband, she became unresponsive. Cardiopulmonary resuscitation (including administration of intravenous epinephrine, bicarbonate and calcium), was performed at a local emergency room (ER), but was unsuccessful. The subject's last dose of study medication was on Day 24. The husband stated that the subject had experienced dyspnea for a few days with some chest pain. The death certificate reported sudden death as the immediate cause of death, with diabetes, hypertension, and morbid obesity as contributing conditions. The eGFR reported during the ER visit was '23.4 mL/min'. Limited additional information was provided in the CRF and CSR. However, given the long-standing history of diabetes, chronic kidney disease, and poorly controlled cardiovascular risk factors, establishing a causal association to study medication for this subject would be difficult. The investigator considered this death to be unrelated to IP.

Although I concur that this early death was not due directly to ertugliflozin, it is unknown whether ertugliflozin may have been a contributing factor (e.g., unconfirmed 50% reduction in eGFR).

8.4.2. Serious Adverse Events

The occurrence of SAEs, as defined in Section 8.4.2, for both the short-term (Placebo Pool) and the long-term (4-MSU Pool) safety populations will be discussed in this section. The non-fatal SAEs associated with AESI will be discussed further in the relevant sections of this review (please refer to Section 8.5).

The proportions of SAEs in the Placebo Pool were similar across treatment arms, occurring in 2.9% and 2.8% of subjects in the placebo and the combined ertugliflozin and treatment groups (Table 17). Generally, no relevant imbalances were noted between treatment arms in this safety pool. The MedDRA PTs were diverse, with only 'osteoarthritis' and 'hypertension' reported as SAEs in more than one ertugliflozin-treated subject. Additionally, evaluation of subgroups (e.g., age, renal function) was not informative due to the limited number of events.

Table 17: Summary of Serious Adverse Events (Placebo Pool)

MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	All Ertugliflozin (n=1029)
Total SAEs — no. (%)	**15 (2.9)**	**17 (3.3)**	**12 (2.4)**	**29 (2.8)**
Osteoarthritis	0	2 (0.4)	0	2 (0.2)
Hypertension	0	2 (0.4)	0	2 (0.2)
Angina pectoris	0	1 (0.2)	0	1 (0.1)
Appendicitis	0	1 (0.2)	0	1 (0.1)
Atrial fibrillation	0	0	1 (0.2)	1 (0.1)
Bipolar disorder	0	1 (0.2)	0	1 (0.1)
Blindness transient	0	1 (0.2)	0	1 (0.1)
Breast cancer	0	1 (0.2)	0	1 (0.1)
Cerebral haemorrhage	0	0	1 (0.2)	1 (0.1)
Acute myocardial infarction	2 (0.4)	1 (0.2)	0	1 (0.1)
Cholelithiasis	0	0	1 (0.2)	1 (0.1)
Diabetes mellitus inadequate control	1 (0.2)	1 (0.2)	0	1 (0.1)
Epistaxis	0	0	1 (0.2)	1 (0.1)
Femur fracture	0	1 (0.2)	0	1 (0.1)
Goitre	0	1 (0.2)	0	1 (0.1)
Haemorrhoidal haemorrhage	0	0	1 (0.2)	1 (0.1)

MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	All Ertugliflozin (n=1029)
Hemiplegia	0	0	1 (0.2)	1 (0.1)
Cholecystitis acute	1 (0.2)	1 (0.2)	0	1 (0.1)
Intervertebral disc disorder	0	0	1 (0.2)	1 (0.1)
Invasive ductal breast carcinoma	0	1 (0.2)	0	1 (0.1)
Laceration	0	0	1 (0.2)	1 (0.1)
Myocardial ischaemia	0	0	1 (0.2)	1 (0.1)
Accidental overdose	0	0	1 (0.2)	1 (0.1)
Periorbital abscess	0	0	1 (0.2)	1 (0.1)
Periorbital cellulitis	0	0	1 (0.2)	1 (0.1)
Pneumonia	0	1 (0.2)	0	1 (0.1)
Prostate cancer	0	0	1 (0.2)	1 (0.1)
Soft tissue necrosis	0	1 (0.2)	0	1 (0.1)
Spinal compression fracture	0	1 (0.2)	0	1 (0.1)
Squamous cell carcinoma of the cervix	0	0	1 (0.2)	1 (0.1)
Transient ischaemic attack	0	0	1 (0.2)	1 (0.1)
Urge incontinence	0	1 (0.2)	0	1 (0.1)
Abdominal pain lower	1 (0.2)	0	0	0
Bacterial infection	1 (0.2)	0	0	0
Cholecystitis	1 (0.2)	0	0	0
Chronic obstructive pulmonary disease	1 (0.2)	0	0	0
Gastritis haemorrhagic	1 (0.2)	0	0	0
Hyperglycaemia	1 (0.2)	0	0	0
Ischaemic stroke	1 (0.2)	0	0	0
Joint injury	1 (0.2)	0	0	0
Non-cardiac chest pain	1 (0.2)	0	0	0
Otitis media chronic	1 (0.2)	0	0	0
Stress urinary incontinence	1 (0.2)	0	0	0
Subcutaneous abscess	1 (0.2)	0	1 (0.2)	0

Source: Derived from the ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at:
Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Abbreviations: no., number; and SAE, serious adverse event.

In the 4-MSU Pool (
Table 18), the proportions of subjects with SAEs were again similar between the combined ertugliflozin and non-ertugliflozin treatment arms (i.e., 6.4% [218/3409 subjects] vs. 6.1% [88/1450 subjects], respectively). System organ classes (SOCs) that included at least two subjects with events and higher proportions of subjects with SAEs in the combined ertugliflozin treatment arms compared to the non-ertugliflozin arm included the 'Cardiac disorders' (1.4%

vs. 1.0%), 'Neoplasms benign, malignant and unspecified' (0.9% vs. 0.5%), 'Musculoskeletal and connective tissue disorders' (0.4% vs. 0.3%), and 'Blood and lymphatics system disorders' (0.1% vs. 0%) SOCs. By MedDRA PTs, all events were relatively low (≤0.3%), without obvious treatment imbalances.

Review of SAEs was further assessed based on MedDRA hierarchy (i.e., High Level Terms [HLTs] and High Level Group Terms [HLGTs]). Of the HLTs, the highest proportion of events were coded as 'Coronary necrosis and vascular insufficiency', with higher numbers reported in the combined ertugliflozin group (1.0% [35/3409] vs. 0.6% [9/1450] of subjects, respectively). The MedDRA PTs coded to this HLT that were reported more frequently in ertugliflozin-treated subjects included: 'angina pectoris' 0.2% (8/3409) vs. 0%; 'myocardial ischaemia' 0.1% (3/3409) vs. 0%; 'acute coronary syndrome' <0.1% (1/3409) vs. 0%; 'coronary artery stenosis' <0.1% (1/3409) vs. 0%; and 'microvascular coronary artery disease' <0.1% (1/3409) vs. 0%. A review of the clinical narratives for the 35 ertugliflozin-treated subjects indicated that these subjects were at risk for CV events, based on age, established CV disease, multiple risk factors, comorbidities, and long-standing T2D. Of the HLGTs, 'Arteriosclerosis, stenosis, vascular insufficiency and necrosis' included the largest number of SAEs (i.e., 1.4% [48/3409] vs. 1.0% [15/1450], respectively).

Events were also reviewed by age and baseline renal function. Although imbalances between treatment arms were not observed for subjects ages 65 and older, higher proportions of ertugliflozin-treated subjects with a baseline eGFR <60 mL/min/1.73m^2 experienced SAEs (i.e., 15% [58/387] vs. 11.6% [22/190]), of which approximately 75% were classified as Chronic Kidney Disease (CKD) stage 3a (eGFR 45 to <60 mL/min/1.73 m^2).[96] As observed with the entire 4-MSU safety population, the 'Cardiac disorders' SOC included the highest proportions of reported SAEs in this subgroup, occurring in 5.4% (21/387) vs. 3.2% (6/190) of ertugliflozin- and non-ertugliflozin-treated subjects, respectively. The SAEs reported more frequently in this SOC for the combined ertugliflozin arm included 'angina pectoris' (1.3% [5/387] vs. 0% [0/190]); 'myocardial ischaemia' (0.8% [3/387] vs. 0%); 'acute myocardial infarction' (0.8% [3/387] vs. 0.5% [1/190]); 'coronary artery stenosis' (0.5% [2/387] vs. 0%); 'myocardial infarction' (0.5% vs. 0%); 'atrial fibrillation' (0.3% [1/387] vs. 0%); 'sinus node dysfunction' (0.3% [1/387] vs. 0%); and 'cardiac failure' 0.3% [1/387] vs. 0%). Even though the SAE rates were relatively low for this subgroup the risk-benefit profile associated with the use of ertugliflozin in subjects with an eGFR <60 mL/min/1.73 m^2 does not appear to be favorable, considering that Trial P001/1016 (the dedicated moderate renal impairment trial) failed on its primary efficacy endpoint (i.e., baseline to week 26 placebo-subtracted change in HbA1c).

Table 18: Summary of Non-Fatal Serious Adverse Events by System Organ Class (4-MSU)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total SAEs — no. (%)	**88 (6.1)**	**117 (6.8)**	**101 (6.0)**	**218 (6.4)**
Age ≥65 years	37/378 (9.8)	47/449 (10.5)	43/427 (10.1)	90/876 (10.3)
eGFR <60 mL/min/1.73 m^2	25/189 (13.2))	32/196 (16.3)	33/190 (17.4)	65/386 (16.8)
45 to <60 mL/min/1.73 m^2	16/126 (12.7)	23/141 (16.3)	20/135 (14.8)	43/276 (15.6)
CARDIAC DISORDERS	**14 (1.0)**	**25 (1.5)**	**24 (1.4)**	**49 (1.4)**
Angina pectoris	0	3 (0.2)	5 (0.3)	8 (0.2)
Coronary artery disease	3 (0.2)	5 (0.3)	3 (0.2)	8 (0.2)
Acute myocardial infarction	3 (0.2)	4 (0.2)	3 (0.2)	7 (0.2)
Myocardial infarction	1 (0.1)	2 (0.1)	3 (0.2)	5 (0.1)
Cardiac failure	0	1 (0.1)	3 (0.2)	4 (0.1)
Myocardial ischaemia	0	1 (0.1)	3 (0.2)	4 (0.1)
Atrial fibrillation	1 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Angina unstable	3 (0.2)	3 (0.2)	1 (0.1)	4 (0.1)
Acute coronary syndrome	0	2 (0.1)	0	2 (0.1)
Cardiac failure congestive	1 (0.1)	2 (0.1)	0	2 (0.1)
Coronary artery stenosis	0	2 (0.1)	0	2 (0.1)
Sinus node dysfunction	0	0	2 (0.1)	2 (0.1)
Cardiac failure chronic	0	1 (0.1)	0	1 (0.0)
Cardiomyopathy	0	1 (0.1)	0	1 (0.0)
Microvascular coronary artery disease	0	1 (0.1)	0	1 (0.0)
Bundle branch block left	1 (0.1)	0	0	0
Bradycardia	1 (0.1)	0	0	0
INFECTIONS AND INFESTATIONS	**19 (1.3)**	**22 (1.3)**	**20 (1.2)**	**42 (1.2)**
Pneumonia	4 (0.3)	6 (0.3)	3 (0.2)	9 (0.3)
Urinary tract infection	1 (0.1)	1 (0.1)	5 (0.3)	6 (0.2)
Cellulitis	0	0	5 (0.3)	5 (0.1)
Appendicitis	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Sepsis	1 (0.1)	2 (0.1)	0	2 (0.1)
Pyelonephritis acute	1 (0.1)	2 (0.1)	0	2 (0.1)
Gastroenteritis	1 (0.1)	2 (0.1)	0	2 (0.1)
Gangrene	0	1 (0.1)	1 (0.1)	2 (0.1)
Diverticulitis	1 (0.1)	1 (0.1)	0	1 (<0.1)
Influenza	0	1 (0.1)	0	1 (<0.1)
Klebsiella sepsis	0	0	1 (0.1)	1 (<0.1)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Labyrinthitis	0	0	1 (0.1)	1 (<0.1)
Lymphangitis	0	1 (0.1)	0	1 (<0.1)
Cellulitis orbital	0	1 (0.1)	0	1 (<0.1)
Cystitis	0	0	1 (0.1)	1 (<0.1)
Pelvic inflammatory disease	0	0	1 (0.1)	1 (<0.1)
Periorbital abscess	0	0	1 (0.1)	1 (<0.1)
Periorbital cellulitis	0	0	1 (0.1)	1 (<0.1)
Pneumococcal sepsis	0	0	1 (0.1)	1 (<0.1)
Cellulitis of male external genital organ	0	1 (0.1)	0	1 (<0.1)
Pneumonia influenzal	0	1 (0.1)	0	1 (<0.1)
Pulmonary tuberculosis	0	0	1 (0.1)	1 (<0.1)
Pyelonephritis	0	1 (0.1)	0	1 (<0.1)
Osteomyelitis acute	0	1 (0.1)	0	1 (<0.1)
Cervicitis	0	0	1 (0.1)	1 (<0.1)
Osteomyelitis	0	1 (0.1)	0	1 (<0.1)
Viral infection	0	1 (0.1)	0	1 (<0.1)
Bacterial infection	1 (0.1)	0	0	0
Bone tuberculosis	1 (0.1)	0	0	0
Cellulitis staphylococcal	1 (0.1)	0	0	0
Diabetic gangrene	1 (0.1)	0	0	0
Diarrhoea infectious	1 (0.1)	0	0	0
Escherichia urinary tract infection	1 (0.1)	0	0	0
Extradural abscess	1 (0.1)	0	0	0
Gastroenteritis norovirus	1 (0.1)	0	0	0
Lower respiratory tract infection	1 (0.1)	0	0	0
Otitis media chronic	1 (0.1)	0	0	0
Peritonitis	1 (0.1)	0	0	0
Postoperative wound infection	1 (0.1)	0	0	0
Subcutaneous abscess	1 (0.1)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**7 (0.5)**	**12 (0.7)**	**18 (1.1)**	**30 (0.9)**
Uterine leiomyoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Malignant melanoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Prostate cancer	0	1 (0.1)	1 (0.1)	2 (0.1)
Breast cancer	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Invasive ductal breast carcinoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Colon cancer	0	1 (0.1)	1 (0.1)	2 (0.1)
Chronic lymphocytic leukaemia	0	1 (0.1)	0	1 (<0.1)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Endometrial adenocarcinoma	0	0	1 (0.1)	1 (<0.1)
Hepatic cancer metastatic	0	0	1 (0.1)	1 (<0.1)
Carcinoma in situ of skin	0	0	1 (0.1)	1 (<0.1)
Benign ear neoplasm	0	1 (0.1)	0	1 (<0.1)
Basal cell carcinoma	1 (0.1)	1 (0.1)	0	1 (<0.1)
Myelodysplastic syndrome	0	1 (0.1)	0	1 (<0.1)
Nodal marginal zone B-cell lymphoma stage III	0	1 (0.1)	0	1 (<0.1)
Non-Hodgkin's lymphoma	0	0	1 (0.1)	1 (<0.1)
Ovarian adenoma	0	0	1 (0.1)	1 (<0.1)
Pancreatic carcinoma	0	0	1 (0.1)	1 (<0.1)
Pancreatic neoplasm	0	0	1 (0.1)	1 (<0.1)
Pelvic neoplasm	0	0	1 (0.1)	1 (<0.1)
Plasma cell myeloma	0	1 (0.1)	1 (0.1)	1 (<0.1)
Lip squamous cell carcinoma	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma of lung	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma of the cervix	0	0	1 (0.1)	1 (<0.1)
Adenocarcinoma gastric	0	1 (0.1)	0	1 (<0.1)
Intraductal papilloma of breast	1 (0.1)	0	0	0
Papillary thyroid cancer	1 (0.1)	0	0	0
Prostatic adenoma	1 (0.1)	0	0	0
Squamous cell carcinoma of skin	1 (0.1)	0	0	0
Bladder cancer	1 (0.1)	0	0	0
NERVOUS SYSTEM DISORDERS	**9 (0.6)**	**14 (0.8)**	**4 (0.2)**	**18 (0.5)**
Cerebrovascular accident	1 (0.1)	3 (0.2)	0	3 (0.1)
Ischaemic stroke	5 (0.3)	2 (0.1)	0	2 (0.1)
Cerebral infarction	0	2 (0.1)	0	2 (0.1)
Sciatica	0	1 (0.1)	1 (0.1)	2 (0.1)
Transient ischaemic attack	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Syncope	0	2 (0.1)	0	2 (0.1)
Cerebral haemorrhage	0	0	1 (0.1)	1 (<0.1)
Sciatic nerve palsy	0	1 (0.1)	0	1 (<0.1)
Carotid artery stenosis	1 (0.1)	1 (0.1)	0	1 (<0.1)
Encephalopathy	0	0	1 (0.1)	1 (<0.1)
Hemiplegia	0	0	1 (0.1)	1 (<0.1)
Carotid arteriosclerosis	0	1 (0.1)	0	1 (<0.1)
Epilepsy	1 (0.1)	0	0	0

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
GASTROINTESTINAL DISORDERS	**8 (0.6)**	**12 (0.7)**	**4 (0.2)**	**16 (0.5)**
Vomiting	0	2 (0.1)	0	2 (0.1)
Abdominal pain	1 (0.1)	0	2 (0.1)	2 (0.1)
Inguinal hernia	0	1 (0.1)	1 (0.1)	2 (0.1)
Anal ulcer	0	1 (0.1)	0	1 (<0.1)
Cyclic vomiting syndrome	0	0	1 (0.1)	1 (<0.1)
Duodenal ulcer haemorrhage	1 (0.1)	1 (0.1)	0	1 (<0.1)
Anal fistula	0	1 (0.1)	0	1 (<0.1)
Gastric ulcer	0	1 (0.1)	0	1 (<0.1)
Gastritis	0	1 (0.1)	0	1 (<0.1)
Haematochezia	0	1 (0.1)	0	1 (<0.1)
Haemorrhoidal haemorrhage	0	0	1 (0.1)	1 (<0.1)
Femoral hernia	0	1 (0.1)	0	1 (<0.1)
Pancreatitis	2 (0.1)	1 (0.1)	0	1 (<0.1)
Pancreatitis acute	0	1 (0.1)	0	1 (<0.1)
Peritoneal haemorrhage	0	1 (0.1)	0	1 (<0.1)
Umbilical hernia	0	1 (0.1)	0	1 (<0.1)
Abdominal hernia	0	0	1 (0.1)	1 (<0.1)
Gastritis haemorrhagic	1 (0.1)	0	0	0
Gastrointestinal haemorrhage	1 (0.1)	0	0	0
Small intestinal obstruction	1 (0.1)	0	0	0
Abdominal pain lower	1 (0.1)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**5 (0.3)**	**10 (0.6)**	**5 (0.3)**	**15 (0.4)**
Osteoarthritis	1 (0.1)	4 (0.2)	0	4 (0.1)
Intervertebral disc protrusion	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Spinal column stenosis	0	2 (0.1)	0	2 (0.1)
Pain in extremity	0	1 (0.1)	1 (0.1)	2 (0.1)
Musculoskeletal pain	0	1 (0.1)	0	1 (<0.1)
Necrotising myositis	0	1 (0.1)	0	1 (<0.1)
Intervertebral disc disorder	0	0	1 (0.1)	1 (<0.1)
Musculoskeletal chest pain	0	0	1 (0.1)	1 (<0.1)
Lumbar spinal stenosis	1 (0.1)	1 (0.1)	0	1 (<0.1)
Cervical spinal stenosis	0	0	1 (0.1)	1 (<0.1)
Rotator cuff syndrome	2 (0.1)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**9 (0.6)**	**10 (0.6)**	**5 (0.3)**	**15 (0.4)**
Femur fracture	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Craniocerebral injury	0	1 (0.1)	0	1 (<0.1)
Face injury	0	1 (0.1)	0	1 (<0.1)
Chest injury	0	1 (0.1)	0	1 (<0.1)
Ankle fracture	1 (0.1)	0	1 (0.1)	1 (<0.1)
Head injury	0	0	1 (0.1)	1 (<0.1)
Humerus fracture	0	1 (0.1)	0	1 (<0.1)
Joint injury	1 (0.1)	0	1 (0.1)	1 (<0.1)
Laceration	0	0	1 (0.1)	1 (<0.1)
Ligament rupture	0	0	1 (0.1)	1 (<0.1)
Ligament sprain	1 (0.1)	0	1 (0.1)	1 (<0.1)
Lumbar vertebral fracture	0	1 (0.1)	0	1 (<0.1)
Multiple injuries	0	1 (0.1)	0	1 (<0.1)
Overdose	0	1 (0.1)	0	1 (<0.1)
Spinal compression fracture	0	1 (0.1)	0	1 (<0.1)
Tibia fracture	0	1 (0.1)	0	1 (<0.1)
Toxicity to various agents	0	1 (0.1)	0	1 (<0.1)
Limb crushing injury	1 (0.1)	0	0	0
Multiple fractures	1 (0.1)	0	0	0
Muscle strain	1 (0.1)	0	0	0
Spinal column injury	1 (0.1)	0	0	0
Upper limb fracture	1 (0.1)	0	0	0
Ligament injury	1 (0.1)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**8 (0.6)**	**5 (0.3)**	**8 (0.5)**	**13 (0.4)**
Chronic obstructive pulmonary disease	2 (0.1)	0	2 (0.1)	2 (0.1)
Asthma	2 (0.1)	0	1 (0.1)	1 (<0.1)
Bronchial hyperreactivity	0	0	1 (0.1)	1 (<0.1)
Acute respiratory failure	1 (0.1)	1 (0.1)	0	1 (<0.1)
Acute respiratory distress syndrome	0	1 (0.1)	0	1 (<0.1)
Dyspnoea	0	0	1 (0.1)	1 (<0.1)
Epistaxis	1 (0.1)	0	1 (0.1)	1 (<0.1)
Haemoptysis	0	0	1 (0.1)	1 (<0.1)
Pneumothorax	0	0	1 (0.1)	1 (<0.1)
Pulmonary embolism	1 (0.1)	0	1 (0.1)	1 (<0.1)
Pulmonary fibrosis	0	1 (0.1)	0	1 (<0.1)
Respiratory failure	0	1 (0.1)	0	1 (<0.1)
Vocal cord thickening	0	1 (0.1)	0	1 (<0.1)
Nasal polyps	1 (0.1)	0	0	0

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Sleep apnoea syndrome	1 (0.1)	0	0	0
Bronchitis chronic	1 (0.1)	0	0	0
VASCULAR DISORDERS	**4 (0.3)**	**6 (0.3)**	**5 (0.3)**	**11 (0.3)**
Hypertension	1 (0.1)	3 (0.2)	0	3 (0.1)
Peripheral ischaemia	0	0	3 (0.2)	3 (0.1)
Peripheral arterial occlusive disease	0	0	1 (0.1)	1 (<0.1)
Peripheral artery occlusion	0	0	1 (0.1)	1 (<0.1)
Deep vein thrombosis	1 (0.1)	1 (0.1)	0	1 (<0.1)
Aortic dissection	0	1 (0.1)	0	1 (<0.1)
Venous thrombosis limb	0	1 (0.1)	0	1 (<0.1)
Peripheral artery stenosis	1 (0.1)	0	0	0
Diabetic vascular disorder	1 (0.1)	0	0	0
RENAL AND URINARY DISORDERS	**6 (0.4)**	**6 (0.3)**	**4 (0.2)**	**10 (0.3)**
Urinary retention	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Acute kidney injury	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Nephrolithiasis	2 (0.1)	2 (0.1)	0	2 (0.1)
Urge incontinence	0	1 (0.1)	0	1 (<0.1)
Hydronephrosis	0	0	1 (0.1)	1 (<0.1)
Haematuria	0	1 (0.1)	0	1 (<0.1)
Stress urinary incontinence	1 (0.1)	0	0	0
Ureterolithiasis	1 (0.1)	0	0	0
Chronic kidney disease	1 (0.1)	0	0	0
METABOLISM AND NUTRITION DISORDERS	**7 (0.5)**	**3 (0.2)**	**2 (0.1)**	**5 (0.1)**
Diabetic ketoacidosis	0	0	2 (0.1)	2 (0.1)
Diabetes mellitus inadequate control	1 (0.1)	1 (0.1)	0	1 (<0.1)
Obesity	0	1 (0.1)	0	1 (<0.1)
Dehydration	0	1 (0.1)	0	1 (<0.1)
Diabetes mellitus	1 (0.1)	0	0	0
Hyperglycaemia	2 (0.1)	0	0	0
Hyperkalaemia	1 (0.1)	0	0	0
Hypoglycaemia	1 (0.1)	0	0	0
Hypomagnesaemia	1 (0.1)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**2 (0.1)**	**1 (0.1)**	**3 (0.2)**	**4 (0.1)**
Chest discomfort	0	0	1 (0.1)	1 (<0.1)
Chest pain	0	1 (0.1)	0	1 (<0.1)
Incarcerated hernia	0	0	1 (0.1)	1 (<0.1)
Asthenia	0	0	1 (0.1)	1 (<0.1)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Non-cardiac chest pain	2 (0.1)	0	0	0
EYE DISORDERS	**4 (0.3)**	**2 (0.1)**	**2 (0.1)**	**4 (0.1)**
Cataract	1 (0.1)	0	1 (0.1)	1 (<0.1)
Retinal artery occlusion	0	1 (0.1)	0	1 (<0.1)
Retinal detachment	0	0	1 (0.1)	1 (<0.1)
Blindness transient	0	1 (0.1)	0	1 (<0.1)
Papilloedema	1 (0.1)	0	0	0
Ulcerative keratitis	1 (0.1)	0	0	0
Keratitis	1 (0.1)	0	0	0
INVESTIGATIONS	**1 (0.1)**	**3 (0.2)**	**1 (0.1)**	**4 (0.1)**
Aspartate aminotransferase increased	0	1 (0.1)	0	1 (<0.1)
Blood potassium decreased	0	1 (0.1)	0	1 (<0.1)
Blood sodium decreased	0	1 (0.1)	0	1 (<0.1)
Glomerular filtration rate decreased	0	0	1 (0.1)	1 (<0.1)
Intraocular pressure increased	0	1 (0.1)	0	1 (<0.1)
Alanine aminotransferase increased	0	1 (0.1)	0	1 (<0.1)
Blood pressure increased	1 (0.1)	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0**	**1 (0.1)**	**2 (0.1)**	**3 (0.1)**
Lymph node haemorrhage	0	0	1 (0.1)	1 (<0.1)
Lymphadenopathy	0	0	1 (0.1)	1 (<0.1)
Iron deficiency anaemia	0	1 (0.1)	0	1 (<0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**1 (0.1)**	**0**	**2 (0.1)**	**2 (0.1)**
Vaginal haemorrhage	0	0	1 (0.1)	1 (<0.1)
Balanoposthitis	0	0	1 (0.1)	1 (<0.1)
Menometrorrhagia	1 (0.1)	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1 (0.1)**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**
Skin ulcer	0	0	1 (0.1)	1 (<0.1)
Diabetic foot	0	1 (0.1)	0	1 (<0.1)
Angioedema	1 (0.1)	0	0	0
EAR AND LABYRINTH DISORDERS	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Hypoacusis	0	0	1 (0.1)	1 (<0.1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Phimosis	0	0	1 (0.1)	1 (<0.1)
ENDOCRINE DISORDERS	**0**	**1 (0.1)**	**0**	**1 (<0.1)**
Goitre	0	1 (0.1)	0	1 (<0.1)
PSYCHIATRIC DISORDERS	**3 (0.2)**	**1 (0.1)**	**0**	**1 (<0.1)**

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Bipolar disorder	0	1 (0.1)	0	1 (<0.1)
Depression	2 (0.1)	0	0	0
Confusional state	1 (0.1)	0	0	0
IMMUNE SYSTEM DISORDERS	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Allergy to arthropod sting	0	0	1 (0.1)	1 (<0.1)

Source: Derived from the iss-broad and sur-iss adsl.xpt and aerpt.xpt and aeplus.xpt datasets, available at:
Application 209803 - Sequence 0014 - 5.3.5.3 [[Study ID]] - [[Study Title]] - sur - Integrated Summary of Safety - SUR
Abbreviations: 4-MSU, Four-Month Safety Update; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and SAE, serious adverse event.

Ertugliflozin/Sitagliptin (NDA 209805) and Ertugliflozin/Metformin (209806) FCDPs:

For the three trials used to support the ertugliflozin/sitagliptin FCDP, and in the Ertugliflozin/Metformin safety pool, SAEs were limited and without obvious imbalances between treatment arms (data not shown).

In Trial P005/1019 (ertugliflozin plus sitagliptin factorial study, the proportions of subjects with reported SAEs in the five treatment arms were: 1.6% (4/247) in the sitagliptin 100 mg arm; 3.2% (8/250) in the ertugliflozin 5 mg arm; 1.2% (3/248) in the ertugliflozin 15 mg arm; 2.5% (6/243) in the ertugliflozin 5 mg plus sitagliptin 100 mg arm; and 1.6% (4/244) in the ertugliflozin 15 mg plus sitagliptin 100 mg arm. The incidences of SAEs were also similar among treatment arms in Trials P006/1015 (i.e., placebo 3.3% [5/153], ertugliflozin 5 mg 4.5% [7/156], and ertugliflozin 15 mg 2% [3/153]) and P017/1047 (i.e., placebo 5.2% [5/97], ertugliflozin 5 mg plus sitagliptin 100 mg 2% [2/98], and ertugliflozin plus sitagliptin 100 mg 3.1% [3/96].

In the Ertugliflozin/Metformin safety pool, non-fatal SAEs were reported in 3.6% (13/362), 2.8% (10/363), and 2.8% (10/358) of subjects in the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms, respectively.

The incidences of SAEs for both FCDP programs were few, and therefore the ability to assess and evaluate trends was limited.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs during treatment exposure (Phase A plus B treatment periods) that were included reported in the 4-MSU safety population are presented in Table 19. More ertugliflozin-treated subjects discontinued study drug due to AEs associated with SGLT2 inhibitors. There were numerically more subjects in the combined ertugliflozin treatment arms that discontinued due to events related to renal and urinary disorders (i.e., 'glomerular

filtration rate decreased', 'acute kidney injury', 'pollakiuria', 'blood creatinine increased', 'dysuria', 'polyuria', 'haematuria', 'nephropathy', 'peripheral swelling', 'urinary retention', and 'urinary incontinence'). Additionally, discontinuations due to genital mycotic infections ('balanoposthitis', 'vulvovaginal mycotic infection', 'vulvovaginal candidiasis', 'vulvovaginal pruritus', 'genital candidiasis', 'pruritus genital', 'genital infection', 'urogenital infection fungal', 'vaginal infection', and 'vulvovaginitis') were more common in ertugliflozin-treated patients. Review of discontinuations by MedDRA hierarchy (i.e., HLT, HLGT and SOC) revealed similar findings (data not shown). Subjects age 65 and older, and those with impaired renal function were more likely to discontinue IP due to AEs in the ertugliflozin treatment arms. For the ≥65-year-old subset, the MedDRA PTs reported in at least two ertugliflozin-treated subjects, at a higher incidence than the non-ertugliflozin arm, included: 'glomerular filtration rate decreased'; 'vulvovaginal candidiasis'; 'acute myocardial infarction'; 'balanoposthitis'; 'dysuria'; 'genital candidiasis'; and 'rash'. For the subset of subjects with Stage 3a CKD, 'glomerular filtration rate decreased' was reported more frequently in the ertugliflozin-treated subjects (i.e., 1.8% [5/276] vs. 0.8% [1/126] in the non-ertugliflozin arm).

Table 19: Summary of Discontinuations Due to Adverse Events (4-MSU)

Discontinuations Due to AEs MedDRA Preferred Terms — no. (%)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total Subjects D/C — no. (%)	**56 (3.9)**	**76 (4.4)**	**78 (4.6)**	**154 (4.5)**
Age ≥65 years	15/378 (4.0)	27/449 (6.0)	22/427 (5.2)	49/876 (5.6)
eGFR <60 mL/min/1.73 m^2	9/189 (4.8))	19/197 (9.6)	13/190 (6.8)	32/386 (8.3)
45 to <60 mL/min/1.73 m^2	6/126 (4.8)	10/141 (7.1)	9/135 (6.7)	19/276 (6.9)
Hyperglycaemia	6 (0.4)	6 (0.3)	8 (0.5)	14 (0.4)
Glomerular filtration rate decreased	2 (0.1)	2 (0.1)	7 (0.4)	9 (0.3)
Balanoposthitis	0	5 (0.3)	1 (0.1)	6 (0.2)
Urinary tract infection	2 (0.1)	2 (0.1)	3 (0.2)	5 (0.1)
Vulvovaginal mycotic infection	0	3 (0.2)	2 (0.1)	5 (0.1)
Acute kidney injury	0	2 (0.1)	2 (0.1)	4 (0.1)
Pollakiuria	0	1 (0.1)	3 (0.2)	4 (0.1)
Vulvovaginal candidiasis	0	1 (0.1)	3 (0.2)	4 (0.1)
Vulvovaginal pruritus	0	2 (0.1)	2 (0.1)	4 (0.1)
Diarrhoea	4 (0.3)	2 (0.1)	1 (0.1)	3 (0.1)
Dizziness	0	3 (0.2)	0	3 (0.1)
Nausea	0	1 (0.1)	2 (0.1)	3 (0.1)
Weight decreased	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Abdominal pain upper	1 (0.1)	2 (0.1)	0	2 (0.1)
Acute myocardial infarction	0	1 (0.1)	1 (0.1)	2 (0.1)
Blood creatinine increased	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)

Discontinuations Due to AEs MedDRA Preferred Terms — no. (%)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Dysuria	0	1 (0.1)	1 (0.1)	2 (0.1)
Genital candidiasis	0	1 (0.1)	1 (0.1)	2 (0.1)
Glycosylated haemoglobin increased	1 (0.1)	0	2 (0.1)	2 (0.1)
Hypoglycaemia	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Insomnia	0	1 (0.1)	1 (0.1)	2 (0.1)
Non-cardiac chest pain	0	1 (0.1)	1 (0.1)	2 (0.1)
Polyuria	0	1 (0.1)	1 (0.1)	2 (0.1)
Pruritus genital	0	1 (0.1)	1 (0.1)	2 (0.1)
Rash	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Renal impairment	2 (0.1)	0	2 (0.1)	2 (0.1)
Rheumatoid arthritis	0	2 (0.1)	0	2 (0.1)
Urinary incontinence	0	0	2 (0.1)	2 (0.1)
Abdominal pain	1 (0.1)	0	1 (0.1)	1 (<0.1)
Adenocarcinoma gastric	0	1 (0.1)	0	1 (<0.1)
Alanine aminotransferase increased	0	1 (0.1)	0	1 (<0.1)
Alopecia	0	0	1 (0.1)	1 (<0.1)
Arthralgia	2 (0.1)	0	1 (0.1)	1 (<0.1)
Aspartate aminotransferase increased	0	1 (0.1)	0	1 (<0.1)
Asthenia	1 (0.1)	1 (0.1)	0	1 (<0.1)
Asthma	0	0	1 (0.1)	1 (<0.1)
Benign ovarian tumour	0	0	1 (0.1)	1 (<0.1)
Blood glucose increased	3 (0.2)	1 (0.1)	0	1 (<0.1)
Breast cancer	0	1 (0.1)	0	1 (<0.1)
Cellulitis	0	0	1 (0.1)	1 (<0.1)
Cerebral infarction	0	1 (0.1)	0	1 (<0.1)
Cerebrovascular accident	1 (0.1)	1 (0.1)	0	1 (<0.1)
Cholelithiasis	0	0	1 (0.1)	1 (<0.1)
Colon cancer	0	0	1 (0.1)	1 (<0.1)
Coronary artery disease	0	1 (0.1)	0	1 (<0.1)
Dermatitis allergic	0	0	1 (0.1)	1 (<0.1)
Diabetic foot	0	1 (0.1)	0	1 (<0.1)
Diabetic ketoacidosis	0	0	1 (0.1)	1 (<0.1)
Diabetic neuropathy	0	1 (0.1)	0	1 (<0.1)
Dry mouth	0	0	1 (0.1)	1 (<0.1)
Dyslipidaemia	0	1 (0.1)	0	1 (<0.1)
Dysphonia	0	0	1 (0.1)	1 (<0.1)
Endometrial adenocarcinoma	0	0	1 (0.1)	1 (<0.1)

Discontinuations Due to AEs MedDRA Preferred Terms — no. (%)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Face injury	0	1 (0.1)	0	1 (<0.1)
Facial paralysis	0	1 (0.1)	0	1 (<0.1)
Fatigue	0	0	1 (0.1)	1 (<0.1)
Fungal skin infection	1 (0.1)	1 (0.1)	0	1 (<0.1)
Genital infection	0	1 (0.1)	0	1 (<0.1)
Haematuria	0	0	1 (0.1)	1 (<0.1)
Head discomfort	0	1 (0.1)	0	1 (<0.1)
Headache	0	0	1 (0.1)	1 (<0.1)
Hepatocellular injury	0	1 (0.1)	0	1 (<0.1)
Humerus fracture	0	1 (0.1)	0	1 (<0.1)
Hunger	0	1 (0.1)	0	1 (<0.1)
Hyperchlorhydria	0	1 (0.1)	0	1 (<0.1)
Jaundice cholestatic	0	0	1 (0.1)	1 (<0.1)
Liver disorder	0	0	1 (0.1)	1 (<0.1)
Malaise	0	0	1 (0.1)	1 (<0.1)
Metabolic acidosis	0	0	1 (0.1)	1 (<0.1)
Mood swings	0	0	1 (0.1)	1 (<0.1)
Musculoskeletal pain	1 (0.1)	1 (0.1)	0	1 (<0.1)
Myocardial infarction	0	1 (0.1)	0	1 (<0.1)
Nephropathy	0	1 (0.1)	0	1 (<0.1)
Nightmare	0	0	1 (0.1)	1 (<0.1)
Nodal marginal zone B-cell lymphoma stage III	0	1 (0.1)	0	1 (<0.1)
Obesity	0	1 (0.1)	0	1 (<0.1)
Oral candidiasis	0	1 (0.1)	0	1 (<0.1)
Osteomyelitis acute	0	1 (0.1)	0	1 (<0.1)
Pain in extremity	1 (0.1)	1 (0.1)	0	1 (<0.1)
Pancreatic neoplasm	0	0	1 (0.1)	1 (<0.1)
Pancreatitis acute	0	1 (0.1)	0	1 (<0.1)
Penile pain	0	0	1 (0.1)	1 (<0.1)
Peripheral ischaemia	0	0	1 (0.1)	1 (<0.1)
Peripheral swelling	0	0	1 (0.1)	1 (<0.1)
Plasma cell myeloma	0	0	1 (0.1)	1 (<0.1)
Prurigo	0	0	1 (0.1)	1 (<0.1)
Pyelonephritis	0	1 (0.1)	0	1 (<0.1)
Pyelonephritis acute	0	1 (0.1)	0	1 (<0.1)
Rash maculo-papular	0	0	1 (0.1)	1 (<0.1)

Discontinuations Due to AEs MedDRA Preferred Terms — no. (%)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Septic shock	0	0	1 (0.1)	1 (<0.1)
Thirst	0	1 (0.1)	0	1 (<0.1)
Urinary retention	0	1 (0.1)	0	1 (<0.1)
Urogenital infection fungal	0	1 (0.1)	0	1 (<0.1)
Vaginal infection	0	1 (0.1)	0	1 (<0.1)
Vision blurred	0	0	1 (0.1)	1 (<0.1)
Vulvovaginitis	0	0	1 (0.1)	1 (<0.1)
Abdominal discomfort	1 (0.1)	0	0	0
Abdominal distension	1 (0.1)	0	0	0
Abdominal pain lower	1 (0.1)	0	0	0
Back pain	1 (0.1)	0	0	0
Bone tuberculosis	1 (0.1)	0	0	0
Chronic kidney disease	1 (0.1)	0	0	0
Creatinine renal clearance decreased	1 (0.1)	0	0	0
Drug-induced liver injury	1 (0.1)	0	0	0
Ear pain	1 (0.1)	0	0	0
Enterocolitis	1 (0.1)	0	0	0
Epigastric discomfort	1 (0.1)	0	0	0
Hepatitis C virus test positive	1 (0.1)	0	0	0
Hyperlipidaemia	1 (0.1)	0	0	0
Hypotension	1 (0.1)	0	0	0
Ischaemic stroke	2 (0.1)	0	0	0
Lethargy	1 (0.1)	0	0	0
Metatarsalgia	1 (0.1)	0	0	0
Nephrolithiasis	1 (0.1)	0	0	0
Pancreatitis	1 (0.1)	0	0	0
Prostatitis	1 (0.1)	0	0	0
Pruritus	1 (0.1)	0	0	0
Pruritus generalised	1 (0.1)	0	0	0
Skin discolouration	1 (0.1)	0	0	0
Subcutaneous abscess	1 (0.1)	0	0	0

Source: Derived from the iss-broad and sur-iss adsl.xpt, aerpt.xpt and aeplus.xpt datasets, available at:
Application 209803 - Sequence 0014 - 5.3.5.3 [[Study ID]] - [[Study Title]] - sur - Integrated Summary of Safety - SUR
Abbreviations: 4-MSU, Four-Month Safety Update; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and SAE, serious adverse event.

For the trials used to support the ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs, discontinuations due to AEs were limited and not informative (data not shown).

8.4.4. Significant Adverse Events

Adverse events meeting the International Council for Harmonization (ICH) E3 definition of other significant adverse events[97] are primarily discussed in Section 8.5 (Analysis of Submission-Specific Safety Issues). Categorization of AEs, definitions, and search strategies used by the Applicant were described previously in Section 8.3.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of common TEAEs in the Placebo Pool that were reported in ≥2% of ertugliflozin-treated subjects and occurred at a higher incidence in either dose group (5 mg or 15 mg) compared to the non-ertugliflozin arm is presented in Table 20. The listed AEs include events based on custom MedDRA queries (i.e., consisting of multiple PTs) as well as the most common individual PTs. As with other SGLT2 inhibitors, female and male genital mycotic infections, urinary tract infections, and osmotic diuresis were the most common TEAEs, with observed incidences similar to those of currently approved SGLT2 inhibitors.[24-26]

Table 20: Summary of Applicant's Common TEAEs (Placebo Pool)

MedDRA Preferred Terms	Number (%) of Patients		
	Placebo n = 515	Ertugliflozin 5 mg n = 519	Ertugliflozin 15 mg n = 510
Genital mycotic infections	8 (1.6)	33 (6.4)	41 (8.0)
Female genital mycotic infections[†]	7/235 (3.0)	23/252 (9.1)	30/245 (12.2)
Male genital mycotic infections[‡]	1/280 (0.4)	10/267 (3.7)	11/265 (4.2)
Urinary tract infections[§]	20 (3.9)	21 (4.0)	21 (4.1)
Headache	12 (2.3)	18 (3.5)	15 (2.9)
Increased urination[¶]	5 (1.0)	14 (2.7)	12 (2.4)
Nasopharyngitis	12 (2.3)	13 (2.5)	10 (2.0)
Back pain	12 (2.3)	9 (1.7)	13 (2.5)
Weight decreased	5 (1.0)	6 (1.2)	12 (2.4)

Source: Adapted from the Applicant's proposed product labeling, labeled as Table 1, page 7 of 41, available at: \\cdsesub1\evsprod\nda209803\0000\m1\us\01-annotated-uspi-mk8835-t-original.pdf; and derived from the ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy –
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; and TEAEs, treatment-emergent adverse events.
[†] Includes: 'genital candidiasis', 'genital infection fungal', 'vaginal infection', 'vulvitis', 'vulvovaginal candidiasis', 'vulvovaginal mycotic infection', and 'vulvovaginitis'. Percentages calculated with the number of female patients in each group as

denominator: placebo (n=235), ertugliflozin 5 mg (n=252), ertugliflozin 15 mg (n=245).

‡ Includes: 'balanitis candida', 'balanoposthitis', 'genital infection', and 'genital infection fungal'. Percentages calculated with the number of male patients in each group as denominator: placebo (n=280), ertugliflozin 5 mg (n=267), ertugliflozin 15 mg (n=265).

§ Includes: 'cystitis', 'dysuria', 'streptococcal urinary tract infection', 'urethritis', 'urinary tract infection'.

¶ Includes: 'pollakiuria', 'micturition urgency', 'polyuria', 'urine output increased', and 'nocturia'.

For completeness, broad CMQs (that included additional AEs in addition to the Applicant's CMQs) were used to search for additional events and clinical symptoms often associated with the Applicant's 'Special Safety Topics' (please refer to Appendix 13.4 and Table 21). Generally, the findings were similar to those of the Applicant. However, besides the events of genital mycotic infections identified by the Applicant, it is noted that symptoms commonly associated with genital infections (i.e., vulvovaginal pruritus, pruritus genital, and vulvovaginal burning sensation) were reported in 3% (14/497) of ertugliflozin-treated females compared to a single subject (0.4% [1/235]) in the placebo arm. Although not included as female genital mycotic infections, the Applicant mentions events of vulvovaginal pruritus in proposed labeling. Additionally, the MedDRA PTs of 'vulval abscess' (considered a complicated genital infection) and 'Bartholinitis' were not included in the Applicant's primary Genital Mycotic Infection CMQ. These disorders may have multiple underlying infectious etiologies, including but not limited to mycotic infections.

Symptoms (i.e., 'thirst', 'dry mouth', 'polydipsia', and 'dry throat') associated with osmotic diuresis ('increased urination') also were reported more commonly in the ertugliflozin treatment arms (2% [21/1029] vs. 0.8% [4/515]). Although 'thirst' is reported in labeling, it was not included in the table of common TEAEs. These AESI will be discussed further in Section 8.5 (Analysis of Submission-Specific Safety Issues) below.

Generally, the types and frequency of events observed in the short-term Placebo Pool would be anticipated for an SGLT2 inhibitor, and review of these data did not reveal any unexpected safety concerns.

Table 21: Summary of Common TEAEs (Placebo Pool)

MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	All Ertugliflozin (n=1029)
Total TEAEs — no. (%)	**263 (51.1)**	**236 (45.5)**	**257 (50.4)**	**493 (47.9)**
Female genital mycotic infections¶	**10/235 (4.3)**	**29/252 (11.5)**	**36/245 (14.7)**	**65/497 (13.1)**
Vulvovaginal mycotic infection	3 (1.3)	14 (5.6)	14 (5.7)	28 (5.6)
Vulvovaginal candidiasis	3 (1.3)	5 (2.0)	7 (2.9)	12 (2.4)
Vulvovaginal pruritus*	1 (0.4)	5 (2.0)	6 (2.4)	11 (2.2)
Vaginal infection	1 (0.4)	2 (0.8)	6 (2.4)	8 (1.6)
Genital infection fungal	0	1 (0.4)	2 (0.8)	3 (0.6)
Vulvovaginitis	0	1 (0.4)	1 (0.4)	2 (0.4)
Pruritus genital*	0	2 (0.8)	0	2 (0.4)

MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	All Ertugliflozin (n=1029)
Vulval abscess*	1 (0.4)	1 (0.4)	0	1 (0.2)
Vulvitis	0	0	1 (0.4)	1 (0.2)
Vulvovaginal burning sensation*	0	1 (0.4)	0	1 (0.2)
Genital candidiasis	0	1 (0.4)	0	1 (0.2)
Bartholinitis*	1 (0.4)	0	0	0
Male genital mycotic infections[¶]	**2/280 (0.7)**	**10/267 (3.7)**	**13/265 (4.9)**	**23/532 (4.3)**
Balanoposthitis	1 (0.4)	6 (2.2)	6 (2.3)	12 (2.3)
Genital infection fungal	0	3 (1.1)	2 (0.8)	5 (0.9)
Balanitis candida	0	1 (0.4)	2 (0.8)	3 (0.6)
Genital infection	0	0	1 (0.4)	1 (0.2)
Genital rash*	0	0	1 (0.4)	1 (0.2)
Phimosis*	1 (0.4)	1 (0.4)	0	1 (0.2)
Cellulitis of male external genital organ	0	0	1 (0.4)	1 (0.2)
Urinary tract infections[¶]	**20 (3.9)**	**22 (4.2)**	**22 (4.3)**	**44 (4.3)**
Urinary tract infection	17 (3.3)	14 (2.7)	12 (2.4)	26 (2.5)
Cystitis	1 (0.2)	3 (0.6)	6 (1.2)	9 (0.9)
Dysuria	1 (0.2)	3 (0.6)	4 (0.8)	7 (0.7)
Prostatitis*	0	1 (0.2)	1 (0.2)	2 (0.2)
Streptococcal urinary tract infection	0	1 (0.2)	0	1 (0.1)
Asymptomatic bacteriuria*	0	1 (0.2)	0	1 (0.1)
Urethritis	1 (0.2)	0	0	0
Increased urination[¶]	**8 (1.6)**	**23 (4.4)**	**17 (3.3)**	**40 (3.9)**
Pollakiuria	2 (0.4)	8 (1.5)	6 (1.2)	14 (1.4)
Thirst*	1 (0.2)	4 (0.8)	5 (1.0)	9 (0.9)
Dry mouth*	2 (0.4)	8 (1.5)	1 (0.2)	9 (0.9)
Polyuria	0 (0.0)	2 (0.4)	6 (1.2)	8 (0.8)
Polydipsia*	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
Micturition urgency	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)
Dry throat*	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)
Urine output increased	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.1)
Nocturia	3 (0.6)	1 (0.2)	0 (0.0)	1 (0.1)
Headache	12 (2.3)	18 (3.5)	15 (2.9)	33 (3.2)
Nasopharyngitis	12 (2.3)	13 (2.5)	10 (2.0)	23 (2.2)
Back pain	12 (2.3)	9 (1.7)	13 (2.5)	22 (2.1)
Weight decreased	5 (1.0)	6 (1.2)	12 (2.4)	18 (1.7)

Source: Derived from the ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at:
Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Abbreviations: CMQ, Custom MedDRA Query; no., number; and TEAE, treatment-emergent adverse event.

* MedDRA PTs not listed in the common adverse reactions table of the proposed product labeling. Please refer to the Applicant's Proposed USPI, labeled as Table 1, page 7 of 41, available at: \\cdsesub1\evsprod\nda209803\0000\m1\us\01-annotated-uspi-mk8835-t-original.pdf

¶ Preferred terms included in this list were derived from existing broad MedDRA SMQs plus CMQs derived from other SGLT2 inhibitor, DPP-4 inhibitor CMQs (please refer to Appendix 13.4).

The Applicant performed an analysis of AEs by SOC (that included at least four subjects in one or more treatment arms). The results of these analyses indicated that AEs coded to the 'Renal and urinary disorders' and the 'Reproductive system and breast disorders' SOCs occurred in significantly more ertugliflozin-treated subjects (i.e., in the 15 mg and 5 mg treatment arms, respectively; Table 22). Review of the associated MedDRA PTs suggests that events in the 'Renal and urinary disorders' SOC were more commonly associated with symptoms of diuresis, while those of the 'Reproductive system and breast disorders' SOC were more commonly associated with genital mycotic infections.

Table 22: Analysis of SOCs with a Higher Incidence in the Ertugliflozin Treatment Arms (Placebo Pool)

System Organ Class MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)
Renal and urinary disorders — no. (%)	**11 (2.1)**	**22 (4.2)**	**25 (4.9)**
% Difference vs. Placebo — estimate (95% CI)*	**—**	**2.1 (-0.1, 4.4)**	**2.8 (0.5, 5.2)**
Polyuria	0	3 (0.6)	6 (1.2)
Pollakiuria	2 (0.4)	8 (1.5)	6 (1.2)
Haematuria	1 (0.2)	0	4 (0.8)
Dysuria	1 (0.2)	3 (0.6)	4 (0.8)
Renal failure	0	1 (0.2)	1 (0.2)
Urinary incontinence	0	1 (0.2)	1 (0.2)
Diabetic nephropathy	0	0	1 (0.2)
Chromaturia	0	1 (0.2)	1 (0.2)
Micturition urgency	0	1 (0.2)	1 (0.2)
Hypertonic bladder	0	0	1 (0.2)
Proteinuria	0	1 (0.2)	0
Urge incontinence	0	1 (0.2)	0
Pyelocaliectasis	1 (0.2)	0	0
Stress urinary incontinence	1 (0.2)	0	0
Renal impairment	2 (0.4)	1 (0.2)	0
Nocturia	3 (0.6)	2 (0.4)	0
Reproductive system & breast disorders — no. (%)	**7 (1.4)**	**20 (3.9)**	**16 (3.1)**
% Difference vs. Placebo — estimate (95% CI)*	**—**	**2.5 (0.6, 4.7)**	**1.8 (-0.0, 3.8)**
Vulvovaginal pruritus	1 (0.2)	5 (1.0)	6 (1.2)
Balanoposthitis	1 (0.2)	6 (1.2)	6 (1.2)

System Organ Class MedDRA Preferred Terms	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)
Genital rash	0	0	1 (0.2)
Genital paraesthesia	0	0	1 (0.2)
Prostatitis	0	1 (0.2)	1 (0.2)
Pelvic haemorrhage	0	0	1 (0.2)
Pelvic pain	0	0	1 (0.2)
Cervical dysplasia	0	1 (0.2)	1 (0.2)
Polymenorrhoea	0	0	1 (0.2)
Penis disorder	0	2 (0.4)	0
Prepuce redundant	0	1 (0.2)	0
Vulvovaginal burning sensation	0	1 (0.2)	0
Pruritus genital	0	2 (0.4)	0
Retrograde ejaculation	0	1 (0.2)	0
Semen discolouration	0	1 (0.2)	0
Vulva cyst	0	1 (0.2)	0
Erectile dysfunction	0	1 (0.2)	0
Perineal pain	1 (0.2)	0	0
Menstruation delayed	1 (0.2)	0	0
Benign prostatic hyperplasia	1 (0.2)	0	0
Postmenopausal haemorrhage	1 (0.2)	0	0
Scrotal pain	1 (0.2)	0	0

Source: Adapted from the Applicant's Integrated Summary of Safety, labeled as Table 68, page 184/9829, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\iss.pdf
Derived from the ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Abbreviations: CI, confidence interval; and no., number.
* Analyses were conducted by the Applicant using the Miettinen & Nurminen method stratified by study.[98]

The common TEAEs (as defined above for the Placebo Pool) reported in the 4-MSU are presented in Table 23 (sorted by the combined ertugliflozin treatment arms). Broad CMQs were again used to search these safety data for genital mycotic infections and osmotic diuresis. Similar to the Placebo Pool, TEAEs associated with female and male genital mycotic infections and osmotic diuresis were the most common TEAEs reported in the ertugliflozin arms. However, the proportions of subjects with TEAEs coded as urinary tract infections was higher in the non-ertugliflozin treatment arms (i.e., 8.3% [120/1450] vs. 7.3% [125/1716] in the ertugliflozin 5 mg arm and 7.7% [130/1693] in the ertugliflozin 15 mg arm).

Table 23: Summary of Common TEAEs (4-MSU)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total TEAEs — no. (%)	**961 (66.3)**	**1107 (64.5)**	**1071 (63.3)**	**2178 (63.9)**
Female genital mycotic infections¶	**30/663 (4.5)**	**96/831 (11.6)**	**127/849 (15.0)**	**223/1680 (13.3)**
Vulvovaginal mycotic infection	4 (0.6)	36 (4.3)	34 (4.0)	70 (4.2)
Vulvovaginal candidiasis	11 (1.7)	14 (1.7)	25 (2.9)	39 (2.3)
Vulvovaginal pruritus*	4 (0.6)	11 (1.3)	20 (2.4)	31 (1.8)
Vaginal infection	3 (0.5)	10 (1.2)	16 (1.9)	26 (1.5)
Pruritus genital*	2 (0.3)	8 (1.0)	9 (1.1)	17 (1.0)
Genital infection fungal	3 (0.5)	5 (0.6)	8 (0.9)	13 (0.8)
Vulvovaginitis	0	8 (1.0)	4 (0.5)	12 (0.7)
Genital candidiasis	0	4 (0.5)	2 (0.2)	6 (0.4)
Vaginal discharge*	0	3 (0.4)	2 (0.2)	5 (0.3)
Vulvitis	0	0	4 (0.5)	4 (0.2)
Urogenital infection fungal*	1 (0.2)	2 (0.2)	2 (0.2)	4 (0.2)
Vaginal haemorrhage	1 (0.2)	1 (0.1)	2 (0.2)	3 (0.2)
Vulval abscess	1 (0.2)	1 (0.1)	0	1 (<0.1)
Vulvovaginal dryness*	0	0	1 (0.1)	1 (<0.1)
Pelvic inflammatory disease*	0	0	1 (0.1)	1 (<0.1)
Genital infection	0	1 (0.1)	0	1 (<0.1)
Vulvovaginal swelling*	0	1 (0.1)	0	1 (<0.1)
Vaginal inflammation	0	1 (0.1)	0	1 (<0.1)
Vulvovaginal burning sensation*	1 (0.2)	1 (0.1)	0	1 (<0.1)
Endometriosis*	1 (0.2)	0	0	0
Bartholinitis*	1 (0.2)	0	0	0
Male genital mycotic infections¶	**7/787 (0.9)**	**48/885 (5.4)**	**48/844 (5.7)**	**96/1729 (5.6)**
Balanoposthitis	1 (0.1)	28 (3.2)	18 (2.1)	46 (2.7)
Genital infection fungal	2 (0.3)	9 (1.0)	10 (1.2)	19 (1.1)
Balanitis candida	0 (0.0)	5 (0.6)	4 (0.5)	9 (0.5)
Phimosis	1 (0.1)	2 (0.2)	6 (0.7)	8 (0.5)
Prostatitis*	2 (0.3)	4 (0.5)	4 (0.5)	8 (0.5)
Pruritus genital*	0 (0.0)	0 (0.0)	4 (0.5)	4 (0.2)
Genital candidiasis	0 (0.0)	2 (0.2)	2 (0.2)	4 (0.2)
Genital infection	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.2)
Cellulitis of male external genital organ	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Genital rash*	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Epididymitis*	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)

MedDRA Preferred Terms	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Prostate infection*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Increased urination¶	**24 (1.7)**	**65 (3.8)**	**61 (3.6)**	**126 (3.7)**
Pollakiuria	10 (0.7)	24 (1.4)	21 (1.2)	45 (1.3)
Dry mouth*	6 (0.4)	17 (1.0)	15 (0.9)	32 (0.9)
Thirst*	1 (0.1)	9 (0.5)	13 (0.8)	22 (0.6)
Polyuria	1 (0.1)	10 (0.6)	11 (0.6)	21 (0.6)
Nocturia	6 (0.4)	10 (0.6)	5 (0.3)	15 (0.4)
Polydipsia	0	2 (0.1)	4 (0.2)	6 (0.2)
Micturition urgency	2 (0.1)	1 (<0.1)	3 (0.2)	4 (0.1)
Urine output increased	2 (0.1)	2 (0.1)	0	2 (0.1)
Dry throat*	1 (0.1)	0	1 (0.1)	1 (<0.1)
Cough	28 (1.9)	41 (2.4)	34 (2.0)	75 (2.2)
Constipation	26 (1.8)	40 (2.3)	33 (1.9)	73 (2.1)
Dizziness	28 (1.9)	36 (2.1)	30 (1.8)	66 (1.9)
Weight decreased	11 (0.8)	23 (1.3)	42 (2.5)	65 (1.9)
Pain in extremity	26 (1.8)	34 (2.0)	27 (1.6)	61 (1.8)

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at:
Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: 4-MSU, Four-Month Safety Update; no., number; and TEAE, treatment-emergent adverse event.
* MedDRA PTs not included in the Applicant's Special Safety Topics Tables for 'genital mycotic infections' (Table 2.7.4: 60-61, pages 407-408 of 486) and 'osmotic diuresis' ('increased urination'; Table 2.7.4:56, page 401 of 486) included in the 4-MSU available at:
\\cdsesub1\evsprod\nda209803\0014\m2\27-clin-sum\summary-clin-safety.pdf
¶ Preferred terms included in this list were derived from existing broad MedDRA SMQs plus CMQs derived from other SGLT-1 inhibitor, DPP-4 inhibitor CMQs (please refer to Appendix 13.4).

Overall, the additional safety data submitted in the 4-MSU did not reveal additional safety concerns besides those already identified in the Broad Pool.

TEAEs: Ertugliflozin/Sitagliptin and Ertugliflozin/Metformin FCDPs

Two of the three trials included in the Placebo Pool also were used to evaluate the safety of the ertugliflozin/sitagliptin (i.e., P006/1015) and ertugliflozin/metformin (i.e., P006/1015 and P007/1017) FCDPs. The incidences and types of events observed in these trials were similar to what was observed in the Placebo Pool (data not shown).

8.4.6. Laboratory Findings

This section will primarily focus on prespecified marked laboratory abnormalities, referred to as predefined limits of change (PDLC) by the Applicant, and the observed changes from baseline in

relevant laboratory tests. Since the 4-MSU did not include additional laboratory data (as agreed at the time of the preNDA Meeting), only the data from the Placebo and Broad Pools are presented. The Placebo Pool is the primary safety population of interest for assessing clinical laboratory changes from baseline, while the Broad Pool is useful for evaluating long-term changes.

Predefined Limits of Change

A summary of the PDLC reported in the Placebo and Broad Pools is presented in Table 24. The Applicant used the Miettinen and Nurminen method to provide 95% confidence intervals (CI) for between-treatment differences in the proportions of subjects with these events.[98] These analyses were stratified by study and computed when at least four subjects had an event in at least one treatment arm. The point estimates (95% CIs) are presented only for the PDLC results that showed statistically significant differences between ertugliflozin and comparator arms.

For the Placebo Pool, the Applicant reported nominally statistically significant percent differences (95% CI) from placebo for the following PDLC: hemoglobin decreases (reported as negative percentage) and increases; blood urea nitrogen increases; and phosphate decreases (reported as negative percentages) and increases. Similar trends were observed in the Broad Pool, which also included higher proportions of ertugliflozin-treated subjects with increases in serum uric acid and parathyroid hormone (PTH) concentrations.

The clinical relevance of these laboratory abnormalities is unknown, and is discussed further below when appropriate.

Table 24: Summary of Predefined Laboratory Limits of Change (Placebo and Broad Pools)

Laboratory Parameter	Placebo Pool			Broad Pool		
Predefined Limits of Change	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
Hematology						
COMPLETE BLOOD COUNT						
Hgb ↓ ≥1.5 gm/dL	27/481 (5.6)	13/493 (2.6)	7/483 (1.4)	130/1357 (9.6)	68/1620 (4.2)¶	47/1590 (3.0)¶
% Difference vs. Placebo (95% CI)	—	*-3.0% (- 5.7, -0.5)¶*	*-4.2% (-6.7, -1.9)¶*	—	*-5.5% (-7.5, -3.7)¶*	*-6.5% (-8.4, -4.8)¶*
Hgb ↑ >2.0 gm/dL	3/481 (0.6)	23/493 (4.7)	20/483 (4.1)	20/1357 (1.5)	109/1620 (6.7)¶	110/1590 (6.9)¶
% Difference vs. Placebo (95% CI)	—	*4.0% (2.2, 6.4)¶*	*3.5% (1.7, 5.8)¶*	—	*0.8% (0.3, 1.3)¶*	*1.3% (0.7, 2.0)¶*
Hgb ↑ >2.0 gm/dl and value > ULN	0/481	2/493 (0.4)	6/483 (1.2)	1/1357 (<0.1)	13/1620 (0.8)¶	21/1590 (1.3)¶
% Difference vs. Placebo (95% CI)	—	—	*1.2% (0.3, 2.7)¶*	—	*5.5% (4.1, 7.0)¶*	*5.6% (4.2, 7.2)¶*
Leukocytes ($10^3/\mu L$) ↓ ≥50% and value <LLN	0/481	0/493	0/483	4/1357 (0.3)	0/1620	2/1588 (0.1)
Leukocytes ($10^3/\mu L$) ↑ ≥20% and value >ULN	9/481 (1.9)	8/493 (1.6)	7/481 (1.5)	39/1357 (2.9)	42/1620 (2.6)	53/1588 (3.3)
Neutrophils ($10^3/\mu L$) ↓ ≥20% and value <LLN	12/481 (2.5)	9/492 (1.8)	9/477 (1.9)	30/1352 (2.2)	36/1609 (2.2)	23/1572 (1.5)

Laboratory Parameter	Placebo Pool			Broad Pool		
Predefined Limits of Change	**Placebo (n=515)**	**Ertugliflozin 5 mg (n=519)**	**Ertugliflozin 15 mg (n=510)**	**Non-Ertugliflozin (n=1450)**	**Ertugliflozin 5 mg (n=1716)**	**Ertugliflozin 15 mg (n=1693)**
Neutrophils (10^3/µL) ↑ ≥20% and value >ULN	13/481 (2.7)	13/492 (2.6)	12/477 (2.5)	57/1352 (4.2)	74/1609 (4.6)	77/1572 (4.9)
Lymph (10^3/µL) ↓ ≥20% and value <LLN	3/481 (0.6)	8/492 (1.6)	4/477 (0.8)	26/1352 (1.9)	38/1609 (2.4)	28/1572 (1.8)
Lymph (10^3/µL) ↑ ≥20% and value >ULN	20/481 (4.2)	28/492 (5.7)	14/477 (2.9)	75/1352 (5.5)	90/1609 (5.6)	76/1572 (4.8)
PLT (10^3/µL) ↓ ≥25% and value <LLN	0/474	3/487 (0.6)	2/478 (0.4)	9/1344 (0.7)	16/1600 (1.0)	13/1574 (0.8)
PLT (10^3/µL) ↑ ≥100% and value >ULN	0/474	0/487	0/478	1/1344 (<0.1)	0/1600	1/1574 (<0.1)
Clinical Chemistry						
ELECTROLYTE PANEL						
CO_2 (bicarbonate) <15 mEq/L	0/498	0/504	1/497 (0.2)	2/1411 (0.1)	6/1675 (0.4)	5/1645 (0.3)
Na ↓ ≥10 mEq/L and value <LLN	0/491	0/496	0/490	2/1384 (0.1)	5/1641 (0.3)	6/1620 (0.4)
Na ↑ ≥10 mEq/L and value >ULN	3/491 (0.6)	1/496 (0.2)	0/490	9/1384 (0.7)	12/1641 (0.7)	5/1620 (0.3)
Na >155 mEq/L	0/498	0/505	0/497	2/1411 (0.1)	2/1676 (0.1)	1/1645 (<0.1)
K ↓ ≥1.0 mEq/L and value <LLN	0/487	0/494	0/488	1/1380 (<0.1)	4/1636 (0.2)	0/1612
K ↑ ≥1.0 mEq/L and value >ULN	25/487 (5.1)	21/494 (4.3)	23/488 (4.7)	111/1380 (8.0)	139/1636 (8.5)	147/1612 (9.1)
K >5.4 mEq/L and value ↑ by 15% above Baseline	24/487 (4.9)	20/494 (4.0)	26/488 (5.3)	98/1380 (7.1)	126/1636 (7.7)	143/1612 (8.9)
K ≥6.0 mEq/L	10/498 (2.0)	6/505 (1.2)	7/497 (1.4)	55/1411 (3.9)	61/1676 (3.6)	52/1644 (3.2)
UA (mg/dL) ↑ ≥50% and value >ULN	12/491 (2.4)	6/495 (1.2)	8/488 (1.6)	63/1383 (4.6)	37/1639 (2.3)¶	41/1618 (2.5)¶
% Difference vs. Placebo (95% CI)	—	—	—	—	*-2.2% (-3.6, -0.9)*¶	*-2.0% (-3.4, -0.6)*¶
RENAL PANEL						
BUN (mg/dL) ↑ ≥50% and value >ULN	25/491 (5.1)	39/496 (7.9)	48/489 (9.8)	135/1383 (9.8)	225/1639 (13.7)¶	253/1620 (15.6)¶
% Difference vs. Placebo (95% CI)	—	—	*4.7% (1.5, 8.2)*¶	—	*4.2% (2.0, 6.5)*¶	*6.2% (3.9, 8.6)*¶
eGFR (mL/min/1.73 m^2) ↓ >30%	14/498 (2.8)	13/504 (2.6)	14/497 (2.8)	73/1411 (5.2)	95/1674 (5.7)	101/1645 (6.1)
eGFR (mL/min/1.73m^2) ↓ >50%	1/498 (0.2)	0/504 (0.0)	1/497 (0.2)	8/1411 (0.6)	2/1674 (0.1)	9/1645 (0.5)
Mineral Panel/PTH						
Ca ↓ ≥1.0 mg/dL and value <LLN	8/491 (1.6)	10/495 (2.0)	4/489 (0.8)	25/1382 (1.8)	37/1636 (2.3)	28/1615 (1.7)
Ca ↑ ≥1.0 mg/dL and value >ULN	11/491 (2.2)	14/495 (2.8)	15/489 (3.1)	54/1382 (3.9)	78/1636 (4.8)	72/1615 (4.5)
Mg ↓ ≥1.0 mEq/dL and value <LLN	0/491	0/496	0/489	0/1383	0/1639	0/1616
Mg ↑ ≥1.0 mEq/L and value >ULN	0/491	0/496	1/489 (0.2)	1/1383 (<0.1)	1/1639 (<0.1)	3/1616 (0.2)
Phos ↓ ≥0.5 mg/dL and value <LLN	26/491 (5.3)	5/495 (1.0)	2/488 (0.4)	92/1382 (6.7)	47/1638 (2.9)¶	40/1619 (2.5)¶
% Difference vs. Placebo (95% CI)	—	*-4.3% (-6.7, -2.2)*¶	*-4.9% (-7.3, -3.0)*¶	—	*-3.5% (-5.1, -1.9)*¶	*-4.0% (-5.6, -2.5)*¶
Phos ↑ ≥0.5 mg/dL and value >ULN	36/491 (7.3)	70/495 (14.1)¶	73/488 (15.0)¶	165/1382 (11.9)	303/1638 (18.5)¶	371/1619 (22.9)¶
% Difference vs. Placebo (95% CI)	—	*6.8% (3.0, 10.8)*¶	*7.6% (3.7, 11.6)*¶	—	*6.6% (4.0, 9.2)*¶	*10.8% (8.1, 13.5)*¶
PTH (pg/mL) ↑ ≥20% and value >ULN	NR	NR	NR	29/323 (9.0)	35/320 (10.9)	27/318 (8.5)
PTH (pg/mL) ↑ ≥30%	NR	NR	NR	97/323 (30.0)	122/320 (38.1)¶	107/318 (33.6)
% Difference vs. Placebo (95% CI)	NR	NR	NR	—	*8.2% (0.9, 15.4)*¶	—
Hepatic Panel						
ALP (IU/L >1.5 x ULN	4/498 (0.8)	1/504 (0.2)	5/497 (1.0)	16/1411 (1.1)	18/1675 (1.1)	25/1645 (1.5)
ALT (IU/L) >3 x ULN	5/498 (1.0)	2/504 (0.4)	2/497 (0.4)	17/1411 (1.2)	13/1675 (0.8)	15/1644 (0.9)
AST (IU/L) ≥3 x ULN	2/498 (0.4)	1/504 (0.2)	0/497	4/1411 (0.3)	6/1675 (0.4)	10/1644 (0.6)
AST (IU/L) or ALT (IU/L) ≥3 x ULN	6/498 (1.2)	2/504 (0.4)	2/497 (0.4)	19/1411 (1.3)	13/1675 (0.8)	17/1644 (1.0)

Laboratory Parameter	Placebo Pool			Broad Pool		
Predefined Limits of Change	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
ALT (IU/L) >5 x ULN	1/498 (0.2)	0/504	0/497	2/1411 (0.1)	3/1675 (0.2)	4/1644 (0.2)
AST (IU/L) >5 x ULN	1/498 (0.2)	1/504 (0.2)	0/497	1/1411 (<0.1)	3/1675 (0.2)	3/1644 (0.2)
AST (IU/L) or ALT (IU/L) >5 x ULN	1/498 (0.2)	1/504 (0.2)	0/497	2/1411 (0.1)	4/1675 (0.2)	4/1644 (0.2)
ALT (IU/L) >10 x ULN	1/498 (0.2)	0/504	0/497	1/1411 (<0.1)	0/1675	1/1644 (<0.1)
AST (IU/L) >10 x ULN	0/498	0/504	0/497	0/1411	0/1675	0/1644
AST (IU/L) or ALT (IU/L) >10 x ULN	1/498 (0.2)	0/504	0/497	1/1411 (<0.1)	0/1675	1/1644 (<0.1)
ALT (IU/L) >20 x ULN	0/498	0/504	0/497	0/1411	0/1675	0/1644
AST (IU/L) >20 x ULN	0/498	0/504	0/497	0/1411	0/1675	0/1644
AST (IU/L) or ALT (IU/L) >20 x ULN	0/498	0/504	0/497	0/1411	0/1675	0/1644
TBILI (mg/dL) >2 x ULN	2/498 (0.4)	0/504	0/497	2/1411 (0.1)	3/1676 (0.2)	1/1645 (<0.1)
ALT ≥3 x ULN and TBILI ≥2 x ULN	2/498 (0.4)	0/504	0/497	2/1411 (0.1)	0/1676	0/1645
AST ≥3 x ULN and TBILI ≥2 x ULN	1/498 (0.2)	0/504	0/497	1/1411 (<0.1)	0/1676	0/1645
ALT (IU/L) or AST (IU/L) ≥3 x ULN and TBILI (mg/dL) ≥2 x ULN	2/498 (0.4)	0/504	0/497	2/1411 (0.1)	0/1676	0/1645

Source: Adapted from the Applicant's Integrated Summary of Safety, labeled as Table 431, pages 2437-2446/9829, and Table 433, pages 2457-2466/9829, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\iss.pdf
These data also were derived/confirmed from the iss and iss-broad adsl.xpt and adlb.xpt datasets, available at:
Application 209803 - Sequence 0000 - Analysis Dataset Legacy –
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Abbreviations: —, not applicable; ↓, decrease; ↑, increase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CO2, bicarbonate; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease [MDRD] equation); Hgb, hemoglobin; K, potassium; LLN, lower limit of normal; Lymph, lymphocytes; Mg, magnesium; Na, sodium; NR, not reported; Phos, phosphate; PLT, platelets; PTH, parathyroid hormone; TBILI, total bilirubin; UA, uric acid; ULN, and upper limit of normal.

¶ Note: Higher percent differences (95% CI) vs. placebo (Miettinen and Nurminen method stratified by study[98]) reported in the Applicant's analyses (computed when ≥4 subjects had an event in ≥1 treatment arm).

Similar trends (data not shown) were observed in the Ertugliflozin/Metformin Pool (Trials P007/1017 and P006/1015). Since the data from the three individual Phase 3 trials used to support the ertugliflozin/sitagliptin FCDP (i.e., Trials P005/1019, P006/1015, and P017/1047) were not pooled, these data were limited, and imbalances in PDLC events with coadministration of ertugliflozin plus sitagliptin in each trial were not evident.

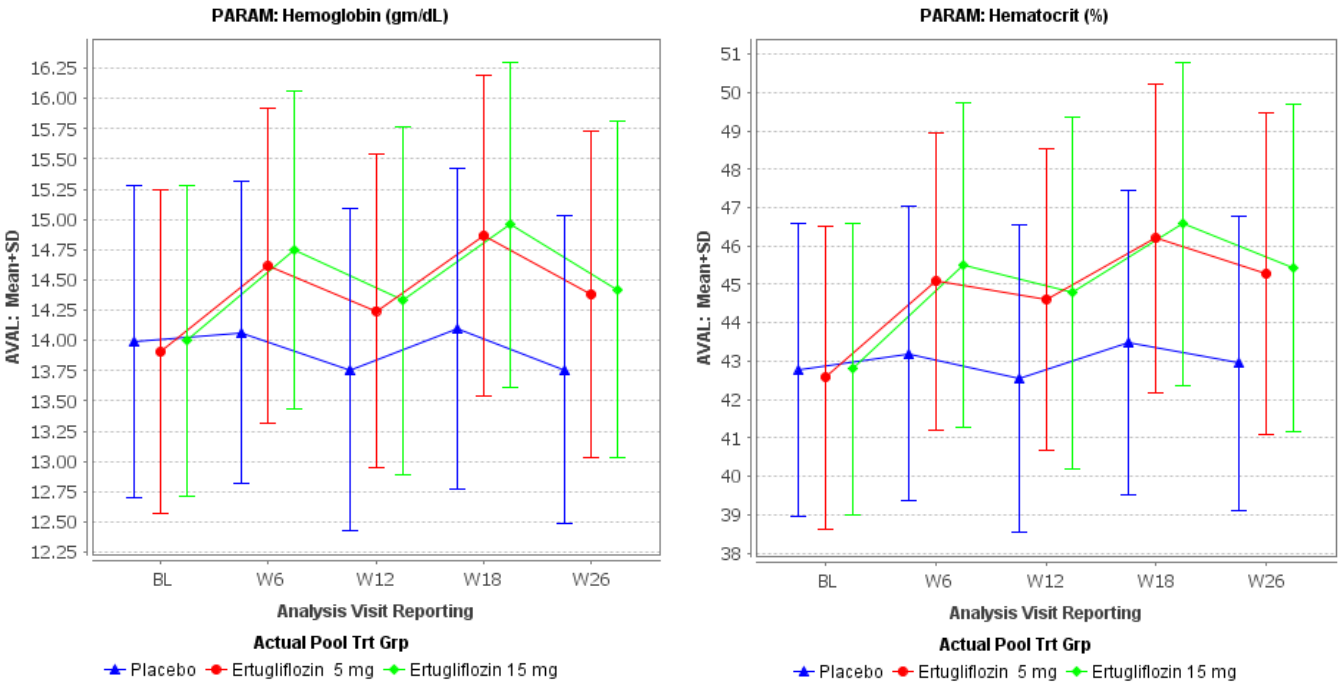
Hematology

The SGLT2 inhibitor pharmacologic class is associated with small increases in hemoglobin and hematocrit (Hct),[99-106] which has been attributed to osmotic diuresis. Potential risks associated with possible drug-induced volume depletion and hemoconcentration may include viscosity-mediated embolic events, such as stroke.[102,105,107-111] The Applicant assessed changes in Hgb and Hct throughout the treatment periods, and small increases from baseline to Week 26 were observed for both ertugliflozin treatment arms in the Placebo Pool (Figure 2). The baseline Hgb concentrations were 14.0 gm/dL in the placebo arm, 13.9 gm/dL in the ertugliflozin 5 mg arm, and 14 gm/dL in the ertugliflozin 15 mg arm. The mean (± SD) Hgb changes from baseline to

Week 26 were -0.2 ± 0.7 gm/dL (range, -3.6 to 2.4), 0.5 ± 0.5 gm/dL (range, -3.7 to 4.1), and 0.5 ± 0.8 gm/dL (range, -4.2 to 2.9) for the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg arms, respectively.

The baseline Hct concentrations were 42.8% in the placebo arm, 42.6% in the ertugliflozin 5 mg arm, and 42.8% in the ertugliflozin 15 mg arm. Baseline to Week 26 Hct changes were 0.2 ± 2.3% (range, -7.5 to 7.5), 2.6 ± 2.7% (range, -10.9 to 13.4), and 2.8 ± 2.5% (range, -10.1 to 11.5), respectively.

Figure 2: Mean (SD) Changes from Baseline to Week 26 in Hemoglobin and Hematocrit (Placebo Pool)



Source: Derived from the iss adsl.xpt and adlb.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy –

Higher proportions of subjects (Table 24) had Hgb increases >2 gm/dL in both the ertugliflozin 5 mg (4.7%) and 15 mg (4.1%) arms compared to the placebo arm (0.6%) in the Placebo Pool. Similarly, approximately 7% of ertugliflozin-treated subjects and 1.5% of non-ertugliflozin-treated subjects in the Broad Pool met this PDLC criteria. A review of the 34 ertugliflozin-treated subjects with Hgb increases >2.0 gm/dl plus values >ULN for possible thromboembolic events, revealed a single subject who experienced an acute myocardial infarction (Subject 0100604) and a second had a retinal artery embolism (Subject 0104215). Both subjects had been randomized to the ertugliflozin 15 mg treatment arm. Brief narrative summaries are provided below. No events of venous thromboembolism were observed in subjects with this

PDLC.

Ertugliflozin 15 mg arm:

> **Subject 0100604**: a 79-year-old Caucasian female who participated in Trial P001/1016 (i.e., the dedicated moderate renal impairment trial) experienced an acute myocardial infarction (non-ST-elevation) on Study Day 261 (reported as severe in intensity and unrelated to IP by the investigator), resulting in discontinuation of IP. The subject denied chest pain in the preceding months, but reported frequent palpitations. Within six days of hospitalization, she experienced angina, and was admitted with 'persistent, stronger, crushing and constricting chest pain'. Blood pressure measurements during treatment exposure, did not reveal hypotension/orthostasis. Her medical history included T2D (baseline HbA1c 8.1%), chronic kidney disease (baseline eGFR of 38 mL/min/1.73 m^2), myocardial ischemia/myocardial infarction (MI), hyperlipidemia, hypertension, diabetic neuropathy and obesity (baseline BMI 36.7 kg/m^2). Relevant prior and concomitant medications included sitagliptin, gliclazide, amlodipine, atorvastatin, hydrochloro-thiazide/valsartan, nebivolol, nitroglycerin 5.2 mg daily, trimetazidine, molsidomine, potassium, aspirin, and furosemide. Her baseline Hgb was 13.4 gm/dL (normal range 11-16.1 gm/dL), with reported post-baseline values of 14.7 gm/dL (Day 45), 15.4 gm/dL (Day 129), 15.2 gm/dL (Day 185), and 16.3 gm/dL (Day 241). No changes in eGFR were observed.

Based on the subject's age, cardiovascular risk factors, preexisting history of coronary artery disease, and chronic kidney disease,[112-117] as well as concomitant thiazide/loop diuretic use, I do not believe that ertugliflozin caused this event. Whether it could have been a contributing factor in this at-risk subject is uncertain.

> **Subject 0104215**: a 62-year-old Caucasian female who participated in Trial P001/1016 experienced a retinal artery embolism (reported as mild in intensity and unrelated to IP by the investigator) on Study Day 116. The subject continued study medication, with the last dose received on Day 365. Her medical history included T2D (baseline HbA1c 9%), chronic kidney disease (baseline eGFR of 68 mL/min/1.73 m^2), hyperlipidemia, hypertension, obesity (baseline BMI 40.1 kg/m^2), peripheral neuropathy, and intermittent claudication. Relevant prior and concomitant medications included the use of simvastatin, lisinopril, furosemide, aspirin, cilostazol, metformin, and glimepiride. Her baseline Hgb was 14.5 gm/dL (normal range 11.6-16.2 gm/dL), with reported post-baseline values of 16 gm/dL (Day 43), 14.8 gm/dL (Day 127), 17.2 gm/dL (Day 183), 16.6 gm/dL (Day 196), 15 gm/dL (Day 239), 15.8 gm/dL (Day 296), 16.7 (Day 365), and 14.9 gm/dL (Day 379).

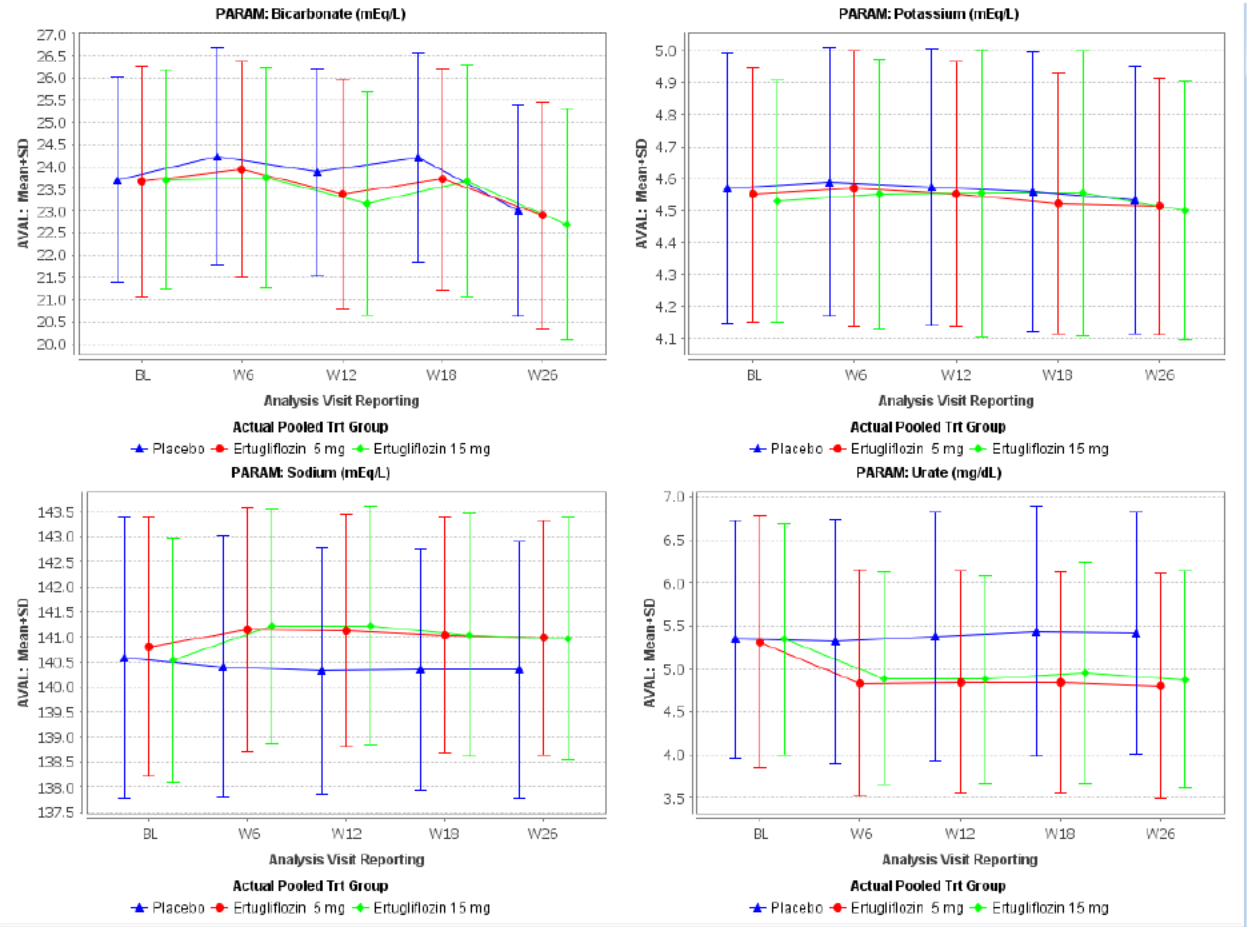
Due to the presence of comorbidities, including peripheral vascular disease, concomitant loop diuretic use, and a reported Hgb concentration of 14.8 gm/dL near the time of the event, a causal association of ertugliflozin with retinal artery embolism is unlikely.

The Applicant did not include PDLC criteria for marked changes in Hct, and these data were not included in the laboratory datasets for either the Broad Pool or the 4-MSU. However, in the Placebo Pool, no subjects had Hct concentrations ≥65% (considered a critical value). Additionally, none of ertugliflozin-treated subjects with Hct concentrations ≥55% (n=22 subjects) had reported thromboembolic AEs, and only two had symptoms of volume depletion (i.e., hypotension and orthostatic hypotension TEAEs).

Clinical Chemistry

In the Placebo and Broad Pools, the proportions of subjects with PDLC for many of the analytes (Table 24), as well as mean serum bicarbonate and potassium changes from baseline to Week 26 (Figure 3), were generally similar across arms without obvious trends, while sodium concentrations increased (approximately 0.26 to 0.38 mEq/L) and uric acid levels decreased (approximately -0.44 to -0.53 mg/dL) in ertugliflozin-treated subjects. In the Broad Pool, more ertugliflozin-treated subjects experienced uric acid and blood urea nitrogen increases that met PDLC criteria. Additionally, higher proportions of ertugliflozin-treated subjects in both safety pools had increased or decreased phosphate concentrations, while the ertugliflozin 5 mg arm for the Broad Pool also had a higher proportion of subjects with parathyroid hormone (PTH) increases of ≥30%. Although the clinical relevance of any of these laboratory changes is uncertain, none resulted in death, were coded as SAEs, or led to treatment discontinuation.

Figure 3: Mean (SD) Changes from Baseline to Week 26 in Serum Electrolytes (Placebo Pool)



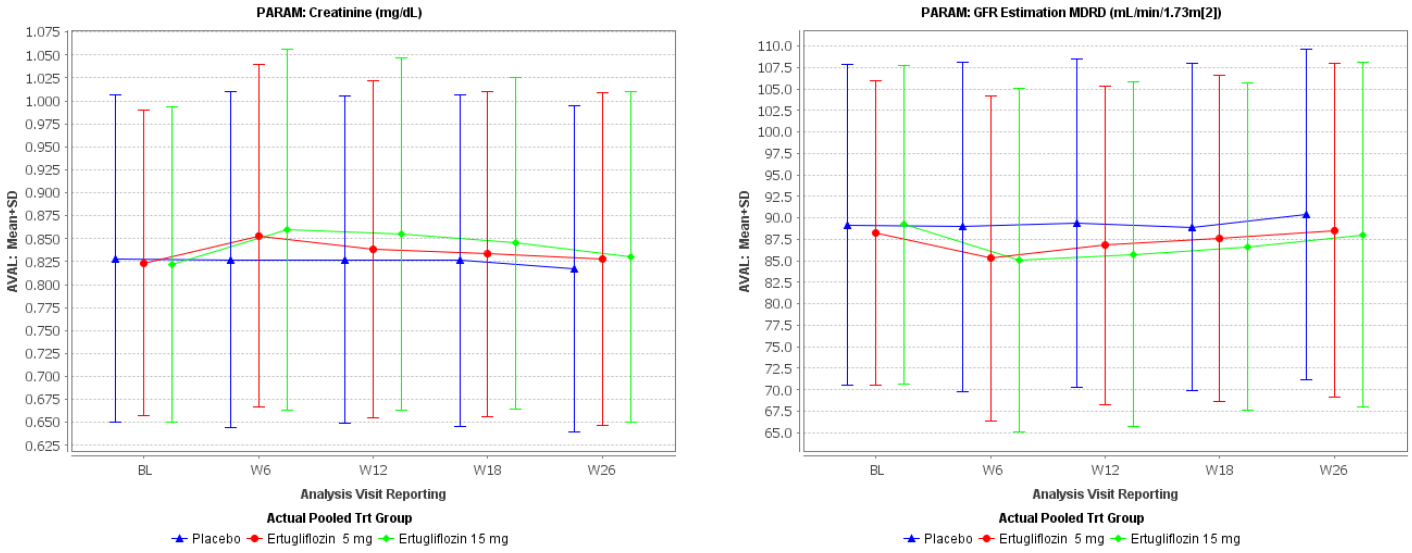
Source: Derived from the iss adsl.xpt and adlb.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy –

Renal Function Tests and Adverse Events

Sodium-glucose cotransport 2 inhibitors have been associated with postmarketing reports of acute kidney injury (AKI).[118] On June 14, 2016, the FDA strengthened the existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin.[119] Proposed mechanisms for these events have included osmotic diuresis, resulting in hyperosmolarity and dehydration, transient hypotensive episodes, uricosuria-mediated tubular injury, and stimulation of chemokines, local inflammation, and tubular injury.[120,121]

In the Placebo Pool, the mean and median changes in serum creatinine were small across all three treatment arms at Weeks 26 (Figure 4). The mean change from baseline in eGFR at Week 26 was 0.67 ± 11.12 ml/min/1.73 m^2 in placebo arm vs. 0.52 ± 11.66 ml/min/1.73 m^2 in the ertugliflozin 5 mg arm vs. -0.58 ± 12.27 ml/min/1.73 m^2 in the 15 mg arm. Maximum reductions in eGFR for the ertugliflozin 5 mg (-2.67 ± 10.69 ml/min/1.73 m^2) and 15 mg (-3.14 ± 12.13 ml/min/1.73 m^2) arms were observed at Week 6.

Figure 4: Mean (SD) Changes from Baseline to Week 26 in Serum Creatinine and Estimated Glomerular Filtration Rate (Placebo Pool)



Source: Derived from the iss adsl.xpt and adlb.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy –

The Applicant's PDLC criteria and results for impaired renal function are presented in Table 24. Although there appeared to be a dose-response associated with the PDLC criteria for BUN increase of ≥50% (Table 24), the proportions of subjects meeting the serum creatinine and eGFR PDLC criteria were generally similar across all three treatment arms for both the Placebo and Broad Safety Pools.

In the Applicant's dedicated moderate renal impairment trial (P001/1016), a larger reduction in eGFR was observed in ertugliflozin-treated subjects with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73 m^2). The mean baseline eGFR ranged from 46.0-46.9 mL/min/1.73 m^2 across the three treatment arms. Similar to what was observed in the Placebo Pool, the maximum decrease from baseline in eGFR was observed at Week 6 (i.e., ertugliflozin 5 mg, -3.2 mL/min/1.73 m^2; and 15 mg, -4.1 mL/min/1.73 m^2). The eGFR reductions remained below baseline through Week 26, with greater LS mean decreases in eGFR reported in the ertugliflozin 5 mg and 15 mg arms (-2.61 and -2.81 mL/min/1.73 m^2, respectively) compared to the placebo arm (-0.54 mL/min/1.73 m^2). Renal-related AEs (e.g., acute kidney injury, renal impairment, acute prerenal failure) were reported in 1.3% (2/155), 0.6% (1/154 subjects), and 2.5% (4/158) of subjects treated with placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg, respectively.

Additionally, custom searches of the Placebo and Broad Pool datasets were performed to evaluate potential adverse renal events and/or laboratory changes suggestive of renal impairment (that also included the Applicant's PDLC criteria). Based on these criteria, a modest dose-response and treatment effect was observed, with higher proportions of subjects reported in the ertugliflozin treatment arms for both safety populations (Table 43).

In the Applicant's 4-MSU report, they reported cumulative renal-related AEs by using the Acute Renal Failure SMQ. Based on these data, they observed a dose-related increase in 'Renal and urinary disorders' PTs ('acute kidney injury', 'acute prerenal failure', 'renal failure' and 'renal impairment'), occurring in 0.4% (6/1450), 0.6% (10/1716), and 0.8% (14/1693) for the non-ertugliflozin, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms, respectively. Using a broad CMQ (Table 25) there also appeared to be a modest dose-related increase in MedDRA PTs of 'glomerular filtration rate decreased' and 'blood creatinine increased'.

Table 25: Summary of Treatment-Emergent Renal Adverse Events (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
TEAEs – no. (%)	**64 (4.4)**	**79 (4.6)**	**91 (5.4)**	**170 (5.0)**
Hyperkalaemia	12 (0.8)	17 (1.0)	15 (0.9)	32 (0.9)
Glomerular filtration rate decreased	6 (0.4)	9 (0.5)	20 (1.2)	29 (0.9)
Blood creatinine increased	3 (0.2)	11 (0.6)	16 (0.9)	27 (0.8)
Blood potassium increased	12 (0.8)	6 (0.3)	11 (0.6)	17 (0.5)
Microalbuminuria	7 (0.5)	10 (0.6)	4 (0.2)	14 (0.4)
Acute kidney injury*	2 (0.1)	6 (0.3)	5 (0.3)	11 (0.3)
Renal impairment*	4 (0.3)	3 (0.2)	8 (0.5)	11 (0.3)
Blood urea increased	2 (0.1)	6 (0.3)	3 (0.2)	9 (0.3)
Chronic kidney disease	3 (0.2)	6 (0.3)	2 (0.1)	8 (0.2)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Hypocalcaemia	3 (0.2)	4 (0.2)	3 (0.2)	7 (0.2)
Hyponatraemia	0	3 (0.2)	3 (0.2)	6 (0.2)
Proteinuria	4 (0.3)	3 (0.2)	3 (0.2)	6 (0.2)
Blood phosphorus increased	0	1 (0.1)	2 (0.1)	3 (0.1)
Leukocyturia	2 (0.1)	0	3 (0.2)	3 (0.1)
Metabolic acidosis	0	1 (0.1)	2 (0.1)	3 (0.1)
Renal failure*	0	1 (0.1)	2 (0.1)	3 (0.1)
Urine albumin/creatinine ratio increased	2 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Diabetic nephropathy	2 (0.1)	0	2 (0.1)	2 (0.1)
Hyperphosphataemia	1 (0.1)	2 (0.1)	0	2 (0.1)
Nephropathy	0	1 (0.1)	1 (0.1)	2 (0.1)
Acute prerenal failure*	0	1 (0.1)	0	1 (<0.1)
Blood parathyroid hormone increased	1 (0.1)	1 (0.1)	0	1 (<0.1)
Blood sodium decreased	1 (0.1)	1 (0.1)	0	1 (<0.1)
Encephalopathy	0	0	1 (0.1)	1 (<0.1)
Hypercreatininaemia	0	0	1 (0.1)	1 (<0.1)
Nephritis	0	0	1 (0.1)	1 (<0.1)
Nephrogenic anaemia	0	0	1 (0.1)	1 (<0.1)
Nephrosclerosis	0	0	1 (0.1)	1 (<0.1)
Normochromic normocytic anaemia	0	0	1 (0.1)	1 (<0.1)
Pericarditis	0	0	1 (0.1)	1 (<0.1)
White blood cells urine positive	3 (0.2)	1 (0.1)	0	1 (<0.1)
Albuminuria	1 (0.1)	0	0	0
Blood calcium decreased	1 (0.1)	0	0	0
Creatinine renal clearance decreased	1 (0.1)	0	0	0
Hypertensive nephropathy	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: 4-MSU, Four-Month Safety Update; no., number; MedDRA, Medical Dictionary for Regulatory Activities; and TEAE, treatment-emergent adverse event.
*Terms reported in the Applicant's 4-MSU for renal-related AEs.

A Clinical Events Committee (CEC) provided independent causality assessment of events of substantial deterioration in laboratory measures of renal function and other selected renal events. In total, there were five renal-related adverse events adjudicated as causally related to IP; one in the non-ertugliflozin arm (possible, 'chronic kidney disease'), two in the ertugliflozin 5 mg arm (very likely, 'acute kidney injury' and possible, 'blood creatinine increased'), and two in

the ertugliflozin 15 mg arm (possible 'acute kidney injury' and 'renal failure').[(1)]

Acute kidney injury and impairment in renal function is currently included in the WARNINGS AND PRECAUTIONS section of other SGLT2 inhibitor product labeling,[24-26] and also is described in this section of the Applicant's proposed product labeling ('Impairment in Renal Function') for ertugliflozin and the ertugliflozin FCDPs. Additionally, postmarketing reports of acute renal failure in patients taking sitagliptin is described in the ertugliflozin/sitagliptin FCDP labeling. [(b) (4)] [(b) (4)] Based on the data submitted for the 4-MSU safety pool, use of ertugliflozin in this subset of subjects was associated with a higher incidence of adverse outcomes that included deaths, SAEs, and discontinuations due to AEs; accounting—in total—for 20.3% (56/276) of ertugliflozin-treated subjects compared to 16.7% (21/126) of subjects in the non-ertugliflozin treatment arm. Although I do not believe that this difference represents a major safety concern, these findings should be considered in the context of the Applicant's failed dedicated renal impairment study (Trial P001/1016), in which no difference was reported between the placebo and ertugliflozin 5 mg or 15 mg treatment arms for the primary efficacy endpoint (i.e., HbA1c change from baseline to Week 26). Therefore, I would not recommend the use of ertugliflozin-containing products in patients with an eGFR <60 mL/min/1.73 m^2.

Mineral Panel / Parathyroid Hormone / Biomarkers of Bone Resorption and Formation

It is thought that diabetic patients may have an increased fracture risk, in part due to decreases in mineralized surface area, rate of mineral apposition, osteoid surface, osteoblast activity, and numbers of osteoclasts.[122] Additionally, these patients may have increased urinary excretion of calcium and magnesium, accumulation of glycation end products, and oxidative stress potentially leading to altered bone strength, metabolism and structure.[122] SGLT2 inhibitors further alter renal tubular transport of several minerals (e.g., phosphorus, calcium and magnesium), and may be associated with increases in parathyroid hormone concentrations and decreases in 1,25-dihydroxyvitamin D concentrations.[123-125] Increased bone resorption markers, such as collagen type 1 beta-carboxy telopeptide (beta-CTX), and decreased bone mineral density (BMD) could potentially be associated with SGLT2 inhibitor-mediated weight loss.[126,127] Elevations in serum parathyroid hormone (PTH) with dapagliflozin,[128] and serum beta-CTX with canagliflozin.[123] have been previously reported.

In the Placebo Pool, there were small mean increases from baseline to Week 26 in serum

[(1)] Adjudicated definitions: 'Very Likely'—Event cannot be reasonably explained by an alternative explanation, and the relationship in time is very suggestive; and 'Possible'—Event might be due to the use of IP, and the relationship in time is reasonable.

calcium (placebo [0.04 ± 0.58 mg/dL] vs. ertugliflozin 5 mg [0.08 ± 0.41 mg/dL] vs. ertugliflozin 15 mg [0.06 ± 0.38 mg/dL]); magnesium (placebo [-0.02 ± 0.14 mEq/dL] vs. ertugliflozin 5 mg [0.11 ± 0.14 mEq/dL] vs. ertugliflozin 15 mg [0.14 ± 0.15 mEq/dL]) and phosphate concentrations (placebo [0.04 ± 0.46 mg/dL] vs. ertugliflozin 5 mg [0.21 ± 0.50 mg/dL] vs. ertugliflozin 15 mg [0.26 ± 0.50 mg/dL] vs.) in subjects receiving ertugliflozin.

Based on the data included in the 4-MSU, there were no deaths, SAEs, or discontinuations from study due to hypercalcemia, hypermagnesemia, hyperphosphatemia, or hyperparathyroidism. The Applicant intends to include information related to changes in serum phosphate concentrations in product labeling.

Additional laboratory measures that may reflect ertugliflozin effects on bone (Table 26), such as serum PTH, carboxy terminal cross linking telopeptides of type I collagen (CTX; a biomarker of bone resorption) and procollagen type 1 N-terminal propeptide (P1NP; a biomarker of bone formation), were assessed in the Applicant's dedicated Moderate Renal Impairment Study (P001/1016), and in Trial P007/1017 (in which 41% of 621 subjects were either postmenopausal women or had a history of bilateral oophorectomy for ≥3 years).

In Trial P001/1016, small increases in PTH from baseline to Week 26 were reported in both ertugliflozin treatment arms. Similarly, increases in PTH concentrations were reported for Trial P007/1017. Changes from baseline in serum P1NP were minimal for ertugliflozin- and placebo-treated subjects in both trials, while CTX increased more in the ertugliflozin arms. The long-term clinical implications of these laboratory changes on bone metabolism and fracture risk are unknown. The laboratory and clinical data following completion of these ongoing trials, as well as the fracture data from the Applicant's CVOT (Trial P004/1021), will be useful for assessing the relevance of these findings on bone safety.

Table 26: PTH and Bone Biomarker Changes from Baseline (Trials P001/1016 and P007/1017)

Treatment	Baseline		Week 26		Change from Baseline at Week 26	
	N	Mean (SD)	N	Mean (SD)		
PTH (ng/L)						
Trial P001/1016*					**Mean (SD)**	**Range**
Placebo	148	50 (32.1)	125	46.0 (29.5)	-4.5 (25.4)	-105, 63
Ertugliflozin 5 mg	149	44.7 (29.8)	130	48.7 (31.1)	4.5 (23.9)	-93, 82
Ertugliflozin 15 mg	147	44.6 (27.0)	125	47.8 (27.3)	2.2 (20.5)	-76, 98
Trial P007/1017[¶]					**Mean (SD)**	**95% CI**
Placebo	202	19.29 (8.17)	186	18.11 (7.91)	-0.98 (6.71)	-1.95, -0.01
Ertugliflozin 5 mg	194	19.52 (6.91)	182	19.60 (8.34)	0.28 (7.52)	-0.82, 1.38
Ertugliflozin 15 mg	198	19.88 (7.71)	184	20.26 (7.77)	0.14 (7.53)	-0.95, 1.24

Treatment	Baseline		Week 26		Change from Baseline at Week 26	
	N	Mean (SD)	N	Mean (SD)		
CTX (ng/L)						
Trial P001/1016*					**Mean (SD)**	**Range**
Placebo	149	830.3 (5162.9)	120	429.0 (239.4)	-508.9 (5735.9)	-62799, 380
Ertugliflozin 5 mg	147	391.1 (197.1)	124	500.1 (259.5)	95.3 (186.3)	-336, 1207
Ertugliflozin 15 mg	149	400.0 (200.3)	125	513.7 (241.8)	109.1 (153.3)	-339, 599
Trial P007/1017¶					**Mean (SD)**	**95% CI**
Placebo	200	268.3 (132.9)	185	280.6 (150.4)	10.8 (106.6)	-4.7, 26.3
Ertugliflozin 5 mg	196	266.9 (129.9)	179	319.8 (154.3)	51.9 (121.9)	33.9, 69.8
Ertugliflozin 15 mg	193	272.2 (135.6)	180	353.6 (166.9)	80.2 (149.7)	58.2, 102.2
P1NP (µg/L)						
Trial P001/1016*					**Mean (SD)**	**Range**
Placebo	149	49.1 (29.3)	122	54.5 (36.4)	4.0 (31.6)	-177, 171
Ertugliflozin 5 mg	148	45.9 (20.4	127	52.5 (22.3)	5.9 (20.4)	-40, 142
Ertugliflozin 15 mg	149	44.9 (20.9)	126	50.0 (23.9)	5.8 (14.9)	-40, 65
Trial P007/1017¶					**Mean (SD)**	**95% CI**
Placebo	200	32.0 (15.0)	186	32.7 (13.1)	0.5 (11.7)	-1.2, 2.2
Ertugliflozin 5 mg	198	32.8 (14.5)	183	33.4 (12.6)	0.8 (12.1)	-0.9, 2.6
Ertugliflozin 15 mg	196	31.5 (16.6)	183	32.3 (11.7)	0.5 (15.0)	-1.7, 2.7

Source: Adapted from the Applicant's Clinical Study Reports for P001V01, Tables 14.3.7.1.1, 14.3.7.2.1, 14.3.7 3.1, pages 2272, 2277, and 2280/2401, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p001v01\p001v01.pdf
and P007/1017, Table 66, page 270/3124, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01.pdf
Abbreviations: CI, confidence interval; CTX, carboxy terminal cross-linking telopeptides of Type I collagen; N, number of subjects with measurement at both baseline and time point; P1NP, procollagen type I N terminal propeptide; PTH, parathyroid hormone; SD, standard deviation.
*Trial P001/1016, measurements included data after bone rescue medications.
¶ In Trial P007/1017, measurements excluded data after bone rescue medications.

Lipid Panel

The Applicant considered changes in serum lipids to be a Special Safety Topic. Small, possibly dose-related increases in mean low-density lipoprotein cholesterol (LDL-C) concentrations have been reported with the use of SGLT2 inhibitors,[129-137] which are described in Warnings and Precautions section of product labeling for all three currently approved products,[24-26] as well as in the proposed product labeling for ertugliflozin and the ertugliflozin FCDPs. Based on nonclinical data with another SGLT2 inhibitor, it has been suggested that the observed increases in serum LDL-C may be associated with reductions in both hepatic LDL receptor protein expression and LDL-C catabolism under fasting conditions.[138] Further, a metabolic switch toward lipid utilization (i.e., from carbohydrate to fat oxidation) with chronic SGLT2

inhibition, may enhance ketogenesis and hepatic cholesterol synthesis within the liver.[138]

The Applicant's analyses of percent changes from baseline to Week 26 for select lipid parameters from the Placebo Pool is presented in Table 27 . Based on these results, there were statistically significant placebo-subtracted, dose-related increases in LDL-C and total cholesterol (Total-C) in the ertugliflozin 15 mg treatment arm (i.e., 5.4% and 4%, respectively), while both ertugliflozin arms resulted in reductions in triglycerides and increases in high-density lipoprotein cholesterol (HDL-C). Although these findings are consistent with other SGLT2 inhibitors, the long-term CV risks associated the observed lipid changes are unknown.

Table 27: Percent Lipid (mg/dL) Changes from Baseline to Week 26 (Placebo Pool)

Treatment	Baseline		Week 26		Percent Change from baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
LDL-C (mg/dL)							
Placebo	501	97.69 (35.41)	452	94.87 (33.12)	470	3.21 (34.09)	2.75 (-0 20, 5.70)
Ertugliflozin 5 mg	505	96.85 (33.91)	475	98.89 (35.06)	482	5.82 (35.47)	5.33 (2.45, 8.22)
Ertugliflozin 15 mg	490	96.61 (34.38)	455	100.22 (33.71)	460	8.37 (31.47)	8.14 (5.18, 11.09)
Estimated Difference					Difference in LS Means (95% CI)[†]		
Ertugliflozin 5 mg vs. Placebo					2.58 (-1.43, 6.59)		
Ertugliflozin 15 mg vs. Placebo					5.39 (1.33, 9.45)		
Total-C (mg/dL)							
Placebo	503	179.74 (42.18)	455	177.25 (39.60)	473	1.07 (19.06)	1.06 (-0.57, 2.69)
Ertugliflozin 5 mg	506	178.46 (42.18)	479	180.70 (40.12)	485	2.83 (18.73)	2.59 (1.00, 4.19)
Ertugliflozin 15 mg	495	176.65 (41.65)	463	183.00 (41.15)	466	5.69 (18.37)	5.06 (3.44, 6.68)
Estimated Difference					Difference in LS Means (95% CI)[†]		
Ertugliflozin 5 mg vs. Placebo					1.53 (-0.68, 3.74)		
Ertugliflozin 15 mg vs. Placebo					4.00 (1.77, 6.23)		
Conditional Pooled SD of Percent Change from Baseline					17.05		
TG (mg/dL)		Median (SD)		Median (SD)	Median (SD)		M-Estimate
Placebo	503	143.0 (106.0)	444	147.5 (92.6)	4.5 (45.7)		3.7
Ertugliflozin 5 mg	508	144.5 (101.4)	470	140.5 (84.7)	-3.9 (41.1)		-3.3
Ertugliflozin 15 mg	496	141.0 (82.8)	450	134.5 (80.0)	-1.7 (41.6)		-1.3
Estimated Difference					Difference in M-Estimates (95% CI)[¶]		
Ertugliflozin 5 mg vs. Placebo					-7.0 (-11.5, -2.4)		
Ertugliflozin 15 mg vs. Placebo					-4.9 (-9.5, -0.3)		
HDL-C (mg/dL)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	503	47.12 (13.45)	455	47.51 (13.02)	473	1.89 (17.57	1.68 (0.18, 3.18)
Ertugliflozin 5 mg	506	47.56 (13.44)	479	49.71 (13.89)	485	6.25 (16.65)	6.23 (4.77, 7.70)
Ertugliflozin 15 mg	495	47.31 (11.72)	463	50.39 (12.38)	466	7.56 (16.11)	7.52 (6.02, 9.02)
Estimated Difference					Difference in LS Means (95% CI)[†]		
Ertugliflozin 5 mg vs. Placebo					4.56 (2.49, 6.63)		
Ertugliflozin 15 mg vs. Placebo					5.84 (3.75, 7.93)		
Conditional Pooled SD of Percent Change from Baseline					16.05		

Treatment	Baseline		Week 26		Percent Change from baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Percent Change from Baseline at Week 26, N is the number of subjects in the ASaT population (i.e., randomized subjects who took at least 1 dose of study medication) and had a baseline measurement and at least one assessment after baseline. The Mean and SD for the Percent Change from baseline are based on non-missing values.

[†] Based on cLDA model with fixed effects for trial, treatment, time, baseline eGFR (continuous) and the interaction of time by treatment. Time is treated as a categorical variable.

[¶] M-Estimates, 95% CI were obtained from fitting a robust regression model with terms for trial, treatment, and covariates baseline triglycerides and baseline eGFR (continuous), after imputing for missing values using multiple imputation.

Source: Adapted from the Applicant's Integrated Summary of Safety, labeled as Tables 371, 383, 395, and 407, pages 2377, 2389, 2401, and 2413 of 9829, respectively, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\iss.pdf
Abbreviations: ASaT, all subjects as treated; CI, confidence interval; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SD, standard deviation; TG, triglycerides; and Total-C, total cholesterol.

A search for MedDRA PTs associated with dyslipidemia did not reveal differences between treatment arms in the Placebo Pool (Table 28), while in the 4-MSU Pool, there appeared to be a dose-related increase in events (i.e., 2.1%, 2.9% and 3.7% of subjects in the non-ertugliflozin, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms, respectively). Events of 'dyslipidaemia', 'hypercholesterolaemia', and 'hyperlipidaemia' were the most commonly reported AEs in the ertugliflozin 15 mg treatment arm. None of the AEs associated with dyslipidemia were coded as SAEs.

Table 28: Subjects with Adverse Events of Dyslipidemia (Placebo Pool and 4-MSU)

MedDRA Preferred Terms	Placebo Pool			Broad Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
DYSLIPIDEMIA – no. (%)	**10 (1.9)**	**7 (1.3)**	**9 (1.8)**	**30 (2.1)**	**50 (2.9)**	**62 (3.7)**
Dyslipidaemia	3 (0.6)	3 (0.6)	4 (0.8)	13 (0.9)	22 (1.3)	23 (1.4)
Hypercholesterolaemia	2 (0.4)	0	1 (0.2)	3 (0.2)	5 (0.3)	14 (0.8)
Hyperlipidaemia	1 (0.2)	0	1 (0.2)	6 (0.4)	7 (0.4)	10 (0.6)
Hypertriglyceridaemia	2 (0.4)	2 (0.4)	2 (0.4)	3 (0.2)	6 (0.3)	8 (0.5)
Blood triglycerides increased	2 (0.4)	2 (0.4)	1 (0.2)	3 (0.2)	10 (0.6)	8 (0.5)
Blood cholesterol increased	0	1 (0.2)	0	1 (0.1)	1 (0.1)	2 (0.1)
Apolipoprotein B increased	0	0	0	0	0	1 (0.1)
High density lipoprotein decreased	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)
Lipid metabolism disorder	0	0	0	0	0	1 (0.1)
Lipids increased	0	0	0	0	0	1 (0.1)
Xanthelasma	0	0	0	1 (0.1)	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: 4-MSU, Four-Month Safety Update; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and TEAE, treatment-emergent adverse event.

Hepatic Panel

Based on the data presented in Table 24, the proportions of subjects with liver laboratory abnormalities as defined by the PDLC were similar across the three treatment arms. Additionally, no cases of ertugliflozin-induced liver injury were observed in the Applicant's clinical program. Changes from baseline to Week 26 in serum liver tests in the Placebo Pool also were not informative (data not shown). (b) (4)

Please refer to Section 8.5.9 for discussion related to adjudicated hepatic events.

8.4.7. Vital Signs

Since the SGLT2 pharmacologic class is associated with diuresis and volume depletion,[24-26,139] assessments of vital signs were performed throughout the treatment periods. In the Placebo Pool, baseline vital signs were similar across treatment arms (Table 29). Small mean reductions in body weight, systolic blood pressure, and diastolic blood pressure from baseline to Week 26 were reported for all treatment arms, with numerically larger mean reductions observed in ertugliflozin-treated subjects. Minimal changes were observed in pulse rate across arms. Weight and blood pressure changes also were evaluated as secondary efficacy endpoints. Please refer to Section 6.1.8 for further discussion.

Table 29: Vital Sign Changes from Baseline to Week 26 (Placebo Pool)*

Treatment	Baseline		Week 26		Change from baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	Mean (SD)	Median	Range
Body Weight (kg)							
Placebo	515	88.0 (21.2)	453	86.1 (20.3)	-1.2 (2.8)	-1.0	-16 to 8
Ertugliflozin 5 mg	519	88.4 (20.7)	480	85.6 (20.1)	-3.1 (3.0)	-3.0	-19 to 7
Ertugliflozin 15 mg	510	87.3 (18.1)	460	84.0 (17.3)	-3.1 (3.0)	-2.9	-16 to 10
All Ertugliflozin	1029	87.9 (19.4)	940	84.8 (18.8)	-3.1 (3.0)	-3.0	-19 to 10
SBP (mmHg) ¶							
Placebo	504	129.72 (14.50)	443	129.55 (14.040	-0.78 (11.83)	-0.3	-51.4 to 34.7
Ertugliflozin 5 mg	512	130.99 (13.30)	475	126.40 (13.43)	-4.84 (11.69)	-4.3	-38.0 to 50.0
Ertugliflozin 15 mg	502	130.48 (13.00)	453	126.13 (13.10)	-4.78 (11.98)	-5.3	-40.0 to 49.4
All Ertugliflozin	1014	130.74 (13.15)	926	126.27 (13.26)	-4.81 (11.82)	-4.7	-40.0 to 50.0
DBP (mmHg) ¶							
Placebo	504	77.97 (7.53)	443	78.15 (8.11)	-0.09 (7.59)	-0.30	-23.7 to 37.3
Ertugliflozin 5 mg	512	78.45 (7.94)	475	76.61 (8.43)	-1.97 (7.46)	-2.00	-31.0 to 26.0
Ertugliflozin 15 mg	502	78.42 (7.47)	453	76.77 (8.52)	-1.71 (7.22)	-1.60	-23.0 to 28.3
All Ertugliflozin	1014	78.43 (7.71)	926	76.69 (8.47)	-1.84 (7.34)	-1.70	-31.0 to 28.3

Treatment	Baseline		Week 26		Change from baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	Mean (SD)	Median	Range
Heart Rate (bpm) ¶							
Placebo	443	72.61 (9.23)	443	72.87 (9.44)	0.23 (8.41)	-0.30	-30.0 to 26.3
Ertugliflozin 5 mg	473	72.82 (10.01)	473	71.51 (10.36)	-1.00 (8.26)	-1.30	-46.0 to 29.6
Ertugliflozin 15 mg	453	72.64 (9.33)	453	71.21 (9.85)	-1.18 (7.97)	-1.30	-37.7 to 28.3
All Ertugliflozin	926	72.73 (9.68)	926	71.37 (10.11)	-1.09 (8.12)	-1.30	-46.0 to 29.6

Source: Adapted from the Applicant's Integrated Summary of Safety, labeled as Tables 461, 463, 477, and 479, pages 8486-8487, 8490-8491, 8506-8507, and 8510-8511 of 9829, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\iss.pdf
Abbreviations: BPM, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SD, standard deviation.
* All subjects as treated including rescue.
¶ Measured in the sitting position.

Additionally, the Placebo Pool and the 4-MSU were searched for AEs associated with vital sign changes (Table 30). Outside of 'weight decreased' in both safety pools, and 'hypotension'/ 'orthostatic hypotension' AEs in the Broad Pool, which were reported in higher proportions of ertugliflozin-treated subjects, events were similar across treatment arms. Both body weight and blood pressure changes were evaluated as efficacy endpoints.

Table 30: Subjects with Adverse Events of Abnormal Vital Signs (Placebo Pool and 4-MSU)

MedDRA Preferred Terms	Placebo Pool			Broad Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
VITAL SIGN-RELATED AES – no. (%)	**27 (5.2)**	**22 (4.2)**	**25 (4.9)**	**101 (7.0)**	**129 (7.5)**	**142 (8.4)**
Weight decreased	5 (1.0)	6 (1.2)	12 (2.4)	11 (0.8)	23 (1.3)	42 (2.5)
Dizziness	8 (1.6)	4 (0.8)	4 (0.8)	28 (1.9)	36 (2.1)	30 (1.8)
Hypertension	6 (1.2)	5 (1.0)	2 (0.4)	27 (1.9)	33 (1.9)	29 (1.7)
Weight increased	0	1 (0.2)	1 (0.2)	7 (0.5)	7 (0.4)	11 (0.6)
Hypotension	1 (0.2)	0	0	2 (0.1)	12 (0.7)	11 (0.6)
Orthostatic hypotension	2 (0.4)	0	2 (0.4)	2 (0.1)	4 (0.2)	7 (0.4)
Palpitations	1 (0.2)	1 (0.2)	1 (0.2)	6 (0.4)	6 (0.3)	6 (0.4)
Presyncope	2 (0.4)	0	2 (0.4)	2 (0.1)	1 (0.1)	4 (0.2)
Blood pressure increased	2 (0.4)	1 (0.2)	0	12 (0.8)	2 (0.1)	3 (0.2)
Sinus bradycardia	0	0	0	1 (0.1)	0	2 (0.1)
Heart rate increased	0	0	0	1 (0.1)	0	2 (0.1)
Hypertensive crisis	0	0	0	4 (0.3)	3 (0.2)	2 (0.1)
Syncope	1 (0.2)	2 (0.4)	0	5 (0.3)	8 (0.5)	2 (0.1)
Sinus tachycardia	0	0	0	0	1 (0.1)	1 (<0.1)
Abnormal loss of weight	0	0	0	0	0	1 (<0.1)
Dizziness postural	1 (0.2)	1 (0.2)	0	1 (<0.1)	2 (0.1)	1 (<0.1)
Bradycardia	0	0	1 (0.2)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Essential hypertension	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)

MedDRA Preferred Terms	Placebo Pool			Broad Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
Tachycardia paroxysmal	0	0	0	0	1 (<0.1)	0
Tachycardia	0	0	0	2 (0.1)	1 (<0.1)	0

Source: Derived from the iss and sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at:
Application 209803 - Sequence 0000 - Analysis Dataset Legacy –
Application 209803 - Sequence 0000 - Analysis Dataset Legacy –
Abbreviations: 4-MSU, Four-month safety update; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and no., number.

8.4.8. Electrocardiograms (ECGs)

The Applicant reported no "clinically meaningful" differences in ECG findings (e.g., PR, QRS, and QTcF intervals) across treatment arms for subjects in the Placebo Pool. Additionally, no ertugliflozin-treated subjects had a QTcF interval ≥500 msec or a QRS complex ≥200 msec during the treatment period, while a single subject each had a PR interval >300 msec (i.e., an increase from 266 msec at baseline to 301 msec on Day 181 in a 69-year-old female subject receiving 15 mg) and QTcF increase from baseline ≥60 msec (i.e., increase from 381 to 458 msec on Day 183 in a 32-year-old female subject receiving 5 mg). Neither of these subjects had relevant clinical laboratory changes or conduction/rhythm-related AEs.

8.4.9. QT

A Thorough QT (TQT) study (P010/1025) was conducted for this Application. In this randomized, placebo-and positive-controlled 3-period crossover study, ertugliflozin was administered as a single dose of 100 mg (6.7 times the maximum recommended human dose of 15 mg/day, with a maximum plasma concentration [C_{max}] approximately 6.5 times higher) to 42 healthy volunteers. The upper bound of the 2-sided 90% CIs for each of the 10 time-matched (0.5 to 48 hours post dose) placebo-subtracted mean differences in the QTcF intervals were less than 10 msec, with the highest reported upper bound value reported as 4.3 msec. Additionally, post ertugliflozin administration, no subjects experienced a PR interval ≥300 msec, QRS complex ≥200 msec, or QTcF ≥480 msec or ≥60 msec from baseline. Based on these data, ertugliflozin does not appear to prolong the QTc to a clinically relevant extent.

8.4.10. Immunogenicity

Not applicable. Please refer to Section 8.5 below for discussion of AESI, which includes hypersensitivity AEs.

8.5. Analysis of Submission-Specific Safety Issues

This section will primarily discuss relevant safety findings associated with known/evolving safety concerns associated with SGLT2 inhibitors, DPP-4 inhibitors and metformin. The Applicant considered the following events to be relevant safety events ('Special Safety Topics'): malignancy, osmotic diuresis, volume depletion, changes in renal function (please refer to Section 8.4.6 for more detailed discussion), genital infection, urinary tract infection, hypoglycemia, bone safety/fracture, hepatic events, pancreatitis, hypersensitivity, changes in lipids (please refer to Section 8.4.6), venous thromboembolism, ketoacidosis, and amputation/peripheral revascularization.

8.5.1. Malignancies

The Applicant considered malignancy as a Special Safety Topic. They identified potential malignancy events using the SMQ, 'Malignant or unspecified tumours', and reported cases using an intention-to-treat approach (i.e., inclusion of all malignancy events, regardless of time relative to the last dose of IP). Since the latency period between treatment exposure and drug-associated malignancy may take years, a broad CMQ search also was performed in this review that included additional PTs of premalignant conditions (Appendix 13.4). Results from this CMQ are presented in Table 31.

The overall incidence of malignancy reported by the Applicant in the 4-MSU was numerically higher in the ertugliflozin 15 mg arm (1.3%; 22/1693), compared to the ertugliflozin 5 mg (0.6%; 10/1716 subjects) and non-ertugliflozin (0.6%; 8/1450) treatment arms. Review of these events by HLT and HLGT using the Applicant's CMQ did not reveal any obvious trends (data not shown). For the cases occurring following at least a six-month of treatment exposure, malignancy was reported in 0.6%, 0.3% and 1% of subjects in the non-ertugliflozin, ertugliflozin 5 mg and ertugliflozin 15 mg arms, respectively. Based on my review of all the malignancy data (including premalignant conditions; Table 31), there did not appear to be any obvious trends or imbalances in the types of malignancies between treatment arms, and no new safety signals were identified. However, these data were limited in terms of assessing causal associations or tumor promoting properties for individual malignancies.

Table 31: Summary of Malignancies and Premalignant Conditions (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total TEAEs – no. (%)	**15 (1.0)**	**19 (1.1)**	**27 (1.6)**	**46 (1.3)**
Large intestine polyp*	3 (0.2)	5 (0.3)	2 (0.1)	7 (0.2)
Cervical dysplasia*	0	2 (0.1)	1 (0.1)	3 (0.1)
Gastric polyps*	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Basal cell carcinoma	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Pancreatic carcinoma¶	0	0	2 (0.1)	2 (0.1)
Plasma cell myeloma	0	1 (0.1)	1 (0.1)	2 (0.1)
Prostate cancer	0	1 (0.1)	1 (0.1)	2 (0.1)
Invasive ductal breast carcinoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Colon cancer	0	1 (0.1)	1 (0.1)	2 (0.1)
Malignant melanoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Breast cancer	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Endometrial adenocarcinoma	0	0	1 (0.1)	1 (<0.1)
Hepatic cancer metastatic	0	0	1 (0.1)	1 (<0.1)
Colon adenoma*	2 (0.1)	1 (0.1)	0	1 (<0.1)
Keratoacanthoma	0	0	1 (0.1)	1 (<0.1)
Chronic lymphocytic leukaemia	0	1 (0.1)	0	1 (<0.1)
Leukaemia	0	0	1 (0.1)	1 (<0.1)
Leukoplakia oral*	0	1 (0.1)	0	1 (<0.1)
Lip squamous cell carcinoma	0	0	1 (0.1)	1 (<0.1)
Carcinoma in situ of skin	0	0	1 (0.1)	1 (<0.1)
Monoclonal gammopathy*	0	0	1 (0.1)	1 (<0.1)
Mucoepidermoid carcinoma of salivary gland	0	0	1 (0.1)	1 (<0.1)
Myelodysplastic syndrome*	0	1 (0.1)	0	1 (<0.1)
Nodal marginal zone B-cell lymphoma stage III	0	1 (0.1)	0	1 (<0.1)
Non-Hodgkin's lymphoma	0	0	1 (0.1)	1 (<0.1)
Anal polyp*	0	1 (0.1)	0	1 (<0.1)
Pancreatic neoplasm¶	0	0	1 (0.1)	1 (<0.1)
Pelvic neoplasm	0	0	1 (0.1)	1 (<0.1)
Adenocarcinoma gastric	0	1 (0.1)	0	1 (<0.1)
Actinic keratosis*	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma of lung	0	0	1 (0.1)	1 (<0.1)
Squamous cell carcinoma of the cervix	0	0	1 (0.1)	1 (<0.1)
Uterine cancer	0	1 (0.1)	0	1 (<0.1)
Bladder cancer	1 (0.1)	0	0	0
Breast calcifications*	1 (0.1)	0	0	0

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Colorectal cancer	1 (0.1)	0	0	0
Hepatic cancer	1 (0.1)	0	0	0
Papillary thyroid cancer	1 (0.1)	0	0	0
Squamous cell carcinoma of skin	1 (0.1)	0	0	0
Acute myeloid leukaemia	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -

Abbreviations: 4-MSU, Four-Month Safety Update; MedDRA, Medical Dictionary for Regulatory Activities; no., number; no., number; and TEAE, treatment-emergent adverse event.

*MedDRA PTs of premalignant conditions not reported in the Applicant's list of malignancies.

¶Note: In error, Subject 0502519 had the same SAE of pancreatic cancer event (i.e., 'pancreatic carcinoma' and 'pancreatic neoplasm') reported twice.

Additionally, the possibility that malignancies could be related to the pharmacologic drug class or mechanisms of action was also considered for this safety review. The Applicant claims that "*to date, there has been no reported plausible mechanism of action to support a causal relationship between SGLT2 inhibition and tumor promotion*." In their nonclinical program (i.e., the two-year rat carcinogenicity study), the Applicant reported an increase in the incidence of adrenal medullary pheochromocytoma in male rats receiving ertugliflozin doses of 15 mg/kg/day, which was attributed to altered calcium homeostasis and considered not to be relevant to humans. Additionally, the potential risk of bladder or breast cancers with SGLT2 inhibitors remains uncertain,[140] and there is some concern whether or not incretin-based antihyperglycemic medications, such as sitagliptin, may be associated with a risk of pancreatic carcinomas.[141-146]

No cases of pheochromocytoma or bladder cancer have been reported in the ertugliflozin clinical development program, and breast cancers that occurred after at least six months of treatment exposure were reported in only one non-ertugliflozin- and two ertugliflozin 15 mg-treated subjects. However, there were two subjects with pancreatic carcinomas/neoplasms; both randomized to the ertugliflozin 15 mg/sitagliptin 100 mg arm in Trial P005/1019. Brief narrative summaries of these two cases are described below. The Applicant does not believe either of these to be related to exposure to study drug.

Ertugliflozin 15 mg + Sitagliptin 100 mg Arm:

Subject 0502519: a 54-year-old white male with T2D for approximately 4 years was randomized to the ertugliflozin15 mg/sitagliptin 100 mg treatment arm. His medical history included smoking and alcohol use. Prior concomitant medication was not relevant. On Day 215, the subject presented with abdominal pain after eating fatty foods, which did not improve with dietary changes. The subject had experienced progressive weight loss (approximately 12 kg in 20 days), and IP was discontinued on Day 239. He was admitted to the hospital on Day 242 for further workup (CT and abdominal ultrasound) of his epigastric pain. The CT scan

showed a rounded picture in pancreas head (36x30 cm), with homogenous enhancement after intravenous contrast. Multiple hypodense images in the liver and gallstones also were noted. Similarly, the abdominal ultrasound showed an enlarged pancreatic head along with gallstones. The SAE was coded as pancreatic neoplasm (Day 242). Abnormal laboratory results included a serum lactate dehydrogenase (LDH) of 1029 U/L (ULN 450 U/L) and a white blood cell count (WBC) of 11900 mm^3 (ULN 10000 mm^3). A cholecystectomy and two liver biopsies were performed on Day 245, and the subject was discharged on Day 246. However, no improvement in abdominal symptoms was noted, and the subject was readmitted with jaundice (SAE of 'malignant pancreas tumor worsening') on Day 256. Serum transaminase, BILI, ALP concentrations were elevated, and results from a repeat abdominal ultrasound showed hepatomegaly and multiple foci in the liver. On Day 266, clinical laboratory abnormalities included ALT 142 mg/dL, AST 122 mg/dL (ULN 34 mg/dL), bilirubin conjugated 16.5 mg/dL (ULN 0.3 mg/dL), TBILI 18.9 mg/dL (ULN 1 mg/dL), and WBC count 14,500 mg/dL (ULN 10000 mg/dL). On Day 270, the subject experienced 'arterial hypotension', 'cardiac arrest', and died. The liver biopsy results showed a morphological and immunological profile consistent with adenocarcinoma of the liver (samples were positive for carcinoembryonic antigen, caudal type homeobox 2, keratin 18, keratin 17, and had isolated positive cells for keratin 20). The investigator considered the SAE of pancreatic carcinoma to be unrelated to IP, and reported this SAE as fatal.

Subject 0502213: a 47-year-old white male with T2D for approximately 11 years was randomized to the ertugliflozin15 mg/sitagliptin 100 mg. On Day 108 he was hospitalized for abdominal bloating/discomfort with nausea and vomiting, and discharged on this same day. On Day 115 he was readmitted with abdominal pain and obstructive jaundice (scleral icterus and abdominal tenderness). The subject did not have a history of alcohol abuse, chronic pancreatitis, or liver cirrhosis, and prior medication use was not relevant. Clinical laboratory results were significant for a total TBILI 13.4 mg/dL (UNL 1.3 mg/dL), direct BILI 7.8 mg/dL (ULN 0.3 mg/dL), AST 116 U/L (ULN 69 U/L), ALP 329 U/L (ULN 126 U/L), lipase 4154 U/L (ULN 300 U/L), and amylase 298 U/L (ULN 110 U/L). A CT scan showed a 5 cm mass at the head of the pancreas. The subject was scheduled to be transferred to another facility for further evaluation and management as well as surgical intervention as needed. On Day 120, he experienced worsening biliary obstruction, with a reported SAE coded as pancreatic carcinoma (it is noted that in the Summary of Clinical Safety, the onset date is reported as Day 36). Laboratory test results at that time included TBILI 15 mg/dL (ULN 1.3 mg/dL), ALT 155 U/L (ULN 72 U/L), AST 74 U/L (ULN 55 U/L), ALP 283 U/L (ULN 126 U/L), and lipase 2338 U/L (ULN 232 U/L). An endoscopic retrograde cholangiopancreatography (ERCP) of the upper gastrointestinal tract showed a large duodenal infiltrative mass. An endoscopic ultrasound showed a round hypoechoic and heterogeneous mass (50x40 mm in diameter) in the pancreatic head, and fine needle biopsy confirmed adenocarcinoma. The subject underwent a rendezvous procedure (Day 123) with stenting of the common bile duct from liver to intestine. Laboratory test results included TBILI 19.3 mg/dl (ULN 1.2 mg/dL), AST 77 U/L (ULN 55 U/L), ALT 133 U/L (ULN 72 U/L), ALP 216 U/L (ULN 126 U/L), and lipase 2338 U/L (ULN 232 U/L). The subject was discharged on Day 125, with plans for follow-up discussion regarding therapeutic options. The last dose of IP was taken on Day 92. The investigator considered the SAE to be not related to IP.

Due to the relatively short latency periods between the diagnosis of pancreatic carcinoma and treatment exposure (i.e., approximately 4 and 7 months, respectively), as well as preexisting risk factors (i.e., smoking/alcohol use and duration of T2D, respectively), I concur that a causal association with ertugliflozin plus sitagliptin for both subjects is not likely. In the three trials that included ertugliflozin plus sitagliptin treatment arms, subjects were exposed to ertugliflozin plus sitagliptin combination therapy for a mean duration of approximately 173 days. It has been suggested that the time span from initiation of tumorigenesis (e.g., an initiated pancreatic intraepithelial neoplasia lesion) to a parental clone (which will initiate an infiltrating pancreatic carcinoma) is approximately 12 years.[144,147] However, whether

ertugliflozin and/or sitagliptin may have tumor promoting properties remains unknown. It has been reported that pharmacological therapies that mimic or increase GLP-1 activity (e.g., DPP-4 inhibitors) may have the potential to increase β-cell proliferation, increase β-cell neogenesis, and decrease β-cell apoptosis, resulting in a situation where cells containing damaged DNA survive and proliferate.[144,145]

8.5.2. **Osmotic Diuresis**

The pharmacodynamic effects of SGLT2 inhibitors include glucosuria, urinary caloric loss, osmotic diuresis and increases in urine volume.[24-26,139,148] Using a broad CMQ (Appendix 13.4), the safety datasets were searched for AEs associated with diuresis and related symptoms. Based on these queries, higher proportions of ertugliflozin-treated subjects in both the Placebo (Table 21) and the 4-MSU (Table 23) Pools had increased urination-related AEs, and these events are reported as common adverse reactions in proposed ertugliflozin product labeling. Please refer to Section 8.4.5 for a complete listing of these events. Additionally, in the 4-MSU Pool, a single SAE ('urge incontinence') was reported in a subject randomized to the ertugliflozin 5 mg arm, and the following AEs, potentially associated with increased diuresis, resulted in discontinuation of IP in ertugliflozin-treated subjects (Table 19): 'pollakiuria' (n=4), 'dizziness' (n=3), 'weight decreased' (n=3), 'dysuria' (n=2), 'polyuria' (n=2), and 'thirst' (n=1).

8.5.3. **Volume Depletion**

As noted in the previous section, SGLT2 inhibitors are associated with osmotic diuresis. This pharmacologic effect could potentially result in intravascular volume contraction, predisposing patients to acute kidney injury, especially in individuals with impaired renal function, heart failure, dehydration, elderly patients, or patients receiving loop diuretics, ACEIs, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs).[119,120]

Although volume depletion and related AEs (e.g., hypotension, dehydration, hypovolemia) were limited in the 4-MSU Pool, higher proportions were reported in the ertugliflozin treatment arms (Table 32). The incidences of events were reported as 1.2% in the non-ertugliflozin arm, and 1.9% and 1.6% in the ertugliflozin 5 mg and 15 mg arms, respectively, with 'hypotension' and 'orthostatic hypotension' being the most common MedDRA PTs. Use of a broad CMQ (Appendix 13.4), did not reveal any additional volume depletion-related events.

Table 32: Summary of Volume Depletion Related Adverse Events (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total TEAEs – no. (%)	**17 (1.2)**	**33 (1.9)**	**27 (1.6)**	**60 (1.8)**
Hypotension	2 (0.1)	12 (0.7)	11 (0.6)	23 (0.7)
Orthostatic hypotension	2 (0.1)	4 (0.2)	7 (0.4)	11 (0.3)
Dehydration	4 (0.3)	6 (0.3)	4 (0.2)	10 (0.3)
Syncope	5 (0.3)	8 (0.5)	2 (0.1)	10 (0.3)
Presyncope	2 (0.1)	1 (0.1)	4 (0.2)	5 (0.1)
Dizziness postural	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Diastolic hypotension	0	1 (0.1)	0	1 (<0.1)
Circulatory collapse	0	1 (0.1)	0	1 (<0.1)
Hypovolaemia	0	0	1 (0.1)	1 (<0.1)
Orthostatic intolerance	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: 4-MSU, Four-Month Safety Update; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and TEAE, treatment-emergent adverse event.

8.5.4. Renal Failure/Impairment

As previously mentioned in Section 8.4.6, ertugliflozin labeling will include acute kidney injury and impairment of renal function in Section 5 (WARNINGS AND PRECAUTIONS). For detailed discussion of treatment-emergent changes in renal function and renal impairment-related AEs please refer to this section of the review.

8.5.5. Genital Infections

Diabetic patients, especially those with poor glycemic control, are at risk for developing genital mycotic infections, such as vulvovaginal candidiasis in women and candida balanitis in men.[149] SGLT2 inhibitors appear to increase this risk,[150-154] possibly mediated through glucosuria. The Applicant includes the risk of genital mycotic infections in proposed labeling for both ertugliflozin and the ertugliflozin FCDPs.

In the ertugliflozin clinical program, dose-related increases in AEs of genital mycotic infections and related symptoms were reported in ertugliflozin-treated subjects in both the Placebo (Table 21) and the 4-MSU (Table 23) Pools. Please refer to Section 8.4.5 for a complete listing of these adverse events.

In the Placebo Pool, the Applicant reported genital infections in 3% (7/235), 9.1% (23/252) and 12.2% (30/245) of females in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment

arms, and in 0.4% (1/280), 3.7% (10/267), and 4.2% (11/265) of males, respectively. Additionally, in ertugliflozin-treated male subjects, events of genital mycotic infection were more frequent in uncircumcised men (5.2% [16/305]) relative to those who were circumcised (1.9% [3/156 subjects]).

In the 4-MSU, the Applicant reported that 3% (20/663), 8.9% (74/831), and 10.8% (92/849) of females had at least one genital mycotic infection in the non-ertugliflozin, ertugliflozin 5 mg and ertugliflozin 15 mg arms, respectively. In males, genital mycotic infections were reported in 0.4% (3/787), 4.7% (42/885) and 3.9% (33/844), respectively. 'Vulvovaginal mycotic infection' and 'vulvovaginal candidiasis' were the two most common MedDRA PTs for females in both safety pools, while 'balanoposthitis' and 'genital infection fungal' were the most commonly reported events in males.

Across the entire clinical program, complicated genital infections (defined as an SAE, or AE considered potentially medically significant, within the Applicant's genital mycotic infection CMQ) were limited, reported in two female subjects each from the non-ertugliflozin ('vulval abscess' and 'vaginal haemorrhage'), ertugliflozin 5 mg ('vulval abscess' and 'vaginal haemorrhage'), and ertugliflozin 15 mg (both 'vaginal haemorrhage'), treatment arms. For males, complicated infections were reported in one non-ertugliflozin-treated subject ('phimosis') and in three subjects in the ertugliflozin 5 mg arm (n=2 'phimosis, and n=1 'cellulitis of male external genital organ') and eight subjects in the ertugliflozin 15 mg arm (n=6 'phimosis', n=1 'cellulitis of male external genital organ', and n=1 balanoposthitis). It is noted that four of eight male ertugliflozin-treated subjects with phimosis required circumcision.

In the Broad Pool, recurrent genital infections (≥2 events) occurred in 0.6% (4/663) and 2.5% (42/1680) of females in the non-ertugliflozin and ertugliflozin treatment arms, respectively, while 0.1% (1/787) of non-ertugliflozin-treated males and 0.8% (14/1729) of ertugliflozin-treated males had recurrent infections.

8.5.6. **Urinary Tract Infections**

As previously noted with genital infections, T2D patients receiving SGLT2 inhibitors also are at increased risk for urinary tract infections (UTIs).[151,154] Both the common adverse reactions tables and WARNINGS AND PRECAUTIONS sections of proposed product labeling for ertugliflozin and the ertugliflozin FCDPs include information related to this risk.

The proportions of subjects with UTIs reported by the Applicant were similar across treatment arms for both the short-term and long-term safety populations, occurring in 3.9% (20/515), 4.0% (21/519) and 4.1% (21/510) of subjects in the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms, respectively in the Placebo Pool (Table 20), and in 8.3% (120/1450), 7.3% (125/1716), and 7.7% (130/1693) of non-ertugliflozin-, ertugliflozin 5 mg- and ertugliflozin

15 mg-treated subjects, respectively in the 4-MSU Pool. Using a broad CMQ (Appendix 13.4) that included the UTI-related AEs, as well as the MedDRA PTs used in the Applicant's CMQ, the events were similar across treatment arms (i.e., 8.8% in the non-ertugliflozin arm vs. 7.8% in the ertugliflozin 5 mg arm and 8.3% in the ertugliflozin 15 mg arm; Table 33). None of the additional events were coded as SAEs, and a review of the PTs did not reveal any additional safety concerns.

Table 33: Summary of Urinary Tract Infections and Related Adverse Events (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total TEAEs – no. (%)	**128 (8.8)**	**134 (7.8)**	**141 (8.3)**	**275 (8.1)**
Urinary tract infection	97 (6.7)	99 (5.8)	98 (5.8)	197 (5.8)
Dysuria	10 (0.7)	15 (0.9)	18 (1.1)	33 (1.0)
Cystitis	5 (0.3)	12 (0.7)	13 (0.8)	25 (0.7)
Asymptomatic bacteriuria*	2 (0.1)	7 (0.4)	2 (0.1)	9 (0.3)
Prostatitis*	2 (0.1)	4 (0.2)	4 (0.2)	8 (0.2)
Urogenital infection fungal	1 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Leukocyturia*	2 (0.1)	0	3 (0.2)	3 (0.1)
Pyelonephritis	0	1 (0.1)	2 (0.1)	3 (0.1)
Urinary tract infection fungal*	1 (0.1)	0	3 (0.2)	3 (0.1)
Pyelonephritis acute	2 (0.1)	2 (0.1)	0	2 (0.1)
Urethritis	2 (0.1)	2 (0.1)	0	2 (0.1)
Urinary tract inflammation*	0	0	2 (0.1)	2 (0.1)
Urine leukocyte esterase positive*	0	0	2 (0.1)	2 (0.1)
Bacteriuria*	0	1 (0.1)	0	1 (0.0)
Cystitis klebsiella	0	0	1 (0.1)	1 (0.0)
Escherichia urinary tract infection	2 (0.1)	1 (0.1)	0	1 (0.0)
Kidney infection	1 (0.1)	0	1 (0.1)	1 (0.0)
Nephritis*	0	0	1 (0.1)	1 (0.0)
Nitrite urine present*	0	0	1 (0.1)	1 (0.0)
Pyelonephritis chronic	0	0	1 (0.1)	1 (0.0)
Streptococcal urinary tract infection	1 (0.1)	1 (0.1)	0	1 (0.0)
Urinary tract infection bacterial	1 (0.1)	0	1 (0.1)	1 (0.0)
White blood cells urine positive*	3 (0.2)	1 (0.1)	0	1 (0.0)
Candiduria*	2 (0.1)	0	0	0
Pyuria*	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -

Abbreviations: 4-MSU, Four-Month Safety Update; MedDRA, Medical Dictionary for Regulatory Activities; no., number; and TEAE, treatment-emergent adverse event.

* UTI-related MedDRA PTs not reported in the Applicant's list of UTI AEs.

Complicated UTIs (defined as SAEs, or AEs considered potentially medically significant, within the Applicant's UTI CMQ) were reported in 0.3% (5/1450) of subjects in the non-ertugliflozin treatment arm, and in 0.2% (4/1716) and 0.6% (10/1693) of subjects in the ertugliflozin 5 mg and 15 mg arms, respectively. In the 14 ertugliflozin-treated subjects, these events included 'cystitis' (n=1); 'kidney infection' (n=1); 'pyelonephritis'/'pyelonephritis acute'/'pyelonephritis chronic' (n=6); and 'urinary tract infection' (n=6). No cases of urosepsis were reported in either ertugliflozin treatment arm during treatment exposure.

In the Broad Pool, recurrent UTIs (≥2 events) occurred in 1.5% (22/1450) of subjects in the non-ertugliflozin treatment arm, and in 1.3% (22/1716) and 1.5% (25/1693) of ertugliflozin 5 mg and 15 mg-treated subjects, respectively.

8.5.7. Hypoglycemia

For all clinical trials, hypoglycemia was defined as any documented blood glucose concentration ≤70 mg/dL, regardless of symptoms, while severe hypoglycemia was defined as an event consistent with hypoglycemia where the subject required the assistance of another person to recover, lost consciousness, or experienced a seizure, regardless of whether a low glucose concentration was documented.

In the Placebo Pool, documented and severe hypoglycemic events, regardless of antihyperglycemic rescue, were limited and similar across treatment arms (Table 34). Additionally, based on the Applicant's prespecified analyses (i.e., Miettinen & Nurminen method stratified by study),[98] the percent differences in events between the ertugliflozin treatment arms and placebo were not statistically significant. Results were similar if subjects requiring rescue are excluded (i.e., documented hypoglycemia reported in 2.9%, 5% and 4.5% in the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms, respectively).

Table 34: Summary of Hypoglycemic Events (Placebo Pool)*

Hypoglycemia Events — no. (%)	Placebo Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)
Documented ¶	21 (4.1)	27 (5.2)	25 (4.9)
Asymptomatic	12 (2.3)	19 (3.7)	17 (3.3)
Symptomatic	11 (2.1)	10 (1.9)	9 (1.8)
Severe †	5 (1.0)	2 (0.4)	2 (0.4)
Requiring non-medical assistance	3 (0.6)	1 (0.2)	1 (0.2)
Requiring medical assistance	2 (0.4)	1 (0.2)	1 (0.2)

Source: Derived from the iss adsl.xpt and adha.xpt datasets, available at: Application 209803 - Sequence 0000 - Analysis Dataset Legacy – ; and adapted from the Applicants' Integrated Summary of Safety, labeled as Table 273, page 2120 of 9829, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\iss.pdf
Abbreviations: no., number.
* **Includes rescue.**
¶ **Documented episode**: defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any plasma or capillary glucose value ≤70 mg/dL).
† **Severe episode**: defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained).

The Applicant's summary table of documented (asymptomatic and symptomatic) and severe hypoglycemic events by each Phase 3 trial is presented in Table 44 (Appendix 13.6).

Additionally, the data from the 4-MSU Pool was searched for AEs associated with hypoglycemia using a broad CMQ (Appendix 13.4). Although a higher proportion of events occurred in the non-ertugliflozin treatment arm (Table 35), it is noted that this arm also included data from Trial P002/1013, which compared ertugliflozin to the active comparator, glimepiride. In this trial, documented hypoglycemia (plasma or capillary glucose ≤70) was reported in 27.2% (119/437) of subjects randomized to the glimepiride arm, compared to 5.6% (25/448) and 8.2% (36/440) of ertugliflozin 5 mg and 15 mg-treated subjects, respectively. Excluding data from Trial P002/1013 yields hypoglycemia-related AEs occurring in 11.6% of non-ertugliflozin-treated subjects and 7.7% of ertugliflozin-treated subjects.

Table 35: Summary of Hypoglycemia Related Adverse Events (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total Hypoglycemia AEs – no. (%)	**223 (15.4)**	**118 (6.9)**	**127 (7.5)**	**245 (7.2)**
Hypoglycaemia	223 (15.4)	118 (6.9)	126 (7.4)	244 (7.2)
Hypoglycaemia unawareness	0	0	1 (0.1)	1 (<0.1)
Cold sweat	1 (0.1)	0	0	0
Hypoglycaemic seizure	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: no., number; and TEAE, treatment-emergent adverse event.

For Trial P001/1016 (i.e., the dedicated moderate renal impairment trial), background insulin and/or insulin secretagogues were allowed. Although higher rates of documented hypoglycemic episodes were observed (Table 44), the proportions of subjects were similar between treatment arms (i.e., 36.1% [48/133] of placebo-treated subjects; 35.8% [53/148] of ertugliflozin 5 mg-treated subjects; and 27.3% [39/143] of ertugliflozin 15 mg-treated subjects).

Notably, except for Trial P001/1016, ertugliflozin has not been studied in combination with insulin or insulin secretagogues. Thus, there is limited hypoglycemia data on the use of ertugliflozin in combination with these drugs in the entire patient population that may be exposed to ertugliflozin-containing products. Nevertheless, it is expected that ertugliflozin in combination with either of these would increase the risk for hypoglycemia. Additional data will be available following completion of the Applicant's ongoing CVOT (Trial P004/1021), which includes three glycemic sub-studies of subjects receiving background insulin with/without metformin, sulfonylurea monotherapy, or sulfonylurea plus metformin.

Hypoglycemia: Ertugliflozin/Sitagliptin and Ertugliflozin/Metformin FCDPs

The numbers of hypoglycemic events, particularly severe events, were limited in the clinical trials in which ertugliflozin was used as add-on/combination therapy with sitagliptin and/or metformin. Except for the ertugliflozin plus sitagliptin factorial trial (P005/1019), in which hypoglycemia was observed in 9% (22/244) of subjects in the ertugliflozin 15 mg/sitagliptin 100 mg arm compared to ≤5.6% in all other treatment arms (i.e., sitagliptin 100 mg, ertugliflozin 5 mg, ertugliflozin 15 mg and ertugliflozin 5 mg plus sitagliptin 100 mg), a dose response for hypoglycemic events with ertugliflozin in combination with sitagliptin and/or metformin was not observed.

8.5.8. Bone Safety / Fractures

As discussed in Section 8.4.6, SGLT2 inhibitors have been associated with small increases in PTH concentrations, decreases in 1,25-dihydroxyvitamin D concentrations, and the potential for decreased bone mineral density and/or increased fracture risk.[124,155] In September 2015, the Agency issued a Safety Communication related to decreased bone mineral density and increased fracture risk associated with canagliflozin, and stated that the risk of bone fractures with other drugs in the SGLT2 inhibitor class, including dapagliflozin and empagliflozin, would continue to be evaluated to determine if additional label changes or studies are needed.[156] Although several recent meta-analyses did not observe an increased fracture risk with SGLT2 inhibitor use, interpretation of the results from these reports is limited, as fractures were often not a prespecified AE endpoint in the included trials, and treatment exposures and follow-up were relatively short.[157,158]

Across the ertugliflozin clinical program (i.e., 4-MSU Pool), fractures (low and high trauma fractures) were similar across treatment arms; reported in 0.7% of non-ertugliflozin-treated subjects compared with 0.6% and 0.5% of subjects randomized to the ertugliflozin 5 mg and 15 mg arms, respectively (Table 36).

Table 36: Summary of Confirmed Fractures (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total Fractures – no. (%)	**10 (0.7)**	**11 (0.6)**	**9 (0.5)**	**20 (0.6)**
Low trauma fracture	7 (0.5)	6 (0.3)	6 (0.4)	12 (0.4)
Radius	0	0	3 (0.2)	3 (0.1)
Metatarsals	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)
Humerus	0	2 (0.1)	0	2 (0.1)
Femur	1 (0.1)	0	1 (0.1)	1 (<0.1)
Fibula, Tibia	0	1 (0.1)	0	1 (<0.1)
Lumbar	0	1 (0.1)	0	1 (<0.1)
Metacarpals	0	0	1 (0.1)	1 (<0.1)
Radius, Ulna	0	1 (0.1)	0	1 (<0.1)
Fibula	2 (0.1)	0	0	0
Clavicle	1 (0.1)	0	0	0
Phlanges	1 (0.1)	0	0	0
Tibia	1 (0.1)	0	0	0
High trauma fracture	3 (0.2)	5 (0.3)	3 (0.2)	8 (0.2)
Phlanges	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Cranium	0	1 (0.1)	0	1 (0.0)
Femur, Lumbar	0	1 (0.1)	0	1 (0.0)
Fibula, Tibia	0	0	1 (0.1)	1 (0.0)
Radius	0	1 (0.1)	0	1 (0.0)
Ribs	0	0	1 (0.1)	1 (0.0)
Lumbar, Maxilla, Ribs, Sternum, Tarsals, Tibia	1 (0.1)	0	0	0
Tibia	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: 4-MSU, Four-Month Safety Update; MedDRA, Medical Dictionary for Regulatory Activities; and no., number.

The Applicant also assessed bone mineral density (BMD) in Trial P007/1017. However, since this trial was ongoing at the time of NDA submission, only the results from the 52-week dual-energy x-ray absorptiometry (DXA) measurements were provided (i.e., the 104-week assessments were not available). Based on these data, percent changes from baseline at three (lumbar spine, femoral neck, and distal forearm) of the four anatomic sites evaluated were not statistically different between treatment arms (data not shown). However, the percent change in BMD at the total hip was statistically significantly lower in the ertugliflozin 15 mg treatment arm (LS mean placebo-subtracted difference: -1.13%; 95% CI, -1.46 to -0.80). Similarly, in the all-female subgroup, the BMD at the total hip was lower in the ertugliflozin 15 mg treatment arm (-0.80%; 95% CI, -1.42 to -0.17). In the subsets that included only male subjects or only postmenopausal female subjects, BMD results were not significantly different between treatment arms at all four sites.

Please refer to Section 8.4.6 for discussion of pertinent laboratory findings related to serum PTH, minerals, and bone biomarkers.

8.5.9. **Adjudicated Hepatic Events**

The Applicant acknowledges that hepatic safety is a significant issue in drug development. Therefore, potential AEs of drug-induced liver injury were adjudicated by an independent clinical events committee (i.e., CEC) blinded to treatment allocation. The CEC was composed of two hepatologists and three gastroenterologists. Laboratory abnormalities that met the following criteria were used to identify events to be adjudicated: ALT or AST elevation ≥5x ULN, or ALT or AST ≥3x ULN and total bilirubin ≥2x ULN within 14 days of the transaminase elevation. The Applicant also performed periodic searches of the data using a CMQ based on the MedDRA PTs included in the 'Drug-related Hepatic Disorders' SMQ. Potential hepatic AEs were submitted for adjudication if the laboratory values met the above criteria. Additionally, all events of liver transplant were adjudicated.

Based on the PDLC for hepatic laboratory tests (Table 24), clinically relevant hepatic events were limited, and there did not appear to be obvious differences between treatment arms. In total, hepatic events were adjudicated for 0.2% (3/1450) of subjects in the non-ertugliflozin treatment arm, 0.2% (4/1716) of subjects in the ertugliflozin 5 mg arm, and 0.4% (6/1693) of subjects in the ertugliflozin 15 mg arm. The causality for the four ertugliflozin-treated subjects in the 5 mg arm were adjudicated as 'possible', and the two subjects in the ertugliflozin 15 mg arm as 'possible' (all with transaminase elevation ≥5x ULN); no cases were adjudicated as 'likely' or 'probable'. A 'possible' causal association was defined as an event that might be due to the use of the IP, the relationship in time is suggestive, and an alternative explanation is less likely. Of these six ertugliflozin-treated subjects, two were using acetaminophen (of which one discontinued IP), two had laboratory abnormalities resolved during treatment, one was hepatitis C antibody positive, and one had resolution of transaminase elevations following interruption of IP without subsequent abnormal results following restarting therapy. Based on the temporal association without definitive alternative etiologies, I concur with the CEC adjudication that these events could possibly be related to IP.

Two additional subjects in the ertugliflozin 15 mg arm had a combined transaminase elevation ≥3x ULN and total bilirubin ≥2x ULN, both were adjudicated as 'not related'. One case (Subject 0502519) involved a 54-year-old male who presented with a pancreatic carcinoma on Day 242 (previously described in Section 8.5.1) and the hepatic event reported on Day 252, while the second involved a 56-year-old female (Subject 0200144) who received her last dose of IP on Day 325, with the onset of the hepatic event on Day 634.

I again concur with the CEC that a causal association with IP is unlikely.

8.5.10. **Adjudicated Pancreatitis Events**

Cases of acute pancreatitis associated with SGLT2 inhibitors have been reported in the medical literature.[159-162]

In the ertugliflozin clinical program, potential events of pancreatitis, identified by a CMQ, were sent for confirmation to a blinded adjudication committee (consisting of four gastroenterologists experienced in the diagnosis and management of pancreatitis). The case definition for acute pancreatitis included at least two of the following three criteria: 1) abdominal pain consistent with acute pancreatitis; 2) serum lipase or amylase at least 3x UNL; and 3) characteristic findings on contrast-enhanced computed tomography magnetic resonance imaging or transabdominal ultrasonography.[163,164] The diagnosis of chronic pancreatitis was based on imaging, regardless of the presence or absence of clinical symptoms, or a Cambridge classification score of 3-5 (corresponding to Cambridge class I-III).[165,166]

At the time of the 4-MSU, there were five cases identified for adjudication: two cases in the non-ertugliflozin arm ('pancreatitis' and 'pancreatitis acute'), two in the ertugliflozin 5 mg arm ('pancreatitis' and 'pancreatitis acute'), and one case in the ertugliflozin 15 mg arm ('jaundice cholestatic'). None of these cases were adjudicated as confirmed pancreatitis (acute or chronic). Brief narrative summaries of the three ertugliflozin-treated subjects are as follows:

Ertugliflozin 5 mg Arm:

Subject 0502509: 55-year-old white female with T2D for approximately 14 years, randomized to ertugliflozin 5 mg in Trial P005/1019, was hospitalized on Day 98 for possible pancreatitis associated with a 3-week history of right upper abdominal quadrant pain (worse after meals) and progressive nausea, vomiting, diarrhea, dehydration and weight loss (approximately 5.4 kg within the last 2 weeks). Imaging (ultrasound and computed tomography scan) showed evidence of gallbladder stones/sludge consistent with acute on chronic cholecystitis. Relevant laboratory test included: serum bicarbonate 16.6 mmol/L (20-26 mmol/L), potassium 3.0 mmol/L (3.5-5.1 mmol/L), anion gap 25 mmol/L (6-16 mmol/L), glucose 222 mg/dL (70-100 mg/dL), BUN 99 mg/dL (6-25 mg/dL), creatinine 4.0 mg/dL (0.5-0.8 mg/dL), eGFR 12 ml/min/1.73m^2 (≥60 mL/min/1.73m^2), lipase 666 U/L (73-393 U/L), and WBC 12.0×10^3/µL (4.0 to 11.0×10^3/µL). The urinalysis was significant for glucose, trace ketones, 1+ occult blood, leukocytes, and >100,000 cfu/mL of E. coli. The subject was diagnosed with gallstone pancreatitis. On Day 99, serum lipase decreased to 492 U/L and then to 223 U/L on Day 101. She underwent a laparoscopic cholecystectomy on Day 101, and was discharged on Day 103. Laboratory test results were unremarkable. The study medication was not changed due to the event. The investigator considered the SAE to be not related to IP, and the CEC adjudicated the event as not pancreatitis.

I concur that this AE was likely due to cholelithiasis. Whether IP may have contributed to the presenting clinical symptoms and laboratory findings (i.e., based on the known pharmacologic properties of SGLT2 inhibitors) is uncertain.

> **Subject 0201092:** 64-year-old white female with T2D, randomized to ertugliflozin 5 mg in Trial P002/1013, had an AE coded as 'pancreatitis acute' on Day 524. The CEC was not able to adjudicate the event due to lack of relevant information (e.g., serum lipase/amylase, imaging, and hospital reports).

Due to limited clinical information, I agree with the CEC that adjudication of this case was not possible.

Ertugliflozin 15 mg Arm:

> **Subject 0200171:** 64-year-old white male with T2D for approximately 24 years, receiving metformin 2000 mg daily, was randomized to ertugliflozin 15 mg arm in Trial P002/1013. The subject had no other relevant medical history or prior medications. On Day 455, he experienced cholestatic jaundice leading to discontinuation of the IP. The subject reported nausea and vomiting for 3 weeks, along with bilateral pedal edema, managed with promethazine and furosemide, respectively. Relevant laboratory results included serum albumin 2.8 gm/dL (3.5-5.2), ALP 463 IU/L (40-129), AST 89 (≤37), BILI 13.5 mg/dL (0.2-1.2). IP was discontinued on Day 462 due to the event ('jaundice cholestatic'). The investigator considered the AE to be not related to the IP. The subject's last dose of IP was taken on Day 461. The CEC felt that there was insufficient information to adjudicate this event (i.e., no clinical notes, pertinent labs, such as amylase and/or lipase, or imaging studies).

I agree that there is insufficient information for this subject with long-standing T2D to determine a diagnosis of pancreatitis. Further, both promethazine[167] and furosemide[168,169] have both been associated with cholestatic jaundice.

Ertugliflozin/Sitagliptin FCDP

In March of 2013, the Agency issued a Drug Safety Communication of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for T2D.[143] Pancreatitis is included in the WARNINGS AND PRECAUTIONS section of proposed product labeling for this FCDP.

8.5.11. Hypersensitivity Reactions

Hypersensitivity reactions have been reported in the literature,[170,171] and are listed in the WARNINGS AND PRECAUTIONS and/or ADVERSE REACTIONS sections of several approved SGLT2 inhibitors.[24,25] The Applicant lists 'history of serious hypersensitivity reaction' to ertugliflozin as a contraindication in proposed product labeling, similar to approved labeling for other SGLT2 inhibitors.[24-26]

In the 4-MSU Pool, the proportions of subjects with hypersensitivity AEs were similar across treatment arms, reported in 2.8% (40/1450), 3.5% (60/1716), and 2.5% (43/1693) of subjects in the non-ertugliflozin, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms. Using a broad CMQ (Appendix 13.4) that included MedDRA PTs for hypersensitivity, anaphylactic reactions,

and angioedema, event rates were higher, but again similar between arms (Table 37). Additionally, none of these events were fatal, and there were no obvious imbalances between arms based on discontinuations/interruptions of IP or serious hypersensitivity AEs (data not shown). In the 5 mg and 15 mg ertugliflozin treatment arms, a single subject each had a reported AE of 'exfoliative rash' (Subject 0200044: 'rash scaly' on Day 75) and 'skin exfoliation' (Subject 0311014: 'post-streptococcal skin reaction/skin peeling on hands' on Day 19), respectively. Both events were coded as mild in severity, and resolved without interruption or discontinuation of IP.

Table 37: Summary of Hypersensitivity Adverse Effects (4-MSU)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Hypersensitivity AEs – no. (%)	**98 (6.8)**	**127 (7.4)**	**106 (6.2)**	**233 (6.8)**
Rash	11 (0.8)	16 (0.9)	9 (0.5)	25 (0.7)
Hypotension*	2 (0.1)	12 (0.7)	11 (0.6)	23 (0.7)
Conjunctivitis*	7 (0.5)	14 (0.8)	8 (0.5)	22 (0.6)
Pruritus*	11 (0.8)	10 (0.6)	8 (0.5)	18 (0.5)
Dermatitis	2 (0.1)	6 (0.3)	7 (0.4)	13 (0.4)
Asthma*	12 (0.8)	4 (0.2)	8 (0.5)	12 (0.4)
Peripheral swelling*	5 (0.3)	7 (0.4)	5 (0.3)	12 (0.4)
Rhinitis allergic	3 (0.2)	4 (0.2)	5 (0.3)	9 (0.3)
Urticaria	6 (0.4)	7 (0.4)	2 (0.1)	9 (0.3)
Dermatitis allergic	2 (0.1)	2 (0.1)	6 (0.4)	8 (0.2)
Dyspnoea*	5 (0.3)	2 (0.1)	5 (0.3)	7 (0.2)
Erythema*	2 (0.1)	6 (0.3)	1 (0.1)	7 (0.2)
Oedema peripheral*	10 (0.7)	3 (0.2)	4 (0.2)	7 (0.2)
Eczema	5 (0.3)	2 (0.1)	4 (0.2)	6 (0.2)
Dermatitis contact*	3 (0.2)	4 (0.2)	1 (0.1)	5 (0.1)
Drug hypersensitivity	2 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Eosinophilia*	0	3 (0.2)	1 (0.1)	4 (0.1)
Hypersensitivity	0	4 (0.2)	0	4 (0.1)
Mouth ulceration*	0	3 (0.2)	1 (0.1)	4 (0.1)
Conjunctivitis allergic	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)
Prurigo*	0	0	3 (0.2)	3 (0.1)
Bronchospasm	0	2 (0.1)	0	2 (0.1)
Eosinophil count increased*	1 (0.1)	0	2 (0.1)	2 (0.1)
Genital rash*	0	1 (0.1)	1 (0.1)	2 (0.1)
Genital swelling*	0	1 (0.1)	1 (0.1)	2 (0.1)
Pruritus allergic	0	1 (0.1)	1 (0.1)	2 (0.1)
Pruritus generalised*	3 (0.2)	2 (0.1)	0	2 (0.1)
Rash pruritic	1 (0.1)	2 (0.1)	0	2 (0.1)
Rash pustular	0	2 (0.1)	0	2 (0.1)
Respiratory failure*	0	1 (0.1)	1 (0.1)	2 (0.1)

MedDRA Preferred Terms	4-MSU			
	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Seasonal allergy*	3 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)
Acute respiratory failure*	1 (0.1)	1 (0.1)	0	1 (<0.1)
Allergic bronchitis	0	1 (0.1)	0	1 (<0.1)
Allergic sinusitis	0	1 (0.1)	0	1 (<0.1)
Bronchial hyperreactivity*	0	0	1 (0.1)	1 (<0.1)
Circulatory collapse	0	1 (0.1)	0	1 (<0.1)
Dermatitis atopic	0	0	1 (0.1)	1 (<0.1)
Diastolic hypotension*	0	1 (0.1)	0	1 (<0.1)
Drug eruption	0	1 (0.1)	0	1 (<0.1)
Ear swelling*	0	0	1 (0.1)	1 (<0.1)
Exfoliative rash	0	1 (0.1)	0	1 (<0.1)
Eye pruritus*	0	1 (0.1)	0	1 (<0.1)
Eye swelling	1 (0.1)	1 (0.1)	0	1 (<0.1)
Eyelid oedema	0	1 (0.1)	0	1 (<0.1)
Generalised erythema*	0	0	1 (0.1)	1 (<0.1)
Hand dermatitis	0	0	1 (0.1)	1 (<0.1)
Idiopathic urticaria	0	0	1 (0.1)	1 (<0.1)
Interstitial lung disease*	0	1 (0.1)	0	1 (<0.1)
Ocular hyperaemia*	1 (0.1)	1 (0.1)	0	1 (<0.1)
Oedema*	2 (0.1)	1 (0.1)	0	1 (<0.1)
Penile swelling*	1 (0.1)	1 (0.1)	0	1 (<0.1)
Photosensitivity reaction*	0	0	1 (0.1)	1 (<0.1)
Rash erythematous	0	0	1 (0.1)	1 (<0.1)
Rash maculo-papular	0	0	1 (0.1)	1 (<0.1)
Scrotal swelling*	0	1 (0.1)	0	1 (<0.1)
Skin exfoliation*	0	0	1 (0.1)	1 (<0.1)
Sneezing*	0	0	1 (0.1)	1 (<0.1)
Stomatitis*	0	1 (0.1)	0	1 (<0.1)
Swelling face	0	0	1 (0.1)	1 (<0.1)
Urticaria chronic	0	0	1 (0.1)	1 (<0.1)
Vulvovaginal swelling*	0	1 (0.1)	0	1 (<0.1)
Wheezing*	1 (0.1)	0	1 (0.1)	1 (<0.1)
Angioedema	1 (0.1)	0	0	0
Contrast media reaction	1 (0.1)	0	0	0
Erythema nodosum	1 (0.1)	0	0	0
Hypersensitivity vasculitis	1 (0.1)	0	0	0
Iodine allergy	1 (0.1)	0	0	0
Rhinitis perennial*	1 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: no., number.
* MedDRA PTs not reported in the Applicant's list of hypersensitivity AEs.

8.5.12. **Venous Thromboembolism**

Patients with T2D and associated comorbidities may be at increased risk for venous thromboembolism.[172-176] It also has been reported that diabetics may be more likely to have complications following venous thromboembolism and suffer recurrent events.[175] Since osmotic diuresis and hemoconcentration may occur with the use of SGLT2 inhibitors, T2D subjects have been monitored for venous thromboembolic events in the clinical development programs with these products,[177] and venous thromboembolism was considered a Special Safety Topic in the ertugliflozin clinical program. It should be noted; to maintain the integrity of the Applicant's dedicated CVOT (Trial P004/1021), thromboembolic events from this ongoing trial were not included in this review.

The cumulative numbers of subjects with venous embolic and thrombotic adverse events at the time of the 4-MSU were limited, reported in only three subjects in the non-ertugliflozin arm (i.e., 'pulmonary embolism', 'deep vein thrombosis', and 'venous thrombosis'), three subjects in the ertugliflozin 5 mg arm ('deep vein thrombosis', 'thrombophlebitis superficial', and 'venous thrombosis limb') and one subject in the ertugliflozin 15 mg arm ('pulmonary embolism'). None of the events in the ertugliflozin-treated subjects appeared to be related to volume depletion and/or hemoconcentration. However, one of these events (Subject 0710319) was associated with hospitalization for peripheral ischemia and 'left femoral amputation'.

Ertugliflozin 15 mg Arm:

Subject 0710319: 63-year-old white male with T2D for approximately 28 years, randomized to the ertugliflozin 15 mg treatment arm in Trial P007/1017, experienced a pulmonary embolism (PE) on Day 352. Relevant medical history included embolism ('thromboembolism of popliteal'; postsurgical in 2005), hypertension, hyperlipidemia, atrial fibrillation, congestive cardiomyopathy, coronary artery disease, ischemic stroke, and peripheral artery aneurysm (popliteal in 2005). At the time of randomization his concomitant medications included indapamide/perindopril, atorvastatin, carvedilol, aspirin/bisoprolol, piracetam, pentoxifylline, and acenocoumarol. On Day 334, the subject presented with peripheral ischemia. Relevant clinical labs (Day 339) included: C-reactive protein (CRP) 218.5 mg/L (normal range: 0-10 mg/L), international normalized ratio (INR) 4.93 (2-3), blood glucose 14.6 mmol/L (3.6-6.1 mmol/L), and WBC: 16.33 x 10^9/L (4.5-11 x 10^9/L). The subject was hospitalized on Day 340 and underwent left femoral amputation on Day 342 (IP discontinued). During hospitalization, he experienced a pulmonary embolism (Day 352; confirmed by CT on Day 354) and cardiac failure (Day 354), and was started on enoxaparin. The subject also experienced AEs of hypokalemia (Day 349; 3 mEq/L), ileus (Day 348), and metabolic acidosis (Day 354; arterial blood gases not available) during hospitalization. On Day 472, he was discharged from the hospital.

This subject had a prior history of thromboembolism, significant comorbidities, limited mobility, and was off IP for approximately 10 days prior to experiencing a PE. While I do not believe that ertugliflozin was the primary cause for the PE, limb ischemia and/or amputation, its role as a possible contributing factor in these events remains uncertain.

8.5.13. **Ketoacidosis**

Ketoacidosis has emerged as a potentially serious safety concern with the use of SGLT2 inhibitors.[178-213] The pharmacologic mechanisms by which SGLT2 inhibitors may induce ketoacidosis remain uncertain. Predisposing and precipitating risk factors of ketoacidosis have not been well characterized, but may include known precipitating events of ketoacidosis (e.g., surgery, intercurrent illness, pancreatic disorders, dehydration, reduction or omission of insulin doses, excessive alcohol ingestion, caloric/dietary restrictions, weight loss and long-standing T2D).[182,184,185,210,213]

On May 15, 2015, the FDA issued a Drug Safety Communication to alert the public of the potential risk of ketoacidosis with the use of SGLT2 inhibitors; subsequently ketoacidosis was added to product labeling for all SGLT2 inhibitors.[214] Hence, the Applicant's proposed labeling for ertugliflozin and the ertugliflozin FCDPs includes class labeling information of ketoacidosis in the respective WARNINGS AND PRECAUTIONS sections.

The Applicant noted that ketoacidosis had only emerged as a possible safety concern with SGLT2 inhibitors late in Phase 3 development of ertugliflozin. In response to this concern, possible events of ketoacidosis were identified using a prespecified ascertainment strategy, which included narrative searches and the use of a CMQ with the following MedDRA PTs: 'diabetic ketoacidosis'; 'diabetic ketoacidotic hyperglycaemic coma'; 'ketoacidosis'; 'ketonuria'; 'ketosis'; 'urine ketone body present'; 'acidosis'; 'metabolic acidosis'; 'blood ketone body present'; and 'blood ketone body, increased'). Potential cases were reviewed by an Internal Case Review Committee (ICRC), composed of three internal physicians with experience in the diagnosis and management of ketoacidosis. The ICRC members were not part of the ertugliflozin development team, and were blinded to treatment allocation. Determination as to whether a case met the prespecified case definition of ketoacidosis was based on independent review by each member, and majority (2/3) or complete (3/3) agreement. The case definitions were defined as 'certain', 'probable', 'possible', 'unlikely', and 'unclassifiable' (please refer to Appendix 13.7, Table 45).

At the time of the 4-MSU, 8/1450 subjects in the non-ertugliflozin treatment arm, and 9/1716 and 9/1693 ertugliflozin 5 mg and 15 mg-treated subjects, respectively had events sent to the committee for case assessment. Of the 18 ertugliflozin-treated subjects, only three AEs (all in the 15 mg treatment arm) were considered to have met the case definition of 'certain' (n=2,) or 'possible' (n=1) ketoacidosis. There were no cases in the non-ertugliflozin or ertugliflozin 5 mg arms. All three cases involved intercurrent illnesses (n=2 sepsis; and n=1 viral illness). These cases resolved with discontinuation of IP for two subjects and without interruption in therapy for the third. After review of the remaining 15 ertugliflozin cases (14 assessed as 'unlikely' and 1 as 'unclassifiable'), I concur with the ICRC that there were no additional cases that met the case definition of ketoacidosis with 'possible' or 'certain' likelihood.

Ertugliflozin 15 mg Arm: Assessed as 'CERTAIN' Ketoacidosis

Subject 0200144: 56-year-old Asian female with T2D for approximately 9 years (baseline HbA1c 9%; receiving metformin), randomized to the ertugliflozin 15 mg arm in Trial P002/1013, experienced an SAE of *Klebsiella* sepsis on Day 322 (associated with abdominal cramps, fever, nausea, and vomiting), and was treated with oseltamivir. She was subsequently hospitalized (Day 325) with a diagnosis of metabolic acidosis secondary to this event. The subject was treated with cephalexin 2000 mg/day (Days 325-329). She did not have a recent history of dietary changes or prior history of alcohol abuse, diabetic ketoacidosis, or ingestion of ethylene-glycol, salicylates, or methanol. There was no evidence of T1D or secondary causes of diabetes resulting in insulin deficiency. Relevant labs included blood ketones large amount (reference range: negative), sodium 125 and 128 mmol/L (136-145 mmol/L), potassium 5.3 and 3.2 mEq/L (3.5- 5.1 mEq/L), chloride 97 and 102 mmol/L (101-111 mmol/L), and carbon dioxide 10 and 16 mmol/L (22-34 mmol/L). Plasma glucose concentrations ranged from 139-281 mg/dL (72-108). The CBC included lymphocytes 0.6 × 10^9/L (1.5-4.0 × 10^9/L), monocyte 1.4 × 10^9/L; neutrophils 10.4 × 109/L (2-7.5 × 10^9/L), platelet count 107 × 10^9/L (150-400 × 109/L), mean corpuscular hemoglobin concentration (MCHC) 308 g/L (320-360 g/L), mean corpuscular hemoglobin (MCH) 20.5 pg (25-31 pg), mean corpuscular volume (MCV) 67 fL (80-100 fL), leukocytes 12.5 × 109/L (4-11 × 109/L), and erythrocytes 6.20 × 1012/L (3.8-4.8 × 1012/L), and the differential showed band neutrophils 1.01 × 10^9/L (0-0.5 × 10^9/L), lymphocytes 0.13 × 10^9/L, monocytes 0.06 × 10^9/L (.2-0.8 × 10^9/L). The subject's anion gap was 10 mEq/L (5–20 mEq/L; note: reported as '17' and '23' in the Summary of Clinical Safety report), and increased to 12 mEq/L on Day 327. Venous blood cultures were positive for *Klebsiella* pneumonia. The urine cultures did not show any significant growth, and the urinalysis showed protein 0.3 g/L, glucose ≥55 mmol/L, ketones ≥7.8 mmol/L, and a small amount of erythrocytes. Blood gases included: venous blood pH of 7.19 (7.32-7.42), venous pO_2 130 mmHg, venous pCO_2 22 mmHg, and venous bicarbonate 8 mmol/L (20-219 mmol/L). The lactate was normal. The chest X-ray was unremarkable. The subject was diagnosed with diabetic ketoacidosis as a result of a bacterial infection. On Day 328, the subject's leukocyte and erythrocyte levels returned to normal range, and the subject was discharged Day 329. The study medication was interrupted from Day 329 to Day 365 due to the event of Klebsiella sepsis, and then permanently discontinued on Day 365 due to the event of metabolic acidosis.

This case was assessed as 'certain' by the ICRC. This AE of 'metabolic acidosis' met laboratory criteria of ketoacidosis (i.e., venous pH ≤7.30, presence of urine/blood ketones, serum bicarbonate <18 mEq/L, and normal serum lactic acid concentration), and there was no evidence of T1D or secondary causes of insulin deficiency. I agree that this event, triggered by intercurrent illness (i.e., secondary to sepsis), met the case definition of 'certain'.

Subject 0720075: 29-year-old white female with T2D for approximately 19 years, randomized to ertugliflozin 15 mg in Trial P007/1017 (baseline HbA1C 10%; receiving metformin), experienced a serious adverse event of diabetic ketoacidosis (Day 341), resulting in discontinuation of IP. Symptoms on presentation included chills, vomiting, and diarrhea (Day 342). The physical examination was significant for tachypnea, tachycardia, and dehydration, and supraventricular tachycardia was noted on ECG. The venous blood gases showed the following: pH of 6.91 (reference range: 7.31-7.41), pCO2 of 25.8 mmHg (41.0 – 51.0 mmHg), and HCO_3 of 5.0 mmol/L (20.0-26.0 mmol/L). Clinical labs included: serum sodium 127 mmol/L (136-145 mmol/L), potassium of 5.38 mEq/L (3.5-5.1 mEq/L), chloride of 95 mmol/L (98-107 mmol/L), anion gap 28, plasma glucose 401 mg/dL (74-106 mg/dL), beta-hydroxybutyrate 9.83 mM (0.0-0.3 mM), and WBC 11.5 x 10^3/mm^3 (4.8-10.8 x 10^3/mm^3). The subject was rehydrated and administered insulin. On Day 344, her lab results showed: serum sodium of 139 mmol/L, potassium of 3.8 mEq/L, chloride of 110 mmol/L, plasma glucose 165 mg/dL [9.15 mmol/L], and beta-hydroxybutyrate of 1.50 mM, and the subject was discharged from the hospital this same day. Subsequent laboratory test results on

> Day 400 revealed glutamic acid decarboxylase (GAD) antibodies of 5.0 U/mL (0.0-5.0 U/mL) and negative islet cell antibodies. The investigator felt that the event of ketoacidosis was precipitated by a viral infection.

The ICRC assessed this AE of 'diabetic ketoacidosis' meeting the case definition as 'certain' likelihood. A serum bicarbonate <18 mEq/L, blood pH of ≤7.30, and elevated beta-hydroxybutyrate concentrations met the laboratory criteria for ketoacidosis. The committee considered that the event again was triggered by intercurrent illness (respiratory infection/gastroenteritis), and noted that there also was some evidence of possible autoimmune diabetes (positive autoantibodies with the suspicion of latent autoimmune diabetes of adults [LADA]). I concur with this assessment.

> **Subject 0502678:** 47-year-old white female with T2D for approximately 4 years (receiving metformin), randomized to the ertugliflozin 15 mg plus sitagliptin 100 mg arm in Trial P005/1019, experienced SAEs of 'cholecystitis acute' and 'pneumococcal sepsis' (Day 287), with a subsequent SAE of 'diabetic ketoacidosis' on Day 289. Symptoms included acute high fever, right hypochondrium pain, and a poor appetite. Physical examination was significant for a temperature of 38.5°C, moderate dehydration, lethargy, right hypochondrium tenderness, and tachypnea. Laboratory data showed: WBC 28.7 x 10 9/L (reference range: 4-10 × 109/L), blood glucose 15 mmol/L (3.0-6.1 mmol/L), calcium 1.64 mmol/L (2.10-2.55 mmol/L), magnesium 0.5 mmol/L (0.66-1.07 mmol/L), phosphorus 0.52 mmol/L (0.81- 1.45 mmol/L), potassium 2.8 mmol/L (3.4-5.1 mmol/L), ketones of 1.9 mmol/L (0.05-0.29 mmol/L), and a positive blood culture for *Streptococcus* pneumoniae. Urine ketones (2+) were present. Venous blood gas showed a mild metabolic acidosis, and an abdominal ultrasound showed an enlarged gallbladder with a thickened wall. The subject's serum ketone body level decreased following intravenous hydration. She was diagnosed with acute cholecystitis, *Streptococcus* pneumonia sepsis, and diabetic ketoacidosis, and treated with intravenous fluids, insulin, and antibiotics. The investigator felt that the *Streptococcus* pneumoniae septicemia was the precipitating factor for the other associated events. On Day 290, laboratory results showed a pH of 7.414 (7.360 -7.440), serum HCO_3 of 15.8 mmol/L (21.0-25.0 mmol/L) and base excess -6.8 (-3.0 to 3.0). Potassium, calcium, and magnesium levels had returned to within the normal range. Administration of IP was not interrupted.

The ICRC assessed this case as meeting the case definition of ketoacidosis with possible likelihood, as the serum bicarbonate was <18 mEq/L, urine and blood ketones were present, and the pH was not ≤7.30. I agree that this case would not meet the criteria for 'certain' ketoacidosis, and that sepsis was the probable triggering event.

Overall, the event rate of ketoacidosis was limited, and the Applicant intends to label ketoacidosis in the WARNINGS AND PRECAUTIONS section of labeling. Based on the occurrence of several events in the Applicant's clinical program, as well as the existing data related to a possible SGLT2 inhibitor class effect, I think this is reasonable. However, it is noted that all three cases of ketoacidosis involved ertugliflozin in combination with metformin. Considering that these events occurred in the setting of intercurrent illness, of which one subject had normal serum lactate concentrations, and a second had possible autoimmune diabetes, it is unclear whether concomitant use of metformin with ertugliflozin may have contributed to the risk of ketoacidosis/metabolic acidosis in these cases.

8.5.14. **Lower Limb Amputations and Peripheral Revascularization Procedures**

According to the Centers for Disease Control and Prevention (CDC), diabetes remains the leading cause of lower limb amputations,[4] resulting in approximately 108,000 hospitalizations for a lower-extremity amputation each year (i.e., 5 per 1000 persons with diabetes).[7] Compared to nondiabetic individuals, patients with diabetics may have a 10-fold greater risk for lower extremity amputations, and diabetic amputees are more likely to be severely disabled, have an amputation at a younger age, progress to higher-level amputations, or die at a younger age.[215]

Recently, the potential risk of lower limb amputation with the use of SGLT2 inhibitors has emerged as a potential safety concern. On May 18, 2016, the FDA issued a Drug Safety Communication informing the public of the interim clinical trial results from two large canagliflozin CVOTs (i.e., CANVAS, and CANVAS-R) that suggested a possible risk of leg and foot amputations (mostly affecting the toes).[47] In these trials, lower limb amputations occurred in twice as many canagliflozin-treated subjects compared to placebo (i.e., among approximately 6000 subjects receiving canagliflozin, rates of amputation were 5.9 per 1000 patient-years vs. 2.8 per 1000 patient-years in CANVAS, and 7.5 per 1000 patient-years vs. 4.2 per 1000 patient-years in CANVAS-R, respectively). Lower-limb infections, gangrene, diabetic foot ulcers, and ischemia were the more common precipitating factors for amputations in these trials. On May 16, 2017, the Drug Safety Communication was updated, stating that a Boxed Warning would be added to canagliflozin product labeling.[46] In this communication, patients were instructed to notify their healthcare professionals if they develop new pain, tenderness, sores or ulcers, or infections in their legs or feet, and healthcare professionals were informed to consider predisposing risk factors (e.g., prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers) prior to initiating therapy. In a published report of the integrated analysis of the CANVAS Trial Program, the risk of amputation with canagliflozin across both CANVAS studies was 6.3 vs. 3.4 participants per 1000 patient-years (HR, 1.97; 95% CI, 1.41–2.75) for canagliflozin- and placebo-treated subjects, respectively.[216,217] The highest absolute risk reported occurred in subjects with a history of peripheral vascular disease or prior amputation.

During the clinical development programs for other SGLT2 inhibitors, the occurrence of amputations often was not prespecified as an AESI, and these events were often coded as procedures and not as AEs. Therefore, the potential for a class effect with all SGLT2 inhibitors remains uncertain.

In the 4-MSU Pool, non-traumatic limb amputations were reported in 0.1% (1/1450), 0.2% (3/1716) and 0.5% (8/1693) of subjects in the non-ertugliflozin, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms, respectively. A summary table and clinical narratives with graphical patient profiles of these subjects are presented in Appendix 13.8 and 13.9, respectively. The mean age of the 11 ertugliflozin-treated patients with lower limb amputations was 63 (range 52-74) years, of which 10 were male, and nine had a history of CV, cerebrovascular, and/or peripheral arterial disease (the remaining two subjects had risk factors,

such as smoking history, hypertension, and/or dyslipidemia). The median duration of exposure at the time of the first surgical procedure was 228 days (mean 271; range 36-577 days), with a risk of approximately 3 amputations per 1000 patient-years of exposure for ertugliflozin-treated subjects compared to approximately 0.6 amputations per 1000 patient-years of exposure for the comparator arm. SAEs occurring prior to amputations included cellulitis, diabetic vascular disorders, diabetic foot infections, gangrene, osteomyelitis, peripheral arterial occlusive disease, and peripheral ischemia.

The Applicant noted that the number of cases was limited, involved subjects with baseline risk factors for these events (e.g., peripheral neuropathy, peripheral artery disease), and did not appear to be associated with volume depletion and/or hemoconcentration. I concur that there were few amputations in the study population, and that these events occurred in at-risk subjects. However, the observed numeric imbalance favoring the non-ertugliflozin comparator arm (i.e., 1 in the non-ertugliflozin arm vs. 11 in the combined ertugliflozin arms), of which one ertugliflozin-treated subject also required a peripheral revascularization procedure and a second required an additional amputation, is somewhat concerning.

Due to the limited number of cases of lower limb amputations and continued uncertainty whether the above imbalance in events represented a possible treatment-related safety concern or chance finding, the Division requested (September 26, 2017) that the Applicant provide information regarding amputation events from their ongoing CVOT (i.e., Trial P004/1021). In an email request for clarification (dated September 28, 2017), the Applicant proposed that the requested data be prepared by the Data Monitoring Committee (DMC) support team, and that the analysis be routed to the firewalled cardiovascular meta-analysis (CVMA) team using the same process as followed for submission of the CVMA report in their NDAs. They assured the Division that this proposal would not result in any unblinding of Applicant personnel beyond those individuals already involved in the preparation of the CVMA report and would be consistent with their data access plan.

On October 12, 2017, the Applicant provided the requested amputation data for Trial P004/1021 (presented in Table 38 below). Based on these data, higher event rates on treatment were observed in the ertugliflozin treatment arms (6.8 per 1000 patient-years in the 5 mg arm and 5 per 1000 patient-years in the 15 mg arm) vs. the comparator arm (4.3 per 1000 patient-years).

Table 38: Subjects with Amputations (All Subjects As Treated*)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2744		2746		2747		5493		8237	
with one or more Amputations	**16**	**(0.6)**	**26**	**(0.9)**	**19**	**(0.7)**	**45**	**(0.8)**	**61**	**(0.7)**
with no Amputations	2728	(99.4)	2720	(99.1)	2728	(99.3)	5448	(99.2)	8176	(99.3)
Surgical and medical procedures										
Toe amputation	8	(0.3)	19	(0.7)	9	(0.3)	28	(0.5)	36	(0.4)
Leg amputation	5	(0.2)	4	(0.1)	5	(0.2)	9	(0.2)	14	(0.2)
Foot amputation	5	(0.2)	3	(0.1)	4	(0.1)	7	(0.1)	12	(0.1)
Amputation	0		1	(<0.1)	1	(<0.1)	2	(<0.1)	2	(<0.1)
Finger amputation	0		1	(<0.1)	0		1	(<0.1)	1	(<0.1)
Limb amputation	1	(<0.1)	0		1	(<0.1)	1	(<0.1)	2	(<0.1)
Metatarsal excision	1	(<0.1)	0		0		0		1	(<0.1)
Event/Subject-Years Exposure Time (1000-Subject-Years Incidence Rate)	**16/3745.5 (4.3)**		**26/3830.2 (6.8)**		**19/3806.6 (5.0)**					

Source: Adapted from the Applicant's CVOT amputation rates – multi-module-info-amendment-12oct2017, labeled as Tables 10.011 and 14.3.1.1.10, pages 3-4 of 4, available at: \\CDSESUB1\evsprod\NDA209803\0037\m1\us\multi-module-info-amendment-12oct2017.pdf

Note: Every subject was counted a single time for each applicable row and column. Three subjects (i.e., Ertugliflozin 5 mg arm with a toe amputation; ertugliflozin 15 mg arm with a leg amputation; and placebo arm with a ray amputation) had amputations identified via SAE comment text search and are not represented in the table. Queries have been sent to investigators to enter these procedures into the procedures database. A finger amputation due to squamous cell carcinoma for a subject in the ertugliflozin 5 mg arm was included in this table.

*Surgical procedures that occurred between the first dose of treatment and final dose of treatment + 14 days, including events after initiation of glycemic rescue medication (i.e., on-treatment events).

The Applicant also provided amputation event rates for the CVOT based on the total post-randomization follow-up (i.e., on-study event/subject-years follow-up time). The incidence rates were 4.5 events, 7.3 events, and 5.2 events per 1000 subject-years of follow-up for the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg treatment arms, respectively (see Appendix 13.10; Table 47).

The findings with respect to lower limb amputations from the overall ertugliflozin Phase 3 clinical program and from the ongoing CVOT (Trial P004/1021) both point toward an increased risk with ertugliflozin. Based on the preliminary data from the CVOT, the on-treatment and on-study amputation event rates were similar to those observed in the SGLT2 inhibitor treatment arms of CANVAS and CANVAS-R. Although the Applicant does not intend to include information related to lower limb amputations in proposed product labeling for any of their three NDAs, I feel that healthcare providers and patients should be adequately informed of these data, especially considering the uncertainty of a potential SGLT2 inhibitor class effect.

In addition to amputations, the Applicant also searched the narratives and datasets of the Phase 3 ertugliflozin program for the occurrence of peripheral revascularization procedures. Only three subjects had revascularization procedures (two in the non-ertugliflozin arm and one in the ertugliflozin 15 mg arm). Risk factors (hypertension, hyperlipidemia) again were present in these subjects.

8.5.15. **Cardiovascular Safety**

Dr. Eland Baro conducted the statistical review (dated August 15, 2017) of the cardiovascular safety of ertugliflozin. Currently, all drugs intended for the treatment of T2D are expected to meet the standards outlined in the FDA Guidance entitled "*Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*".[218] Specifically, the guidance states that, before submission of an NDA, "Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8."

To demonstrate an acceptable level of CV safety, the Applicant is using a preplanned, two-stage approach, which includes a premarketing, program-wide CVMA (Stage 1), as well postmarketing completion of a dedicated CVOT (Stage 2). The CVMA was conducted using the data from nine clinical trials; the seven Phase 3 trials used to support safety and efficacy of ertugliflozin and the ertugliflozin FCDPs, a 12-week Phase 2 trial (P042/1004), and the ongoing CVOT (P004/1021). The anticipated completion of the CVOT is 2019 (i.e., dependent on accrual of adjudicated CV events). To protect the integrity of this trial, the interim data and detailed results from the CVMA will not be discussed in this review.

The primary endpoint for the CVMA was Major Adverse Cardiovascular Endpoint-plus ("MACE-plus"), a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Blinded adjudication of all CV events, thromboembolic events, hospitalization for heart failure, and deaths was performed by an independent Clinical Adjudication Committee (CAC), composed of five cardiovascular specialists and three vascular neurology specialists.

The external Data Monitoring Committee (DMC) reviewed the results of the CVMA (data cut April 18, 2016) and reported that the upper bound of the adjusted 95% CI for the hazard ratio for MACE-plus was <1.8, ruling out an 80% increase in CV risk relative to the non-ertugliflozin comparator arm; meeting the Agency's requirements for an antihyperglycemic New Drug Application (NDA). Based on the Agency review, Dr. Baro concurred that the 1.8 risk margin for MACE-plus was excluded. Please refer to her review for a detailed discussion.

Additionally, a review of the CV or cerebrovascular AEs submitted for the ertugliflozin NDAs was conducted based on reported investigator-reported terms. Please refer to Sections 8.4.1, 8.4.2, and 8.4.3 for a review of relevant deaths, SAEs, and discontinuations due to AEs, respectively. No safety concerns were identified in the 4-MSU data using the CV SMQs and broad CMQs described in Appendix 13.4.

8.5.16. Other AEs Associated with DPP-4 Inhibitors and SGLT2 Inhibitors

Using broad CMQs, the AE datasets also were queried for other AESI associated with DPP-4 Inhibitors and SGLT2 Inhibitors, which included arthropathies; bone and joint infections; bone disorders; bone, joint and vascular therapeutic procedures; dermal diabetic complications; venous embolic and thrombotic events; ketoacidosis; osmotic diuresis; opportunistic infections; stomatitis/mouth ulceration; and vascular insufficiency. Event counts for many of these CMQs were limited/non-informative, and no trends were readily identified that suggested apparent imbalances between treatment arms for subjects with these AESI.

8.6. Specific Safety Studies/Clinical Trials

Not applicable.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

In the 2-year mouse carcinogenicity study, there were no ertugliflozin-related neoplastic findings with doses up to 40 mg/kg/day (approximately 41 times human exposure at the maximum recommended human dose [MRHD] of 15 mg/day based on AUC). In the 2-year rat carcinogenicity study, ertugliflozin was administered at doses up to 15 mg/kg/day. Ertugliflozin-related neoplastic findings included an increased incidence of benign and combined benign and malignant adrenal medullary pheochromocytoma in male rats at 15 mg/kg/day. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis, which has been associated with pheochromocytoma development in rats and has unclear relevancy to human risk. The no-observed-effect level (NOEL) for neoplasia was 5 mg/kg/day (approximately 18 times human exposure at the MRHD of 15 mg/day based on exposure).

Based on the nonclinical data, ertugliflozin was not mutagenic or clastogenic (microbial reverse mutation, *in vitro* cytogenetic, and *in vivo* rat micronucleus assays).

8.7.2. **Human Reproduction and Pregnancy**

In the rat fertility and embryonic development study, male and female rats were administered ertugliflozin at 5, 25, and 250 mg/kg/day. No effects on fertility were observed at the 250 mg/kg/day dose (approximately 480 and 570 times male and female human exposures at the proposed MRHD of 15 mg/day).

Female participants in the Applicant's clinical protocols who were biologically capable of having children and sexually active were asked to use acceptable methods of contraception throughout the active treatment period and for at least 14 days after the last dose of IP. Should a pregnancy occur during the trial, the investigator(s) or their designees were required to report them to the Applicant, IP was discontinued, and the subject was to be followed until the completion/termination of the pregnancy.

In their clinical program, there have been two pregnancies; one in a 39-year-old female (Subject 0200629) in the ertugliflozin 5 mg arm (positive pregnancy testing on Days 247 and 251) that ended in an elective abortion on Day 254, and the other in a 34-year-old white female (Subject 0311794) in the placebo arm that resulted in a spontaneous abortion on Day 205.

Currently, there is limited clinical experience with the use of ertugliflozin as monotherapy or in combination with sitagliptin or metformin in pregnant or lactating women, and therefore the (b) (4) I concur that the available data are insufficient to inform the use of ertugliflozin during pregnancy. Product labeling will include language recommending that ertugliflozin not be used during the second and third trimesters of pregnancy, as adverse renal changes were observed in rats when

ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy.

It is noted that postmarketing enhanced pharmacovigilance for pregnancy outcomes was required for dapagliflozin and canagliflozin approval. Though there are concerns that exposure to SGLT2 inhibitors during pregnancy (particularly in the 2nd and 3rd trimesters) may result in adverse outcomes, it is unclear how much useful information will be obtained through enhanced pharmacovigilance. Additionally, current prescribing practices would likely result in patients being switched to insulin therapy, thus exposure in the later part of pregnancy is unlikely. As such, it was decided that this would not be a post-marketing requirement for empagliflozin. The Applicant includes contact information for their sitagliptin surveillance program (i.e., Merck Pregnancy Registry) in proposed labeling for the ertugliflozin/sitagliptin FCDP, as this program monitors pregnancy outcomes in women exposed to sitagliptin during pregnancy. Similar information is not included in proposed labeling for the other two products (i.e., ertugliflozin and the ertugliflozin/metformin FCDP).

Dr. Carrie Ceresa, from the Division of Pediatric and Maternal Health (DPMH), was consulted to provide input for appropriate format and content of the pregnancy, lactation, and females and males of reproductive potential sections of proposed product labeling (i.e., PLLR format) for all three NDAs. Based on the 10-year data from the Applicant's sitagliptin surveillance program, there were no congenital anomalies observed out of 29 prospective reports (i.e., 13 were lost to follow-up, one report was pending, 14 resulted in live births, and two spontaneous abortions) for JANUVIA (sitagliptin) and JANUMET (sitagliptin/metformin FCDP). In her review (dated August 25, 2017), Dr. Ceresa noted that there were few pregnancies in the Applicant's ertugliflozin clinical program, and that published literature related to sitagliptin and metformin exposure during pregnancy are not sufficient to demonstrate or rule-out a drug-associated risk to the fetus. However, she acknowledged that poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications and the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

8.7.3. **Pediatrics and Assessment of Effects on Growth**

No pediatric subjects were enrolled in the ertugliflozin (including the proposed FCDPs) clinical development program. Although metformin (immediate-release) is approved for use in children with T2D, pediatric clinical trials and/or assessments on growth and development for either ertugliflozin or sitagliptin have not been completed.

The Pediatric Review Committee (PeRC) convened on August 21, 2013, to review the initial Pediatric Study Plan (iPSP) for a proposed plan to request a partial waiver and deferral for ertugliflozin (IND 106447). The iPSP included a partial waiver for pediatric subjects ages 0 to

<10 years. In accordance with 21 CFR 314.55(c)3(ii),[219] the Applicant noted that the necessary studies would be impossible or highly impracticable to conduct because the number of patients in this age group is so small that clinical trials could not be reasonably conducted, and there is not a significant therapeutic need in the population under the age of 10 years.

The Applicant also requested a deferral of a study in pediatric subjects ages 10 to <18 years until the safety and efficacy of ertugliflozin was evaluated in their completed adult core Phase 3 trials, (b) (4)

The iPSP for ertugliflozin (NDA 209803) was agreed on August 26, 2013. For additional information, please refer to:

\\cdsesub1\evsprod\nda209803\0000\m1\us\req-pediatric-waiver.pdf
\\cdsesub1\evsprod\nda209803\0000\m1\us\req-pediatric-deferral.pdf
\\cdsesub1\evsprod\nda209803\0000\m1\us\proposed-pediatric-request.pdf

The iPSP for NDA 209805 (ertugliflozin/sitagliptin FCDP), which requested a full waiver of pediatric studies, was agreed upon on August 20, 2015. For this product, the Applicant stated that conduct of appropriate studies in all pediatric populations would be impossible or highly impracticable to conduct.

For the same reasons that applied to NDA 209803 (ertugliflozin), the Applicant proposed to request a partial waiver for the study of pediatric subjects ages 0 to <10 years for NDA 209806 (ertugliflozin/metformin FCDP). Since the proposed pediatric study for ertugliflozin also applies to their ertugliflozin/metformin FCDP—as it will be conducted on the background of metformin—the Agency agreed to the Applicant's plan to request a deferral for the study of pediatric subjects ages 10 to <18 years. The iPSP was agreed upon on August 20, 2015.

The Applicant states that there are concerns with the potential effects of ertugliflozin on bone metabolism and bone health. (b) (4)

The Division does not agree. Based on the 52-week interim data from this trial, findings from the nonclinical studies conducted in the ertugliflozin development program, and experience with approved SGLT2 inhibitors, the Division does not view the 2-year BMD data as necessary to inform the study of ertugliflozin in pediatric patients. Markers of bone health should be monitored in the planned pediatric trial regardless of findings in adults.

8.7.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The Applicant states that there is no data available related to overdose of ertugliflozin as monotherapy or in combination sitagliptin or metformin. In their clinical development program,

single doses up to 300 mg (i.e., 20 x the maximum proposed ertugliflozin dose) and multiple daily doses (≤14 days) up to 100 mg (approximately 7 x the maximum dose) have been administered, and were generally tolerated.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Ertugliflozin, and the ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs are not approved in any country, and therefore there is no postmarketing experience with these products.

8.8.2. Expectations on Safety in the Postmarket Setting

Ertugliflozin is intended to be prescribed as an adjunct to diet and exercise to improve glycemic control in adults with T2D. As with other SGLT2 inhibitors, ertugliflozin may increase the risk of hypotension and volume depletion (especially in patients with renal impairment, the elderly or concomitant diuretic use), ketoacidosis, renal impairment, urosepsis, and/or hypoglycemia in combination with insulin or an insulin secretagogue. No new or unanticipated safety concerns were identified from review of the safety data that would be considered unique to ertugliflozin or other SGLT2 inhibitors administered as monotherapy or in combination with metformin or sitagliptin. The main safety concern was an imbalance in the number of subjects who experienced lower limb amputations (11 ertugliflozin-treated subjects vs. 1 non-ertugliflozin-treated subject). I believe that this safety signal will be better evaluated in the Applicant's dedicated CVOT (i.e., Trial P004/1021), and that this issue can be addressed at the time of approval with appropriate labeling and routine pharmacovigilance.

8.9. Additional Safety Issues from Other Disciplines

No additional safety issues were identified by the other review disciplines that would affect regulatory decision-making, product labeling, or postmarketing requirements (PMRs). However, at the time of this review, there were 11 ongoing tracked safety issues (TSIs) related to SGLT2 inhibitor and DPP-4 inhibitor pharmacologic classes (Table 39). There are currently no TSIs open that involve metformin. A TSI is a significant safety issue associated with a marketed drug product that requires follow-up and triggers the creation of a Reporting and Regulatory Tracking System (DARRTS) TSI (i.e., an FDA-generated application created for the purpose of tracking and archiving regulatory activities associated with a significant safety issue related to a marketed prescription or over-the-counter drug).[220] Review of the safety database from the ertugliflozin clinical program did not reveal any additional safety signals beyond those already labeled or previously identified as TSIs with other related drug products.

Table 39: Active and Ongoing Tracked Safety Issues for SGLT2 Inhibitors and DPP-4 Inhibitors

TSI No.	Drug Class	Safety Issue	Create Date	Status*
000893	DPP-4 inhibitors	Pancreatitis	4/20/2010	Ongoing
000907	DPP-4 inhibitors	Angioedema	5/18/2010	Ongoing
000909	DPP-4 inhibitors	Pancreatic malignancy	5/18/2010	Ongoing
001366	DPP-4 inhibitors	Hospitalization for HF	3/25/2015	Ongoing
001441	SGLT2 inhibitors	Stroke and thromboembolic events	6/18/2015	Ongoing
001459	DPP-4 inhibitors	Oral soft tissue conditions	7/16/2015	Active
001511	DPP-4 inhibitors	Renal failure	8/18/2015	Ongoing
001513	SGLT2 inhibitors	Fracture	8/18/2015	Ongoing
001680	SGLT2 inhibitors	Amputations	4/6/2016	Ongoing
001704	SGLT2 inhibitors	Acute pancreatitis	6/15/2016	Ongoing
001767	SGLT2 inhibitors	Nephrolithiasis	6/15/2016	Ongoing
001823	DPP-4 inhibitors	Rhabdomyolysis	6/23/2017	Active
001844	SGLT2 inhibitors	Fournier's gangrene	10/10/2017	Active

Abbreviations: DPP-4, dipeptidyl peptidase-4; HF, heart failure; SGLT2, sodium-glucose cotransporter 2; and TSI, tracked safety issue.

Definitions:** ***Active, an issue for which there are activities pending (e.g., submissions or reviews are being evaluated, responses from sponsors are pending and expected within a few months, or regulatory actions are being contemplated, requested, or required); and ***Ongoing***, an issue has not been resolved; however, the awaited data are expected to take months or years to be submitted.[220]

During the review cycle, the Division of Pharmacovigilance-I (DPV-I)/Office of Surveillance and Epidemiology (OSE), conducted a pharmacovigilance review evaluating the risk of nephrolithiasis (TSI #001767) associated with SGLT2 inhibitors. This safety signal was identified from the Food and Drug Administration Amendments Act (FDAAA) Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis for other SGLT2 inhibitors. Based on the review, DPV-I felt that labeling of nephrolithiasis is not warranted at this time because additional data is needed to better assess a causal association, identify factors to mitigate the potential risk, and determine at-risk populations. This TSI is now closed. Please refer to the Pharmacovigilance Review of Drs. Christine Chamberlain and Paolo Fanti (dated May 25, 2017) for additional information.

Since obesity[221] and T2D[222] are considered possible risk factors for nephrolithiasis, and because of uncertainty as to whether several pharmacodynamic effects associated with SGLT2 inhibitors

could be additional contributing/predisposing factors (e.g., volume depletion,[24-26] metabolic acidosis,[178-213] uricosuria,[223,224] increased serum parathyroid hormone concentrations,[128] and urinary tract infections[225,226]), the 4-MSU datasets were screened for cases of nephrolithiasis and related TEAEs (Table 40). Based on these data, there were no apparent imbalances between treatment arms for these AEs.

Table 40: Nephrolithiasis and Related Adverse Events (4-MSU)

MedDRA PT – no. (%)	Non-ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)	All Ertugliflozin (n=3409)
Total Events	**10 (0.7)**	**7 (0.4)**	**10 (0.6)**	**17 (0.5)**
Nephrolithiasis	5 (0.3)	3 (0.2)	3 (0.2)	6 (0.2)
Renal colic	2 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Hydronephrosis	0	2 (0.1)	1 (0.1)	3 (0.1)
Calculus urinary	1 (0.1)	0	2 (0.1)	2 (0.1)
Urinary sediment abnormal	0	0	2 (0.1)	2 (0.1)
Urinary sediment present	0	0	1 (0.1)	1 (0.0)
Pyelocaliectasis	1 (0.1)	0	0	0
Ureterolithiasis	2 (0.1)	0	0	0

Source: Derived from the sur-ISS adsl.xpt, adae.xpt, aeplus.xpt, and aerpt.xpt datasets, available at: Application 209803 - Sequence 0014 - Data Analysis Data -
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; no., number; and PT, preferred term.

Additionally, several cases of Fournier's gangrene in diabetic patients receiving SGLT2 inhibitors were identified through the FDA Adverse Event Reporting System (FAERS) and published literature,[227,228] resulting in OSE opening a TSI on October 10, 2017 (Table 39). Fournier's gangrene is a serious, potentially fatal (reported mortality rates of 3-75%[229-238]), rapidly progressive infective necrotizing fasciitis that commonly affects the perineal, genital or perianal areas.[229-232,239] These infections may be associated with a breach in the integrity of the gastrointestinal or urethral mucosa in individuals with a compromised immune system (e.g., diabetes), and potentially trigger an obliterative endarteritis of the surrounding vasculature, with subsequent thrombosis and ischemia.[229,232,239-241] Diabetes is a known risk factor, present in approximately 10-77% of cases.[230,231,237,242,243] Although more common in older men, Fournier's gangrene can occur in children,[244-248] and also may involve the vulva and perineum in females.[239,249-252] Because of risks of genitourinary infections and hypoperfusion (e.g., amputations, acute kidney injury) associated with the use of SGLT2 inhibitors in diabetic patients, the Division felt that this emerging safety signal should be further evaluated for SGLT2 inhibitor applications.

To identify potential cases, the 4-MSU datasets were screened for the following MedDRA PTs: Cellulitis of male external genital organ, Erosive balanitis, Fascial infection, Fasciitis, Gangrenous

balanitis, Necrotising fasciitis, Necrotising fasciitis fungal, Necrotising fasciitis staphylococcal, Necrotising fasciitis streptococcal, Necrotising myositis, Necrotising soft tissue infection, Penile abscess, Perineal abscess, Perineal infection, Perineal necrosis, Scrotal abscess, Vulval abscess, and Vulval cellulitis. Based on this search, there were limited events identified (i.e., one case each of 'Vulval abscess' in the non-ertugliflozin and the ertugliflozin 5 mg treatment arms). Both cases were coded as mild in severity, and resolved without discontinuation in study medication (please refer to Section 8.5.5 above).

Two SAEs also were identified ('Cellulitis of male external genital organ', and 'Necrotising myositis') and are discussed as follows:

> **Subject 030376:** 63-year-old white uncircumcised male with T2D, randomized to ertugliflozin 5 mg in Trial P003/1022, experienced SAEs of cellulitis of male external genital organ, acute respiratory failure, and sepsis, resulting in hospitalization on Day 358. Other concurrent AEs included acute kidney injury, hypoxia, cardiomyopathy, hypotension, pneumonia, hypokalemia, hypomagnesemia, and chronic obstructive pulmonary disease. Relevant medical history included morbid obesity, asthma and sleep apnea syndrome; but there was no prior history of genital infections. On Day 281, he had non-serious AEs of genital infection fungal and tinea cruris (genital and groin area), which were treated with fluconazole on Days 281 to 311 and betamethasone dipropionate plus clotrimazole cream from Days 281 through 356. Study medication was not interrupted. An ultrasound scan of the scrotum showed wall thickening, but no soft tissue gas, abscess or fluid collection; both urine and blood cultures were negative. On Day 361, the subject experienced AEs of cardiac failure congestive and atrial flutter. The subject received fluconazole and broad spectrum intravenous antibiotics (cefepime, vancomycin, and metronidazole) for the cellulitis and supportive therapy for all other events. All AEs resolved on Day 367.

Although this case does not represent Fournier's gangrene (negative ultrasound findings and resolution with broad spectrum antibiotics alone), ertugliflozin may have contributed to the SAEs and associated hospitalization for this subject.

> **Subject 0720325:** 42-year-old Asian female with T2D receiving metformin, randomized to ertugliflozin 5 mg in Trial P007/1017, experienced a SAE of soft tissue necrosis ('right thigh necrotising myositis status post debridement, soft tissue defect with femoral bone exposure worsening') on Day 70. Relevant medical history included fasciectomy (right leg wound), debridement (right leg wound), myositis, necrotizing myositis, arthritis bacterial, carbuncle, cellulitis, sepsis, two soft tissue flap operations of the right leg, synovectomy, and soft tissue necrosis. There was no relevant medication at the time of randomization. The subject had been experiencing soft tissue defect with muscle pain prior to study. Since the soft tissue defect and wound muscle pain persisted but had not worsened, the subject came to the outpatient department on Day 70. On examination, it was noted that upper 1/3 of the wound was healing well and lower third of the wound had poor granulation. The subject was hospitalized on Day 76 for a soft tissue flap operation. No X-ray of the affected limb was performed, and there was no surgical removal of necrotic tissue. Administration of study medication was not interrupted (ertugliflozin was continued to Week 104). The subject was discharged on Day 85, with resolution of the SAE on Day 110.

This case, involving a subject with a preexisting history of soft tissue necrosis and associated surgical procedures, also does not represent Fournier's gangrene. The effect of ertugliflozin on wound healing in this case is uncertain.

8.10. Integrated Assessment of Safety

The safety profile of ertugliflozin is consistent with the safety profile of the other SGLT2 inhibitors. The most common adverse reactions, reported in ≥2% of subjects and more frequently in ertugliflozin-treated subjects than placebo-treated subjects, included female and male genital mycotic infections, urinary tract infections, headache, vaginal symptoms, increased urination, nasopharyngitis, back pain, weight decreased, and thirst. Although hypoglycemia is a risk with any antihyperglycemic medication, the occurrence of hypoglycemic events (i.e., blood glucose concentrations ≤70 mg/dL) when ertugliflozin was administered as monotherapy was relatively low (2.6%), with higher rates reported in combination with sitagliptin (≤6.1%), metformin (≤7.8%), and sitagliptin plus metformin (≤4.5%). There were few events of severe hypoglycemia (i.e., requiring assistance, lost consciousness, or experienced a seizure regardless of blood glucose).

(b) (4)

(b) (4) efficacy was not established in their dedicated renal impairment trial (P001/1016) at this level of renal function. Further, based on the data submitted for the 4-MSU safety pool, use of ertugliflozin in this subset of subjects was associated with numerically higher incidences of adverse outcomes, including deaths, SAEs, and discontinuations due to AEs. Therefore, I do not recommend the use of ertugliflozin-containing products in patients with an eGFR <60 mL/min/1.73 m^2.

Ketoacidosis, a potentially fatal condition, has been identified in clinical trials and postmarketing surveillance with other SGLT2 inhibitors. Across the ertugliflozin clinical program, events of ketoacidosis were adjudicated as 'certain' or 'possible' in three of 3,409 (0.1%) ertugliflozin-treated subjects, with no adjudicated events occurring in the non-ertugliflozin treatment arm. These cases were each associated with intercurrent illness (infection/sepsis, gastroenteritis), with a possibility of autoimmune diabetes in one of the three. As with SGLT2 inhibitor class labeling, the proposed product labeling includes information on ketoacidosis in the WARNINGS AND PRECAUTIONS section. Based on the existing data, this should be adequate.

A somewhat concerning finding in the pooled safety analysis was an imbalance in the number of subjects who experienced lower limb amputations. An increased risk for lower limb amputations has been seen with another SGLT2 inhibitor. Across the clinical program, non-traumatic limb amputations were reported in one of 1450 (0.1%) subjects in the non-ertugliflozin arm, three of 1716 (0.2%) in the ertugliflozin 5 mg arm, and eight of 1693 (0.5%) in the ertugliflozin 15 mg arm, of which one of these subjects underwent two separate procedures

(left second toe and left third toe amputations), and a second had both a peripheral revascularization procedure and toe amputation. The most frequently reported procedure was toe amputation, which was the surgical procedure for eight of the 11 ertugliflozin-treated patients, while the remaining three subjects had lower limb amputations. All patients had preexisting risk factors, such as peripheral neuropathy, peripheral artery disease, diabetic foot, and/or current or past smoking history. The most common precipitating medical events included those related to limb infection, peripheral artery disease, and gangrene. It will be important that product labeling adequately inform prescribers and patients of this risk and recommend monitoring for associated signs and symptoms.

In accordance with the 2008 FDA Guidance ("*Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*"),[218] the Applicant has conducted a program-wide cardiovascular meta-analysis to support the CV safety of ertugliflozin. Based on data from nine clinical trials (including interim data from Trial P004/1021, their dedicated CVOT), the upper bound of the adjusted 95% CI for the hazard ratio for the composite MACE-plus endpoint was <1.8, ruling out an 80% increase in CV risk relative to the non-ertugliflozin comparator arm. Since Trial P004/1021 is ongoing, detailed results will not be provided in order to maintain the data integrity of this CVOT.

Based on the totality of the safety data submitted, and the observed adverse event findings, no new safety signals were identified. The risks associated with the use of ertugliflozin as monotherapy or in combination with sitagliptin or metformin are anticipated, monitorable, and similar to those observed in other SGLT2 inhibitor clinical programs.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. No Advisory Committee was held to discuss the three Applications which are the subject of this review.

10 Labeling Recommendations

10.1. Prescribing Information

The proposed labeling for ertugliflozin, and the ertugliflozin/sitagliptin and ertugliflozin/metformin FCDPs conform to the final rule governing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 24, 2006, available at:

https://www.fda.gov/ohrms/dockets/98fr/06-545.pdf

The Applicant proposed the following indications for the three products that are the subject of this review:

> **NDA 209803 (ertugliflozin):** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
>
> **NDA 209805 (ertugliflozin/sitagliptin FCDP):** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.
>
> **NDA 209806 (ertugliflozin/metformin FCDP):** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

As noted at the time of the pre-NDA meeting (dated September 6, 2016; please see Section 3.2, Table 2) all clinical trials used to support the ertugliflozin/metformin FDCP were designed as add-on to background metformin therapy, and not in treatment-naïve subjects. Therefore, the contribution of metformin to the FCDP is difficult to determine, and I recommend that the indication for this product be revised as follows:

> *"As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are* (b) (4)

(b) (4) their dedicated moderate renal impairment study (Trial P001/1016) failed to show a difference between treatment arms (i.e., placebo vs. ertugliflozin 5 mg or 15 mg) in HbA1c changes from baseline to Week 26. Further, in this trial and across the entire clinical program (Table 41), the Applicant reported numerically more adverse outcomes (discontinuations due to SAEs, SAEs, and deaths) for ertugliflozin-treated subjects compared to subjects in the placebo or non-ertugliflozin arms, (b) (4). I recommend that ertugliflozin-containing products not be used in patients with an eGFR <60 mL/min/1.73 m2.

Table 41: Adverse Outcomes from Trial P001/1016 and 4-MSU for Subjects with an eGFR <60 mL/min/1.73 m^2

Events — no. (%)	eGFR (mL/min/1.73 m^2)	Trial P001		4-MSU	
		Placebo (n=515)	ALL Ertu (n=1029)	Non-Ertu (n=1450)	ALL Ertu (n=3409)
Deaths*	45 to <60	0/99	2/202 (1.0)	1/126 (0.8)	6/276 (2.2)
	<60	1/154(0.6)	3/313 (1.0)	3/180 (1.6)	9/386 (2.3)
SAEs	45 to <60	8/99 (8.1)	20/202 (9.9)	16/126 (12.7)	43/276 (15.6)
	<60	17/154 (11.0)	34/313 (10.9)	25/189 (13.2)	65/386 (16.80
D/C due to SAEs	45 to <60	0/99	2/202 (1.0)	1/126 (0.8)	5/276 (1.8)
	<60	1/154 (0.6)	7/313 (2.2)	3/189 (1.6)	12/386 (3.1)

Source: Adapted from the Applicant's MidCycle Presentation (Dated June 5, 2017).
Abbreviations: 4-MSU, Four-Month Safety Update; D/C, discontinuations; eGFR, estimated glomerular filtration rate; Ertu, ertugliflozin; no., number; Non-Ertu, non-ertugliflozin; and SAEs, serious adverse events.

Additionally, a numeric imbalance of lower limb amputations that favored the comparator arm was observed across the ertugliflozin clinical program (please refer to Section 8.5.14), and should be included in the labeling for all three ertugliflozin products.

For Section 14 (Clinical Studies) of all three products, the Office of Biostatistics' preferred analysis for the primary efficacy endpoint (i.e., HbA1c change from baseline to Week 26) is the de facto estimand, which estimates the difference that actually occurred as a result of being randomized to the experimental vs. control arm.

Further, for the FCDPs, the data (b) (4)

Changes in blood pressure and body weight are not considered pertinent to the proposed indications, (b) (4)

For NDA 209803 (ertugliflozin) and NDA 209806 (ertugliflozin/metformin FCDP), the Division recommends that limited information for the ertugliflozin/sitagliptin factorial study be included in respective labeling, since this trial is not considered relevant to either product.

For NDA 209805 (ertugliflozin/sitagliptin FCDP), bullous pemphigoid, a recent safety concern for all DPP-4 inhibitors, is not listed in any of the relevant sections of proposed labeling. This information should be added.

Labeling negotiations are ongoing at the time of finalization of this review, and additional labeling recommendations may be communicated to the Applicant.

10.2. Patient Labeling

Labeling negotiations are ongoing. Please refer to Section 10.1 above for preliminary/potential labeling review issues.

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy (REMS) is recommended for the products that are the subject of this review.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

No Risk Evaluation and Management Strategy is recommended for NDA 209803, NDA 209805, and NDA 209806.

12 Postmarketing Requirements and Commitments

I have the following recommendations for postmarketing requirements (PMRs):

1. Completion of the ongoing cardiovascular outcomes study (Trial P004/1021) to meet the requirements outlined in "FDA Guidance for Industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes". In addition to evaluating cardiovascular outcomes, data on other AESI (i.e. changes in renal function, and occurrence of amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, and malignancies) and pregnancy outcomes should be assessed.

2. Performance of studies in pediatrics as required under the Pediatric Research Equity Act (PREA). (b) (4) Please refer to Section 8.7.3 for further discussion of postmarketing pediatric assessments.

13 Appendices

13.1. References

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13.2. Antihyperglycemic Products Approved in the United States

Table 42: Summary Table of Approved Antihyperglycemic Products

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
Alpha-Glucosidase Inhibitors				
GLYSET (meglitol)	020682 (December 18, 1996)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. DOSAGE/ADMINISTRATION: • Initial dose: 25 mg orally 3 times daily at the start of each meal. • May increase to 50 mg 3 times daily after 4-8 weeks. • Maximum recommended dose: 100 mg 3 times daily.	**Not recommended if serum creatinine is >2 mg/dL or CrCl <25 mL/min.** • Miglitol is eliminated by renal excretion as unchanged drug. Following a 25 mg dose, over 95% of the dose is recovered in the urine within 24 hours. At higher doses, the cumulative recovery of drug from urine is somewhat lower due to the incomplete bioavailability. • Plasma concentrations of meglitol in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. • Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with meglitol is not recommended. • Because miglitol is excreted primarily by the kidneys, accumulation of miglitol is expected in patients with renal impairment. Patients with creatinine clearance <25 mL/min taking 25 mg 3 times daily, exhibited a greater than two-fold increase in miglitol plasma levels as compared to subjects with creatinine clearance >60 mL/min. Dosage adjustment to correct the increased plasma concentrations is not feasible because miglitol acts locally. Little information is available on the safety of miglitol in patients with creatinine clearance <25 mL/min. Therefore, treatment of these patients with	CONTRAINDICATIONS: • Diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, predisposition to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine, hypersensitivity to the drug or any of its components. WARNINGS AND PRECAUTIONS: • Sulfonylurea agents or insulin may cause hypoglycemia. • When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary. DISADVANTAGES: • Generally modest HbA1c efficacy;

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			miglitol is not recommended.	gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[20]
PRECOSE (acarbose)	020482 (September 6, 1995)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • Initial dose: 25 mg orally 3 times daily at the start of each meal. • May increase to 50 mg 3 times daily after 4-8 weeks. • Maximum recommended dose: 100 mg 3 times daily (50 mg 3 times daily for patients ≤60 kg).	**Not recommended if serum creatinine is >2 mg/dL.** • The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given intravenously, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an oral dose was recovered in the urine as active (that is, parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. • Plasma concentrations of acarbose in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. • Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with acarbose is not recommended. • Patients with severe renal impairment (CrCl <25 mL/min/1.73m^2) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function.	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug, diabetic ketoacidosis or cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, predisposition to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine. **WARNINGS AND PRECAUTIONS:** • Sulfonylurea agents or insulin may cause hypoglycemia. • In long-term studies (up to 12 months, and including acarbose doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) above the upper limit of normal (ULN), greater than 1.8 times the ULN, and greater than 3 times the ULN occurred in 14%, 6%, and 3%, respectively, of acarbose-treated patients as compared to 7%, 2%, and 1%, respectively, of placebo-treated patients. • When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may

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				occur. At such times, temporary insulin therapy may be necessary. **DISADVANTAGES:** • Generally modest HbA1c efficacy; gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[20]
Amylin Mimetics				
SYMLIN (pramlintide)	021332 (March 16, 2005)	**INDICATION:** As an adjunctive treatment in patients with T1D or T2D who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy. **DOSAGE/ADMINISTRATION:** • T1D: Start at 15 mcg subcutaneously before major meals. Increase in 15 mcg increments to a maximum premeal dose of 30 or 60 mcg; if not tolerated, reduce to 30 mcg, as tolerated. • T2D: Start at 60 mcg subcutaneously before major meals then increase to 120 mcg before meals, as tolerated.	**No dosage adjustments are provided in product labeling.** • No studies have been conducted in patients with ESRD. • In a single-dose pharmacokinetic study in patients with type 1 diabetes, 60 mcg of pramlintide was administered to 4 patients with normal renal function (CrCl >90 mL/min), 9 patients with mild renal impairment (CrCl 60-89 mL/min), 5 patients with moderate renal impairment (CrCl 30-59 mL/min) and 3 patients with severe renal impairment (CrCl 15-29 mL/min). No statistically significant differences were noted in total (AUC0-∞) and peak (Cmax) exposure of pramlintide for mild, moderate, and severe renal impairment categories in comparison to patients with normal renal function; although, inter-patient variability in pharmacokinetic parameters was high.	**BOXED WARNING:** • Use with insulin has been associated with an increased risk of severe hypoglycemia, particularly in patients with T1D. **CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to pramlintide or its ingredients, confirmed diagnosis of gastroparesis, or hypoglycemia unawareness. **WARNINGS AND PRECAUTIONS:** • Severe hypoglycemia: Increased risk particularly for type 1 diabetes. Upon initiation of pramlintide, reduce mealtime insulin dose by 50% and frequently monitor blood glucoses. • Never share a pramlintide pen injector between patients, even if the needle is changed. • Do not mix pramlintide and insulin: Mixing can alter the pharmaco-kinetics of both products. Administer as separate injections. • Slows gastric emptying: Administer concomitant oral medications at

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				least 1 hour before or 2 hours after pramlintide if rapid onset or threshold concentration is critical. **DISADVANTAGES:** • Generally modest HbA1c efficacy; gastrointestinal side effects (e.g., nausea, vomiting); hypoglycemia unless insulin dose is simultaneously reduced; injectable; frequent dosing schedule; and training requirements.[20]
Biguanides				
FORTAMET (metformin) **GLUCOPHAGE** (metformin) **GLUCOPHAGE XR** (metformin extended-release) **GLUMETZA** (metformin extended-release) **RIOMET** (metformin)	021574 (April 27, 2004) 020357 (March 3, 1995) 021202 (October 13, 2000) 021748 (June 3, 2005) 021591 (September 11, 2003)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • Extended-release tablet is 500 to 1000 mg once daily with the evening meal, although 500 mg may be utilized when clinically appropriate. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg (GLUMETZA, GLUCOPHAGE XR) to 2500 mg (FORTAMET) once daily with the evening meal. • Immediate-release tablet or solution: Adults ≥17 years: Initial: 500 mg twice daily or 850 mg once daily; titrate in increments of 500 mg weekly or 850 mg every other week; may also titrate from 500 mg twice a day to 850 mg twice a day after 2 weeks. If a dose >2,000 mg daily is required, it may be better tolerated in 3 divided doses with meals. Maximum recommended	• Metformin use is contraindicated in patients with an eGFR <30 mL/minute/1.73 m^2. • Obtain an eGFR prior to initiating metformin therapy. • Initiating metformin in patients with an eGFR between 30 to 45 mL/min/1.73 m^2 is not recommended. • Obtain an eGFR at least annually in all patients taking metformin; assess renal function more frequently in patients at increased risk for renal impairment (e.g., elderly patients). • Assess the benefits of continuing metformin treatment in patients whose eGFR falls below 45 mL/min/1.73 m^2; discontinue metformin if the eGFR falls below 30 mL/min/1.73 m^2. • Discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR between 30 to 60 mL/min/1.73 m^2, in patients with a history of hepatic disease, alcoholism, or heart failure, and/or in patients who will receive intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours following the imaging procedure; metformin may be reinitiated once renal function is stable. • Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in	**BOXED WARNING:** • Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. **CONTRAINDICATIONS:** • Use is contraindicated in patients with an eGFR <30 mL/minute/1.73

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		dose: 2,550 mg daily (2000 mg daily in pediatric patients 10-16 years of age). **GLUCOVANCE INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inadequate glycemic control on diet and exercise alone: 1.25 mg/250 mg once daily with a meal; patients with HbA1c >9% or FPG >200 mg/dL may start with 1.25 mg/250 mg twice daily with meals. • Inadequate glycemic control on a sulfonylurea and/or metformin: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals. Dosage may be increased in increments no greater than 5 mg/500 mg; maximum daily dose: 20 mg/2000 mg.	the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than CrCl, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. • In patients with decreased renal function (based on measured CrCl), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in CrCl.	m^2, known hypersensitivity to metformin (or components of combination product), metabolic acidosis, including diabetic ketoacidosis. **WARNINGS AND PRECAUTIONS:** • Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. • Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents (i.e., glyburide or glipizide) can lead to hemolytic anemia. **DISADVANTAGES:** • Gastrointestinal side effects (diarrhea, abdominal cramping); lactic acidosis risk (rare); vitamin B_{12} deficiency; multiple contraindications.[20] *Also, refer to Sulfonylureas for sulfonylurea-containing FCDPs and to DPP-4 inhibitors for DPP-4 inhibitor-containing FCDPs.*
Combination Products **GLUCOVANCE** (glyburide + metformin)	021178 (July 31, 2000)			
METAGLIP (glipizide + metformin)	021460 (October 21, 2002)	**METAGLIP:** • Inadequate glycemic control on diet and exercise alone: Glipizide 2.5 mg/metformin 250 mg once a day. In patients with FPG 280 to 320 mg/dL, initiate therapy with glipizide 2.5 mg/metformin 500 mg twice daily. Increase dose every 2 weeks per glycemic response. Maximum dose: Glipizide 10 mg/metformin 2,000 mg per day in divided doses. • Patients with inadequate glycemic control on a sulfonylurea and/or metformin: Glipizide 2.5 mg/metformin 500 mg or glipizide 5 mg/metformin 500 mg twice daily.		

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		The starting dose of glipizide/metformin should not exceed the daily doses of glipizide (b) (4) and metformin already being taken. Increase dose in increments of no more than glipizide 5 mg/metformin 500 mg. Maximum dose: Glipizide 20 mg/metformin 2,000 mg per day (b) (4)		
Bile Acid Sequestrants				
WELCHOL (colesevelam)	21176 (January 18, 2008)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • The recommended dose of colesevelam for T2D is 6 tablets (3.75 g) orally once daily or 3 tablets (1.875 g) twice daily. Colesevelam should be taken with a meal and liquid.	**No dosage adjustment necessary; not absorbed from the GI tract.** • Excretion: In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine. • T2D: Of the 2048 patients enrolled in the six diabetes studies, 807 (39%) had mild renal insufficiency (CrCl 50-<80 mL/min), 61 (3%) had moderate renal insufficiency (CrCl 30 to <50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with CrCl <50 mL/min (n=53) and those with a CrCl ≥50 mL/min (n=1075) in the add-on to metformin, sulfonylureas, and insulin diabetes studies. In the monotherapy study and add-on to pioglitazone study only 3 and 5 patients respectively had moderate renal insufficiency.	**CONTRAINDICATIONS:** • Colesevelam is contraindicated in patients with a history of bowel obstruction, serum TG concentrations >500 mg/dL, or a history of hypertriglyceridemia-induced pancreatitis. • Postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia. **WARNINGS AND PRECAUTIONS:** • Can increase TG, particularly when used with insulin or sulfonylureas. • Not recommended in patients at risk of bowel obstruction (e.g., patients with gastroparesis, other gastrointestinal motility disorders or a history of major gastrointestinal surgery). • Reduces gastrointestinal absorption of some drugs. • Oral Suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet.

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				DISADVANTAGES: • Generally modest HbA1c efficacy; constipation; increase in triglycerides; and may decrease the absorption of other medications.[20]
Dopamine-2 Agonists				
CYCLOSET (bromocriptine)	020866 (May 5, 2009)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • Initial: 0.8 mg orally once daily; may increase at weekly intervals in 0.8 mg increments as tolerated; usual dose: 1.6 to 4.8 mg once daily (maximum: 4.8 mg/day)	(b) (4) • The major route of excretion of bromocriptine is in the bile with the remaining 2-6% of an oral dose excreted via the urine. • No pharmacokinetic studies have been conducted in patients with renal impairment. Although the kidney is a minor pathway for elimination of bromocriptine, caution should be used in patients with renal impairment.	**CONTRAINDICATIONS:** • Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients. • Patients with syncopal migraine (increases the likelihood of a hypotensive episode) among patients with syncopal migraine. • Women who are nursing their children (may inhibit lactation, and there are postmarketing reports of stroke in this patient population). **WARNINGS AND PRECAUTIONS:** • Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. • May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. • May cause somnolence. • Effectiveness and safety are unknown in patients already taking dopamine receptor agonists (b) (4) (b) (4) **DISADVANTAGES:** • Generally modest HbA1c efficacy; dizziness/syncope; nausea; fatigue; and rhinitis.[20]

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DPP-4 Inhibitors				
JANUVIA (sitagliptin)	021995 (October 16, 2006)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • 100 mg orally once daily.	**FOR SITAGLIPTIN MONOTHERAPY:** **CrCl >50 mL/min: No dosage adjustment necessary.** **CrCl ≥30 to <50 mL/min (approximate serum creatinine of >1.7 to ≤3 mg/dL [males] or >1.5 to ≤2.5 mg/dL [females]): 50 mg once daily.** **CrCl <30 mL/min (approximate serum creatinine >3 mg/dL [males] or >2.5 mg/dL [females]): 25 mg once daily.** **End-stage renal disease requiring hemodialysis or peritoneal dialysis: 25 mg once daily; administer without regard to timing of hemodialysis.** • Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal half-life following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. • Compared to normal healthy control subjects, an approximate 1.1-to 1.6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. Because increases of this magnitude are	**CONTRAINDICATIONS:** • Metabolic acidosis, including diabetic ketoacidosis. • History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to one of the product components. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. • Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of sitagliptin in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms • There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. • There is an increased risk of hypoglycemia when added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. • There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.
Combination Products				
JANUMET (sitagliptin + metformin)	022044 (March 30, 2007)	**JANUMET:** • Sitagliptin 100 mg daily plus current daily dose of metformin given in 2 equally divided doses; maximum: sitagliptin 100 mg/metformin 2000 mg daily. Patients currently receiving metformin 850 mg twice daily should receive an initial dose of sitagliptin 50 mg and metformin 1000 mg twice daily.		
JANUMET XR (sitagliptin + metformin extended-release)	202270 (February 2, 2012)	**JANUMET XR:** • Sitagliptin 100 mg daily plus current daily dose of metformin given once daily; maximum: sitagliptin 100 mg/metformin 2000 mg daily. Patients currently receiving immediate release metformin 850 to 1000 mg twice daily should receive sitagliptin/metformin extended release at an initial dose of sitagliptin 100 mg and metformin 2000 mg once daily.		

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JUVISYNC (sitagliptin + simvastatin)	202343 (October 7, 2011)	**JUVISYNC:** • Initial dose: Sitagliptin 100 mg and simvastatin 40 mg once daily. Patients already taking simvastatin <40 mg daily (with or without sitagliptin 100 mg daily) can be converted to the comparable equivalent of the combination product. Dose adjustments should be made at intervals of ≥4 weeks.	not clinically relevant, dosage adjustment in patients with mild renal insufficiency is not necessary. Plasma AUC levels of sitagliptin were increased approximately 2-fold and 4-fold in patients with moderate renal insufficiency and in patients with severe renal insufficiency, including patients with ESRD on hemodialysis, respectively. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3to 4-hour hemodialysis session starting 4 hours post dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring dialysis. *Also, refer to Biguanides for metformin-containing FCDPs.* **FOR JUVISYNC:** **CrCl >50 mL/min: No dosage adjustment necessary.** **CrCl ≥30 to <50 mL/min (approximate serum creatinine of >1.7 to ≤3 mg/dL [males] or >1.5 to ≤2.5 mg/dL [females]): Sitagliptin 50 mg and simvastatin 40 mg once daily.** **CrCl <30 mL/min (approximate serum creatinine >3 mg/dL [males] or >2.5 mg/dL [females]): Use is not recommended.** **ESRD: Use is not recommended.**	• Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. **DISADVANTAGES:** • Angioedema/urticaria and other immune-mediated dermatological effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class.[20] *Also, refer to Biguanides for metformin-containing FCDPs.*
NESINA (alogliptin)	022271 (January 25, 2013)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended dose in patients with normal renal function or mild renal impairment is 25 mg orally once daily.	**FOR ALOGLIPTIN MONOTHERAPY:** **CrCl ≥60 mL/min: No dosage adjustment is necessary.** **CrCl ≥30 to <60 mL/min: 12.5 mg once daily.** **CrCl ≥15 to <30 mL/min or ESRD (CrCl <15 mL/min or hemodialysis): 6.25 mg once daily. Administer without regard to the timing of dialysis.** **Peritoneal dialysis: There is no dosage adjustment**	**CONTRAINDICATIONS:** • History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions or severe cutaneous adverse reactions. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing

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			provided in product labeling (has not been studied). • The primary route of elimination of [^{14}C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr. • A single-dose, open-label study was conducted to evaluate the pharmacokinetics of alogliptin 50 mg in patients with chronic renal impairment compared with healthy subjects. In patients with mild renal impairment (creatinine clearance [CrCl] ≥60 to <90 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed. Because increases of this magnitude are not considered clinically relevant, dose adjustment for patients with mild renal impairment is not recommended. In patients with moderate renal impairment (CrCl ≥30 to <60 mL/min), an approximate two-fold increase in plasma AUC of alogliptin was observed. To maintain similar systemic exposures of alogliptin to those with normal renal function, the recommended dose is 12.5 mg once daily in patients with moderate renal impairment. In patients with severe renal impairment (CrCl ≥15 to <30 mL/min) and end-stage renal disease (ESRD) (CrCl <15 mL/min or requiring dialysis), an approximate three- and four-fold increase in plasma AUC of alogliptin were observed, respectively. Dialysis removed approximately 7% of the drug during a three-hour dialysis session. Alogliptin may be administered without regard to the timing of the dialysis. To maintain similar systemic exposures of alogliptin to those with normal renal function, the recommended dose is 6.25 mg once daily in patients with severe renal impairment, as well as in patients with ESRD requiring dialysis.	reports of acute pancreatitis. • Heart failure: consider the risks and benefits of NESINA prior to initiating treatment in patients at risk for heart failure. • There have been postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. • Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. • When an insulin secretagogue (e.g., sulfonylurea) or insulin is used in combination with NESINA, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. • Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. **DISADVANTAGES:** • Angioedema/urticaria and other immune-mediated dermatological effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class.[20]

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Combination Products **KAZANO** (alogliptin + metformin)	203414 (January 25, 2013)	**KAZANO:** • Individualize the starting dose based on the patient's current regimen. • Should be taken twice daily with food. • May adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.	**FOR KAZANO:** **Prior to initiation, assess renal function with eGFR.** **Do not use in patients with eGFR below 60 mL/min/1.73 m^2.** **CONTRAINDICATION: Severe renal impairment eGFR below 30/mL/min/1.73 m^2.**	
OSENI (alogliptin + pioglitazone)	022426 (January 25, 2013)	**OSENI:** • Individualize the starting dose based on the patient's current regimen and concurrent medical condition but do not exceed a daily dose of alogliptin 25 mg and pioglitazone 45 mg. • Can be taken with or without food. • Limit initial dose of pioglitazone to 15 mg once daily in patients with NYHA Class I or II heart failure. • Adjust dose if moderate renal impairment.	**FOR OSENI:** **Adjust dose with moderate renal impairment (CrCl ≥30 to <60 mL/min): 12.5 mg/15 mg, 12.5 mg/30 mg or 12.5 mg/45 mg once daily.** **Not recommended for patients with severe renal impairment or ESRD requiring dialysis.** *Also, refer to Biguanides for metformin-containing FCDPs and to Thiazolidinediones for pioglitazone-containing FCDPs.*	
ONGLYZA (saxagliptin)	022350 (July 31, 2009)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. • 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g.,	**FOR SAXAGLIPTIN MONOTHERAPY:** **(b) (4) No dosage adjustment is recommended.** **CrCl (b) (4) mL/min: 2.5 mg once daily.** **ESRD (CrCl <15 mL/min or hemodialysis): 2.5 mg once daily after hemodialysis.** **Peritoneal dialysis: No dosage adjustments are provided in product labeling (has not been studied).**	**CONTRAINDICATIONS:** • History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to ONGLYZA. **WARNINGS AND PRECAUTIONS:** • Acute pancreatitis. • Heart failure: Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart

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		ketoconazole.	• Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of saxagliptin 5 mg to healthy subjects, the mean plasma terminal half-life for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively. • A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (b) (4) compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. (b) (4) [redacted] The degree of renal impairment did not affect the Cmax of saxagliptin or its active metabolite (b) (4) (b) (4) [redacted]	failure. • When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. • Hypersensitivity-related events (e.g., urticaria, facial edema): More common in patients treated with ONGLYZA than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. • Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. **DISADVANTAGES:** • Angioedema/urticaria and other immune-mediated dermatological effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class (statistically significant increase incidence observed in the CVOT, SAVOR).[20]

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Combination Products **KOMBIGLYZE XR** (saxagliptin+metformin extended-release)	200678 (November 5, 2010)	**KOMBIGLYZE XR:** • Administer orally once daily with the evening meal. • Individualize the starting dose based on the patient's current regimen then adjust the dosage based on effectiveness and tolerability. • Do not exceed a daily dosage of 5 mg saxagliptin/2000 mg metformin HCl extended-release. • Swallow whole. Never crush, cut, or chew.	(b) (4) [redacted] renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis. **FOR KOMBIGLYZE XR:** **Do not use in patients with eGFR below 30 mL/min/1.3 m^2.** **Initiation is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.** **Assess risk benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2.** **Limit the saxagliptin component to 2.5 mg daily if eGFR is less than 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls below 30 mL/min/1.73 m^2.** *Also, refer to Biguanides for metformin-containing FCDPs and to SGLT2 inhibitor-containing FCDPs*	
TRADJENTA (linagliptin)	201280 (May 2, 2011)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended dose is 5 mg orally once daily. • Can be taken with or without food.	**FOR LINAGLIPTIN MONOTHERAPY:** **No dosage adjustment is recommended for patients with renal impairment.** • Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.	**CONTRAINDICATIONS:** • History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperactivity. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis,

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Combination Products **JENTADUETO** (linagliptin + metformin)	201281 (January 30, 2012)	**JENTADUETO INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both linagliptin and metformin is appropriate. • Individualize the starting dose based on the patient's current regimen. • The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin twice daily. • Should be given twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.	• Under steady-state conditions, linagliptin exposure in patients with mild renal impairment (CrCl 50 to <80 mL/min) was comparable to healthy subjects. • In patients with moderate renal impairment (CrCl 30 to <50 mL/min) under steady-state conditions, mean exposure of linagliptin increased (AUCτ,ss by 71% and Cmax by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with T2D and severe renal impairment (CrCl <30 mL/min) showed steady-state exposure approximately 40% higher than that of patients with T2D and normal renal function (increase in AUCτ,ss by 42% and Cmax by 35%). For both T2D groups, renal excretion was below 7% of the administered dose. These findings were further supported by the results of population pharmacokinetic analyses. **For JENTADUETO and JENTADUETO XR:** **Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).** **Do not use in patients with eGFR below 30 mL/min/1.73 m^2.** **Initiation is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.** **Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls below 30 mL/min/173 m^2.**	including fatal pancreatitis. • Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of linagliptin in patients who have known risk factors for heart failure. Monitor for signs and symptoms. • When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. • There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin including anaphylaxis, angioedema, and exfoliative skin conditions. • Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. **DISADVANTAGES:** • Angioedema/urticaria and other immune-mediated dermatological effects; uncertain risk for acute pancreatitis; and uncertain increased risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class.[20]

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JENTADUETO XR (linagliptin + metformin extended-release)	208026 (May 27, 2016)	**JENTADUETO XR INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both linagliptin and metformin is appropriate. • Individualize the starting dose based on the patient's current regimen. • Do not exceed a total daily dose of linagliptin 5 mg and metformin 2000 mg. • Give once daily with a meal. • Swallow whole; do not split, crush, dissolve, or chew.		
GLYXAMBI (empagliflozin/linagliptin)	206073 (January 30, 2015)	**GLYXAMBI INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and linagliptin is appropriate. • The recommended dose is 10 mg empagliflozin/5 mg linagliptin orally once daily, taken in the morning with or without food. • Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.	**FOR GLYXAMBI:** **Assess renal function before initiating.** **Do not initiate Glyxambi if eGFR is below 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls persistently below 45 mL/min/1.73 m^2.** *Also, refer to Biguanides for metformin-containing FCDPs and SGLT2 inhibitors for empagliflozin-containing FCDRs.*	
GLP-1 Receptor Agonists				
ADLYXIN (lixisenatide)	208471 (July 27, 2016)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20	**FOR LIXISENATIDE MONOTHERAPY:** **eGFR ≥30 to 89 mL/min/1.73 m^2: No dosage adjustment necessary; monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function.**	**CONTRAINDICATIONS:** • Hypersensitivity to lixisenatide or any product components. **WARNINGS AND PRECAUTIONS:** • Anaphylaxis and serious hypersensitivity reactions.

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Combination Products **SOLIQUA** (insulin glargine + lixisenatide)	208673 (November 21, 2016)	mcg once daily. • Administer once daily within one hour before the first meal of the day. • Inject subcutaneously in the abdomen, thigh or upper arm. **SOLIQUA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide. • In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily. • In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily. • Inject once a day within the hour prior to the first meal of the day. • Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). • SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. • Use alternative antidiabetic products if patients require a SOLIQUA 100/33 daily dosage below 15 units or over 60 units. • Inject subcutaneously in thigh, upper arm, or abdomen.	**eGFR 15 to 29 mL/min/1.73 m^2: There are no dosage adjustments provided in product labeling (limited data); exposure is increased in these patients. Monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function.** **eGFR <15 mL/min/1.73 m^2: Use is not recommended (has not been studied).** • Lixisenatide is presumed to be eliminated through glomerular filtration, and proteolytic degradation. After multiple dose administration in patients with T2D, the mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h. • Compared to healthy subjects [CrCl using Cockcroft-Gault ≥90 mL/min (N=4)], plasma Cmax of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild [CrCl 60–89 mL/min (N=9)], moderate [CrCl 30–59 mL/min (N=11)], and severe [CrCl 15–29 mL/min (N=8)] renal impairment. Plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively. • In patients with mild renal impairment (eGFR: 60–89 mL/min/1.73 m^2) no dose adjustment is required, but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because a higher incidence of hypoglycemia, nausea and vomiting were observed in these patients. • In a cardiovascular outcome study, 655 (22%) lixisenatide treated patients had moderate renal impairment (eGFR: 30 to less than 60 mL/min/1.73 m^2). No dosing adjustment is recommended in patients with moderate renal impairment, but close monitoring for lixisenatide related adverse gastrointestinal reactions	• Pancreatitis. • Never share ADLYXIN pen between patients, even if the needle is changed. • Hypoglycemia with concomitant use of sulfonylurea or basal insulin. • Acute kidney injury. • Immunogenicity. **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[20]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Do not administer intravenously, intramuscularly, or by an infusion pump. • Do not dilute or mix with any other insulin products or solutions.	and for changes in renal function is recommended because these may lead to dehydration and acute renal failure and worsening of chronic failure in these patients. • Clinical experience in patients with severe renal impairment is limited as there were only 5 patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) exposed to lixisenatide in all controlled studies. Lixisenatide exposure was higher in these patients. Patients with severe renal impairment exposed to lixisenatide should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes in renal function. • There is no therapeutic experience in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use lixisenatide in this population.	
BYDUREON (exenatide extended-release) **BYDUREON BCISE** (exenatide extended-release) **BYETTA** (exenatide)	022200 (January 27, 2012) 209210 (October 20, 2017) 021919 (October 30, 2009)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Administer 2 mg by subcutaneous injection once every seven days, at any time of day and with or without meals. • Administer immediately after the dose is prepared. **BYETTA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately six hours or	**For BYDUREON/BYDUREON BCISE:** **CrCL <30 mL/min, eGFR <30 mL/min/1.73 m^2 or ESRD: Use is not recommended.** **CrCL 30-50 mL/min or eGFR 30-50 mL/min/1.73 m^2 (BYDUREON), CrCL 30-59 mL/min or eGFR 30-59 mL/min/1.73 m^2 (BYDUREON BCISE), or renal transplantation: Use with caution.** • Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 hours post-dose, whereas following administration of exenatide extended-release, plasma exenatide concentrations generally fall below the minimal detectable concentration of 10 pg/mL approximately 10 weeks after discontinuation of	**BOXED WARNING:** • Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including MTC in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to exenatide or any of the product components. **WARNINGS AND PRECAUTIONS:**

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		more apart. • Initiate 5 mcg per dose twice daily; increase to 10 mcg twice daily after one month based on clinical response.	therapy. • Population pharmacokinetic analysis of renally impaired patients receiving 2 mg exenatide extended-release indicate that there is a 62% and 33% increase in exposure in moderate (N=10) and mild (N=56) renally impaired patients, respectively, as compared to patients with normal renal function (N=84). • In a study of exenatide in subjects with ESRD receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function.	• Acute pancreatitis: Including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been reported. • Hypoglycemia: When used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia. • Acute kidney and impairment of renal function: Sometimes requiring hemodialysis and kidney transplantation. Not recommended if patient has severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal impairment. • Gastrointestinal disease: Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). • Immunogenicity: Patients may develop antibodies to exenatide. • Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. • Injection-site reactions: Serious injection-site reactions with or without subcutaneous nodules have been reported. **DISADVANTAGES:** • Gastrointestinal side effects

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				(nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[20]
TANZEUM (albiglutide)	(BLA) 125431 (April 15, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Administer once weekly at any time of day, without regard to meals. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control. • If a dose is missed, administer within 3 days of missed dose.	**No dosage adjustment necessary. Use caution when initiating or escalating doses.** • Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed. Because albiglutide is an albumin fusion protein, it likely follows a metabolic pathway similar to native human serum albumin which is catabolized primarily in the vascular endothelium. The mean apparent clearance of albiglutide is 67 mL/h with an elimination half-life of approximately 5 days, making albiglutide suitable for once-weekly administration. • In a population pharmacokinetic analysis including a Phase 3 trial in patients with mild, moderate, and severe renal impairment, exposures were increased by approximately 30% to 40% in severe renal impairment compared with those observed in T2D patients with normal renal function.	**BOXED WARNING:** • Carcinogenicity of albiglutide could not be assessed in rodents, but other GLP-1 receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether albiglutide causes thyroid C-cell tumors, including MTC, in humans. • Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to albiglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors. • Pancreatitis. • Hypoglycemia: Can occur when used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin. • Hypersensitivity reactions. • Renal impairment.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				DISADVANTAGES: • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[20]
TRULICITY (dulaglutide)	(BLA) 125469 (September 18, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Administer once weekly at any time of day. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 0.75 mg subcutaneously once weekly. • Dose can be increased to 1.5 mg once weekly for additional glycemic control. • If a dose is missed, administer within three days of missed dose.	**No dosage adjustments necessary; use caution when initiating or escalating doses.** • Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways. The mean apparent clearance at steady state of dulaglutide is approximately 0.111 L/h for the 0.75 mg dose, and 0.107 L/h for the 1.5 mg dose. The elimination half-life of dulaglutide for both doses is approximately 5 days. • Dulaglutide systemic exposure was increased by 20, 28, 14 and 12% for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in Cmax were 13, 23, 20 and 11%, respectively.	**BOXED WARNING:** • Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether dulaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance could not be determined from clinical or nonclinical studies. • Dulaglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to dulaglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors in animals. • Pancreatitis: Has been reported in clinical trials. • Hypoglycemia: When used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia. • Hypersensitivity reactions.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• Renal impairment. **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[20]
VICTOZA (liraglutide)	022341 (January 25, 2010)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. To reduce the risk of major adverse CV events in adults with T2D and established CV disease. • Inject subcutaneously in the abdomen, thigh or upper arm. • Administer once daily at any time of day, independently of meals. • Initiate at 0.6 mg per day for one week then increase to 1.2 mg. • Dose can be increased to 1.8 mg for additional glycemic control	**No dosage adjustments are provided in product labeling; however, use with caution, due to reports of acute renal failure and exacerbation of chronic renal failure and limited experience in patients with severe renal impairment.** • During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration. • The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated CrCl 50-80 mL/min) to severe (estimated CrCl <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to liraglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors in animals. • Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. • Never share the liraglutide pen between patients, even if the needle is changed.
Combination Products **XULTOPHY** (insulin degludec/liraglutide)	208583 (November 21, 2016)	**XULTOPHY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Recommended starting dosage is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily. • Administer once daily at same time each day with or without food. • Maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide). • XULTOPHY 100/3.6 pen delivers doses from 10 to 50 units with each injection; each XULTOPHY 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide. • Use alternative antidiabetic products if patients require a XULTOPHY 100/3.6 daily dosage: Persistently below 16 units, or over 50 units. • Inject subcutaneously in thigh, upper arm or abdomen. • Do not administer intravenously, intramuscularly, or by an infusion pump. • Do not dilute or mix with any other insulin products or solutions.	to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively.	• Serious hypoglycemia: When used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia. • Renal impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. • Hypersensitivity reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[20]
Insulins and Insulin Analogues				
Rapid-Acting Analogs **AFREZZA** (inhaled insulin human) **APIDRA** (insulin glulisine) **FIASP**	022472 (June 27, 2014) 021629 (April 16, 2004) 208751	Most patients with T1D should be treated with multiple daily injections of prandial insulin (e.g., rapid-acting insulin analogs to reduce hypoglycemia risk) and basal insulin or continuous subcutaneous insulin infusion. ADA recommendations suggest a starting insulin dose based on weight, with total insulin doses ranging	**No dosage adjustments are provided in product labeling. Insulin dose requirements may be reduced due to changes in insulin clearance or metabolism; increased circulating levels of insulin may occur in patients with renal impairment/failure. Careful glucose monitoring and dose adjustments of insulin may be necessary.**	**CONTRAINDICATIONS (AFREZZA):** • Patients with chronic lung disease (e.g., asthma, COPD) with inhaled insulin. **DISADVANTAGES:** • Hypoglycemia, weight gain, uncertain mitogenic effects, injectable (except inhaled insulin),

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(insulin aspart)	(September 29, 2017)	from 0.4 to 1.0 units/kg/day, and potentially higher amounts during puberty. The ADA/JDRF Type 1 Diabetes Sourcebook notes 0.5 units/kg/day as a typical starting dose in patients who are metabolically stable, with higher weight-based dosing required immediately following presentation with ketoacidosis.[21] ***Inhaled Insulin:*** AFREZZA • Administer using a single inhalation per cartridge • Administer at the beginning of a meal • Dosing must be individualized. ***Injectable Insulins*** • The dosage must be must be individualized (e.g., based on the route of administration, metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use). • **For rapid-acting analogs (SC):** **APIDRA:** Administer within 15 minutes before a meal or within 20 minutes after starting a meal. **FIASP:** Administer at the start of the meal or within 20 minutes after starting a meal. **HUMALOG:** Administer within 15 minutes before a meal or immediately after a meal. **NOVOLOG:** Administer within 5-10 minutes before a meal.	• In adults, the following adjustments have been previously suggested for insulin products:[253,254] — CrCl >50 mL/min: No adjustment necessary. — CrCl 10-50 mL/min: Administer at 75% of recommended dose. — CrCl <10 mL/min: Administer at 50% of recommended dose and monitor glucose closely. — Hemodialysis: Because of a large molecular weight (6000 daltons), insulin is not significantly removed by either peritoneal or hemodialysis; supplemental dose is not necessary. — CRRT: Administer at 75% of recommended dose. • Polypeptides and low-molecular proteins, such as insulin, can be actively reabsorbed by the proximal tubules through luminal endocytosis, followed by hydrolysis by the digestive enzymes in the lysosomes to peptide fragments and amino acids. The amino acids are then reabsorbed by a carrier-mediated, energy-dependent transport mechanism. Approximately one-third of the insulin dose may undergo degradation in the kidneys. Azotemia may be associated with a prolonged half-life of insulin, and an increased risk of hypoglycemia. Patients with CKD treated with insulin should closely monitor their blood glucose to minimize this risk, and dose adjustments made as necessary. Initiation of peritoneal dialysis may require an increase in the insulin dosage due to the absorption of glucose from the dialysate through the peritoneal cavity.[255,256]	patient and provider reluctance, training requirements, pulmonary toxicity (inhaled insulin).[20,21] Spirometry (FEV_1) testing prior to and after starting inhaled insulin therapy. **WARNINGS AND PRECAUTIONS:** • Never share insulin pen injectors, syringes, or needles. • Hyper- or hypoglycemia (e.g., with changes in insulin regimen). • Medication errors. • Hypersensitivity reactions. • Hypokalemia. • Fluid retention and heart failure with concomitant use of thiazolidinediones. • May require a reduction in dose with renal or hepatic impairment.
Short-Acting **HUMULIN R** (insulin human)	018780 (October 28, 1982)			
NOVOLIN R (insulin human)	019938 (June 25, 1991)			
Intermediate-Acting **HUMULIN N** (insulin isophane)	018781 (October 28, 1982)			
Basal Analogs **BASAGLAR** (insulin glargine)	205692 (August 18, 2014)			
LANTUS (insulin glargine)	021081 (April 20, 2000)			
LEVEMIR (insulin detemir)	021536 (June 16, 2005)			
[redacted] (b) (4)				
TOUJEO (insulin glargine)	206538 (February 25, 2015)			
TRESIBA (insulin degludec)	203314 (September 25, 2015)			

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
Combination Products **HUMALOG MIX** (insulin lispro protamine + insulin lispro) **NOVOLOG MIX** (insulin aspart protamine + insulin aspart) **RYZODEC** (insulin degludec + insulin aspart)	021017 (December 22, 1999) 021018 December 22, 1999 021172 (November 1, 2001) 203313 (September 25, 2015)	• **For short-acting (SC):** **HUMULIN R AND NOVOLIN R:** Administer approximately 30 minutes before a meal.		
Meglitinides				
PRANDIN (repaglinide)	020741 (December 22, 1997)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • For patients not previously treated or whose HbA1c is <8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA1c is ≥8%, the initial dose is 1 or 2 mg with each meal preprandially. • The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.	**No dosage adjustment is required with mild to moderate renal impairment. Initiate with a 0.5 mg dose, and subsequently titrate carefully with severe renal impairment.** • Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces. • Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with T2D and normal renal function (CrCl >80 mL/min), mild to moderate renal function impairment (CrCl = 40-80 mL/min), and severe renal function impairment (CrCl = 20-40 mL/min). Both AUC and Cmax of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced	**CONTRAINDICATIONS:** • Diabetic ketoacidosis, with or without coma. • T1D. • Co-administration of gemfibrozil. • Known hypersensitivity to the drug or its inactive ingredients. **WARNINGS AND PRECAUTIONS:** • Not indicated for use in combination with NPH insulin. • All oral antihyperglycemic drugs are capable of producing hypoglycemia. • Use with caution in patients with moderate to severe liver disease because such patients have not been studied. • May need to discontinue and temporarily use insulin if glycemic control deteriorates during periods of stress or if there is decreased

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Combination Products **PRANDIMET** (repaglinide + metformin)	022386 (June 23, 2008)	**PRANDIMET INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D who are already treated with a meglitinide and metformin HCl or who have inadequate glycemic control on a meglitinide alone or metformin HCl alone. • The dosage should be individualized. • Start with 1 mg/500 mg twice daily unless the patient is already taking higher co-administered doses of repaglinide and metformin HCl. • Do not exceed 10 mg repaglinide/2500 mg metformin HCl daily or 4 mg repaglinide/1000 mg metformin HCl per meal. • Give in divided doses within 15 minutes prior to meals. • Patients who skip a meal should skip the dose for that meal.	renal function had elevated mean AUC and Cmax values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. However, patients with T2D who have severe renal function impairment should initiate repaglinide therapy with the 0.5 mg dose, and, subsequently, patients should be carefully titrated. Studies were not conducted in patients with CrCl <20 mL/min or patients with renal failure requiring hemodialysis. *Also, refer to Biguanides for metformin-containing FCDPs.*	intake of fluids and food (e.g., infection, surgery). **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[20] *Also, refer to Biguanides for metformin-containing FCDPs.*
STARLIX (nateglinide)	021204 (December 22, 2000)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Nateglinide should be taken one to 30 minutes prior to meals. • The recommended starting and maintenance dose, alone or in combination with metformin or a thiazolidinedione, is 120 mg three times daily before meals. • The 60 mg dose, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA1C	**No dosage adjustment necessary with renal impairment. However, use with caution with severe renal impairment; patients may be more susceptible to glucose-lowering effects.** • Transient nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered ^{14}C-nateglinide was recovered in the urine. Eighty-three percent of the ^{14}C-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ^{14}C-nateglinide was excreted in the urine as parent compound. In all studies of healthy volunteers and patients with T2D, nateglinide plasma	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug or its inactive ingredients. • T1D. • DKA. **WARNINGS AND PRECAUTIONS:** • (b) (4) . • All oral antihyperglycemic drugs are capable of producing hypoglycemia. • May need to discontinue and temporarily use insulin if glycemic control deteriorates during periods of stress or if there is decreased

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		when treatment is initiated.	concentrations declined rapidly with an average elimination half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days. • Compared to healthy matched subjects, patients with T2D and moderate-to-severe renal insufficiency (CrCl 15-50 mL/min) not on dialysis displayed similar apparent clearance, AUC, and Cmax. Patients with T2D and renal failure on dialysis exhibited reduced overall drug exposure. However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.	intake of fluids and food (e.g., infection, surgery). **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[20]
SGLT2 Inhibitors				
FARXIGA (dapagliflozin)	202293 (January 8, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. • Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control.	**FOR DAPAGLIFLOZIN MONOTHERAPY:** **eGFR ≥60 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR 30 to <60 mL/minute/1.73 m^2: Use is not recommended for initiation of therapy or when eGFR is persistently between 30 and <60 mL/minute/1.73 m^2.** **eGFR <30 mL/minute/1.73 m^2, ESRD, or hemodialysis: Use is contraindicated.** • Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to FARXIGA. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. **WARNINGS AND PRECAUTIONS:** • Hypotension: Before initiating FARXIGA, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. • Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, (b) (4) (b) (4) • Acute kidney injury and Impairment

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			of dapagliflozin 10 mg. • At steady state (20 mg once-daily dapagliflozin for 7 days), patients with T2D with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean (GM) systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with T2D with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with T2D and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.	in Renal Function. • Urosepsis and pyelonephritis. • Hypoglycemia: In patients taking insulin or an insulin secretagogue with FARXIGA, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. • Genital mycotic infections. • Increased LDL-C. • Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. FARXIGA should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer. **DISADVANTAGES:** • Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[20]
Combination Products **QTERN** (dapagliflozin+saxagliptin)	209091 (February 27, 2017)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin. • Administer 10 mg dapagliflozin/5 mg saxagliptin once daily in the morning with or without food. • Swallow whole. Do not split or cut the tablets. • Assess renal function before initiating. Do not initiate or continue if eGFR is	**FOR QTERN:** **eGFR <45 mL/minute/1.73 m^2, ESRD, or dialysis: Use is contraindicated.**	*Also, refer to DPP-4 inhibitors for DPP-4 inhibitor-containing FCDPs.*

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		below 60 mL/min/1.73 m^2. • Do not coadminister with strong cytochrome P450 3A4/5 inhibitors.		-*
XIGDUO XR (dapagliflozin+metformin)	205649 (October 29, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both dapagliflozin and metformin is appropriate. • Individualize the starting dose based on the patient's current treatment. • Administer once daily in the morning with food. • Swallow whole. Never crush, cut, or chew. • Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release. • Assess renal function before initiating. Do not initiate or continue if eGFR is below 60 mL/min/1.73 m^2. • No dosage adjustment is indicated in patients with mild renal impairment. • XIGDUO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.	**FOR XIGDUO XR:** **eGFR <60 mL/minute/1.73 m^2, ESRD, ESRD, or dialysis: Use is contraindicated.** *Also, refer to Biguanides for metformin-containing FCDPs.*	**XIGDUO XR BOXED WARNING:** • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. *Also, refer to Biguanides for metformin-containing FCDPs.*
INVOKANA (canagliflozin)	204042 (March 29, 2013)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 100 mg once daily, taken before the first meal of the day.	**FOR CANAGLIFLOZIN MONOTHERAPY:** **eGFR ≥60 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR 45 to <60 mL/minute/1.73 m^2: Maximum dose: 100 mg once daily. If patient receiving concurrent UDP-glucuronosyl transferase (UGT) enzyme inducers (e.g., rifampin, phenytoin, phenobarbital, ritonavir)**	**INVOKANA/INVOKANAMET /INVOKANAMET XR BOXED WARNING:** • In patients with type 2 diabetes who have established CVD or at risk for CVD, canagliflozin has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved

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Combination Products **INVOKAMET** (canagliflozin + metformin)	204353 (August 8, 2014)	• Dose can be increased to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control. **INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both canagliflozin and metformin is appropriate. • Individualize based on the patient's current regimen. • Take one INVOKAMET tablet twice daily with meals, recommended starting dose of canagliflozin is 50 mg twice daily and metformin 500 mg twice daily. • Canagliflozin dose can be increased to 150 mg twice daily in patients tolerating canagliflozin 50 mg twice daily who have eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control. Do not exceed a total daily canagliflozin dose of 300 mg. • Gradually escalate metformin dose to reduce the gastrointestinal side effects while not exceeding total daily dose of 2000 mg. • Assess renal function before initiating and periodically thereafter.	**and eGFR 45 to <60 mL/minute/1.73 m^2 at baseline, consider the use of another antihyperglycemic agent.** **eGFR ≥30 to <45 mL/minute/1.73 m^2: Use not recommended for initiation of therapy or when eGFR is persistently <45 mL/minute/1.73 m^2.** **eGFR <30 mL/minute/1.73 m^2: Use is contraindicated.** **ESRD: Use is contraindicated.** **Hemodialysis: Use is contraindicated.** • Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible. Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min. Mean systemic clearance of canagliflozin was approximately 192 mL/min in healthy subjects following intravenous administration. • A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD eGFR formula) compared to healthy subjects. Renal impairment did not affect the Cmax of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than	the leg. **CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to INVOKANA. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. **WARNINGS AND PRECAUTIONS:** • Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. • Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, and glycogen storage disorders).[184] • Acute kidney injury and Impairment in Renal Function. • Hyperkalemia. • Urosepsis and pyelonephritis. • Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with canagliflozin. • Genital mycotic infections. • Hypersensitivity reactions. • Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKANA. • Increased LDL-C.

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			60 and 15 to less than 30 mL/min/1.73 m^2, respectively), but was similar for ESRD (N=8) subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment. Canagliflozin was negligibly removed by hemodialysis.	**DISADVANTAGES:** Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[20]
INVOKAMET XR (canagliflozin + metformin extended-release)	205879 (September 20, 2016)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both canagliflozin and metformin is appropriate. • Individualize based on the patient's current regimen. • Take two tablets once daily with the morning meal. • In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets, each tablet containing canagliflozin 50 mg and metformin 500 mg. • In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same total daily dose of canagliflozin and the same, or nearest appropriate, total daily dose of metformin. • In patients that require additional glycemic control that are taking a total daily dose of canagliflozin 100 mg, the INVOKAMET XR dose can be increased to canagliflozin 300 mg once daily. Do not	**FOR INVOKAMET AND INVOKAMET XR:** **Contraindicated in patients with an estimated eGFR <45 mL/min/1.73 m^2.** **Limit the dose of canagliflozin component to 50 mg twice daily (INVOKAMET) or to two tablets, each contain 50 mg, once daily (INVOKAMET XR) in patients with an eGFR of 45 to <60 mL/min/1.73 m^2.** **May need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.** *Also, refer to Biguanides for metformin-containing FCDPs.*	**INVOKAMET AND INVOKAMET XR BOXED WARNING:** • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. *Also, refer to Biguanides for metformin-containing FCDPs.*

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		exceed a total daily canagliflozin dose of 300 mg. • Gradually escalate metformin dose to reduce the gastrointestinal side effects while not exceeding a total daily dose of 2000 mg. • Assess renal function before initiating and periodically thereafter • Swallow whole. Never crush, cut, or chew.		
JARDIANCE (empagliflozin) *Combination Products* GLYXAMBI (empagliflozin + linagliptin)	204629 (August 1, 2014) 206073 (January 30, 2015)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. To reduce the risk of cardiovascular death in adult patients with T2D and established cardiovascular disease. • The recommended dose is 10 mg once daily, taken in the morning, with or without food. • Dose may be increased to 25 mg once daily. • Assess renal function before initiating. GLYXAMBI INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and linagliptin is appropriate. • The recommended dose is 10 mg empagliflozin/5 mg linagliptin once daily, taken in the morning, with or without food.	FOR EMPAGLIFLOZIN MONOTHERAPY AND GLYXAMBI: **eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR <45 mL/minute/1.73 m^2: Do not initiate therapy; in patients already taking empagliflozin, discontinue therapy when eGFR is persistently <45 mL/minute/1.73 m^2** **eGFR <30 mL/minute/1.73 m^2: Use is contraindicated. ESRD, dialysis: Use is contraindicated.** • The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.	CONTRAINDICATIONS: • History of serious hypersensitivity reaction to JARDIANCE. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. WARNINGS AND PRECAUTIONS: • Hypotension: Before initiating JARDIANCE, assess and correct volume status in patients with renal impairment, the elderly, in patients with low SBP, and in patients on diuretics. • Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, and glycogen storage disorders).[184] • Acute kidney injury and impairment in renal function. • Urosepsis and pyelonephritis. • Hypoglycemia: Consider lowering the dose of insulin secretagogues or insulin to reduce the risk of

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		• Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily. • Assess renal function before initiating.	• In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.	hypoglycemia when initiating JARDIANCE. • Genital mycotic infections. • Increased LDL-C. **DISADVANTAGES:** • Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[20]
SYNJARDY (empagliflozin + metformin)	206111 (August 26, 2015)	**SYNJARDY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. • Individualize the starting dose of SYNJARDY based on the patient's current regimen. • The maximum recommended dose is 12.5 mg empagliflozin/1000 mg metformin twice daily. • Take twice daily with meals, with gradual dose escalation to reduce the	**FOR SYNJARDY:** **eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR <45 mL/minute/1.73 m^2, ESRD, or dialysis: Use is contraindicated.** *Also, refer to Biguanides for metformin-containing FCDPs and to DPP-4 inhibitors for linagliptin-containing FCDPs.*	

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		gastrointestinal side effects due to metformin. • Assess renal function before initiating.		
Sulfonylureas				
DIABINESE (chlorpropamide)	011641 (October 28, 1958)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Initial dose: 250 mg orally daily in mild to moderate diabetes in middle-aged, stable patients. • In debilitated or malnourished patients, the initial dosing should be conservative to avoid hypoglycemic reactions. • After 5-7 days of initiation, subsequent daily dosages may be increased or decreased by 50-125 mg at 3- to 5-day intervals. • The maintenance dose is 100-250 mg daily (500 mg/day may be required; avoid doses >750 mg/day).	**No specific dosage adjustment provided in product labeling. In patients with impaired renal function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.** (b) (4) [redacted] • Chorpropamide undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as hydroxylated or hydrolyzed metabolites. The biological half-life of chlorpropamide averages about 36 hours. Within 96 hours, 80% to 90% of a single oral dose is excreted in the urine. However, long-term administration of therapeutic doses does not result in undue accumulation in the blood, since absorption and excretion rates become stabilized in about 5 to 7 days after the initiation of therapy. • Chlorpropamide impairs water excretion. Renal insufficiency also affect the disposition of chlorpropamide and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. The elimination half-life with ESRD may be increased to 50-200 hours, and prolonged hypoglycemia may occur in azotemic patients.	**CONTRAINDICATIONS:** • Known hypersensitivity to any component of this medication. • T1D, and DKA, with or without coma. **WARNINGS AND PRECAUTIONS:** • Hypoglycemia: All sulfonylurea drugs, including chlorpropamide, are capable of producing severe hypoglycemia, which may result in coma, and may require hospitalization. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue DIABINESE and administer insulin. • Hemolytic anemia: Treatment of patients with glucose G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Geriatric use: Chlorpropamide is identified in the Beers Criteria as a

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				potentially inappropriate medication to be avoided in patients 65 years and older (independent of diagnosis or condition) because of its prolonged half-life in older adults, which may cause prolonged hypoglycemia.[257] In addition, chlorpropamide may cause SIADH. • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20]
AMARYL (glimepiride)	020496 (November 30, 1995)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Recommended starting dose is 1 or 2 mg once daily. • Increase in 1 or 2 mg increments no more frequently than every 1-2 weeks based on glycemic response. • Maximum recommended dose is 8 mg once daily. • Administer with breakfast or first meal of the day.	**FOR GLIMEPIRIDE MONOTHERAPY:** **The initial dose is 1 mg once daily with renal impairment; with careful titration** (b) (4) (b) (4) • When ^{14}C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80 to 90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in	**CONTRAINDICATIONS:** • Hypersensitivity to glimepiride or any of the product's ingredients. • Hypersensitivity to sulfonamide derivatives. **WARNINGS AND PRECAUTIONS:** • Hypoglycemia: May be severe. Ensure proper patient selection, dosing, and instructions, particularly in at-risks populations (e.g., elderly, renally impaired) and when used with other antihyperglycemic medications).

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Use 1 mg starting dose and titrate slowly in patients at increased risk for hypoglycemia (e.g., elderly, patients with renal impairment).	one subject. In animals, M1 possesses about one- third of the pharmacological activity of glimepiride, and M2 is inactive. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed. • A single-dose, open-label study glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CrCl): Group I consisted of 5 patients with mild renal impairment (CrCl > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CrCl = 20 to 50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CrCl < 20 mL/min). Although, glimepiride serum concentrations decreased with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III. • A multiple-dose titration study was conducted in 16 patients with T2D and renal impairment using doses ranging from 1 mg to 8 mg daily for 3 months. Baseline CrCl ranged from 10 to 60 mL/min. The pharmacokinetics of glimepiride were evaluated in the multiple-dose titration study and the results were consistent with those observed in patients enrolled in a single-dose study. In both studies, the relative total clearance of glimepiride increased when kidney function was impaired. Both studies also demonstrated	• Hypersensitivity reactions: Postmarketing reports include anaphylaxis, angioedema, and Stevens-Johnson Syndrome. • Hemolytic anemia: Can occur if G6PD deficient. • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			that the elimination of the two major metabolites was reduced in patients with renal impairment. *Also, refer to thiazolidinediones for TZD-containing FCDPs.*	
GLUCOTROL (glipizide)	017783 (May 8, 1984)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 5 mg, given orally before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. • Dosage adjustments should ordinarily be in increments of 2.5–5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. • If response to a single dose is not satisfactory, dividing that dose may prove effective. • The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. • The maximum recommended total daily dose is 40 mg.	**FOR GLIPIZIDE MONOTHERAPY:** **There are no specific dosage adjustments provided in product labeling.** **Glipizide is primarily converted to inactive metabolites and may be less likely to cause hypoglycemia in patients with renal impairment compared to other sulfonylureas.** **A reduced dose may be necessary,**[258] (b) (4) (b) (4) (b) (4) • The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). • The pharmacokinetics of glipizide has not been evaluated in patients with varying degree of renal impairment. Limited data indicates that glipizide biotransformation products may remain in circulation for a longer time in subjects with renal impairment than that seen in subjects with normal renal function. *Also, refer to Biguanides for metformin-containing FCDPs.*	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • T1D. • DKA, with or without coma. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, quinolones and beta adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20]
GLUCOTROL XL (glipizide extended-release)	020329 (April 26, 1994)	**GLUCOTROL XL INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Recommended starting dose is 5 mg orally once daily.		**GLUCOTROL XL CONTRAINDICATIONS:** • Known hypersensitivity to glipizide or any of the product's ingredients. • Hypersensitivity to sulfonamide derivatives. **GLUCOTROL XL WARNINGS AND**

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Daily adjustment can be made based on the patient's glycemic control. • Maximum recommended dose is 20 mg once daily. • Administer with breakfast or the first meal of the day • For combination therapy with other antihyperglycemic agents, initiate at the lowest recommended dose, and observe patients for hypoglycemia.		**PRECAUTIONS:** • Hypoglycemia: May be severe. Ensure proper patient selection, dosing, and instructions, particularly in at-risk populations (e.g., elderly, renally impaired) and when used with other antihyperglycemic medications. • Hemolytic anemia: Can occur if G6PD deficient. • Cardiovascular mortality: Potential increased risk of cardiovascular mortality with sulfonylureas. (b) (4) (b) (4)
GLYNASE (glyburide)	020051 (March 4, 1992)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The suggested starting dose is 1.5 to 3 mg daily, administered orally with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 0.75 mg daily. • The usual maintenance dose is in the range of 0.75 to 12 mg daily, which may be given as a single dose or in divided doses. • Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals based upon the patient's blood glucose response. • Daily doses of more than 12 mg are	**FOR GLYBURIDE MONOTHERAPY:** **There are no specific dosage adjustments provided in product labeling;** (b) (4) • Glyburide is excreted as weakly active metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine. • This drug is known to be substantially excreted by the kidney. Renal insufficiency may cause elevated drug levels of glyburide, which increase the risk of serious hypoglycemic reactions. Dose selection should include assessment of renal function. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • DKA, with or without coma. • T1D. • Concomitant administration of bosentan. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) • Hypoglycemia: All sulfonylurea drugs

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		not recommended.	*Also, refer to Biguanides for metformin-containing FCDPs.*	are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glyburide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, quinolones and beta-adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of

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DIABETA (glyburide)	017532 (May 1, 1984)	**DIABETA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The usual starting dose as initial therapy is 2.5 to 5 mg daily, administered orally with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily.		delivery. This has been reported more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20] **DIABETA CONTRAINDICATIONS:** • Known hypersensitivity to the drug or any of its excipients. • T1D. • DKA, with or without coma. • Treated with bosentan. **DIABETA WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress

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				such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glyburide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, ACE inhibitors, disopyramide, fluoxetine, clarithromycin, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, (b) (4) monoamine oxidase inhibitors, and beta-adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.
(Tolazamide)	A070259¶ (November 7, 1986)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D.	**There are no specific dosage adjustments provided in product labeling for patients with renal impairment; however, conservative initial and maintenance doses are recommended because tolazamide is metabolized to active metabolites, which are eliminated in the urine.**	CONTRAINDICATIONS: • Known hypersensitivity to the drug. • DKA, with or without coma • T1D.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• The usual starting dose of tolazamide tablets for the mild to moderately severe T2D patient is 100 mg to 250 mg daily administered orally with breakfast or the first main meal. • Generally, if the fasting blood glucose is less than 200 mg/dL the starting dose is 100 mg/day as a single daily dose. If the fasting blood glucose value is greater than 200 mg/dL, the starting dose is 250 mg/day as a single dose. If the patient is malnourished, underweight, elderly, or not eating properly, the initial therapy should be 100 mg once a day.	• Tolazamide is metabolized to five major metabolites ranging in hypoglycemic activity from 0-70%. They are excreted principally in the urine. Following a single oral dose of tritiated tolazamide, 85% of the dose was excreted in the urine and 7% in the feces over a five-day period. Most of the urinary excretion of the drug occurred within the first 24 hours post administration. • Renal insufficiency may cause elevated blood levels of tolazamide, which increase the risk of serious hypoglycemic reactions. Elderly patients are prone to develop renal insufficiency, which may put them at risk of hypoglycemia. Dose selection should include assessment of renal function.	**WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs (b) (4) be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue (b) (4) and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				inflammatory agents, (b) (4) and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, (b) (4) and beta-adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20]
(Tolbutamide)	A086445† (April 10, 1979)	As an adjunct to diet (b) (4) with T2D. • The usual starting dose is 1 to 2 grams orally daily. This may be increased or decreased, depending on individual patient response. • Transfer of patients from other oral antihyperglycemic regimens to tolbutamide tablets should be done conservatively.	**There is no dosage adjustment provided in product labeling for patients with renal impairment; however, conservative initial and maintenance doses are recommended.** (b) (4) • (b) (4), and has an elimination half-life of 4.5-6.5 hours. Approximately 75 (b) (4)% is eliminated in the urine, primarily as metabolites.	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • DKA, with or without coma • T1D. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. (b) (4) (b) (4) • Hypoglycemia: All sulfonylurea drugs

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue (b) (4) and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, (b) (4) and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, (b) (4) and beta adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of

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				delivery. This has been reported more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[20]
Thiazolidinediones				
ACTOS (pioglitazone) *Combination Products* **ACTOPLUS MET** (pioglitazone + metformin) **ACTOPLUS MET XR** (pioglitazone + metformin extended-release) **DUETACT** (pioglitazone + glimepiride) **OSENI** (pioglitazone + alogliptin)	021073 (July 15, 1999) 021842 (August 29, 2005) 022024 (May 12, 2009) 021925 (July 28, 2006) 022426 (January 25, 2013)		**FOR PIOGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/h. • The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance [CrCl] 30 to 50 mL/min) and severe (CrCl <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required with pioglitazone monotherapy. • In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related. In postmarketing experience, reports of new onset or	**BOXED WARNING:** • Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients. After initiation of Actos, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of ACTOS must be considered. ACTOS is not recommended in patients with symptomatic heart failure. **CONTRAINDICATIONS:** • Initiation in patients with established NYHA Class III or IV heart failure. • Known hypersensitivity to pioglitazone or any other component of ACTOS. **WARNINGS AND PRECAUTIONS:** • Congestive heart failure: Fluid retention may occur and can

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			worsening edema have been received. Pioglitazone should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, pioglitazone should be used with caution in patients at risk for congestive heart failure. (b) (4) *Also, refer to Biguanides for metformin-containing FCDPs, DPP-4 inhibitors for alogliptin-containing FCDPs, and Sulfonylureas for glimepiride-containing FCDPs.*	exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms. • Hypoglycemia: When used with insulin or an insulin secretagogue, a lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia. • Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ACTOS and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ACTOS if liver injury is confirmed and no alternate etiology can be found. • Bladder cancer: May increase the risk of bladder cancer. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. • Edema: Dose-related edema may occur. • Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. • Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes

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				according to current standards of care with prompt evaluation for acute visual changes. • Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOS (b) (4) **DISADVANTAGES:** • Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[20]
AVANDIA (rosiglitazone) *Combination Products* **AVANDAMET** (rosiglitazone + metformin) **AVANDARYL** (rosiglitazone + glimepiride)	021071 (May 25, 1999) 021410 (October 10, 2002) 021700 (November 23, 2005)		**FOR ROSIGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral or intravenous administration of [^{14}C] rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C] related material ranged from 103 to 158 hours. • There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving rosiglitazone monotherapy. • Rosiglitazone should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone should be used with caution in patients at risk for heart failure.	**BOXED WARNING:** • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of AVANDIA, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If these signs or symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered. AVANDIA is not recommended in patients with symptomatic heart failure. **CONTRAINDICATIONS:** • Initiation in patients with established NYHA Class III or IV heart failure. • Hypersensitivity to rosiglitazone or any of the product's ingredients. **WARNINGS AND PRECAUTIONS:**

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			Patients should be monitored for signs and symptoms of heart failure. (b) (4) In controlled clinical trials of patients with T2D, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone. *Also, refer to Biguanides for metformin-containing FCDPs and Sulfonylureas for glimepiride-containing FCDPs.*	• Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects. • Meta-analysis of 52 mostly short-term trials suggested a potential risk of ischemic cardiovascular (CV) events relative to placebo, not confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. • Dose-related edema and weight gain may occur. • Measure liver enzymes prior to initiation and periodically thereafter. Do not initiate therapy in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Discontinue therapy if ALT levels remain >3X the upper limit of normal or if jaundice is observed. • Macular edema has been reported. • Increased incidence of bone fracture was observed in long-term trials. • Dose-related decreases in hemoglobin and hematocrit have occurred. • When used in combination with other hypoglycemic agents, a dose reduction of the concomitant agent may be necessary to reduce the risk of hypoglycemia.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				DISADVANTAGES: • Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[20]

Sources: Product labeling, available at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; Facts & Comparisons eAnswers: http://online.factsandcomparisons.com/; UpToDate: http://www.uptodate.com.ezproxy.nihlibrary.nih.gov/contents/search; and selected literature (as referenced in the table).

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; AUCτ,ss, area under concentration-time curve during dosing interval at steady-state; BLA, Biologics License Application; CL/F, apparent total clearance of the drug from plasma after oral administration; Cmax, maximum plasma concentration; COPD, chronic obstructive lung disease; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FBG, fasting blood glucose; FCDP, fixed combination drug product; FEV, forced expiratory volume; G6PD, 6-phosphate dehydrogenase; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; h, hour; HbA1c, hemoglobin A1c (glycated hemoglobin); JDRF, Juvenile Diabetes Research Foundation; L, liter; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; MEN 2, Multiple endocrine neoplasia syndrome type 2; min, minute; MTC, medullary thyroid carcinoma; NDA, New Drug Application; NYHA, New York Heart Association; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; SC, subcutaneous; SGLT2, sodium-glucose Cotransporter-2; SIADH, syndrome of inappropriate antidiuretic hormone; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; TG, triglyceride; TZD, thiazolidinediones; UKPDS, United Kingdom Prospective Diabetes Study; and ULN, upper limit of normal.

*Original date of approval.

†Dosing guidelines for the mono-component of the FCDP, except in the case of JUVISYNC (sitagliptin + simvastatin).

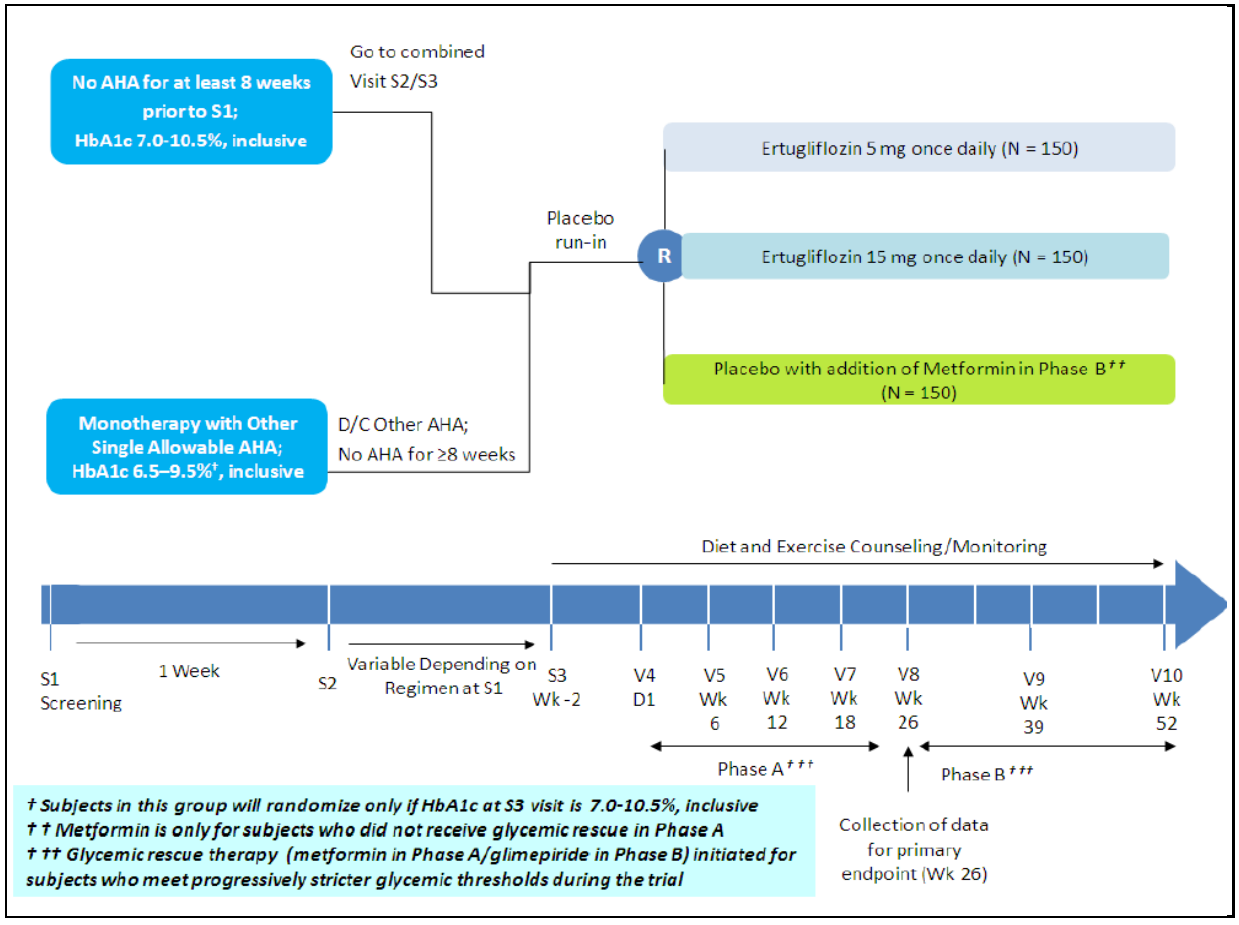
¶Reference Listed Drug (RLD); approved under an Abbreviated New Drug Application (ANDA).

‡Contraindications and Warnings and Precautions relate to the mono-component of the FCDP unless specified otherwise.

13.3. Study Designs for the Relevant Phase 3 Trials

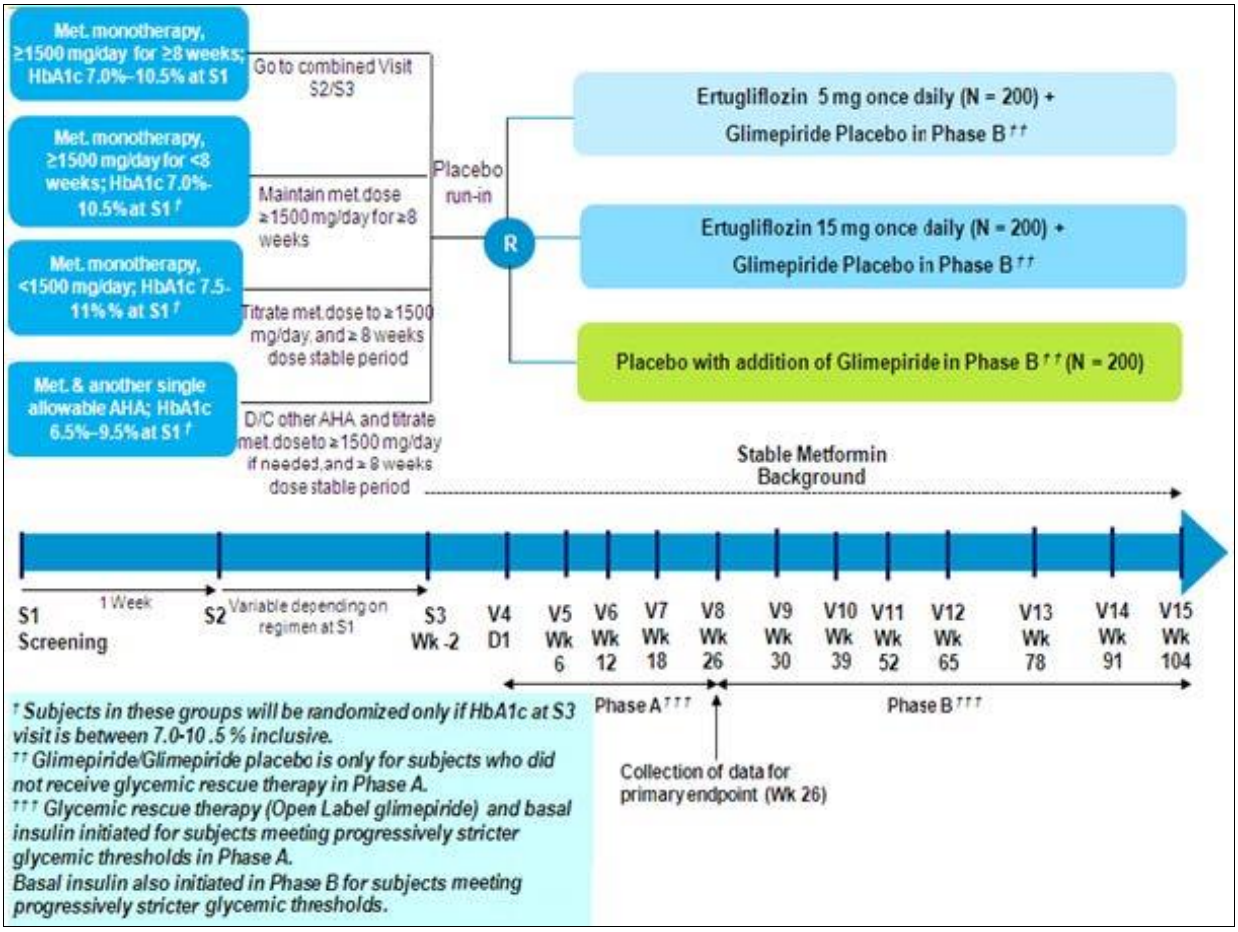
The study designs for the seven Phase 3 clinical trials relevant to NDA 209803/NDA 209805/NDA 209806 are presented below.

Figure 5: Study Design of Trial P003/1022



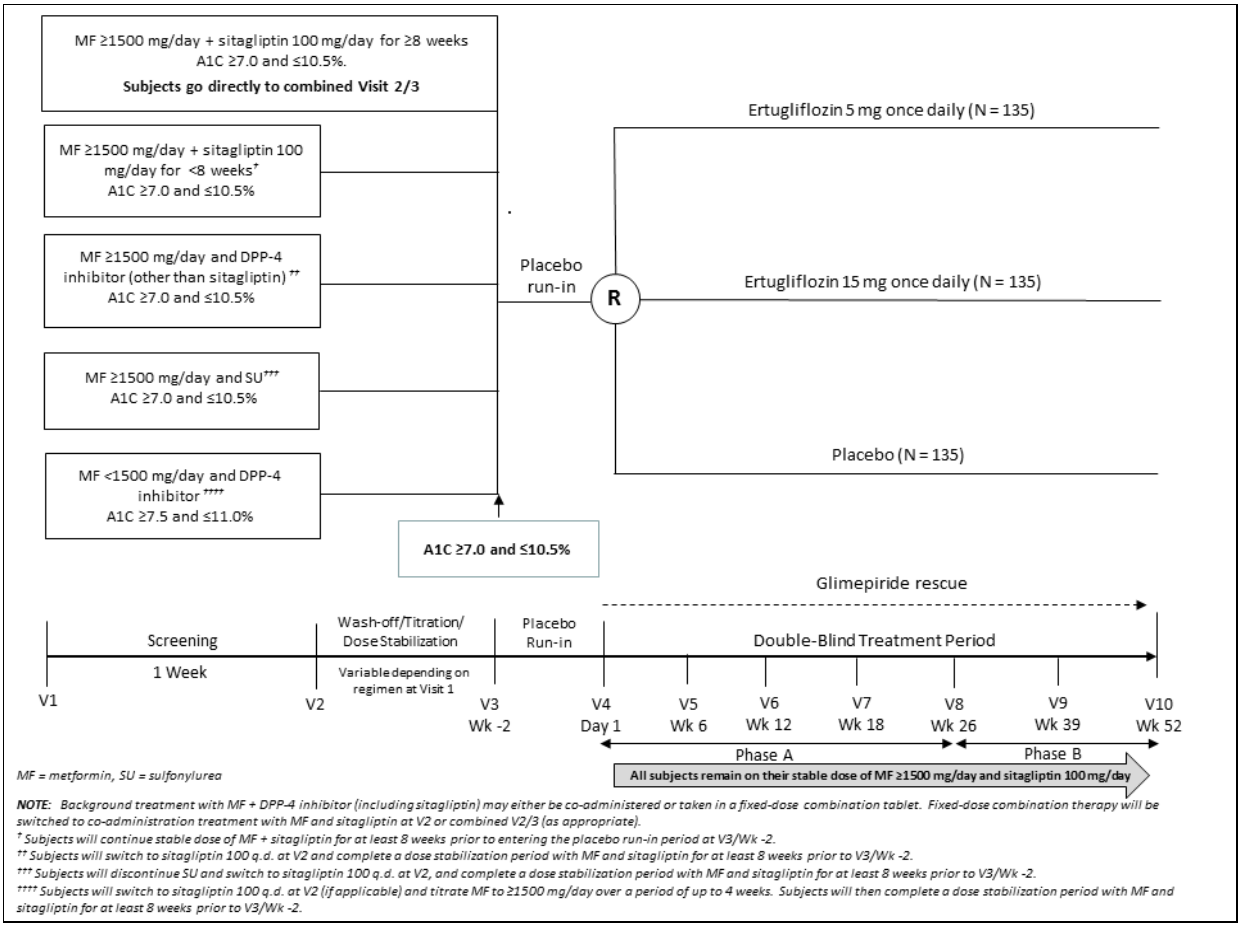
Source: Reproduced from the Applicant's Clinical Study Report, Protocol MK-8835-003/B1521022, labeled as Figure 1, page 66 of 3191, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p003v01\p003v01.pdf

Figure 6: Study Design of Trial P007/1017



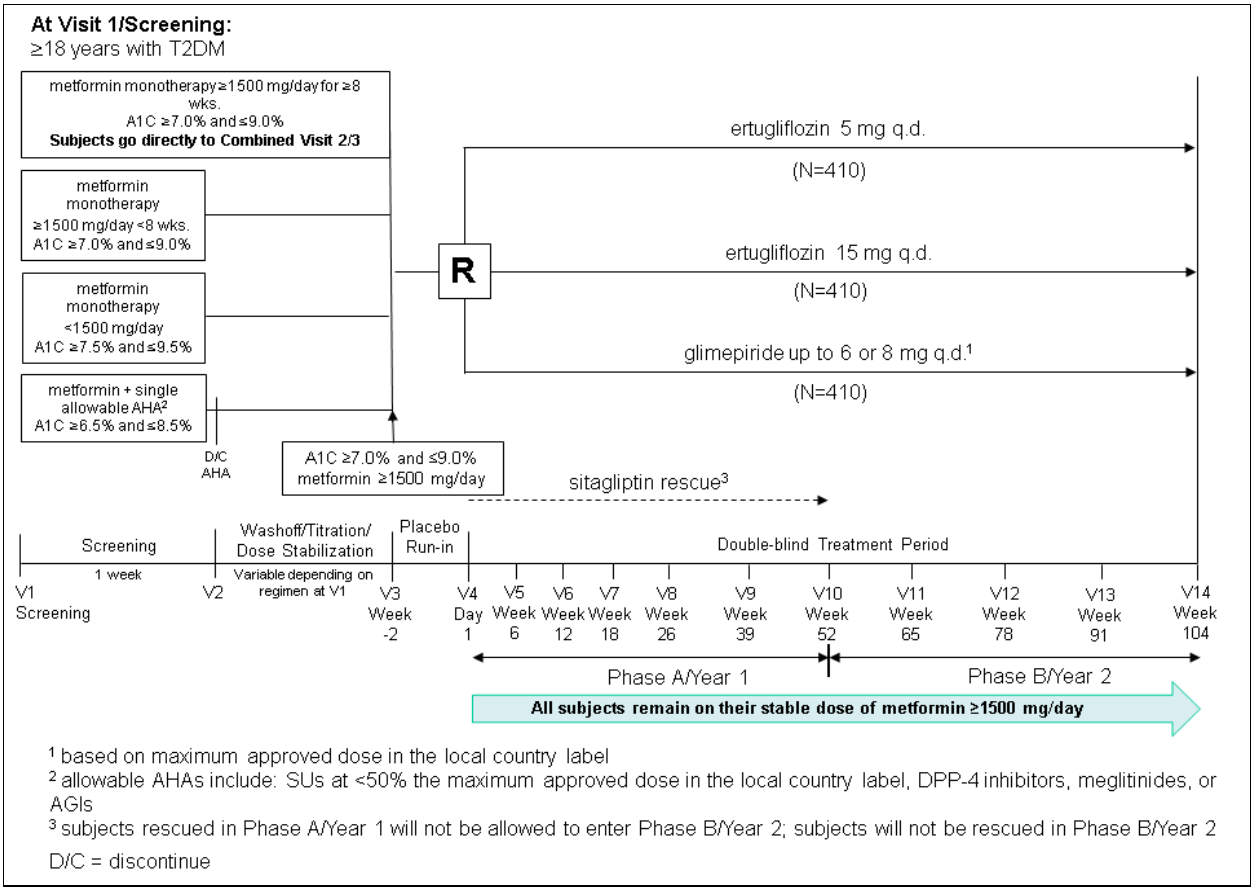
Source: Reproduced from the Applicant's Clinical Study Report, Protocol MK-8835-007/B1521017, labeled as Figure 1, page 76 of 3124, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01.pdf

Figure 7: Study Design of Trial P006/1015



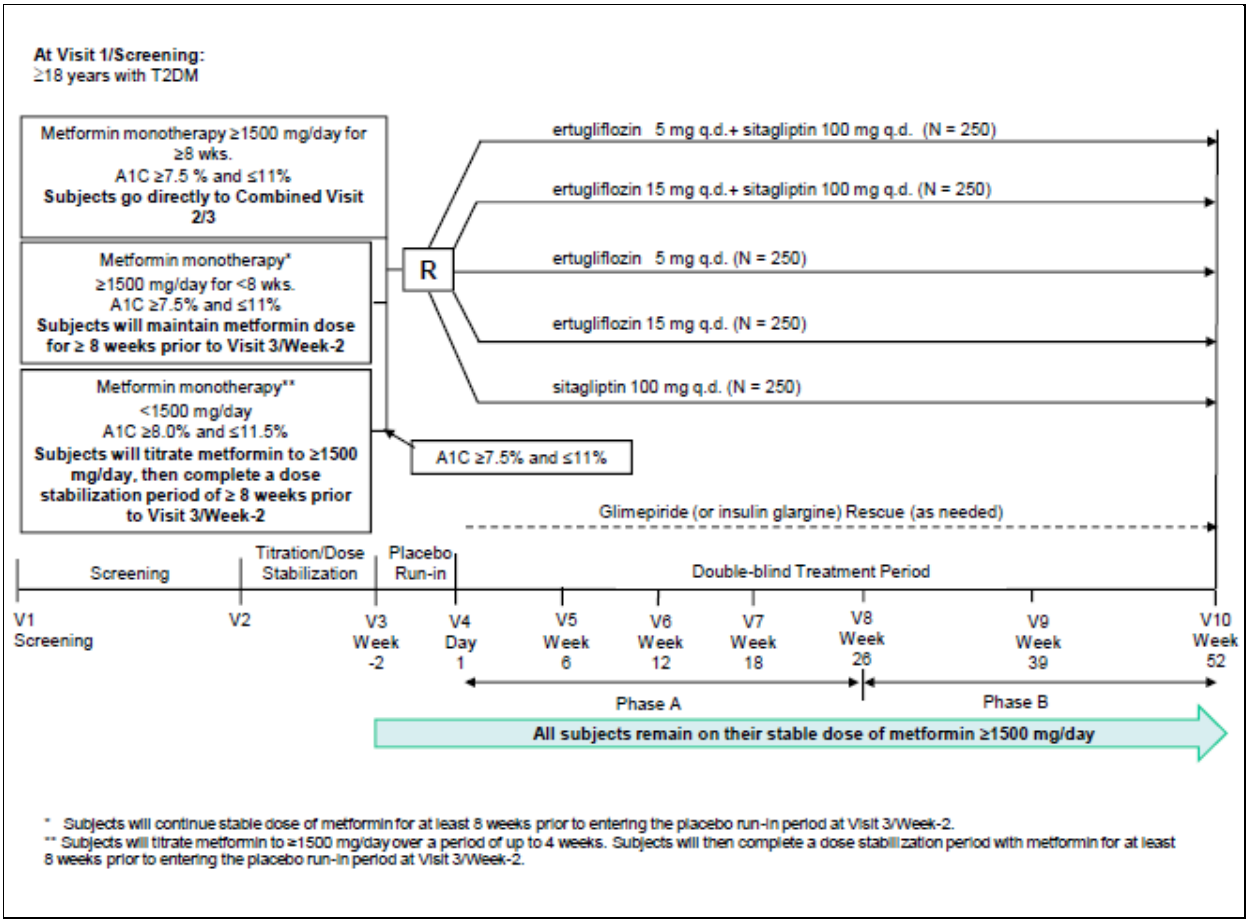
Source: Reproduced from the Applicant's Clinical Study Report P006V01, labeled as Figure 9-1, page 67 of 1074, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p006v01\p006v01.pdf

Figure 8: Study Design of Trial P002/1013



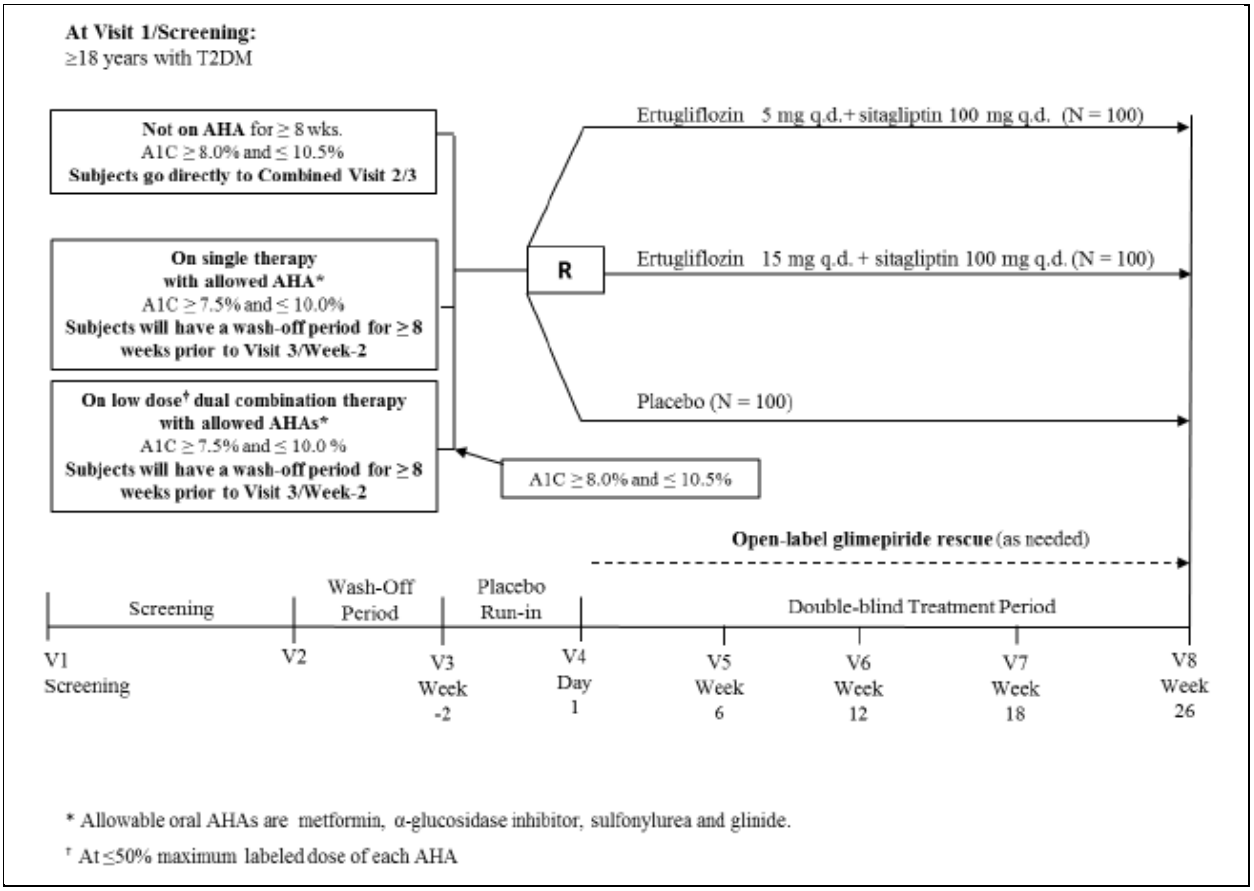
Source: Reproduced from the Applicant's Clinical Study Report P002V01, labeled as Figure 9-1, page 75 of 2209, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p002v01\p002v01.pdf

Figure 9: Study Design of Trial P005/1019



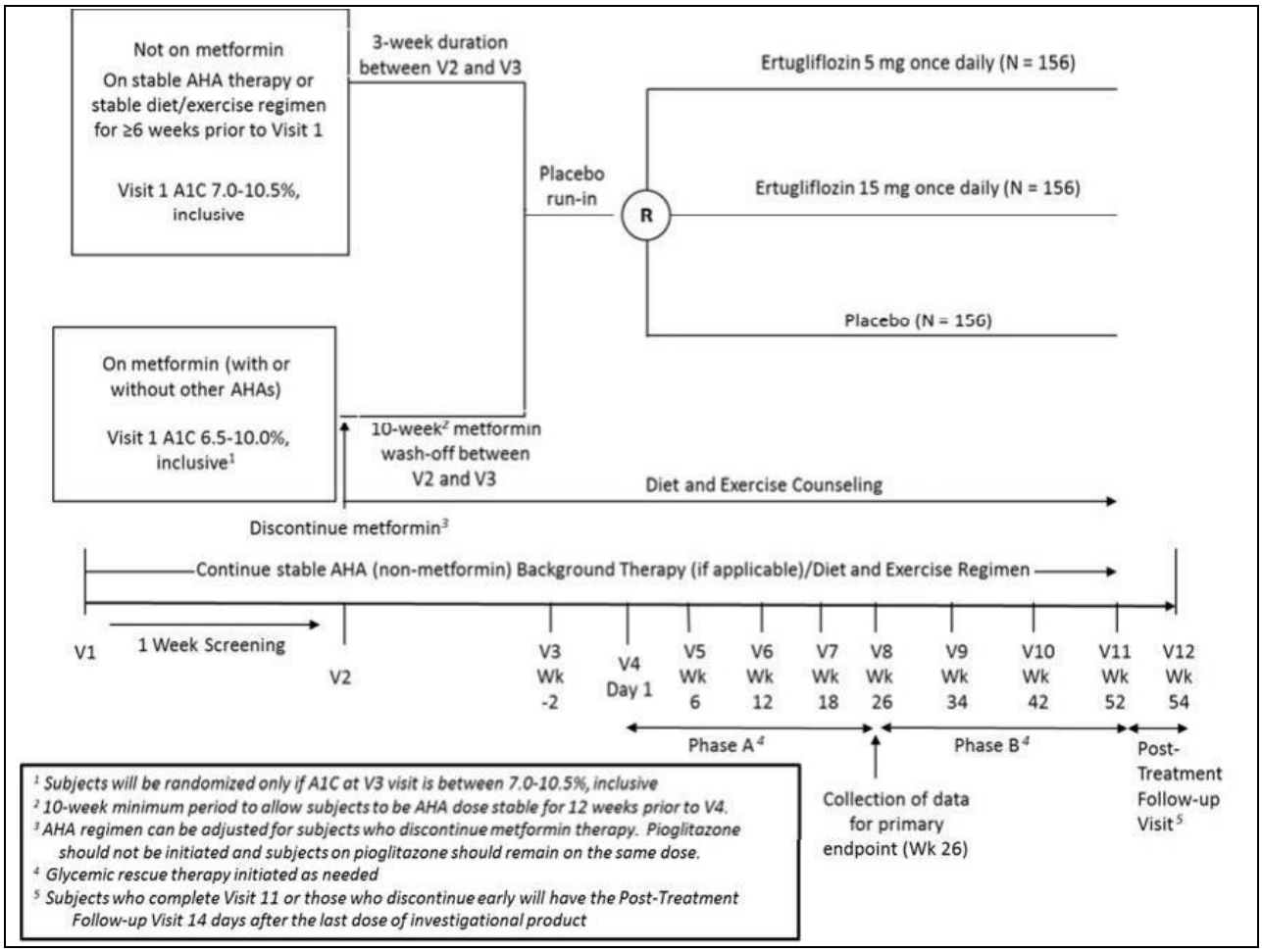
Source: Reproduced from the Applicant's Clinical Study Report P005V01, labeled as Figure 9-1, page 90 of 2273, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p005v01\p005v01.pdf

Figure 10: Study Design of Trial P017/1047



Source: Reproduced from the Applicant's Clinical Study Report P017, labeled as Figure 9-1, page 71 of 1028, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p007v01\p007v01.pdf

Figure 11: Study Design of Trial P001/1016



Source: Reproduced from the Applicant's Clinical Study Report P001, labeled as Figure 9-1, page 131 of 2401, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p001v01\p001v01.pdf

13.4. Adverse Events of Special Interest (System/Custom MedDRA Queries)

Note: MedDRA v19 was used, and SMQs/CMQs were derived from existing MedDRA SMQs and/or from SGLT2 inhibitor and/or DPP-4 inhibitor Applications

ACUTE KIDNEY INJURY AND CHRONIC RENAL FAILURE

MedDRA PTs: Acquired cystic kidney disease; Acute kidney injury; Acute phosphate nephropathy; Acute prerenal failure; Albumin urine present; Albuminuria; Aluminium overload; Anuria; Artificial kidney device user; Autoimmune nephritis; Azotaemia; Biopsy kidney abnormal; Blood 1,25-dihydroxycholecalciferol decreased; Blood bicarbonate abnormal; Blood bicarbonate decreased; Blood calcium abnormal; Blood calcium decreased; Blood creatinine abnormal; Blood creatinine increased; Blood erythropoietin abnormal; Blood erythropoietin decreased; Blood parathyroid hormone abnormal; Blood parathyroid hormone increased; Blood phosphorus abnormal; Blood phosphorus increased; Blood potassium abnormal; Blood potassium increased; Blood sodium abnormal; Blood sodium decreased; Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratio increased; Bloody peritoneal effluent; Bone cyst; C3 glomerulopathy; Calcification of muscle; Calciphylaxis; Chronic allograft nephropathy; Chronic kidney disease; Coma uraemic; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Diabetic end stage renal disease; Diabetic nephropathy; Dialysis; Dialysis amyloidosis; Dialysis device insertion; Dialysis disequilibrium syndrome; Dialysis membrane reaction; Dialysis related complication; Diffuse mesangial sclerosis; Effective peritoneal surface area increased; Encephalopathy; End stage renal disease; Eosinophils urine present; Extensive interdialytic weight gain; Fibrillary glomerulonephritis; Focal segmental glomerulosclerosis; Fractional excretion of sodium; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Glomerulonephritis; Glomerulonephritis chronic; Glomerulonephritis membranoproliferative; Glomerulonephritis membranous; Glomerulonephritis minimal lesion; Glomerulonephritis proliferative; Glomerulonephritis rapidly progressive; Glomerulonephropathy; Glomerulosclerosis; Goodpasture's syndrome; Haemodialysis; Haemodialysis complication; Haemodialysis-induced symptom; Haemofiltration; Haemolytic uraemic syndrome; Haemorrhagic diathesis; Haemorrhagic fever with renal syndrome; Hepatitis virus-associated nephropathy; Hepatorenal failure; Hepatorenal syndrome; High turnover osteopathy; HIV associated nephropathy; Hypercalcaemic nephropathy; Hypercreatininaemia; Hyperkalaemia; Hyperparathyroidism; Hyperparathyroidism secondary; Hyperphosphataemia; Hypertensive nephropathy; Hypervolaemia; Hypoalbuminaemia; Hypocalcaemia; Hyponatraemia; IgA nephropathy; IgM nephropathy; Immunotactoid glomerulonephritis; Inadequate haemodialysis; Intercapillary glomerulosclerosis; Intradialytic parenteral nutrition; Inulin renal clearance abnormal; Inulin renal clearance decreased; Ischaemic nephropathy; Kidney fibrosis; Kidney injury molecule-1; Kidney small; Leukocyturia; Low turnover osteopathy; Lupus nephritis; Mesangioproliferative glomerulonephritis; Metabolic acidosis; Microalbuminuria; Neonatal anuria; Nephritic syndrome; Nephritis; Nephrogenic anaemia; Nephrogenic systemic fibrosis; Nephropathy; Nephropathy toxic; Nephrosclerosis; Nephrotic syndrome; Normochromic normocytic anaemia; Obstructive nephropathy; Oedema due to renal disease; Oliguria; Osteomalacia; Pancreatorenal syndrome; Paraneoplastic glomerulonephritis; Paraneoplastic nephrotic syndrome; Parathyroid gland enlargement; Pericarditis; Pericarditis uraemic; Peritoneal cloudy effluent; Peritoneal dialysis; Peritoneal dialysis complication; Peritoneal effluent abnormal; Peritoneal effluent erythrocyte count increased; Peritoneal effluent leukocyte count increased; Peritoneal equilibration test abnormal; Peritoneal fluid analysis abnormal; Peritoneal fluid protein abnormal; Peritoneal fluid protein increased; Peritoneal permeability increased; Pigment nephropathy; Polyomavirus-associated nephropathy; Postoperative renal failure; Postrenal failure; Potassium wasting nephropathy; Prerenal failure; Protein urine present; Proteinuria; Red blood cells urine positive; Reflux nephropathy; Renal amyloidosis; Renal and liver transplant; Renal and pancreas transplant; Renal atrophy; Renal failure; Renal failure neonatal; Renal function test abnormal; Renal impairment; Renal impairment neonatal; Renal injury; Renal osteodystrophy; Renal papillary necrosis; Renal replacement therapy; Renal rickets; Renal transplant; Renal tubular atrophy; Renal tubular disorder; Renal tubular necrosis; Secondary hypertension; Tubulointerstitial nephritis; Ultrafiltration failure; Ultrasound kidney abnormal; Uraemia odour; Uraemic acidosis; Uraemic encephalopathy; Uraemic gastropathy; Uraemic myopathy; Uraemic neuropathy; Uraemic pruritus; Urate nephropathy; Urea renal clearance decreased; Uridrosis; Urinary casts present; Urine albumin/creatinine ratio abnormal; Urine albumin/creatinine ratio increased; Urine output decreased; Urine protein/creatinine ratio abnormal; Urine protein/creatinine ratio increased; Vascular calcification; Venogram renal abnormal; White blood cells urine positive

Relevant Clinical Laboratory Changes: Increase in serum creatinine from baseline ≥0.3 mg/dL; increase in serum creatinine from baseline ≥1 mg/dL (medical history of renal impairment/chronic kidney disease); increase in serum creatinine ≥1.5 x baseline value; serum creatinine ≥2.5 mg/dL; increase in serum creatinine ≥2 x baseline value; confirmed (≥2 measurements)/sustained (≥30 days) serum creatinine ≥6 mg/dL; confirmed (≥2 measurements)/sustained (≥30 days) 40% decline in eGFR; confirmed (≥2 measurements)/sustained (≥30 days) eGFR <15 mL/min/1.73m2; 30% decline in eGFR; 50% decline in eGFR; downward shift in eGFR from ≥90 to 60-89 mL/min/1.73m2, 60-89 to 45-59 mL/min/1.73m2, 45-59 to 30-44 mL/min/1.73m2, 30-44 to 15-29 mL/min/1.73m2, and 15-29 to <15 mL/min/1.73m2; and downward shift in eGFR from ≥60 to 45-59 mL/min/1.73m2, 45-59 to 30-44 mL/min/1.73m2, 30-44 to 15-29 mL/min/1.73m2, and 15-29 to <15 mL/min/1.73m2; urine output = 0 mL/kg/h x12 hours; urine output <0.3 mL/kg/h x 24 h; urine albumin-to-creatinine change from baseline from <30 to ≥30-≤300 mg/g, and ≥30-≤300 to >300 mg/g; serum potassium ≥6 mEq/L; serum potassium ≥5.4 mEq/L and increase ≥15% above baseline; serum potassium increase ≥1 mEq/L and value >ULN; BUN >60 mg/dL; death plus AE terms below; blood urea nitrogen increase ≥50% and value >ULN; serum sodium decrease ≥10 mEq/L and value <LLN; serum phosphate increase ≥0.5 mg/dL and value >ULN

Arthropathies

MedDRA PTs: Amyloid arthropathy; Ankle arthroplasty; Ankylosing spondylitis; Arthralgia; Arthritis; Arthritis allergic; Arthritis bacterial; Arthritis climacteric; Arthritis enteropathic; Arthritis fungal; Arthritis gonococcal; Arthritis helminthic; Arthritis infective; Arthritis reactive; Arthritis rubella; Arthritis salmonella; Arthritis viral; Arthrodesis; Arthropathy; Arthroscopy abnormal; Arthrotoxicity; Articular calcification; Aspiration joint abnormal; Autoimmune arthritis; Axial spondyloarthritis; Caplan's syndrome; Carcinomatous polyarthritis; Chondrocalcinosis; Chondrocalcinosis pyrophosphate; Chondromalacia; Crystal arthropathy; Enteropathic spondylitis; Epidemic polyarthritis; Facet joint syndrome; Felty's syndrome; Gout; Gouty arthritis; Gouty tophus; Haemophilic arthropathy; Hip arthroplasty; Infusion site joint effusion; Infusion site joint erythema; Infusion site joint infection; Infusion site joint inflammation; Infusion site joint movement impairment; Infusion site joint pain; Infusion site joint swelling; Infusion site joint warmth; Injection site joint effusion; Injection site joint erythema; Injection site joint infection; Injection site joint inflammation; Injection site joint movement impairment; Injection site joint pain; Injection site joint swelling; Injection site joint warmth; Intervertebral discitis; Joint abscess; Joint adhesion; Joint arthroplasty; Joint contracture; Joint crepitation; Joint debridement; Joint destruction; Joint effusion; Joint fluid drainage; Joint range of motion decreased; Joint stiffness; Joint swelling; Joint warmth; Juvenile idiopathic arthritis; Juvenile psoriatic arthritis; Juvenile spondyloarthritis; Knee arthroplasty; Laryngeal rheumatoid arthritis; Medical device site joint infection; Monarthritis; Musculoskeletal stiffness; Neck pain; Neuropathic arthropathy; Nodal osteoarthritis; Osteoarthritis; Osteoarthropathy; Palindromic rheumatism; Paraneoplastic arthritis; Patellofemoral pain syndrome; Periarthritis; Periarthritis calcarea; Periarticular disorder; Peripheral arthritis; Plica syndrome; Polyarthritis; Psoriatic arthropathy; Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome; Rapidly progressive osteoarthritis; Reiter's syndrome; Rheumatic disorder; Rheumatic fever; Rheumatoid arthritis; Rheumatoid nodule removal; Sacroiliitis; Senile ankylosing vertebral hyperostosis; Septic arthritis haemophilus; Septic arthritis neisserial; Septic arthritis staphylococcal; Septic arthritis streptobacillus; Septic arthritis streptococcal; Seronegative arthritis; Shoulder arthroplasty; SLE arthritis; Spinal osteoarthritis; Spinal pain; Spondylitis; Spondyloarthropathy; Still's disease adult onset; Synovectomy; Synovial fluid analysis abnormal; Synovial fluid crystal present; Synovial fluid protein present; Synovial fluid red blood cells positive; Synovial fluid white blood cells positive; Synoviorthesis; Synovitis; Temporomandibular joint syndrome; Traumatic arthritis; Traumatic arthropathy; Vaccination site joint infection

Bone and Joint Infections

MedDRA PTs: Abscess jaw; Administration site joint infection; Application site joint infection; Arthritis infective; Bone abscess; Bone tuberculosis; Bursitis infective; Bursitis infective staphylococcal; Candida osteomyelitis; Infected bunion; Infective chondritis; Infective periostitis; Infective spondylitis; Infusion site joint infection; Injection site joint infection; Intervertebral discitis; Joint abscess; Joint tuberculosis; Medical device site joint infection; Osteomyelitis; Osteomyelitis acute; Osteomyelitis bacterial; Osteomyelitis blastomyces; Osteomyelitis chronic; Osteomyelitis fungal; Osteomyelitis salmonella; Osteomyelitis viral; Paraspinal abscess; Petrositis; Purulent synovitis; Staphylococcal osteomyelitis; Sternitis; Subperiosteal abscess; Vaccination site joint infection; Yaws of bone

Bone, Joint and Vascular Therapeutic Procedures

MedDRA PTs: Amputation; Amputation stump pain ; Angioplasty; Arm amputation; Arterectomy; Arterectomy with graft replacement; Arterial bypass operation; Arterial catheterisation; Arterial catheterisation abnormal; Arterial graft; Arterial repair; Arterial stent insertion; Arterial switch operation; Arterial therapeutic procedure; Arteriovenous fistula operation; Atherectomy; Bone debridement; Calcanectomy; Debridement; Endarterectomy; Finger amputation; Finger repair operation; Foot amputation; Foot operation; Fracture debridement; Hand amputation; Hand repair operation; Hip disarticulation; Interscapulothoracic amputation; Joint debridement; Leg amputation; Limb amputation; Limb immobilisation; Limb operation; Limb reattachment surgery; Limb reconstructive surgery; Metacarpal excision; Metatarsal excision; Microsurgery to hand; Necrectomy; Peripheral artery angioplasty; Peripheral artery bypass; Peripheral artery stent insertion; Peripheral endarterectomy; Peripheral revascularisation; Prosthetic vessel implantation; Spontaneous amputation; Surgical vascular shunt; Talipes correction; Thrombectomy; Thromboembolectomy; Toe amputation; Toe operation; Trapezectomy; Vascular anastomosis; Vascular brachytherapy; Vascular catheterisation; Vascular graft; Vascular operation; Vascular stent insertion; Vasodilation procedure

Bone Disorders

MedDRA PTs: Alveolar osteitis; Aneurysmal bone cyst; Bone callus excessive; Bone contusion; Bone cyst; Bone development abnormal; Bone disorder; Bone erosion; Bone fistula; Bone formation decreased; Bone formation increased; Bone hyperpigmentation; Bone infarction; Bone lesion; Bone loss; Bone marrow oedema; Bone marrow oedema syndrome; Bone pain; Bone swelling; Callus formation delayed; Cemento osseous dysplasia; Coccydynia; Dental alveolar anomaly; Dental cyst; Eagle's syndrome; Enostosis; Erdheim-Chester disease; Exostosis; Exostosis of external ear canal; Exostosis of jaw; Exposed bone in jaw; Extraskeletal ossification; Hyperphosphatasaemia; Hypertrophic osteoarthropathy; Inadequate osteointegration; Jaw cyst; Jaw disorder; Medial tibial stress syndrome; Melorheostosis; Metatarsalgia; Osteitis; Osteitis condensans; Osteitis deformans; Osteolysis; Osteonecrosis; Osteonecrosis of external auditory canal; Osteonecrosis of jaw; Osteoradionecrosis; Osteorrhagia; Osteosclerosis; Osteosis; Os trigonum syndrome; Pain in jaw; Periosteal haematoma; Periostitis; Periostitis hypertrophic; Periostosis; Periprosthetic osteolysis; Post transplant distal limb syndrome; Post-traumatic osteoporosis; Primary sequestrum; Pubic pain; Radiation osteitis; Secondary sequestrum; Skeletal injury; Spinal column injury; Spinal disorder; Spinal pain; Sternal injury; Tertiary sequestrum; Vertebral column mass; Vertebral lesion; Vertebral wedging

Relevant Clinical Laboratory Changes: Serum phosphate increase ≥0.5 mg/dL and value >ULN; serum magnesium increase ≥1.0 mg/dL and value >ULN; serum calcium increase ≥1.0 mg/dL and value >ULN

Bone Fractures

MedDRA PTs: Acetabulum fracture; Ankle fracture; Atypical fracture; Avulsion fracture; Bone fragmentation; Cervical vertebral fracture; Chance fracture; Clavicle fracture; Comminuted fracture; Complicated fracture; Compression fracture; Elevation skull fracture; Epiphyseal fracture; Facial bones fracture; Femoral neck fracture; Femur fracture; Fibula fracture; Foot fracture; Forearm fracture; Fracture; Fracture debridement; Fracture delayed union; Fracture displacement; Fracture malunion; Fracture nonunion; Fracture pain; Fracture reduction; Fractured coccyx; Fractured ischium; Fractured sacrum; Fractured maxilla elevation; Fractured skull depressed; Fractured zygomatic arch elevation; Greenstick fracture; Hand fracture; Hip fracture; Humerus fracture; Ilium fracture; Impacted fracture; Intervertebral disc injury; Jaw fracture; Limb crushing injury; Lower limb fracture; Lumbar vertebral fracture; Multiple fractures; Open fracture; Osteochondral fracture; Osteoporotic fracture; Patella fracture; Pathological fracture; Pelvic fracture; Pubis fracture; Periprosthetic fracture; Radius fracture; Rib fracture; Sacroiliac fracture; Scapula fracture; Skull fracture; Skull fractured base; Spinal compression fracture; Sternal fracture; Stress fracture; Thoracic vertebral fracture; Tibia fracture; Torus fracture; Traumatic fracture; Ulna fracture; Upper limb fracture; Wrist fracture

Dermal Diabetic Complications

MedDRA PTs: Cellulitis gangrenous; Diabetic bullosis; Diabetic cheiroarthropathy; Diabetic dermopathy; Diabetic foot; Diabetic foot infection; Diabetic gangrene; Diabetic ulcer; Infected skin ulcer; Necrobiosis lipoidica diabeticorum; Skin ulcer

Diabetic Microvascular Complications

MedDRA PTs: Acute painful neuropathy of rapid glycaemic control; Acute polyneuropathy; Albumin urine present; Autonomic neuropathy; Chronic kidney disease; Decreased vibratory sense; Demyelinating polyneuropathy; Diabetic end stage renal disease; Diabetic foot; Diabetic foot infection; Diabetic nephropathy; Diabetic neuropathic ulcer; Diabetic neuropathy; Diabetic retinal oedema; Diabetic retinopathy; Diabetic ulcer; Exudative retinopathy; Microalbuminuria; Protein urine; Protein urine present; Proteinuria; Retinal laser coagulation; Retinopathy; Retinopathy proliferative

Venous Embolic and Thrombotic Events

MedDRA PTs: Axillary vein thrombosis; Brachiocephalic vein occlusion; Budd-Chiari syndrome; Catheterisation venous; Cavernous sinus thrombosis; Central venous catheterisation; Cerebral venous thrombosis; Compression stockings application; Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Hepatic vein occlusion; Hepatic vein thrombosis; Homans' sign positive; Iliac vein occlusion; Inferior vena cava syndrome; Inferior vena caval occlusion; Intracranial venous sinus thrombosis; Jugular vein occlusion; Jugular vein thrombosis; Mahler sign; May-Thurner syndrome; Mesenteric vein thrombosis; Mesenteric venous occlusion; Obstetrical pulmonary embolism; Obstructive shock; Ophthalmic vein thrombosis; Ovarian vein thrombosis; Paget-Schroetter syndrome; Pelvic venous thrombosis; Penile vein thrombosis; Phlebectomy; Portal vein cavernous transformation; Portal vein occlusion; Portal vein thrombosis; Portosplenomesenteric venous thrombosis; Post procedural pulmonary embolism; Post thrombotic syndrome; Postoperative thrombosis; Postpartum venous thrombosis; Pulmonary embolism; Pulmonary infarction; Pulmonary microemboli; Pulmonary oil microembolism; Pulmonary thrombosis; Pulmonary vein occlusion; Pulmonary veno-occlusive disease; Pulmonary venous thrombosis; Renal vein embolism; Renal vein occlusion; Renal vein thrombosis; Retinal vein occlusion; Retinal vein thrombosis; SI QIII TIII pattern; Splenic vein occlusion; Splenic vein thrombosis; Subclavian vein thrombosis; Superior sagittal sinus thrombosis; Superior vena cava occlusion; Superior vena cava syndrome; Thrombophlebitis; Thrombophlebitis migrans; Thrombophlebitis neonatal; Thrombophlebitis superficial; Thrombosed varicose vein; Thrombosis; Thrombosis corpora cavernosa; Transverse sinus thrombosis; Vascular graft; Vena cava embolism; Vena cava filter insertion; Vena cava filter removal; Vena cava thrombosis; Venogram abnormal; Venoocclusive disease; Venoocclusive liver disease; Venous angioplasty; Venous occlusion; Venous operation; Venous recanalisation; Venous repair; Venous stent insertion; Venous thrombosis; Venous thrombosis neonatal; Venous thrombosis in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal; Visceral venous thrombosis

Genital Infections

MedDRA PTs: Acquired phimosis; Balanitis candida; Balanoposthitis; Balanoposthitis infective; Bartholin's abscess; Bartholinitis; Candida cervicitis; Cervicitis cystic; Cellulitis of male external genital organ; Endometriosis; Epididymitis; Circumcision; Clitoris abscess; Erosive balanitis; Fallopian tube abscess; Gangrenous balanitis; Genital abscess; Genital burning sensation; Genital candidiasis; Genital discharge; Genital infection; Genital infection female; Genital infection fungal; Genital infection male; Genital rash; Genitourinary tract infection; Hydrocele male infected; Intrauterine infection; Myometritis; Oophoritis; Orchitis; Ovarian abscess; Parametric abscess; Parametritis; Pelvic abscess; Pelvic infection; Pelvic inflammatory disease; Pelvic sepsis; Penile abscess; Penile infection; Perineal abscess; Perineal infection; Phimosis; Prostate infection; Prostatic abscess; Prostatitis; Prostatovesiculitis; Pruritus genital; Pyometra; Pyospermia; Rectovaginal septum abscess; Salpingitis; Salpingo-oophoritis; Scrotal abscess; Scrotal gangrene; Scrotal infection; Seminal vesicular infection; Seminal vesiculitis; Spermatic cord funiculitis; Testicular abscess; Tubo-ovarian abscess; Urogenital infection fungal; Uterine abscess; Uterine infection; Vaginal abscess; Vaginal cellulitis; Vaginal discharge; Vaginal erosion; Vaginal exfoliation; Vaginal haemorrhage; Vaginal infection; Vaginal inflammation; Vaginal lesion; Vaginal odour; Vulval abscess; Vulval cellulitis; Vulval disorder; Vulval oedema; Vulvitis; Vulvovaginal burning sensation; Vulvovaginal candidiasis; Vulvovaginal discomfort; Vulvovaginal disorder; Vulvovaginal dryness; Vulvovaginal mycotic infection; Vulvovaginal pain; Vulvovaginitis; Vulvovaginal erythema; Vulvovaginal pruritus; Vulvovaginal swelling; Vulvovaginal ulceration; Vulvovaginitis

Heart Failure/Cardiomyopathy

MedDRA PTs: Abnormal precordial movement; Acquired cardiac septal defect; Acute left ventricular failure; Acute pulmonary oedema; Acute right ventricular failure; Alcohol septal ablation; Allergic myocarditis; Arrhythmia; Arrhythmia supraventricular; Arrhythmogenic right ventricular dysplasia; Artificial heart implant; Ascites; Atrial hypertrophy; Atrial natriuretic peptide abnormal; Atrial natriuretic peptide increased; Atrial pressure increased; Atrial septal defect acquired; Autoimmune myocarditis; Bendopnoea; Biopsy heart abnormal; Blood pressure diastolic abnormal; Blood pressure diastolic decreased; Blood pressure diastolic increased; Blood pressure fluctuation; Blood pressure inadequately controlled; Blood pressure systolic abnormal; Blood pressure systolic decreased; Blood pressure systolic increased; Brain natriuretic peptide abnormal; Brain natriuretic peptide increased; Cardiac amyloidosis; Cardiac aneurysm; Cardiac arrest; Cardiac asthma; Cardiac cirrhosis; Cardiac contractility modulation therapy; Cardiac electrophysiologic study abnormal; Cardiac failure; Cardiac failure acute; Cardiac failure chronic; Cardiac failure congestive; Cardiac failure high output; Cardiac function test abnormal; Cardiac hypertrophy; Cardiac imaging procedure abnormal; Cardiac index abnormal; Cardiac index decreased; Cardiac index increased; Cardiac monitoring abnormal; Cardiac operation; Cardiac output decreased; Cardiac pseudoaneurysm; Cardiac resynchronisation therapy; Cardiac sarcoidosis; Cardiac septal hypertrophy; Cardiac siderosis; Cardiac ventricular scarring; Cardiac ventriculogram abnormal; Cardiac ventriculogram left abnormal; Cardiac ventriculogram right abnormal; Cardiogenic shock; Cardiomegaly; Cardiomyopathy; Cardiomyopathy acute; Cardiomyopathy alcoholic; Cardiomyopathy neonatal; Cardiopulmonary failure; Cardiorenal syndrome; Cardio-respiratory distress; Cardiothoracic ratio increased; Cardiotoxicity; Cardiovascular disorder; Cardiovascular function test abnormal; Central venous pressure increased; Chest pain; Chest X-ray abnormal; Chronic left ventricular failure; Chronic right ventricular failure; Computerised tomogram thorax abnormal; Congestive cardiomyopathy; Cor pulmonale; Cor pulmonale acute; Cor pulmonale chronic; Coxsackie carditis; Coxsackie myocarditis; Cytomegalovirus myocarditis; Cytotoxic cardiomyopathy; Decreased ventricular preload; Diabetic cardiomyopathy; Diastolic dysfunction; Dilatation atrial; Dilatation ventricular; Directional Doppler flow tests abnormal; Dyspnoea; Dyspnoea paroxysmal nocturnal; ECG signs of ventricular hypertrophy; Echocardiogram abnormal; Ejection fraction abnormal; Ejection fraction decreased; Electrocardiogram abnormal; Electrocardiogram change; Endocardial fibroelastosis; Eosinophilic myocarditis; External counterpulsation; Heart and lung transplant; Heart transplant; Hepatic congestion; Hepatic vein dilatation; Hepatojugular reflux; Hepatomegaly; HIV cardiomyopathy; Hyperdynamic left ventricle; Hypertensive cardiomyopathy; Hypertrophic cardiomyopathy; Hypoplastic left heart syndrome; Increased ventricular preload; Irregular breathing; Ischaemic cardiomyopathy; Jugular vein distension; Kearns-Sayre syndrome; Labile blood pressure; Left atrial dilatation; Left ventricular dysfunction; Left ventricular end-diastolic pressure decreased; Left ventricular failure; Left ventricular heave; Low cardiac output syndrome; Lower respiratory tract congestion; Lupus myocarditis; Malarial myocarditis; Mental status changes; Metabolic cardiomyopathy; Multiple cardiac defects; Multiple gated acquisition scan abnormal; Muscular dystrophy; Myocardiac abscess; Myocardial bridging; Myocardial calcification; Myocardial depression; Myocardial fibrosis; Myocardial haemorrhage; Myocardial necrosis marker increased; Myocarditis; Myocarditis bacterial; Myocarditis helminthic; Myocarditis infectious; Myocarditis meningococcal; Myocarditis mycotic; Myocarditis post infection; Myocarditis septic; Myocarditis syphilitic; Myocarditis toxoplasmal; Myoglobinaemia; Myoglobinuria; Neonatal cardiac failure; Nocturia; Nocturnal dyspnoea; Non-obstructive cardiomyopathy; N-terminal prohormone brain natriuretic peptide abnormal; N-terminal prohormone brain natriuretic peptide increased; Nuclear magnetic resonance imaging thoracic abnormal; Obstructive shock; Oedema; Oedema due to cardiac disease; Oedema neonatal; Oedema peripheral; Orthopnoea; Orthostatic hypotension; Palpitations; Papillary muscle disorder; Papillary muscle haemorrhage; Peripartum cardiomyopathy; Peripheral oedema neonatal; Peripheral swelling; Prohormone brain natriuretic peptide abnormal; Prohormone brain natriuretic peptide increased; Pulmonary arterial wedge pressure increased; Pulmonary congestion; Pulmonary oedema; Pulmonary oedema neonatal; Radiation associated cardiac failure; Radiation myocarditis; Reduction ventriculoplasty; Refeeding syndrome; Restrictive cardiomyopathy; Right atrial dilatation; Right atrial pressure increased; Right ventricle outflow tract obstruction; Right ventricular dysfunction; Right ventricular ejection fraction decreased; Right ventricular failure; Right ventricular heave; Right ventricular systolic pressure decreased; Scan myocardial perfusion abnormal; Stress cardiomyopathy; Stroke volume decreased; Sudden cardiac death; Sudden death; Syncope; Systolic anterior motion of mitral valve; Systolic dysfunction; Tachycardia induced cardiomyopathy; Thyrotoxic cardiomyopathy; Ultrasound Doppler abnormal; Vascular resistance pulmonary increased; Venous pressure increased; Venous pressure jugular abnormal; Venous pressure jugular increased; Ventricular arrhythmia; Ventricular assist device insertion;

Ventricular dysfunction; Ventricular dyskinesia; Ventricular dyssynchrony; Ventricular failure; Ventricular hyperkinesia; Ventricular hypertrophy; Ventricular hypokinesia; Ventricular hypoplasia; Ventricular remodelling; Ventricular septal defect acquired; Viral cardiomyopathy; Viral myocarditis

Hepatotoxicity

MedDRA PTs: 5'nucleotidase increased; Accessory liver lobe; Acquired antithrombin III deficiency; Acquired protein S deficiency; Acute fatty liver of pregnancy; Acute graft versus host disease in liver; Acute hepatic failure; Acute hepatitis B; Acute hepatitis C; Acute on chronic liver failure; Acute yellow liver atrophy; Adenoviral hepatitis; Alagille syndrome; Alanine aminotransferase abnormal; Alanine aminotransferase increased; Alcoholic liver disease; Allergic hepatitis; Ammonia abnormal; Ammonia increased; Anorectal varices; Anorectal varices haemorrhage; Anti factor X activity abnormal; Anti factor X activity decreased; Anti factor X activity increased; Antithrombin III decreased; Ascites; Aspartate aminotransferase abnormal; Aspartate aminotransferase increased; Asterixis; Asymptomatic viral hepatitis; Autoimmune hepatitis; Bacterascites; Benign hepatic neoplasm; Benign hepatobiliary neoplasm; Bile output abnormal; Bile output decreased; Biliary ascites; Biliary cirrhosis; Biliary cirrhosis primary; Biliary fibrosis; Bilirubin conjugated abnormal; Bilirubin conjugated increased; Bilirubin excretion disorder; Bilirubin urine present; Biopsy liver abnormal; Blood alkaline phosphatase abnormal; Blood alkaline phosphatase increased; Blood bilirubin abnormal; Blood bilirubin increased; Blood bilirubin unconjugated increased; Blood cholinesterase abnormal; Blood cholinesterase decreased; Blood fibrinogen abnormal; Blood fibrinogen decreased; Blood thrombin abnormal; Blood thrombin decreased; Blood thromboplastin abnormal; Blood thromboplastin decreased; Bromosulphthalein test abnormal; Cerebrohepatorenal syndrome; Child-Pugh-Turcotte score abnormal; Child-Pugh-Turcotte score increased; Cholaemia; Cholangiosarcoma; Cholestasis; Cholestasis of pregnancy; Cholestatic liver injury; Cholestatic pruritus; Chronic graft versus host disease in liver; Chronic hepatic failure; Chronic hepatitis; Chronic hepatitis B; Chronic hepatitis C; Cirrhosis alcoholic; Coagulation factor decreased; Coagulation factor IX level abnormal; Coagulation factor IX level decreased; Coagulation factor V level abnormal; Coagulation factor V level decreased; Coagulation factor VII level abnormal; Coagulation factor VII level decreased; Coagulation factor X level abnormal; Coagulation factor X level decreased; Coma hepatic; Computerised tomogram liver; Congenital absence of bile ducts; Congenital cystic disease of liver; Congenital hepatic fibrosis; Congenital hepatitis B infection; Congenital hepatobiliary anomaly; Congenital hepatomegaly; Cryptogenic cirrhosis; Cystic fibrosis hepatic disease; Cytomegalovirus hepatitis; Deficiency of bile secretion; Diabetic hepatopathy; Dilatation intrahepatic duct congenital; Drug-induced liver injury; Duodenal varices; Fatty liver alcoholic; Focal nodular hyperplasia; Foetor hepaticus; Galactose elimination capacity test abnormal; Galactose elimination capacity test decreased; Gallbladder varices; Gamma-glutamyltransferase abnormal; Gamma-glutamyltransferase increased; Gastric variceal injection; Gastric variceal ligation; Gastric varices; Gastric varices haemorrhage; Gianotti-Crosti syndrome; Glutamate dehydrogenase increased; Glycogen storage disease type I; Glycogen storage disease type II; Glycogen storage disease type III; Glycogen storage disease type IV; Glycogen storage disease type VI; Glycogen storage disease type VII; Glycogen storage disease type VIII; Graft versus host disease in liver; Granulomatous liver disease; Guanase increased; Haemangioma of liver; Haemorrhagic ascites; Haemorrhagic hepatic cyst; HBV-DNA polymerase increased; Hepaplastin abnormal; Hepaplastin decreased; Hepatectomy; Hepatic adenoma; Hepatic amoebiasis; Hepatic angiosarcoma; Hepatic artery flow decreased; Hepatic atrophy; Hepatic calcification; Hepatic cancer; Hepatic cancer metastatic; Hepatic cancer recurrent; Hepatic cancer stage I; Hepatic cancer stage II; Hepatic cancer stage III; Hepatic cancer stage IV; Hepatic candidiasis; Hepatic cirrhosis; Hepatic congestion; Hepatic cyst; Hepatic cyst infection; Hepatic cyst ruptured; Hepatic echinococciasis; Hepatic encephalopathy; Hepatic encephalopathy prophylaxis; Hepatic enzyme abnormal; Hepatic enzyme decreased; Hepatic enzyme increased; Hepatic failure; Hepatic fibrosis; Hepatic fibrosis marker abnormal; Hepatic fibrosis marker increased; Hepatic function abnormal; Hepatic haemangioma rupture; Hepatic hydrothorax; Hepatic hypertrophy; Hepatic infection; Hepatic infection bacterial; Hepatic infection fungal; Hepatic infection helminthic; Hepatic infiltration eosinophilic; Hepatic lesion; Hepatic mass; Hepatic necrosis; Hepatic neoplasm; Hepatic pain; Hepatic sequestration; Hepatic steato-fibrosis; Hepatic steatosis; Hepatic vascular resistance increased; Hepatitis; Hepatitis A; Hepatitis A antibody abnormal; Hepatitis A antibody positive; Hepatitis A antigen positive; Hepatitis A virus test positive; Hepatitis acute; Hepatitis alcoholic; Hepatitis B antibody positive; Hepatitis B core antibody positive; Hepatitis B core antigen positive; Hepatitis B DNA assay positive; Hepatitis B DNA increased; Hepatitis B e antibody positive; Hepatitis B e antigen positive; Hepatitis B surface antibody positive; Hepatitis B surface antigen positive; Hepatitis B virus test positive; Hepatitis C; Hepatitis C antibody positive; Hepatitis C core antibody positive; Hepatitis C RNA increased; Hepatitis C RNA positive; Hepatitis C virus test positive; Hepatitis cholestatic; Hepatitis chronic active; Hepatitis chronic persistent; Hepatitis D; Hepatitis D antibody positive; Hepatitis D antigen positive; Hepatitis D RNA positive; Hepatitis D virus test positive; Hepatitis E antibody abnormal;

Hepatitis E antibody positive; Hepatitis E antigen positive; Hepatitis E virus test positive; Hepatitis F; Hepatitis fulminant; Hepatitis G; Hepatitis H; Hepatitis infectious; Hepatitis infectious mononucleosis; Hepatitis mumps; Hepatitis neonatal; Hepatitis non-A non-B; Hepatitis non-A non-B non-C; Hepatitis post transfusion; Hepatitis syphilitic; Hepatitis toxic; Hepatitis toxoplasmal; Hepatitis viral; Hepatitis viral test positive; Hepatobiliary cancer; Hepatobiliary cancer in situ; Hepatobiliary disease; Hepatobiliary infection; Hepatobiliary neoplasm; Hepatobiliary scan abnormal; Hepatoblastoma; Hepatoblastoma recurrent; Hepatocellular carcinoma; Hepatocellular damage neonatal; Hepatocellular foamy cell syndrome; Hepatocellular injury; Hepato-lenticular degeneration; Hepatomegaly; Hepatopulmonary syndrome; Hepatorenal failure; Hepatorenal syndrome; Hepatosplenic candidiasis; Hepatosplenomegaly; Hepatosplenomegaly neonatal; Hepatotoxicity; Hereditary haemochromatosis; Herpes simplex hepatitis; Hyperammonaemia; Hyperbilirubinaemia; Hyperbilirubinaemia neonatal; Hypercholia; Hyperfibrinolysis; Hypertransaminasaemia; Hypoalbuminaemia; Hypocoagulable state; Hypofibrinogenaemia; Hypoprothrombinaemia; Hypothrombinaemia; Hypothromboplastinaemia; Icterus index increased; International normalised ratio abnormal; International normalised ratio increased; Intestinal varices; Intestinal varices haemorrhage; Intrahepatic portal hepatic venous fistula; Ischaemic hepatitis; Jaundice; Jaundice cholestatic; Jaundice hepatocellular; Jaundice neonatal; Kayser-Fleischer ring; Kernicterus; Leucine aminopeptidase increased; Liver ablation; Liver abscess; Liver and small intestine transplant; Liver carcinoma ruptured; Liver contusion; Liver dialysis; Liver disorder; Liver function test abnormal; Liver function test decreased; Liver function test increased; Liver induration; Liver injury; Liver iron concentration abnormal; Liver iron concentration increased; Liver operation; Liver palpable; Liver sarcoidosis; Liver scan abnormal; Liver tenderness; Liver transplant; Lupoid hepatic cirrhosis; Lupus hepatitis; Minimal hepatic encephalopathy; Mitochondrial aspartate aminotransferase increased; Mixed hepatocellular cholangiocarcinoma; Mixed liver injury; Model for end stage liver disease score abnormal; Model for end stage liver disease score increased; Molar ratio of total branched-chain amino acid to tyrosine; Neonatal cholestasis; Neonatal hepatomegaly; Nodular regenerative hyperplasia; Non-alcoholic fatty liver; Non-alcoholic steatohepatitis; Non-cirrhotic portal hypertension; Ocular icterus; Oedema due to hepatic disease; Oesophageal varices haemorrhage; Parenteral nutrition associated liver disease; Perihepatic discomfort; Peripancreatic varices; Periportal oedema; Peritoneal fluid protein abnormal; Peritoneal fluid protein decreased; Peritoneal fluid protein increased; Peritoneovenous shunt; Pneumobilia; Polycystic liver disease; Porphyria acute; Porphyria non-acute; Portal fibrosis; Portal hypertension; Portal hypertensive enteropathy; Portal hypertensive gastropathy; Portal pyaemia; Portal shunt; Portal shunt procedure; Portal tract inflammation; Portal vein cavernous transformation; Portal vein dilatation; Portal vein flow decreased; Portal vein pressure increased; Portopulmonary hypertension; Protein C decreased; Protein S abnormal; Protein S decreased; Prothrombin level abnormal; Prothrombin level decreased; Prothrombin time abnormal; Prothrombin time prolonged; Prothrombin time ratio abnormal; Prothrombin time ratio increased; Radiation hepatitis; Renal and liver transplant; Retinol binding protein decreased; Retrograde portal vein flow; Reye's syndrome; Reynold's syndrome; Small-for-size liver syndrome; Spider naevus; Splenic varices; Splenic varices haemorrhage; Splenorenal shunt; Splenorenal shunt procedure; Spontaneous intrahepatic portosystemic venous shunt; Steatohepatitis; Stomal varices; Subacute hepatic failure; Thrombin time abnormal; Thrombin time prolonged; Total bile acids increased; Transaminases abnormal; Transaminases increased; Ultrasound liver abnormal; Urine bilirubin increased; Urobilinogen urine decreased; Urobilinogen urine increased; Varices oesophageal; Varicose veins of abdominal wall; X-ray hepatobiliary abnormal; Yellow skin

Relevant Clinical Laboratory Changes: AST >3x ULN; AST >5x ULN; AST >10x ULN; AST >20x ULN; ALT >3x ULN; ALT >5x ULN; ALT >10x ULN; ALT >20x ULN; TB >2 x ULN; ALP >3x ULN; ALP >1.5x ULN; AST >3x ULN or ALT >3x ULN and TB >2x ULN (within 14 days of AST/ALT elevation) and ALP <2x ULN; AST >3x ULN or ALT >3x ULN and TB >1.5x ULN (within 14 days of AST/ALT elevation) and ALP <2x ULN; INR <1.5; ALT or AST >3x ULN + Fatigue/Nausea/Vomiting/Abdominal pain upper/Abdominal tenderness/Pyrexia /Rash/Eosinophilia/ and/or Allergic eosinophilia

Hypersensitivity/Anaphylactic Reaction/Angioedema

MedDRA PTs: Acute generalised exanthematous pustulosis; Acute respiratory failure; Administration site dermatitis; Administration site eczema; Administration site hypersensitivity; Administration site photosensitivity reaction; Administration site rash; Administration site recall reaction; Administration site urticaria; Administration site vasculitis; Airway remodelling; Allergic bronchitis; Allergic colitis; Allergic cough; Allergic cystitis; Allergic eosinophilia; Allergic gastroenteritis; Allergic granulomatous angiitis; Allergic hepatitis; Allergic keratitis; Allergic myocarditis; Allergic oedema; Allergic otitis externa; Allergic otitis media; Allergic pharyngitis; Allergic respiratory disease; Allergic respiratory symptom; Allergic sinusitis; Allergy to fermented products; Allergy to

immunoglobulin therapy; Allergic transfusion reaction; Allergy alert test positive; Allergy test positive; Allergy to chemicals; Allergy to fermented products; Allergy to immunoglobulin therapy; Allergy to surgical sutures; Allergy to vaccine; Alpha tumour necrosis factor increased; Alveolitis; Alveolitis allergic; Anaphylactic reaction; Anaphylactic shock; Anaphylactic transfusion reaction; Anaphylactoid reaction; Anaphylactoid shock; Anaphylaxis treatment; Angioedema; Antiallergic therapy; Antibody test abnormal; Antibody test positive; Antiendomysial antibody positive; Anti-insulin antibody increased; Anti-insulin antibody increased; Anti-insulin antibody positive; Anti-insulin receptor antibody increased; Anti-insulin receptor antibody positive; Anti-neutrophil cytoplasmic antibody positive vasculitis; Application site dermatitis; Application site eczema; Application site hypersensitivity; Application site rash; Application site recall reaction; Application site urticaria; Application site vasculitis; Arthritis allergic; Aspirin-exacerbated respiratory disease; Asthma; Asthma late onset; Asthma-chronic obstructive pulmonary disease overlap syndrome; Asthmatic crisis; Atopy; Auricular swelling; Blepharitis allergic; Blister; Blood immunoglobulin A abnormal; Blood immunoglobulin A increased; Blood immunoglobulin D increased; Blood immunoglobulin E abnormal; Blood immunoglobulin E increased; Blood immunoglobulin G abnormal; Blood immunoglobulin G increased; Blood immunoglobulin M abnormal; Blood immunoglobulin M increased; Blood pressure decreased; Bromoderma; Bronchial hyperreactivity; Bronchial oedema; Bronchospasm; Bullous impetigo; Caffeine allergy; Capillaritis; Cardiac arrest; Cardio-respiratory arrest; Cardio-respiratory distress; Cardiovascular insufficiency; Catheter site dermatitis; Catheter site eczema; Catheter site hypersensitivity; Catheter site rash; Catheter site urticaria; Catheter site vasculitis; Charcot-Leyden crystals; Choking; Choking sensation; Chronic eosinophilic rhinosinusitis; Chronic hyperplastic eosinophilic sinusitis; Circulatory collapse; Circumoral oedema; Complement factor C1 decreased; Complement factor C1 increased; Complement factor C2 decreased; Complement factor C2 increased; Complement factor C3 decreased; Complement factor C3 increased; Complement factor C4 decreased; Complement factor C4 increased; Complement factor decreased; Complement factor increased; Complement fixation abnormal; Complement fixation test positive; Conjunctivitis; Conjunctivitis allergic; Conjunctival oedema; Contact stomatitis; Contrast media allergy; Contrast media reaction; Corneal exfoliation; Corneal oedema; Cutaneous vasculitis; Cyanosis; Cytokine release syndrome; Cytokine storm; Dennie-Morgan fold; Dermatitis; Dermatitis acneiform; Dermatitis allergic; Dermatitis atopic; Dermatitis bullous; Dermatitis contact; Dermatitis exfoliative; Dermatitis exfoliative generalised; Dermatitis herpetiformis; Dermatitis infected; Dermatitis psoriasiform; Device allergy; Dialysis membrane reaction; Diastolic hypotension; Distributive shock; Documented hypersensitivity to administered product; Drug cross-reactivity; Drug eruption; Drug hypersensitivity; Drug provocation test; Drug reaction with eosinophilia and systemic symptoms; Dyspnoea; Ear swelling; Eczema; Eczema infantile; Eczema nummular; Eczema vaccinatum; Eczema vesicular; Eczema weeping; Encephalitis allergic; Encephalopathy allergic; Endotracheal intubation; Eosinophil count abnormal; Eosinophil count increased; Eosinophil percentage abnormal; Eosinophil percentage increased; Eosinophilia; Eosinophilia myalgia syndrome; Eosinophilic bronchitis; Eosinophilic oesophagitis; Eosinophilic pneumonia; Eosinophilic pneumonia acute; Eosinophilic pneumonia chronic; Epidermal necrosis; Epidermolysis; Epidermolysis bullosa; Epiglottic oedema; Erythema; Erythema multiforme; Erythema nodosum; Exfoliative rash; Eye allergy; Eye oedema; Eye pruritus; Eye swelling; Eyelid oedema; Face oedema; Fixed drug eruption; Flushing; Gastrointestinal oedema; Generalised erythema; Generalised oedema; Genital rash; Genital swelling; Giant papillary conjunctivitis; Gingival oedema; Gingival swelling; Gleich's syndrome; Haemolytic transfusion reaction; Haemorrhagic urticaria; Hand dermatitis; Henoch-Schonlein purpura; Henoch-Schonlein purpura nephritis; Heparin-induced thrombocytopenia; Hereditary angioedema; HLA marker study positive; Hypersensitivity; Hypersensitivity vasculitis; Hyperventilation; Hypotension; Idiopathic angioedema; Idiopathic urticaria; Immediate post-injection reaction; Immune complex level increased; Immune thrombocytopenic purpura; Immune tolerance induction; Immune-mediated adverse reaction; Immunoglobulins abnormal; Immunoglobulins increased; Immunology test abnormal; Implant site dermatitis; Implant site hypersensitivity; Implant site photosensitivity; Implant site rash; Implant site urticaria; Incision site dermatitis; Incision site rash; Infantile asthma; Infusion site dermatitis; Infusion site eczema; Infusion site hypersensitivity; Infusion site photosensitivity reaction; Infusion site rash; Infusion site recall reaction; Infusion site urticaria; Infusion site vasculitis; Injection site dermatitis; Injection site eczema; Injection site hypersensitivity; Injection site photosensitivity reaction; Injection site rash; Injection site recall reaction; Injection site urticaria; Injection site vasculitis; Instillation site hypersensitivity; Instillation site rash; Instillation site urticaria; Interstitial granulomatous dermatitis; Interstitial lung disease; Intestinal angioedema; Iodine allergy; Kaposi's varicelliform eruption; Kounis syndrome; Laryngeal dyspnoea; Laryngeal obstruction; Laryngeal oedema; Laryngitis allergic; Laryngospasm; Laryngotracheal oedema; Leukotriene increased; Limbal swelling; Lip exfoliation; Lip oedema; Lip swelling; Local swelling; Localised oedema; Mast cell degranulation present; Mechanical urticaria; Medical device site dermatitis; Medical device site eczema; Medical device site hypersensitivity; Medical device site photosensitivity reaction; Medical device site rash; Medical device site recall reaction; Medical device site urticaria; Mesenteric panniculitis; Mouth swelling; Mouth ulceration; Mucocutaneous rash; Mucosa vesicle; Mucosal erosion; Mucosal exfoliation; Mucosal necrosis; Mucosal ulceration; Multiple allergies; Nasal

obstruction; Nasal oedema; Necrotising panniculitis; Nephritis allergic; Neurodermatitis; Neutralising antibodies positive; Nikolsky's sign; Nipple oedema; Nipple swelling; Nodular rash; Noninfective conjunctivitis; Non-neutralising antibodies positive; Obstructive airways disorder; Occupational asthma; Occupational dermatitis; Ocular hyperaemia; Oculomucocutaneous syndrome; Oculorespiratory syndrome; Oedema; Oedema genital; Oedema mouth; Oedema mucosal; Oedema neonatal; Oedema peripheral; Oral allergy syndrome; Oral mucosal exfoliation; Orbital oedema; Oropharyngeal blistering; Oropharyngeal spasm ; Oropharyngeal swelling; Palatal oedema; Palatal swelling; Palisaded neutrophilic granulomatous dermatitis; Palpable purpura; Panniculitis; Pathergy reaction; Penile exfoliation; Penile oedema; Penile swelling; Perineal rash; Peripheral oedema neonatal; Periorbital oedema; Peripheral swelling; Perivascular dermatitis; Pharyngeal oedema; Photosensitivity reaction; Pneumonitis; Prurigo; Pruritus; Pruritus allergic; Pruritus generalised; Pulmonary eosinophilia; Radioallergosorbent test positive; Rash; Rash erythematous; Rash follicular; Rash generalised; Rash macular; Rash maculo-papular; Rash maculovesicular; Rash morbilliform; Rash neonatal; Rash papulosquamous; Rash pruritic; Rash pustular; Rash rubelliform; Rash scarlatiniform; Rash vesicular; Reaction to azo-dyes; Reaction to colouring; Reaction to drug excipients; Reaction to preservatives; Reactive airways dysfunction syndrome; Red man syndrome; Respiratory arrest; Respiratory distress; Respiratory failure; Respiratory tract oedema; Reversible airways obstruction; Rhinitis allergic; Rhinitis perennial; Scleral oedema; Scleritis allergic; Scrotal oedema; Scrotal swelling; Seasonal allergy; Sensation of foreign body; Septal panniculitis; Serum sickness; Serum sickness-like reaction; Shock; Shock symptom; Skin erosion; Skin exfoliation; Skin necrosis; Skin oedema; Skin reaction; Skin swelling; Skin test positive; Sneezing; Solar urticaria; Solvent sensitivity; Status asthmaticus; Stevens-Johnson syndrome; Stoma site hypersensitivity; Stoma site rash; Stomatitis; Streptokinase antibody increased; Stridor; Suffocation feeling; Swelling; Swelling face; Swollen tongue; Tachypnoea; Throat tightness; Tongue exfoliation; Tongue oedema; Toxic epidermal necrolysis; Toxic skin eruption; Tracheal obstruction; Tracheal oedema; Tracheostomy; Transplantation associated food allergy; Type I hypersensitivity; Type II hypersensitivity; Type III immune complex mediated reaction; Type IV hypersensitivity reaction; Upper airway obstruction; Urticaria; Urticaria cholinergic; Urticaria chronic; Urticaria contact; Urticaria papular; Urticaria physical; Urticaria pigmentosa; Urticaria vesiculosa; Urticarial vasculitis; Vaccination site dermatitis; Vaccination site eczema; Vaccination site exfoliation; Vaccination site hypersensitivity; Vaccination site photosensitivity reaction; Vaccination site rash; Vaccination site recall reaction; Vaccination site urticaria; Vaccination site vasculitis; Vaccination site vesicles; Vaginal exfoliation; Vaginal oedema; Vaginal ulceration; Vasculitic rash; Vessel puncture site rash; Vessel puncture site vesicles; Visceral oedema; Vulval oedema; Vulval ulceration; Vulvovaginal rash; Vulvovaginal swelling; Vulvovaginal ulceration**;** Wheezing

Hypoglycemia

MedDRA PTs: Cold sweat; Hypoglycaemia; Hypoglycaemia neonatal; Hypoglycaemia unawareness; Hypoglycaemic coma; Hypoglycaemic encephalopathy; Hypoglycaemic seizure; Neuroglycopenia; Hyperinsulinaemia; Hyperinsulinism; Hypoglycaemic unconsciousness; Shock hypoglycaemic

Relevant Clinical Laboratory Changes: Blood glucose <40 mg/dL

Ketoacidosis

MedDRA PTs: Acetonaemia; Acid base balance abnormal; Acid-base balance disorder mixed; Acidosis; Anion gap; Anion gap abnormal; Anion gap increased; Blood bicarbonate abnormal; Blood bicarbonate decreased; Blood gases abnormal; Blood ketone body; Blood ketone body increased; Blood ketone body present; Blood lactic acid abnormal; Blood lactic acid increased; Blood pH abnormal; Blood pH decreased; Coma acidotic; Diabetes with hyperosmolarity; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Diabetic ketoacidosis; Diabetic ketoacidotic hyperglycaemic coma; Diabetic metabolic decompensation; Hyperglycaemic seizure; Hyperlactacidaemia; Hyperosmolar hyperglycaemic state; Hyperosmolar state; Ketoacidosis; Ketonuria; Ketosis; Kussmaul respiration; Lactic acidosis; Metabolic acidosis; Organic acid analysis abnormal; PCO2 abnormal; PCO2 decreased; Respiratory alkalosis; Urine ketone body; Urine ketone body present; Urine lactic acid increased

Relevant Clinical Laboratory Changes: Blood bicarbonate ≤15 mEq/L; blood bicarbonate ≤10 mEq/L; anion gap (sodium – [chloride + bicarbonate]) >12 mEq/L; blood glucose >250 mg/dL; effective serum osmolality (sodium mEq/L + [glucose mg/dL/18]) >320 mOsm/kg; arterial pH ≤7.3; venous pH ≤7.3; serum ketones positive; urine ketones positive

Lactic Acidosis

MedDRA PTs: Acid base balance abnormal; Acidosis; Anion gap abnormal; Anion gap increased; Blood bicarbonate abnormal; Blood bicarbonate decreased; Blood gases abnormal; Blood lactic acid abnormal; Blood lactic acid increased; Blood pH abnormal; Blood pH decreased; Coma acidotic; Hyperlactacidaemia; Kussmaul respiration; Lactic acidosis; Metabolic acidosis; PCO2 abnormal; PCO2 decreased; Urine lactic acid increased

Relevant Clinical Laboratory Changes: Blood bicarbonate ≤15 mEq/L; anion gap (sodium – [chloride + bicarbonate]) >12 mEq/L; serum lactate >4 mmol/L; serum lactate >2 mmol/L plus one of the following: Decreased appetite, Nausea, Acetonaemic vomiting, Vomiting, Vomiting projectile, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Lethargy, Hyperventilation, Hypotension

Lymphopenia

MedDRA PTs: B-lymphocyte abnormalities; B-lymphocyte count decreased; CD4 lymphocytes decreased; CD8 lymphocytes decreased; Lymphocyte count abnormal; Lymphocyte count decreased; Lymphocyte percentage abnormal; Lymphocyte percentage decreased; Lymphocytopenia neonatal; Lymphopenia; T-lymphocyte count abnormal; T-lymphocyte count decreased

Relevant Clinical Laboratory Changes: Lymphocyte count ≤0.5 c/L; lymphocyte count ≤0.75 c/L; lymphocyte count decrease ≥20% and <LLN

Malignancies & Premalignant Conditions

MedDRA PTs: 5q minus syndrome; Abdominal neoplasm; Abdominal wall neoplasm; Abdominal wall neoplasm malignant; Acanthosis nigricans; Acinar cell carcinoma of pancreas; Acinic cell carcinoma of salivary gland; Acquired thalassaemia; Acral lentiginous melanoma; Acral lentiginous melanoma stage I; Acral lentiginous melanoma stage II; Acral lentiginous melanoma stage III; Acral lentiginous melanoma stage IV; Acrokeratosis paraneoplastica; ACTH-producing pituitary tumour; Actinic keratosis; Acute biphenotypic leukaemia; Acute leukaemia; Acute leukaemia in remission; Acute lymphocytic leukaemia; Acute lymphocytic leukaemia (in remission); Acute lymphocytic leukaemia recurrent; Acute lymphocytic leukaemia refractory; Acute megakaryocytic leukaemia; Acute megakaryocytic leukaemia (in remission); Acute monocytic leukaemia; Acute monocytic leukaemia (in remission); Acute myeloid leukaemia; Acute myeloid leukaemia (in remission); Acute myeloid leukaemia recurrent; Acute myelomonocytic leukaemia; Acute promyelocytic leukaemia; Acute undifferentiated leukaemia; Adenocarcinoma; Adenocarcinoma gastric; Adenocarcinoma of appendix; Adenocarcinoma of colon; Adenocarcinoma of salivary gland; Adenocarcinoma of the cervix; Adenocarcinoma pancreas; Adenoid cystic carcinoma; Adenoid cystic carcinoma of external auditory canal; Adenoid cystic carcinoma of salivary gland; Adenomatous polyposis coli; Adenosquamous carcinoma of the cervix; Adenosquamous carcinoma of vagina; Adenosquamous cell carcinoma; Adenosquamous cell lung cancer; Adenosquamous cell lung cancer recurrent; Adenosquamous cell lung cancer stage 0; Adenosquamous cell lung cancer stage I; Adenosquamous cell lung cancer stage II; Adenosquamous cell lung cancer stage III; Adenosquamous cell lung cancer stage IV; Adrenal gland cancer; Adrenal gland cancer metastatic; Adrenal neoplasm; Adrenocortical carcinoma; Adult T-cell lymphoma/leukaemia; Adult T-cell lymphoma/leukaemia recurrent; Adult T-cell lymphoma/leukaemia refractory; Adult T-cell lymphoma/leukaemia stage I; Adult T-cell lymphoma/leukaemia stage II; Adult T-cell lymphoma/leukaemia stage III; Adult T-cell lymphoma/leukaemia stage IV; Aesthesioneuroblastoma; Alcoholisation procedure; Aleukaemic leukaemia; Alpha 1 foetoprotein abnormal; Alpha 1 foetoprotein increased; Alpha interferon therapy; Alveolar rhabdomyosarcoma; Alveolar soft part sarcoma; Alveolar soft part sarcoma metastatic; Alveolar soft part sarcoma recurrent; Amputation of penis; Anal cancer; Anal cancer metastatic; Anal cancer recurrent; Anal cancer stage 0; Anal cancer stage I; Anal cancer stage II; Anal cancer stage III; Anal cancer stage IV; Anal leukoplakia; Anal neoplasm; Anal polyp; Anal polypectomy; Anal squamous cell carcinoma; Anaplastic astrocytoma; Anaplastic large cell lymphoma T- and null-cell types; Anaplastic large cell lymphoma T- and null-cell types recurrent; Anaplastic large cell lymphoma T- and null-cell types refractory; Anaplastic large cell lymphoma T- and null-cell types stage I; Anaplastic large cell lymphoma T- and null-cell types stage II; Anaplastic large cell lymphoma T- and null-cell types stage III; Anaplastic large cell lymphoma T- and null-cell types stage IV; Anaplastic large-cell lymphoma;

Anaplastic lymphoma kinase gene and nucleophosmin gene fusion overexpression; Anaplastic meningioma; Anaplastic oligodendroglioma; Anaplastic thyroid cancer; Androgen therapy; Angiocentric glioma; Angiocentric lymphoma; Angiocentric lymphoma recurrent; Angiocentric lymphoma refractory; Angiocentric lymphoma stage I; Angiocentric lymphoma stage II; Angiocentric lymphoma stage III; Angiocentric lymphoma stage IV; Angiogenesis biomarker increased; Angioimmunoblastic T-cell lymphoma; Angioimmunoblastic T-cell lymphoma recurrent; Angioimmunoblastic T-cell lymphoma refractory; Angioimmunoblastic T-cell lymphoma stage I; Angioimmunoblastic T-cell lymphoma stage II; Angioimmunoblastic T-cell lymphoma stage III; Angioimmunoblastic T-cell lymphoma stage IV; Angiosarcoma; Angiosarcoma metastatic; Angiosarcoma non-metastatic; Angiosarcoma recurrent; Anogenital dysplasia; Antiandrogen therapy; Anti-androgen withdrawal syndrome; Anti-NMDA antibody positive; Antioestrogen therapy; Anti-VGCC antibody positive; Apocrine breast carcinoma; Appendix cancer; APUDoma; Arsenical keratosis; Aspiration bone marrow abnormal; Astrocytoma; Astrocytoma malignant; Atypical fibroxanthoma; Atypical teratoid/rhabdoid tumour of CNS; Autologous bone marrow transplantation therapy; Axillary lymphadenectomy; B precursor type acute leukaemia; Barrett's oesophagus; Basal cell carcinoma; Basosquamous carcinoma; Basosquamous carcinoma of skin; B-cell lymphoma; B-cell lymphoma recurrent; B-cell lymphoma refractory; B-cell lymphoma stage I; B-cell lymphoma stage II; B-cell lymphoma stage III; B-cell lymphoma stage IV; B-cell prolymphocytic leukaemia; B-cell small lymphocytic lymphoma; B-cell small lymphocytic lymphoma recurrent; B-cell small lymphocytic lymphoma refractory; B-cell small lymphocytic lymphoma stage I; B-cell small lymphocytic lymphoma stage II; B-cell small lymphocytic lymphoma stage III; B-cell small lymphocytic lymphoma stage IV; B-cell type acute leukaemia; B-cell unclassifiable lymphoma high grade; B-cell unclassifiable lymphoma low grade; Benign hydatidiform mole; Beta interferon therapy; Bile duct adenocarcinoma; Bile duct adenosquamous carcinoma; Bile duct cancer; Bile duct cancer recurrent; Bile duct cancer stage 0; Bile duct cancer stage I; Bile duct cancer stage II; Bile duct cancer stage III; Bile duct cancer stage IV; Bile duct squamous cell carcinoma; Biliary cancer metastatic; Biliary neoplasm; Biopsy abdominal wall abnormal; Biopsy adrenal gland abnormal; Biopsy anus abnormal; Biopsy artery abnormal; Biopsy bile duct abnormal; Biopsy bladder abnormal; Biopsy blood vessel abnormal; Biopsy bone abnormal; Biopsy bone marrow abnormal; Biopsy brain abnormal; Biopsy breast abnormal; Biopsy bronchus abnormal; Biopsy cartilage abnormal; Biopsy cervix abnormal; Biopsy chest wall abnormal; Biopsy chorionic villous abnormal; Biopsy colon abnormal; Biopsy conjunctiva abnormal; Biopsy cornea abnormal; Biopsy diaphragm abnormal; Biopsy ear abnormal; Biopsy endometrium abnormal; Biopsy epididymis abnormal; Biopsy eyelid abnormal; Biopsy fallopian tube abnormal; Biopsy foetal abnormal; Biopsy heart abnormal; Biopsy intestine abnormal; Biopsy kidney abnormal; Biopsy larynx abnormal; Biopsy ligament abnormal; Biopsy lip abnormal; Biopsy liver abnormal; Biopsy lung abnormal; Biopsy lymph gland abnormal; Biopsy mucosa abnormal; Biopsy muscle abnormal; Biopsy oesophagus abnormal; Biopsy ovary abnormal; Biopsy palate abnormal; Biopsy pancreas abnormal; Biopsy parathyroid gland abnormal; Biopsy penis abnormal; Biopsy pericardium abnormal; Biopsy peripheral nerve abnormal; Biopsy peritoneum abnormal; Biopsy pharynx abnormal; Biopsy pleura abnormal; Biopsy prostate abnormal; Biopsy rectum abnormal; Biopsy retina abnormal; Biopsy salivary gland abnormal; Biopsy sclera abnormal; Biopsy seminal vesicle abnormal; Biopsy site unspecified abnormal; Biopsy skin abnormal; Biopsy small intestine abnormal; Biopsy spinal cord abnormal; Biopsy spleen abnormal; Biopsy stomach abnormal; Biopsy tendon abnormal; Biopsy testes abnormal; Biopsy thymus gland abnormal; Biopsy thyroid gland abnormal; Biopsy tongue abnormal; Biopsy trachea abnormal; Biopsy urethra abnormal; Biopsy uterus abnormal; Biopsy vagina abnormal; Biopsy vocal cord abnormal; Biopsy vulva abnormal; Biotherapy; Biphasic mesothelioma; Bladder adenocarcinoma recurrent; Bladder adenocarcinoma stage 0; Bladder adenocarcinoma stage I; Bladder adenocarcinoma stage II; Bladder adenocarcinoma stage III; Bladder adenocarcinoma stage IV; Bladder adenocarcinoma stage unspecified; Bladder cancer; Bladder cancer recurrent; Bladder cancer stage 0, with cancer in situ; Bladder cancer stage 0, without cancer in situ; Bladder cancer stage I, with cancer in situ; Bladder cancer stage I, without cancer in situ; Bladder cancer stage II; Bladder cancer stage III; Bladder cancer stage IV; Bladder dysplasia; Bladder leukoplakia; Bladder neck resection; Bladder neoplasm; Bladder neoplasm surgery; Bladder polypectomy; Bladder squamous cell carcinoma recurrent; Bladder squamous cell carcinoma stage 0; Bladder squamous cell carcinoma stage I; Bladder squamous cell carcinoma stage II; Bladder squamous cell carcinoma stage III; Bladder squamous cell carcinoma stage IV; Bladder squamous cell carcinoma stage unspecified; Bladder transitional cell carcinoma; Bladder transitional cell carcinoma metastatic; Bladder transitional cell carcinoma recurrent; Bladder transitional cell carcinoma stage 0; Bladder transitional cell carcinoma stage I; Bladder transitional cell carcinoma stage II; Bladder transitional cell carcinoma stage III; Bladder transitional cell carcinoma stage IV; Blast cell count increased; Blast cell crisis; Blast cell proliferation; Blast cells present; Blast crisis in myelogenous leukaemia; Blastic plasmacytoid dendritic cell neoplasia; Blood chromogranin A increased; Bone cancer; Bone cancer metastatic; Bone giant cell tumour; Bone giant cell tumour malignant; Bone marrow infiltration; Bone marrow leukaemic cell infiltration; Bone marrow reticulin fibrosis; Bone marrow tumour cell infiltration; Bone neoplasm; Bone sarcoma; Bone scan abnormal; Borderline mucinous tumour of ovary; Borderline ovarian tumour; Borderline serous tumour of ovary; Bowenoid

papulosis; Bowen's disease; Brachytherapy; Brachytherapy to eye; Brachytherapy to penis; Brachytherapy to tongue; Brachytherapy to tonsil; Brain cancer metastatic; Brain neoplasm; Brain neoplasm malignant; Brain sarcoma; Brain scan abnormal; Brain stem glioma; Brain teratoma; Brain tumour operation; Breast angiosarcoma; Breast angiosarcoma metastatic; Breast calcifications; Breast cancer; Breast cancer female; Breast cancer in situ; Breast cancer male; Breast cancer metastatic; Breast cancer recurrent; Breast cancer stage I; Breast cancer stage II; Breast cancer stage III; Breast cancer stage IV; Breast capsulotomy; Breast conserving surgery; Breast dysplasia; Breast neoplasm; Breast prosthesis implantation; Breast reconstruction; Breast sarcoma; Breast sarcoma metastatic; Breast sarcoma recurrent; Brenner tumour; Bronchial carcinoma; Bronchial neoplasm; Bronchioloalveolar carcinoma; Burkitt's leukaemia; Burkitt's lymphoma; Burkitt's lymphoma recurrent; Burkitt's lymphoma refractory; Burkitt's lymphoma stage I; Burkitt's lymphoma stage II; Burkitt's lymphoma stage III; Burkitt's lymphoma stage IV; Buschke-Lowenstein's tumour; Cancer hormonal therapy; Cancer in remission; Cancer pain; Cancer surgery; Carbohydrate antigen 125 increased; Carbohydrate antigen 15-3 increased; Carbohydrate antigen 19-9 increased; Carbohydrate antigen 27.29 increased; Carbohydrate antigen 549 increased; Carcinoembryonic antigen decreased; Carcinoembryonic antigen increased; Carcinogenicity; Carcinoid crisis; Carcinoid heart disease; Carcinoid syndrome; Carcinoid tumour; Carcinoid tumour of the appendix; Carcinoid tumour of the caecum; Carcinoid tumour of the duodenum; Carcinoid tumour of the gastrointestinal tract; Carcinoid tumour of the pancreas; Carcinoid tumour of the prostate; Carcinoid tumour of the small bowel; Carcinoid tumour of the stomach; Carcinoid tumour pulmonary; Carcinoma ex-pleomorphic adenoma; Carcinoma in situ; Carcinoma in situ of eye; Carcinoma in situ of penis; Carcinoma in situ of skin; Carcinoma in situ of trachea; Carcinomatous polyarthritis; Cardiac neoplasm malignant; Cardiac neoplasm unspecified; Cardiac teratoma; Carotid body tumour; Cartilage neoplasm; CD20 antigen positive; CD25 antigen positive; CD30 expression; Cell marker increased; Cell-free and concentrated ascites reinfusion therapy; Cementoplasty; Central nervous system leukaemia; Central nervous system lymphoma; Central nervous system melanoma; Central nervous system neoplasm; Central nervous system neuroblastoma; Cerebellar tumour; Cerebellopontine angle tumour; Cervical dysplasia; Cervix cancer metastatic; Cervix carcinoma; Cervix carcinoma recurrent; Cervix carcinoma stage 0; Cervix carcinoma stage I; Cervix carcinoma stage II; Cervix carcinoma stage III; Cervix carcinoma stage IV; Cervix neoplasm; Chemotherapy; Chemotherapy cardiotoxicity attenuation; Chemotherapy cytokine prophylaxis; Chemotherapy extravasation management; Chemotherapy multiple agents systemic; Chemotherapy neurotoxicity attenuation; Chemotherapy sensitivity and resistance assay; Chemotherapy single agent systemic; Chemotherapy urothelial toxicity attenuation; Chest wall tumour; Chloroma; Chloroma (in remission); Cholangiocarcinoma; Cholangiosarcoma; Chondrosarcoma; Chondrosarcoma metastatic; Chondrosarcoma recurrent; Chordoma; Choriocarcinoma; Choroid melanoma; Choroid neoplasm; Choroid plexus carcinoma; Choroid tumour excision; Chronic eosinophilic leukaemia; Chronic leukaemia; Chronic leukaemia in remission; Chronic lymphocytic leukaemia; Chronic lymphocytic leukaemia (in remission); Chronic lymphocytic leukaemia recurrent; Chronic lymphocytic leukaemia refractory; Chronic lymphocytic leukaemia stage 0; Chronic lymphocytic leukaemia stage 1; Chronic lymphocytic leukaemia stage 2; Chronic lymphocytic leukaemia stage 3; Chronic lymphocytic leukaemia stage 4; Chronic lymphocytic leukaemia transformation; Chronic myeloid leukaemia; Chronic myeloid leukaemia (in remission); Chronic myeloid leukaemia recurrent; Chronic myeloid leukaemia transformation; Chronic myelomonocytic leukaemia; Chronic myelomonocytic leukaemia (in remission); C-kit gene negative; Clear cell carcinoma of cervix; Clear cell endometrial carcinoma; Clear cell renal cell carcinoma; Clear cell sarcoma of soft tissue; Clear cell sarcoma of the kidney; Clonal evolution; CNS germinoma; Colectomy; Colectomy total; Colon adenoma; Colon cancer; Colon cancer metastatic; Colon cancer recurrent; Colon cancer stage 0; Colon cancer stage I; Colon cancer stage II; Colon cancer stage III; Colon cancer stage IV; Colon dysplasia; Colon neoplasm; Colony stimulating factor therapy; Colorectal adenocarcinoma; Colorectal cancer; Colorectal cancer metastatic; Colorectal cancer recurrent; Colorectal cancer stage I; Colorectal cancer stage II; Colorectal cancer stage III; Colorectal cancer stage IV; Colorectal carcinoma stage 0; Composite lymphoma; Computerised tomogram breast abnormal; Congenital fibrosarcoma; Congenital malignant neoplasm; Congenital melanocytic naevus; Congenital retinoblastoma; Congenital teratoma; Conjunctival melanoma; Conjunctival neoplasm; Conjunctival primary acquired melanosis; Connective tissue neoplasm; Corneoconjunctival intraepithelial neoplasia; Crohn's disease; Cronkhite-Canada syndrome; CSF lymphocyte count abnormal; CSF lymphocyte count increased; Cutaneous T-cell dyscrasia; Cyclotron therapy; Cystadenocarcinoma ovary; Cystoprostatectomy; Cytokeratin 18 increased; Dedifferentiated liposarcoma; Dermatofibrosarcoma protuberans; Dermatofibrosarcoma protuberans metastatic; Desmoplastic melanoma; Desmoplastic mesothelioma; Desmoplastic small round cell tumour; Diaphragm neoplasm; Diffuse large B-cell lymphoma; Diffuse large B-cell lymphoma recurrent; Diffuse large B-cell lymphoma refractory; Diffuse large B-cell lymphoma stage I; Diffuse large B-cell lymphoma stage II; Diffuse large B-cell lymphoma stage III; Diffuse large B-cell lymphoma stage IV; Disseminated large cell lymphoma; Ductal adenocarcinoma of pancreas; Duodenal neoplasm; Duodenal polyp; Duodenectomy; Dysplasia; Dysplastic naevus; Dysplastic naevus syndrome; Ear neoplasm; Ear neoplasm malignant; Eastern Cooperative Oncology Group performance status improved; Eastern Cooperative Oncology Group

performance status worsened; Eccrine carcinoma; Ectopic ACTH syndrome; Ectopic aldosterone secretion; Ectopic antidiuretic hormone secretion; Ectopic calcitonin production; Ectopic chorionic gonadotrophin secretion; Ectopic growth hormone secretion; Ectopic hormone secretion; Ectopic parathyroid hormone production; Ectopic prolactin secretion; Ectopic renin secretion; Electron radiation therapy; Electron radiation therapy to bladder; Electron radiation therapy to blood; Electron radiation therapy to bone; Electron radiation therapy to brain; Electron radiation therapy to breast; Electron radiation therapy to colon; Electron radiation therapy to ear, nose, or throat; Electron radiation therapy to liver; Electron radiation therapy to lung; Electron radiation therapy to pancreas; Electron radiation therapy to prostate; Electron radiation therapy to skin; Electron radiation therapy to soft tissue; Electron radiation therapy to uterus; Elephantiasis nostras verrucosa; Embryonal rhabdomyosarcoma; Endocrine neoplasm; Endocrine neoplasm malignant; Endometrial adenocarcinoma; Endometrial cancer; Endometrial cancer metastatic; Endometrial cancer recurrent; Endometrial cancer stage 0; Endometrial cancer stage I; Endometrial cancer stage II; Endometrial cancer stage III; Endometrial cancer stage IV; Endometrial dysplasia; Endometrial hyperplasia; Endometrial neoplasm; Endometrial sarcoma; Endometrial sarcoma metastatic; Endometrial sarcoma recurrent; Endometrial stromal sarcoma; Endotheliomatosis; Enteropathy-associated T-cell lymphoma; Eosinophilic leukaemia; Ependymoma; Ependymoma malignant; Epidermodysplasia verruciformis; Epididymal cancer; Epididymal neoplasm; Epiglottic carcinoma; Epiglottidectomy; Epithelioid mesothelioma; Epithelioid sarcoma; Epithelioid sarcoma metastatic; Epithelioid sarcoma recurrent; Epstein-Barr virus associated lymphoma; Epstein-Barr virus associated lymphoproliferative disorder; Erythraemic myelosis (in remission); Erythroleukaemia; Erythroplasia; Erythroplasia of lip; Erythroplasia of penis; Erythroplasia of vulva; Essential thrombocythaemia; Ewing's sarcoma; Ewing's sarcoma metastatic; Ewing's sarcoma recurrent; Ex vivo gene therapy; Exploratory operation; Extended radical mastectomy; Extradural neoplasm; Extragonadal primary embryonal carcinoma; Extragonadal primary germ cell tumour; Extragonadal primary germ cell tumour mixed; Extragonadal primary germ cell tumour mixed stage I; Extragonadal primary germ cell tumour mixed stage II; Extragonadal primary germ cell tumour mixed stage III; Extragonadal primary malignant teratoma; Extragonadal primary non-seminoma; Extragonadal primary non-seminoma stage I; Extragonadal primary non-seminoma stage II; Extragonadal primary non-seminoma stage III; Extragonadal primary non-seminoma stage IV; Extragonadal primary seminoma (pure); Extragonadal primary seminoma (pure) stage I; Extragonadal primary seminoma (pure) stage II; Extragonadal primary seminoma (pure) stage III; Extragonadal primary seminoma (pure) stage IV; Extramammary Paget's disease; Extranodal marginal zone B-cell lymphoma (MALT type); Extranodal marginal zone B-cell lymphoma (MALT type) recurrent; Extranodal marginal zone B-cell lymphoma (MALT type) refractory; Extranodal marginal zone B-cell lymphoma (MALT type) stage I; Extranodal marginal zone B-cell lymphoma (MALT type) stage II; Extranodal marginal zone B-cell lymphoma (MALT type) stage III; Extranodal marginal zone B-cell lymphoma (MALT type) stage IV; Extraocular retinoblastoma; Extra-osseous Ewing's sarcoma; Extra-osseous Ewing's sarcoma metastatic; Extra-osseous Ewing's sarcoma recurrent; Extraskeletal chondrosarcoma metastatic; Extraskeletal chondrosarcoma recurrent; Extraskeletal myxoid chondrosarcoma; Extraskeletal osteosarcoma; Extraskeletal osteosarcoma metastatic; Extraskeletal osteosarcoma recurrent; Eyelid tumour; Fallopian tube cancer; Fallopian tube cancer metastatic; Fallopian tube cancer stage I; Fallopian tube cancer stage II; Fallopian tube cancer stage III; Fallopian tube cancer stage IV; Fallopian tube neoplasm; Familial medullary thyroid cancer; Female reproductive neoplasm; Female reproductive tract carcinoma in situ; Fibrosarcoma; Fibrosarcoma excision; Fibrosarcoma metastatic; Fiducial marker placement; Fms-like tyrosine kinase 3 positive; Follicle centre lymphoma diffuse small cell lymphoma; Follicle centre lymphoma diffuse small cell lymphoma recurrent; Follicle centre lymphoma diffuse small cell lymphoma refractory; Follicle centre lymphoma diffuse small cell lymphoma stage I; Follicle centre lymphoma diffuse small cell lymphoma stage II; Follicle centre lymphoma diffuse small cell lymphoma stage III; Follicle centre lymphoma diffuse small cell lymphoma stage IV; Follicle centre lymphoma, follicular grade I, II, III; Follicle centre lymphoma, follicular grade I, II, III recurrent; Follicle centre lymphoma, follicular grade I, II, III refractory; Follicle centre lymphoma, follicular grade I, II, III stage I; Follicle centre lymphoma, follicular grade I, II, III stage II; Follicle centre lymphoma, follicular grade I, II, III stage III; Follicle centre lymphoma, follicular grade I, II, III stage IV; Follicular dendritic cell sarcoma; Follicular thyroid cancer; Free prostate-specific antigen increased; Free prostate-specific antigen positive; Fungating wound; Gallbladder adenocarcinoma; Gallbladder adenoma; Gallbladder adenosquamous carcinoma; Gallbladder cancer; Gallbladder cancer metastatic; Gallbladder cancer recurrent; Gallbladder cancer stage 0; Gallbladder cancer stage I; Gallbladder cancer stage II; Gallbladder cancer stage III; Gallbladder cancer stage IV; Gallbladder neoplasm; Gallbladder squamous cell carcinoma; Gamma interferon therapy; Gamma radiation therapy; Gamma radiation therapy to bladder; Gamma radiation therapy to blood; Gamma radiation therapy to bone; Gamma radiation therapy to brain; Gamma radiation therapy to breast; Gamma radiation therapy to colon; Gamma radiation therapy to ear, nose, or throat; Gamma radiation therapy to liver; Gamma radiation therapy to lung; Gamma radiation therapy to pancreas; Gamma radiation therapy to pleura; Gamma radiation therapy to prostate; Gamma radiation therapy to skin; Gamma radiation therapy to soft tissue; Gamma radiation therapy to thyroid; Gamma radiation

therapy to uterus; Gammopathy; Ganglioglioma; Ganglioneuroblastoma; Garcin syndrome; Gastrectomy; Gastric cancer; Gastric cancer recurrent; Gastric cancer stage 0; Gastric cancer stage I; Gastric cancer stage II; Gastric cancer stage III; Gastric cancer stage IV; Gastric dysplasia; Gastric neoplasm; Gastric polypectomy; Gastric polyps; Gastric sarcoma; Gastric stent insertion; Gastrinoma; Gastrinoma malignant; Gastroenteropancreatic neuroendocrine tumour disease; Gastrointestinal cancer metastatic; Gastrointestinal carcinoma; Gastrointestinal carcinoma in situ; Gastrointestinal dysplasia; Gastrointestinal melanoma; Gastrointestinal neoplasm; Gastrointestinal stromal cancer; Gastrointestinal stromal tumour; Gastrointestinal submucosal tumour; Gastrooesophageal cancer; Genital cancer male; Genital cancer male in situ; Genital neoplasm malignant female; Genitourinary melanoma; Genitourinary tract neoplasm; Germ cell cancer; Germ cell cancer metastatic; Germ cell neoplasm; Gestational trophoblastic tumour; Gingival cancer; Glioblastoma; Glioblastoma multiforme; Glioma; Gliomatosis cerebri; Glioneuronal tumour; Gliosarcoma; Glossectomy; Glottis carcinoma; Glucagonoma; Granular cell tumour; Growth hormone-producing pituitary tumour; Haemangiopericytoma; Haemangiopericytoma of meninges; Haematological malignancy; Haematopoietic neoplasm; Haemorrhagic tumour necrosis; Hairy cell leukaemia; Hairy cell leukaemia recurrent; Head and neck cancer; Head and neck cancer metastatic; Head and neck cancer stage I; Head and neck cancer stage II; Head and neck cancer stage III; Head and neck cancer stage IV; Hemicorporectomy; Hemilaryngectomy; Hemipelvectomy; Hepatectomy; Hepatic angiosarcoma; Hepatic cancer; Hepatic cancer metastatic; Hepatic cancer recurrent; Hepatic cancer stage I; Hepatic cancer stage II; Hepatic cancer stage III; Hepatic cancer stage IV; Hepatic neoplasm; Hepatobiliary cancer; Hepatobiliary cancer in situ; Hepatobiliary neoplasm; Hepatoblastoma; Hepatoblastoma recurrent; Hepatocellular carcinoma; Hepatosplenic T-cell lymphoma; HER-2 positive breast cancer; HER-2 positive gastric cancer; Hereditary leiomyomatosis renal cell carcinoma; Hereditary papillary renal carcinoma; Hidradenocarcinoma; High frequency ablation; High grade B-cell lymphoma Burkitt-like lymphoma; High grade B-cell lymphoma Burkitt-like lymphoma recurrent; High grade B-cell lymphoma Burkitt-like lymphoma refractory; High grade B-cell lymphoma Burkitt-like lymphoma stage I; High grade B-cell lymphoma Burkitt-like lymphoma stage II; High grade B-cell lymphoma Burkitt-like lymphoma stage III; High grade B-cell lymphoma Burkitt-like lymphoma stage IV; High intensity focused ultrasound; Histiocytic medullary reticulosis; Histiocytic sarcoma; Hodgkin's disease; Hodgkin's disease lymphocyte depletion stage I site unspecified; Hodgkin's disease lymphocyte depletion stage I subdiaphragm; Hodgkin's disease lymphocyte depletion stage I supradiaphragm; Hodgkin's disease lymphocyte depletion stage II site unspecified; Hodgkin's disease lymphocyte depletion stage II subdiaphragm; Hodgkin's disease lymphocyte depletion stage II supradiaphragm; Hodgkin's disease lymphocyte depletion type recurrent; Hodgkin's disease lymphocyte depletion type refractory; Hodgkin's disease lymphocyte depletion type stage III; Hodgkin's disease lymphocyte depletion type stage IV; Hodgkin's disease lymphocyte depletion type stage unspecified; Hodgkin's disease lymphocyte predominance stage I site unspec; Hodgkin's disease lymphocyte predominance stage I subdiaphragm; Hodgkin's disease lymphocyte predominance stage I supradiaphragm; Hodgkin's disease lymphocyte predominance stage II site unspec; Hodgkin's disease lymphocyte predominance stage II subdiaphragm; Hodgkin's disease lymphocyte predominance stage II supradiaphragm; Hodgkin's disease lymphocyte predominance type recurrent; Hodgkin's disease lymphocyte predominance type refractory; Hodgkin's disease lymphocyte predominance type stage III; Hodgkin's disease lymphocyte predominance type stage IV; Hodgkin's disease lymphocyte predominance type stage unspecified; Hodgkin's disease mixed cellularity recurrent; Hodgkin's disease mixed cellularity refractory; Hodgkin's disease mixed cellularity stage I site unspecified; Hodgkin's disease mixed cellularity stage I subdiaphragmatic; Hodgkin's disease mixed cellularity stage I supradiaphragmatic; Hodgkin's disease mixed cellularity stage II subdiaphragmatic; Hodgkin's disease mixed cellularity stage II supradiaphragmatic; Hodgkin's disease mixed cellularity stage III; Hodgkin's disease mixed cellularity stage IV; Hodgkin's disease mixed cellularity stage unspecified; Hodgkin's disease nodular sclerosis; Hodgkin's disease nodular sclerosis recurrent; Hodgkin's disease nodular sclerosis refractory; Hodgkin's disease nodular sclerosis stage I; Hodgkin's disease nodular sclerosis stage II; Hodgkin's disease nodular sclerosis stage III; Hodgkin's disease nodular sclerosis stage IV; Hodgkin's disease recurrent; Hodgkin's disease refractory; Hodgkin's disease stage I; Hodgkin's disease stage II; Hodgkin's disease stage III; Hodgkin's disease stage IV; Hodgkin's disease unclassifiable; Hormone refractory breast cancer; Hormone suppression therapy; Hormone therapy; Hormone-dependent prostate cancer; Hormone-refractory prostate cancer; Hormone-secreting ovarian tumour; Huerthle cell carcinoma; Human chorionic gonadotropin increased; Human chorionic gonadotropin positive; Human epidermal growth factor receptor increased; Hypercalcaemia of malignancy; Hypergammaglobulinaemia benign monoclonal; Hyperthermia therapy; Hypopharyngeal cancer; Hypopharyngeal cancer recurrent; Hypopharyngeal cancer stage 0; Hypopharyngeal cancer stage I; Hypopharyngeal cancer stage II; Hypopharyngeal cancer stage III; Hypopharyngeal cancer stage IV; Hypopharyngeal neoplasm; Hypophysectomy; Hysterectomy; Hysterosalpingectomy; Hysterosalpingo-oophorectomy; Ileectomy; Ileocolectomy; Imaging procedure abnormal; Immune enhancement therapy; Immune reconstitution inflammatory syndrome associated Kaposi's sarcoma; Immunoblastic lymphoma; Immunochemotherapy; Implantable pleural catheter insertion; In vivo gene therapy; Infected neoplasm; Inferior vena

cava syndrome; Inflammatory carcinoma of breast recurrent; Inflammatory carcinoma of breast stage III; Inflammatory carcinoma of breast stage IV; Inflammatory carcinoma of the breast; Inflammatory malignant fibrous histiocytoma; Inflammatory myofibroblastic tumour; Insulinoma; Interleukin therapy; Intestinal adenocarcinoma; Intestinal polyp; Intestinal polypectomy; Intestinal resection; Intestinal T-cell lymphoma recurrent; Intestinal T-cell lymphoma refractory; Intestinal T-cell lymphoma stage I; Intestinal T-cell lymphoma stage II; Intestinal T-cell lymphoma stage III; Intestinal T-cell lymphoma stage IV; Intracranial germ cell tumour; Intracranial meningioma malignant; Intracranial tumour haemorrhage; Intraductal papillary breast neoplasm; Intraductal papillary mucinous neoplasm; Intraductal papillary-mucinous carcinoma of pancreas; Intraductal proliferative breast lesion; Intraocular melanoma; Intraperitoneal hyperthermic chemotherapy; Intratumoural aneurysm; Invasive breast carcinoma; Invasive ductal breast carcinoma; Invasive lobular breast carcinoma; Invasive papillary breast carcinoma; Iris melanoma; Iris neoplasm; Jejunectomy; Juvenile chronic myelomonocytic leukaemia; Kaposi's sarcoma; Kaposi's sarcoma AIDS related; Kaposi's sarcoma classical type; Keratinising squamous cell carcinoma of nasopharynx; Keratoacanthoma; Lacrimal duct neoplasm; Langerhans' cell histiocytosis; Large cell lung cancer; Large cell lung cancer metastatic; Large cell lung cancer recurrent; Large cell lung cancer stage 0; Large cell lung cancer stage I; Large cell lung cancer stage II; Large cell lung cancer stage III; Large cell lung cancer stage IV; Large granular lymphocytosis; Large intestinal polypectomy; Large intestine polyp; Laryngeal cancer; Laryngeal cancer metastatic; Laryngeal cancer recurrent; Laryngeal cancer stage 0; Laryngeal cancer stage I; Laryngeal cancer stage II; Laryngeal cancer stage III; Laryngeal cancer stage IV; Laryngeal dysplasia; Laryngeal leukoplakia; Laryngeal neoplasm; Laryngeal polypectomy; Laryngeal squamous cell carcinoma; Laryngopharyngectomy; Laser brain ablation; Leiomyosarcoma; Leiomyosarcoma metastatic; Leiomyosarcoma recurrent; Lentigo maligna; Lentigo maligna recurrent; Lentigo maligna stage I; Lentigo maligna stage II; Lentigo maligna stage III; Lentigo maligna stage IV; Leukaemia; Leukaemia basophilic; Leukaemia cutis; Leukaemia granulocytic; Leukaemia in remission; Leukaemia monocytic; Leukaemia recurrent; Leukaemic cardiac infiltration; Leukaemic infiltration; Leukaemic infiltration extramedullary; Leukaemic infiltration gingiva; Leukaemic infiltration hepatic; Leukaemic infiltration ovary; Leukaemic infiltration pulmonary; Leukaemic infiltration renal; Leukaemic lymphoma; Leukaemic retinopathy; Leukoplakia; Leukoplakia oesophageal; Leukoplakia of penis; Leukoplakia oral; Leukostasis syndrome; Leydig cell tumour of the testis; Linitis plastica; Lip and/or oral cavity cancer; Lip and/or oral cavity cancer recurrent; Lip and/or oral cavity cancer stage 0; Lip and/or oral cavity cancer stage I; Lip and/or oral cavity cancer stage II; Lip and/or oral cavity cancer stage III; Lip and/or oral cavity cancer stage IV; Lip neoplasm; Lip neoplasm malignant stage unspecified; Lip squamous cell carcinoma; Liposarcoma; Liposarcoma metastatic; Liposarcoma recurrent; Liver ablation; Liver carcinoma ruptured; Liver scan abnormal; Lobular breast carcinoma in situ; Lung adenocarcinoma; Lung adenocarcinoma metastatic; Lung adenocarcinoma recurrent; Lung adenocarcinoma stage 0; Lung adenocarcinoma stage I; Lung adenocarcinoma stage II; Lung adenocarcinoma stage III; Lung adenocarcinoma stage IV; Lung cancer metastatic; Lung carcinoma cell type unspecified recurrent; Lung carcinoma cell type unspecified stage 0; Lung carcinoma cell type unspecified stage I; Lung carcinoma cell type unspecified stage II; Lung carcinoma cell type unspecified stage III; Lung carcinoma cell type unspecified stage IV; Lung infiltration malignant; Lung lobectomy; Lung neoplasm; Lung neoplasm malignant; Lung neoplasm surgery; Lung squamous cell carcinoma metastatic; Lung squamous cell carcinoma recurrent; Lung squamous cell carcinoma stage 0; Lung squamous cell carcinoma stage I; Lung squamous cell carcinoma stage II; Lung squamous cell carcinoma stage III; Lung squamous cell carcinoma stage IV; Lymph nodes scan abnormal; Lymphadenectomy; Lymphangiosarcoma; Lymphangiosis carcinomatosa; Lymphatic mapping; Lymphatic system neoplasm; Lymphocyte adoptive therapy; Lymphocyte morphology abnormal; Lymphocytic leukaemia; Lymphocytic lymphoma; Lymphoid leukaemia (in remission); Lymphoid tissue operation; Lymphoma; Lymphoma AIDS related; Lymphoma cutis; Lymphoma operation; Lymphoma transformation; Lymphoplasmacytoid lymphoma/immunocytoma; Lymphoplasmacytoid lymphoma/immunocytoma recurrent; Lymphoplasmacytoid lymphoma/immunocytoma refractory; Lymphoplasmacytoid lymphoma/immunocytoma stage I; Lymphoplasmacytoid lymphoma/immunocytoma stage II; Lymphoplasmacytoid lymphoma/immunocytoma stage III; Lymphoplasmacytoid lymphoma/immunocytoma stage IV; Lymphoproliferative disorder; Lymphoproliferative disorder in remission; Male reproductive tract neoplasm; Malignant anorectal neoplasm; Malignant ascites; Malignant blue naevus; Malignant bowel obstruction; Malignant connective tissue neoplasm; Malignant cranial nerve neoplasm; Malignant dysphagia; Malignant exophthalmos; Malignant fibrous histiocytoma; Malignant fibrous histiocytoma metastatic; Malignant fibrous histiocytoma of bone; Malignant fibrous histiocytoma recurrent; Malignant genitourinary tract neoplasm; Malignant giant cell fibrous histiocytoma; Malignant glioma; Malignant haemangiopericytoma; Malignant haemangiopericytoma metastatic; Malignant haemangiopericytoma recurrent; Malignant histiocytosis; Malignant hydatidiform mole; Malignant lymphoid neoplasm; Malignant lymphoma unclassifiable high grade; Malignant lymphoma unclassifiable low grade; Malignant mast cell neoplasm; Malignant mediastinal neoplasm; Malignant melanoma; Malignant melanoma in situ; Malignant melanoma of eyelid; Malignant melanoma of sites other than skin; Malignant melanoma stage I; Malignant melanoma stage II; Malignant melanoma stage III; Malignant melanoma stage IV; Malignant

meningioma metastatic; Malignant mesenchymoma; Malignant mesenchymoma metastatic; Malignant mesenchymoma recurrent; Malignant mesenteric neoplasm; Malignant middle ear neoplasm; Malignant muscle neoplasm; Malignant neoplasm of ampulla of Vater; Malignant neoplasm of auricular cartilage; Malignant neoplasm of choroid; Malignant neoplasm of conjunctiva; Malignant neoplasm of cornea; Malignant neoplasm of eye; Malignant neoplasm of eyelid; Malignant neoplasm of islets of Langerhans; Malignant neoplasm of lacrimal duct; Malignant neoplasm of lacrimal gland; Malignant neoplasm of orbit; Malignant neoplasm of paraurethral glands; Malignant neoplasm of placenta; Malignant neoplasm of pleura; Malignant neoplasm of pleura metastatic; Malignant neoplasm of renal pelvis; Malignant neoplasm of retina; Malignant neoplasm of seminal vesicle; Malignant neoplasm of spermatic cord; Malignant neoplasm of spinal cord; Malignant neoplasm of thorax; Malignant neoplasm of thymus; Malignant neoplasm of unknown primary site; Malignant neoplasm of uterine adnexa; Malignant neoplasm papilla of Vater; Malignant neoplasm progression; Malignant nervous system neoplasm; Malignant nipple neoplasm; Malignant nipple neoplasm female; Malignant nipple neoplasm male; Malignant oligodendroglioma; Malignant ovarian cyst; Malignant palate neoplasm; Malignant pericardial neoplasm; Malignant peritoneal neoplasm; Malignant pituitary tumour; Malignant pleural effusion; Malignant respiratory tract neoplasm; Malignant splenic neoplasm; Malignant sweat gland neoplasm; Malignant transformation; Malignant urinary tract neoplasm; Mantle cell lymphoma; Mantle cell lymphoma recurrent; Mantle cell lymphoma refractory; Mantle cell lymphoma stage I; Mantle cell lymphoma stage II; Mantle cell lymphoma stage III; Mantle cell lymphoma stage IV; Marginal zone lymphoma; Marginal zone lymphoma recurrent; Marginal zone lymphoma refractory; Marginal zone lymphoma stage I; Marginal zone lymphoma stage II; Marginal zone lymphoma stage III; Marginal zone lymphoma stage IV; Marjolin's ulcer; Mastectomy; Mastocytic leukaemia; Mastoidectomy; Mature B-cell type acute leukaemia; Maxillofacial sinus neoplasm; Mediastinal biopsy abnormal; Mediastinum neoplasm; Medullary carcinoma of breast; Medullary thyroid cancer; Medulloblastoma; Medulloblastoma recurrent; Megaloblasts increased; Meigs' syndrome; Melanoma recurrent; Melanoplakia oral; Meningeal neoplasm; Meningioma malignant; Mesenteric neoplasm; Mesothelioma; Mesothelioma malignant; Mesothelioma malignant recurrent; Metaplastic breast carcinoma; Metastases to abdominal cavity; Metastases to abdominal wall; Metastases to adrenals; Metastases to biliary tract; Metastases to bladder; Metastases to bone; Metastases to bone marrow; Metastases to breast; Metastases to central nervous system; Metastases to chest wall; Metastases to diaphragm; Metastases to Eustachian tube; Metastases to eye; Metastases to fallopian tube; Metastases to gallbladder; Metastases to gastrointestinal tract; Metastases to heart; Metastases to kidney; Metastases to large intestine; Metastases to larynx; Metastases to liver; Metastases to lung; Metastases to lymph nodes; Metastases to meninges; Metastases to mouth; Metastases to muscle; Metastases to nasal sinuses; Metastases to neck; Metastases to nervous system; Metastases to oesophagus; Metastases to ovary; Metastases to pancreas; Metastases to pelvis; Metastases to penis; Metastases to perineum; Metastases to peripheral nervous system; Metastases to peripheral vascular system; Metastases to peritoneum; Metastases to pharynx; Metastases to pituitary gland; Metastases to placenta; Metastases to pleura; Metastases to prostate; Metastases to rectum; Metastases to reproductive organ; Metastases to retroperitoneum; Metastases to salivary gland; Metastases to skin; Metastases to small intestine; Metastases to soft tissue; Metastases to spine; Metastases to spleen; Metastases to stomach; Metastases to testicle; Metastases to the mediastinum; Metastases to the respiratory system; Metastases to thorax; Metastases to thyroid; Metastases to tonsils; Metastases to trachea; Metastases to urinary tract; Metastases to uterus; Metastases to vagina; Metastasis; Metastatic bronchial carcinoma; Metastatic carcinoid tumour; Metastatic carcinoma of the bladder; Metastatic choriocarcinoma; Metastatic gastric cancer; Metastatic glioma; Metastatic glucagonoma; Metastatic lymphoma; Metastatic malignant melanoma; Metastatic neoplasm; Metastatic nervous system neoplasm; Metastatic ocular melanoma; Metastatic pulmonary embolism; Metastatic renal cell carcinoma; Metastatic salivary gland cancer; Metastatic squamous cell carcinoma; Metastatic uterine cancer; Micrographic skin surgery; Mismatch repair cancer syndrome; Mixed adenoneuroendocrine carcinoma; Mixed hepatocellular cholangiocarcinoma; Mixed-type liposarcoma; Modified radical mastectomy; Monoclonal gammopathy; Monocytic leukaemia in remission; Mucinous adenocarcinoma of appendix; Mucinous breast carcinoma; Mucinous cystadenocarcinoma of pancreas; Mucinous cystadenocarcinoma ovary; Mucinous endometrial carcinoma; Mucoepidermoid carcinoma; Mucoepidermoid carcinoma of salivary gland; Mueller's mixed tumour; Multiple gated acquisition scan abnormal; Muscle neoplasm; Musculoskeletal cancer; Myasthenic syndrome; Mycosis fungoides; Mycosis fungoides recurrent; Mycosis fungoides refractory; Mycosis fungoides stage I; Mycosis fungoides stage II; Mycosis fungoides stage III; Mycosis fungoides stage IV; Myectomy; Myeloblastoma; Myelodysplastic syndrome; Myelodysplastic syndrome transformation; Myelodysplastic syndrome unclassifiable; Myelofibrosis; Myeloid leukaemia; Myeloid leukaemia in remission; Myeloid metaplasia; Myeloma cast nephropathy; Myeloproliferative neoplasm; Myxofibrosarcoma; Myxoid liposarcoma; Nasal cavity cancer; Nasal neoplasm; Nasal sinus cancer; Nasopharyngeal cancer; Nasopharyngeal cancer recurrent; Nasopharyngeal cancer stage 0; Nasopharyngeal cancer stage I; Nasopharyngeal cancer stage II; Nasopharyngeal cancer stage III; Nasopharyngeal cancer stage IV; Natural killer-cell leukaemia;

Natural killer-cell lymphoblastic lymphoma; Necrolytic migratory erythema; Needle biopsy site unspecified abnormal; Neoadjuvant therapy; Neobladder surgery; Neonatal leukaemia; Neonatal neuroblastoma; Neoplasm; Neoplasm malignant; Neoplasm of appendix; Neoplasm of cornea unspecified malignancy; Neoplasm of orbit; Neoplasm of thymus; Neoplasm progression; Neoplasm prostate; Neoplasm recurrence; Neoplasm skin; Neoplasm swelling; Nephrectomy; Nephroblastoma; Nephroureterectomy; Nervous system neoplasm; Nervous system neoplasm surgery; Neuroblastoma; Neuroblastoma recurrent; Neuroectodermal neoplasm; Neuroendocrine breast tumour; Neuroendocrine carcinoma; Neuroendocrine carcinoma metastatic; Neuroendocrine carcinoma of the skin; Neuroendocrine tumour; Neuroendoscopy; Neurofibrosarcoma; Neurofibrosarcoma metastatic; Neurofibrosarcoma recurrent; Neuromyotonia; Neurotensinoma; Nipple neoplasm; Nipple resection; Nodal marginal zone B-cell lymphoma; Nodal marginal zone B-cell lymphoma recurrent; Nodal marginal zone B-cell lymphoma refractory; Nodal marginal zone B-cell lymphoma stage I; Nodal marginal zone B-cell lymphoma stage II; Nodal marginal zone B-cell lymphoma stage III; Nodal marginal zone B-cell lymphoma stage IV; Nodular melanoma; Nongerminomatous germ cell tumour of the CNS; Non-Hodgkin's lymphoma; Non-Hodgkin's lymphoma metastatic; Non-Hodgkin's lymphoma recurrent; Non-Hodgkin's lymphoma refractory; Non-Hodgkin's lymphoma stage I; Non-Hodgkin's lymphoma stage II; Non-Hodgkin's lymphoma stage III; Non-Hodgkin's lymphoma stage IV; Non-Hodgkin's lymphoma transformed recurrent; Non-Hodgkin's lymphoma unspecified histology aggressive; Non-Hodgkin's lymphoma unspecified histology aggressive recurrent; Non-Hodgkin's lymphoma unspecified histology aggressive refractory; Non-Hodgkin's lymphoma unspecified histology aggressive stage I; Non-Hodgkin's lymphoma unspecified histology aggressive stage II; Non-Hodgkin's lymphoma unspecified histology aggressive stage III; Non-Hodgkin's lymphoma unspecified histology aggressive stage IV; Non-Hodgkin's lymphoma unspecified histology indolent; Non-Hodgkin's lymphoma unspecified histology indolent stage I; Non-Hodgkin's lymphoma unspecified histology indolent stage II; Non-Hodgkin's lymphoma unspecified histology indolent stage III; Non-Hodgkin's lymphoma unspecified histology indolent stage IV; Nonkeratinising carcinoma of nasopharynx; Non-renal cell carcinoma of kidney; Non-secretory adenoma of pituitary; Non-small cell lung cancer; Non-small cell lung cancer metastatic; Non-small cell lung cancer recurrent; Non-small cell lung cancer stage 0; Non-small cell lung cancer stage I; Non-small cell lung cancer stage II; Non-small cell lung cancer stage III; Non-small cell lung cancer stage IIIA; Non-small cell lung cancer stage IIIB; Non-small cell lung cancer stage IV; Ocular cancer metastatic; Ocular haemangiopericytoma; Ocular lymphoma; Ocular neoplasm; Oesophageal adenocarcinoma; Oesophageal adenocarcinoma metastatic; Oesophageal adenocarcinoma recurrent; Oesophageal adenocarcinoma stage 0; Oesophageal adenocarcinoma stage I; Oesophageal adenocarcinoma stage II; Oesophageal adenocarcinoma stage III; Oesophageal adenocarcinoma stage IV; Oesophageal cancer metastatic; Oesophageal carcinoma; Oesophageal carcinoma recurrent; Oesophageal carcinoma stage 0; Oesophageal dysplasia; Oesophageal neoplasm; Oesophageal polyp; Oesophageal squamous cell carcinoma; Oesophageal squamous cell carcinoma metastatic; Oesophageal squamous cell carcinoma recurrent; Oesophageal squamous cell carcinoma stage 0; Oesophageal squamous cell carcinoma stage I; Oesophageal squamous cell carcinoma stage II; Oesophageal squamous cell carcinoma stage III; Oesophageal squamous cell carcinoma stage IV; Oesophagectomy; Oesophagogastrectomy; Oestrogen receptor assay positive; Oestrogen receptor positive breast cancer; Oligoastrocytoma; Oligodendroglioma; Omentectomy; Oncogenic osteomalacia; Oncologic complication; Oophorectomy; Oophorectomy bilateral; Optic glioma; Optic nerve neoplasm; Oral cavity cancer metastatic; Oral cavity neoplasm surgery; Oral neoplasm; Oral polypectomy; Orchidectomy; Oropharyngeal cancer; Oropharyngeal cancer recurrent; Oropharyngeal cancer stage 0; Oropharyngeal cancer stage I; Oropharyngeal cancer stage II; Oropharyngeal cancer stage III; Oropharyngeal cancer stage IV; Oropharyngeal lymphoepithelioma; Oropharyngeal neoplasm; Oropharyngeal squamous cell carcinoma; Ostectomy; Osteosarcoma; Osteosarcoma metastatic; Osteosarcoma recurrent; Otic cancer metastatic; Ovarian cancer; Ovarian cancer metastatic; Ovarian cancer recurrent; Ovarian cancer stage I; Ovarian cancer stage II; Ovarian cancer stage III; Ovarian cancer stage IV; Ovarian clear cell carcinoma; Ovarian dysgerminoma stage I; Ovarian dysgerminoma stage II; Ovarian dysgerminoma stage III; Ovarian dysgerminoma stage IV; Ovarian dysgerminoma stage unspecified; Ovarian embryonal carcinoma; Ovarian endometrioid carcinoma; Ovarian epithelial cancer; Ovarian epithelial cancer metastatic; Ovarian epithelial cancer recurrent; Ovarian epithelial cancer stage I; Ovarian epithelial cancer stage II; Ovarian epithelial cancer stage III; Ovarian epithelial cancer stage IV; Ovarian germ cell cancer; Ovarian germ cell cancer stage I; Ovarian germ cell cancer stage II; Ovarian germ cell cancer stage III; Ovarian germ cell cancer stage IV; Ovarian germ cell choriocarcinoma; Ovarian germ cell choriocarcinoma stage I; Ovarian germ cell choriocarcinoma stage II; Ovarian germ cell choriocarcinoma stage III; Ovarian germ cell choriocarcinoma stage IV; Ovarian germ cell embryonal carcinoma stage I; Ovarian germ cell embryonal carcinoma stage II; Ovarian germ cell embryonal carcinoma stage III; Ovarian germ cell embryonal carcinoma stage IV; Ovarian germ cell endodermal sinus tumour; Ovarian germ cell endodermal sinus tumour stage I; Ovarian germ cell endodermal sinus tumour stage II; Ovarian germ cell endodermal sinus tumour stage III; Ovarian germ cell endodermal sinus tumour stage IV; Ovarian germ cell polyembryoma; Ovarian germ cell polyembryoma stage I; Ovarian germ cell polyembryoma stage II; Ovarian germ

cell polyembryoma stage III; Ovarian germ cell polyembryoma stage IV; Ovarian germ cell teratoma; Ovarian germ cell teratoma stage I; Ovarian germ cell teratoma stage II; Ovarian germ cell teratoma stage III; Ovarian germ cell teratoma stage IV; Ovarian germ cell tumour; Ovarian germ cell tumour mixed; Ovarian granulosa cell tumour; Ovarian granulosa-theca cell tumour; Ovarian low malignant potential tumour; Ovarian neoplasm; Ovarian Sertoli-Leydig cell tumour; Ovarian stromal cancer; Ovarian stromal hyperplasia; Ovarian theca cell tumour; Paget's disease of nipple; Paget's disease of penis; Paget's disease of the vulva; Palliative care; Pancoast's tumour; Pancreastatin abnormal; Pancreastatin increased; Pancreatectomy; Pancreatic carcinoma; Pancreatic carcinoma metastatic; Pancreatic carcinoma recurrent; Pancreatic carcinoma stage 0; Pancreatic carcinoma stage I; Pancreatic carcinoma stage II; Pancreatic carcinoma stage III; Pancreatic carcinoma stage IV; Pancreatic neoplasm; Pancreatic neuroendocrine tumour; Pancreatic neuroendocrine tumour metastatic; Pancreatic sarcoma; Pancreaticoduodenectomy; Pancreaticosplenectomy; Pancreatoblastoma; Papillary serous endometrial carcinoma; Papillary thyroid cancer; Paraganglion neoplasm; Paraganglion neoplasm malignant; Paranasal biopsy abnormal; Paranasal sinus and nasal cavity malignant neoplasm; Paranasal sinus and nasal cavity malignant neoplasm recurrent; Paranasal sinus and nasal cavity malignant neoplasm stage 0; Paranasal sinus and nasal cavity malignant neoplasm stage I; Paranasal sinus and nasal cavity malignant neoplasm stage II; Paranasal sinus and nasal cavity malignant neoplasm stage III; Paranasal sinus and nasal cavity malignant neoplasm stage IV; Paranasal sinus neoplasm; Paraneoplastic arthritis; Paraneoplastic dermatomyositis; Paraneoplastic encephalomyelitis; Paraneoplastic glomerulonephritis; Paraneoplastic nephrotic syndrome; Paraneoplastic neurological syndrome; Paraneoplastic pemphigus; Paraneoplastic pleural effusion; Paraneoplastic rash; Paraneoplastic syndrome; Parapsoriasis; Parathyroid scan abnormal; Parathyroid tumour; Parathyroid tumour malignant; Parathyroidectomy; Parotidectomy; Pelvic neoplasm; Penile cancer; Penile dysplasia; Penile neoplasm; Penile operation; Penile squamous cell carcinoma; Penile wart; Penile warts excision; Penis carcinoma metastatic; Penis carcinoma recurrent; Penis carcinoma stage I; Penis carcinoma stage II; Penis carcinoma stage III; Penis carcinoma stage IV; Pepsinogen test positive; Percutaneous ethanol injection therapy; Pericardial effusion malignant; Pericardial mesothelioma malignant; Pericardial mesothelioma malignant recurrent; Pericardial neoplasm; Pericarditis malignant; Peripheral nerve sheath tumour malignant; Peripheral nervous system neoplasm; Peripheral neuroepithelioma of bone; Peripheral neuroepithelioma of bone metastatic; Peripheral neuroepithelioma of bone recurrent; Peripheral neuroepithelioma of soft tissue; Peripheral primitive neuroectodermal bone tumour; Peripheral primitive neuroectodermal tumour of soft tissue; Peripheral T-cell lymphoma unspecified; Peripheral T-cell lymphoma unspecified recurrent; Peripheral T-cell lymphoma unspecified refractory; Peripheral T-cell lymphoma unspecified stage I; Peripheral T-cell lymphoma unspecified stage II; Peripheral T-cell lymphoma unspecified stage III; Peripheral T-cell lymphoma unspecified stage IV; Peritoneal carcinoma metastatic; Peritoneal fluid protein increased; Peritoneal mesothelioma malignant; Peritoneal mesothelioma malignant recurrent; Peritoneal neoplasm; Peritoneal sarcoma; Peritonectomy; Peritumoural oedema; Phaeochromocytoma; Phaeochromocytoma crisis; Phaeochromocytoma excision; Phaeochromocytoma malignant; Pharyngeal cancer; Pharyngeal cancer metastatic; Pharyngeal cancer recurrent; Pharyngeal cancer stage 0; Pharyngeal cancer stage I; Pharyngeal cancer stage II; Pharyngeal cancer stage III; Pharyngeal cancer stage IV; Pharyngeal leukoplakia; Pharyngeal neoplasm; Pharyngectomy; Philadelphia chromosome positive; Photodynamic diagnostic procedure; Photon radiation therapy; Photon radiation therapy to bladder; Photon radiation therapy to blood; Photon radiation therapy to bone; Photon radiation therapy to brain; Photon radiation therapy to breast; Photon radiation therapy to colon; Photon radiation therapy to ear, nose, or throat; Photon radiation therapy to liver; Photon radiation therapy to lung; Photon radiation therapy to pancreas; Photon radiation therapy to pleura; Photon radiation therapy to prostate; Photon radiation therapy to skin; Photon radiation therapy to soft tissue; Photon radiation therapy to thyroid; Photon radiation therapy to uterus; Phyllodes tumour; Pilomatrix carcinoma; Pineal germinoma; Pineal neoplasm; Pineal parenchymal neoplasm malignant; Pinealoblastoma; Pinealoma; Pituitary cancer metastatic; Pituitary gland radiotherapy; Pituitary neoplasm malignant recurrent; Pituitary tumour; Pituitary tumour recurrent; Placental neoplasm; Plasma cell leukaemia; Plasma cell leukaemia in remission; Plasma cell myeloma; Plasma cell myeloma in remission; Plasma cell myeloma recurrent; Plasmablastic lymphoma; Plasmacytoma; Pleomorphic adenoma; Pleomorphic liposarcoma; Pleomorphic malignant fibrous histiocytoma; Pleural mesothelioma; Pleural mesothelioma malignant; Pleural mesothelioma malignant recurrent; Pleural neoplasm; Pleural sarcoma; Pleurectomy; PML/RAR alpha expression; Pneumonectomy; POEMS syndrome; Polycythaemia vera; Polyneuropathy in malignant disease; Poorly differentiated thyroid carcinoma; Porocarcinoma; Portal vein embolisation; Post transplant lymphoproliferative disorder; Postcricoid cancer; Posterior fossa syndrome; Postmastectomy lymphoedema syndrome; Precancerous mucosal lesion; Precancerous skin lesion; Precursor B-lymphoblastic lymphoma; Precursor B-lymphoblastic lymphoma recurrent; Precursor B-lymphoblastic lymphoma refractory; Precursor B-lymphoblastic lymphoma stage I; Precursor B-lymphoblastic lymphoma stage II; Precursor B-lymphoblastic lymphoma stage III; Precursor B-lymphoblastic lymphoma stage IV; Precursor T-lymphoblastic lymphoma/leukaemia; Precursor T-lymphoblastic lymphoma/leukaemia recurrent; Precursor T-lymphoblastic

lymphoma/leukaemia refractory; Precursor T-lymphoblastic lymphoma/leukaemia stage I; Precursor T-lymphoblastic lymphoma/leukaemia stage II; Precursor T-lymphoblastic lymphoma/leukaemia stage III; Precursor T-lymphoblastic lymphoma/leukaemia stage IV; Primary cardiac lymphoma; Primary effusion lymphoma; Primary mediastinal large B-cell lymphoma; Primary mediastinal large B-cell lymphoma recurrent; Primary mediastinal large B-cell lymphoma refractory; Primary mediastinal large B-cell lymphoma stage I; Primary mediastinal large B-cell lymphoma stage II; Primary mediastinal large B-cell lymphoma stage III; Primary mediastinal large B-cell lymphoma stage IV; Primary myelofibrosis; Primitive neuroectodermal tumour; Primitive neuroectodermal tumour metastatic; Proctectomy; Proctocolectomy; Progesterone receptor assay positive; Prolactin-producing pituitary tumour; Prolymphocytic leukaemia; Prophylactic chemotherapy; Prostate ablation; Prostate cancer; Prostate cancer metastatic; Prostate cancer recurrent; Prostate cancer stage 0; Prostate cancer stage I; Prostate cancer stage II; Prostate cancer stage III; Prostate cancer stage IV; Prostate cryoablation; Prostate interstitial hyperthermia therapy; Prostatectomy; Prostatic dysplasia; Prostatic specific antigen abnormal; Prostatic specific antigen increased; Pseudoachalasia; Pseudomyxoma peritonei; Pseudosarcoma; Pulmonary resection; Pylorectomy; Pyoderma gangrenosum; Queyrat erythroplasia; Radiation therapy to ear, nose, or throat; Radical cystectomy; Radical hysterectomy; Radical mastectomy; Radical neck dissection; Radical prostatectomy; Radioactive iodine therapy; Radioembolisation; Radiofrequency ablation of oesophagus; Radioisotope scan abnormal; Radiosensitisation therapy; Radiotherapy; Radiotherapy to abdomen; Radiotherapy to adrenal gland; Radiotherapy to blood; Radiotherapy to bone; Radiotherapy to brain; Radiotherapy to breast; Radiotherapy to colon; Radiotherapy to ear; Radiotherapy to eye; Radiotherapy to gallbladder; Radiotherapy to gastrointestinal tract; Radiotherapy to head and neck; Radiotherapy to joint; Radiotherapy to kidney; Radiotherapy to liver; Radiotherapy to lung; Radiotherapy to lymph nodes; Radiotherapy to mediastinum; Radiotherapy to nose; Radiotherapy to oesophagus; Radiotherapy to oral cavity; Radiotherapy to ovary; Radiotherapy to pancreas; Radiotherapy to pleura; Radiotherapy to prostate; Radiotherapy to rectum; Radiotherapy to skin; Radiotherapy to soft tissue; Radiotherapy to spleen; Radiotherapy to stomach; Radiotherapy to throat; Radiotherapy to thymus; Radiotherapy to thyroid; Radiotherapy to urinary bladder; Radiotherapy to uterus; Radiotherapy to vagina; Rectal adenocarcinoma; Rectal cancer; Rectal cancer metastatic; Rectal cancer recurrent; Rectal cancer stage 0; Rectal cancer stage I; Rectal cancer stage II; Rectal cancer stage III; Rectal cancer stage IV; Rectal neoplasm; Rectal polyp; Rectal polypectomy; Rectosigmoid cancer; Rectosigmoid cancer metastatic; Rectosigmoid cancer recurrent; Rectosigmoid cancer stage 0; Rectosigmoid cancer stage I; Rectosigmoid cancer stage II; Rectosigmoid cancer stage III; Rectosigmoid cancer stage IV; Recurrent cancer; Refractory anaemia with an excess of blasts; Refractory anaemia with ringed sideroblasts; Refractory cancer; Refractory cytopenia with multilineage dysplasia; Refractory cytopenia with unilineage dysplasia; Regional chemotherapy; Renal cancer; Renal cancer metastatic; Renal cancer recurrent; Renal cancer stage I; Renal cancer stage II; Renal cancer stage III; Renal cancer stage IV; Renal cell carcinoma; Renal cell carcinoma recurrent; Renal cell carcinoma stage I; Renal cell carcinoma stage II; Renal cell carcinoma stage III; Renal cell carcinoma stage IV; Renal neoplasm; Renal scan abnormal; Renal tumour excision; Respiratory tract carcinoma in situ; Respiratory tract neoplasm; Retinal melanoma; Retinal neoplasm; Retinal tumour excision; Retinoblastoma; Retro-orbital neoplasm; Retroperitoneal cancer; Retroperitoneal neoplasm; Retroperitoneal neoplasm metastatic; Retro-pubic prostatectomy; Rhabdoid tumour; Rhabdoid tumour of the kidney; Rhabdomyosarcoma; Rhabdomyosarcoma recurrent; Richter's syndrome; Round cell liposarcoma; Salivary bypass tube insertion; Salivary gland cancer; Salivary gland cancer recurrent; Salivary gland cancer stage 0; Salivary gland cancer stage I; Salivary gland cancer stage II; Salivary gland cancer stage III; Salivary gland cancer stage IV; Salivary gland neoplasm; Salivary gland resection; Salivary gland scan abnormal; Salpingectomy; Salpingo-oophorectomy; Salpingo-oophorectomy bilateral; Salpingo-oophorectomy unilateral; Sarcoma; Sarcoma excision; Sarcoma metastatic; Sarcoma of skin; Sarcoma uterus; Sarcomatoid mesothelioma; Sarcomatosis; Scan abdomen abnormal; Scan abnormal; Scan adrenal gland abnormal; Scan bone marrow abnormal; Scan gallium abnormal; Scan myocardial perfusion abnormal; Scan with contrast abnormal; Scrotal cancer; Sebaceous carcinoma; Sebaceous naevus; Second primary malignancy; Secondary cerebellar degeneration; Secretory adenoma of pituitary; Seminoma; Serous cystadenocarcinoma of pancreas; Serous cystadenocarcinoma ovary; Sertoli cell testicular tumour; Sezary cells increased; Sigmoidectomy; Signet-ring cell carcinoma; Simple mastectomy; Sinus cancer metastatic; Skin angiosarcoma; Skin cancer; Skin cancer metastatic; Skin cryotherapy; Skin neoplasm bleeding; Skin neoplasm excision; Skin squamous cell carcinoma metastatic; Small cell carcinoma; Small cell carcinoma of the cervix; Small cell lung cancer; Small cell lung cancer extensive stage; Small cell lung cancer limited stage; Small cell lung cancer metastatic; Small cell lung cancer recurrent; Small intestinal polypectomy; Small intestinal resection; Small intestine adenocarcinoma; Small intestine carcinoma; Small intestine carcinoma metastatic; Small intestine carcinoma recurrent; Small intestine carcinoma stage 0; Small intestine carcinoma stage I; Small intestine carcinoma stage II; Small intestine carcinoma stage III; Small intestine carcinoma stage IV; Small intestine leiomyosarcoma; Smooth muscle cell neoplasm; Soft tissue neoplasm; Soft tissue sarcoma; Solid pseudopapillary tumour of the pancreas; Somatostatin receptor scan

abnormal; Somatostatinoma; Spermatocytic seminoma; Spinal cord neoplasm; Spinal meningioma malignant; Spindle cell sarcoma; Spitzoid melanoma; Spleen scan abnormal; Splenectomy; Splenic marginal zone lymphoma; Splenic marginal zone lymphoma recurrent; Splenic marginal zone lymphoma refractory; Splenic marginal zone lymphoma stage I; Splenic marginal zone lymphoma stage II; Splenic marginal zone lymphoma stage III; Splenic marginal zone lymphoma stage IV; Splenic neoplasm malignancy unspecified; Squamous cell carcinoma; Squamous cell carcinoma of head and neck; Squamous cell carcinoma of lung; Squamous cell carcinoma of pharynx; Squamous cell carcinoma of skin; Squamous cell carcinoma of the cervix; Squamous cell carcinoma of the hypopharynx; Squamous cell carcinoma of the oral cavity; Squamous cell carcinoma of the tongue; Squamous cell carcinoma of the vagina; Squamous cell carcinoma of the vulva; Squamous endometrial carcinoma; Stauffer's syndrome; Stem cell transplant; Stewart-Treves syndrome; Stomach scan abnormal; Superficial spreading melanoma stage I; Superficial spreading melanoma stage II; Superficial spreading melanoma stage III; Superficial spreading melanoma stage IV; Superficial spreading melanoma stage unspecified; Superior vena cava occlusion; Superior vena cava syndrome; Suprapubic prostatectomy; Synovial sarcoma; Synovial sarcoma metastatic; Synovial sarcoma recurrent; Targeted cancer therapy; T-cell chronic lymphocytic leukaemia; T-cell lymphoma; T-cell lymphoma recurrent; T-cell lymphoma refractory; T-cell lymphoma stage I; T-cell lymphoma stage II; T-cell lymphoma stage III; T-cell lymphoma stage IV; T-cell prolymphocytic leukaemia; T-cell type acute leukaemia; T-cell unclassifiable lymphoma high grade; T-cell unclassifiable lymphoma low grade; Tendon neoplasm; Teratoma; Testicular cancer metastatic; Testicular choriocarcinoma; Testicular choriocarcinoma recurrent; Testicular choriocarcinoma stage I; Testicular choriocarcinoma stage II; Testicular choriocarcinoma stage III; Testicular embryonal carcinoma; Testicular embryonal carcinoma stage I; Testicular embryonal carcinoma stage II; Testicular embryonal carcinoma stage III; Testicular germ cell cancer; Testicular germ cell cancer metastatic; Testicular germ cell tumour; Testicular germ cell tumour mixed; Testicular germ cell tumour mixed stage I; Testicular germ cell tumour mixed stage II; Testicular germ cell tumour mixed stage III; Testicular leiomyosarcoma; Testicular malignant teratoma; Testicular malignant teratoma stage I; Testicular malignant teratoma stage II; Testicular malignant teratoma stage III; Testicular neoplasm; Testicular scan abnormal; Testicular seminoma (pure); Testicular seminoma (pure) stage I; Testicular seminoma (pure) stage II; Testicular seminoma (pure) stage III; Testicular yolk sac tumour; Testicular yolk sac tumour stage I; Testicular yolk sac tumour stage II; Testicular yolk sac tumour stage III; Testis cancer; Testis cancer recurrent; Throat cancer; Thymic cancer metastatic; Thymoma; Thymoma malignant; Thymoma malignant recurrent; Thyroid B-cell lymphoma; Thyroid cancer; Thyroid cancer metastatic; Thyroid cancer recurrent; Thyroid cancer stage 0; Thyroid cancer stage I; Thyroid cancer stage II; Thyroid cancer stage III; Thyroid cancer stage IV; Thyroid C-cell hyperplasia; Thyroid electron radiation therapy; Thyroid gland scan abnormal; Thyroid neoplasm; Thyroid stimulating hormone-producing pituitary tumour; Thyroidectomy; Tissue polypeptide antigen increased; Tongue cancer metastatic; Tongue cancer recurrent; Tongue carcinoma stage 0; Tongue carcinoma stage I; Tongue carcinoma stage II; Tongue carcinoma stage III; Tongue carcinoma stage IV; Tongue dysplasia; Tongue neoplasm; Tongue neoplasm malignant stage unspecified; Tonsil cancer; Tonsil cancer metastatic; Tonsillar neoplasm; Total adrenalectomy; Tracheal cancer; Tracheal neoplasm; Transcatheter arterial chemoembolisation; Transcranial electrical motor evoked potential monitoring abnormal; Transitional cell cancer of renal pelvis and ureter metastatic; Transitional cell cancer of the renal pelvis and ureter; Transitional cell cancer of the renal pelvis and ureter localised; Transitional cell cancer of the renal pelvis and ureter recurrent; Transitional cell cancer of the renal pelvis and ureter regional; Transitional cell carcinoma; Transitional cell carcinoma metastatic; Transitional cell carcinoma recurrent; Transitional cell carcinoma urethra; Transurethral bladder resection; Transurethral prostatectomy; Triple negative breast cancer; Trousseau's syndrome; Tubular breast carcinoma; Tumour associated fever; Tumour budding; Tumour cell mobilisation; Tumour compression; Tumour embolism; Tumour excision; Tumour exudation; Tumour fistulisation; Tumour flare; Tumour haemorrhage; Tumour invasion; Tumour lysis syndrome; Tumour marker abnormal; Tumour marker decreased; Tumour marker increased; Tumour necrosis; Tumour obstruction; Tumour of ampulla of Vater; Tumour pain; Tumour perforation; Tumour pruritus; Tumour pseudoprogression; Tumour rupture; Tumour thrombosis; Tumour treating fields therapy; Tumour ulceration; Tumour vaccine therapy; Ultrasound scan abnormal; Ultrasound scan vagina abnormal; Undifferentiated carcinoma of colon; Undifferentiated nasopharyngeal carcinoma; Undifferentiated sarcoma; Ureteral neoplasm; Ureteric cancer; Ureteric cancer local; Ureteric cancer metastatic; Ureteric cancer recurrent; Ureteric cancer regional; Urethral cancer; Urethral cancer metastatic; Urethral cancer recurrent; Urethral melanoma metastatic; Urethral neoplasm; Urethrectomy; Urinary bladder sarcoma; Urinary cystectomy; Urinary tract carcinoma in situ; Urinary tract neoplasm; Uterine cancer; Uterine carcinoma in situ; Uterine leiomyosarcoma; Uterine neoplasm; Uterine tumour excision; Uvulectomy; Vaginal adenocarcinoma; Vaginal cancer; Vaginal cancer metastatic; Vaginal cancer recurrent; Vaginal cancer stage 0; Vaginal cancer stage I; Vaginal cancer stage II; Vaginal cancer stage III; Vaginal cancer stage IVA; Vaginal cancer stage IVB; Vaginal dysplasia; Vaginal neoplasm; Vaginectomy; Vascular neoplasm; Vipoma; Vocal cord leukoplakia; Vocal cord neoplasm; Vocal cordectomy; Vulval cancer; Vulval cancer metastatic; Vulval cancer recurrent; Vulval cancer stage 0;

Vulval cancer stage I; Vulval cancer stage II; Vulval cancer stage III; Vulval cancer stage IV; Vulval neoplasm; Vulval operation; Vulval warts removal; Vulvar adenocarcinoma; Vulvar dysplasia; Vulvectomy; Vulvovaginal adenosis; Waldenstrom's macroglobulinaemia; Waldenstrom's macroglobulinaemia recurrent; Waldenstrom's macroglobulinaemia refractory; Waldenstrom's macroglobulinaemia stage I; Waldenstrom's macroglobulinaemia stage II; Waldenstrom's macroglobulinaemia stage III; Waldenstrom's macroglobulinaemia stage IV; X-ray therapy to bladder; X-ray therapy to blood; X-ray therapy to bone; X-ray therapy to brain; X-ray therapy to breast; X-ray therapy to colon; X-ray therapy to ear, nose, or throat; X-ray therapy to joint; X-ray therapy to liver; X-ray therapy to lung; X-ray therapy to pancreas; X-ray therapy to pleura; X-ray therapy to prostate; X-ray therapy to skin; X-ray therapy to soft tissue; X-ray therapy to thyroid; X-ray therapy to uterus; X-ray treatment; Yolk sac tumour site unspecified

Musculoskeletal and Soft Tissue Investigations

MedDRA PTs: Biopsy bone; Biopsy bone abnormal; Bone scan; Bone scan abnormal; X-ray limb; X-ray limb abnormal

Myopathy/Rhabdomyolysis

MedDRA PTs: Acute kidney injury; Acute prerenal failure; Aldolase; Aldolase abnormal; Aldolase increased; Anuria; Back pain; Biopsy muscle abnormal; Blood calcium decreased; Blood creatine abnormal; Blood creatine increased; Blood creatine phosphokinase; Blood creatine phosphokinase abnormal; Blood creatine phosphokinase increased; Blood creatine phosphokinase MM; Blood creatine phosphokinase MM increased; Blood creatinine abnormal; Blood creatinine increased; Chromaturia; Chronic kidney disease; Compartment syndrome; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatine urine; Creatine urine abnormal; Creatine urine increased; Diaphragm muscle weakness; Electromyogram abnormal; End stage renal disease; Flank pain; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Hypercreatinaemia; Hypocalcaemia; Inflammatory pain; Muscle disorder; Muscle enzyme; Muscle enzyme increased; Muscle fatigue; Muscle haemorrhage; Muscle injury; Muscle necrosis; Muscle rupture; Muscle spasms; Muscle spasticity; Muscular weakness; Musculoskeletal chest pain; Musculoskeletal discomfort; Musculoskeletal disorder; Musculoskeletal injury; Musculoskeletal pain; Musculoskeletal stiffness; Myalgia; Myalgia intercostal; Myoglobin blood; Myoglobin blood increased; Myoglobin blood present; Myoglobin urine; Myoglobin urine present; Myoglobinaemia; Myoglobinuria; Myopathy; Myopathy toxic; Myositis; Myositis-like syndrome; Necrotising myositis; Non-cardiac chest pain; Oliguria; Pain in extremity; Prerenal failure; Renal failure; Renal impairment; Renal tubular necrosis; Rhabdomyolysis; Skeletal muscle enzymes; Tendon discomfort

Relevant Clinical Laboratory Changes: Aldolase >3x ULN; creatinine kinase >3x ULN; creatine kinase >5x ULN; creatine kinase >10x ULN; creatine kinase >10x ULN + creatinine ≥0.5 mg/dL from baseline

Opportunistic Infections

MedDRA PTs: Abnormal precordial movement; Acute pulmonary histoplasmosis; Adrenal gland tuberculosis; Arthritis fungal; Atypical mycobacterial infection; Atypical mycobacterial lymphadenitis; Atypical mycobacterial pneumonia; Atypical mycobacterium pericarditis; Bacillary angiomatosis; Bartonellosis; Biliary tract infection cryptosporidial; Biliary tract infection fungal; Bone tuberculosis; Bovine tuberculosis; Bronchitis fungal; Candida osteomyelitis; Candida pneumonia; Candida sepsis; Cerebral fungal infection; Cerebral toxoplasmosis; Chronic pulmonary histoplasmosis; Coccidioides encephalitis; Coccidioidomycosis; Congenital tuberculosis; Conjunctivitis tuberculous; Cryptococcal cutaneous infection; Cryptococcal fungaemia; Cryptococcosis; Cryptosporidiosis infection; Cutaneous coccidioidomycosis; Cutaneous tuberculosis; Cytomegalovirus chorioretinitis; Cytomegalovirus colitis; Cytomegalovirus duodenitis; Cytomegalovirus enteritis; Cytomegalovirus enterocolitis; Cytomegalovirus gastritis; Cytomegalovirus gastroenteritis; Cytomegalovirus gastrointestinal infection; Cytomegalovirus hepatitis; Cytomegalovirus infection; Cytomegalovirus mononucleosis; Cytomegalovirus mucocutaneous ulcer; Cytomegalovirus myelomeningoradiculitis; Cytomegalovirus myocarditis; Cytomegalovirus oesophagitis; Cytomegalovirus pancreatitis; Cytomegalovirus pericarditis; Cytomegalovirus syndrome; Cytomegalovirus test positive; Cytomegalovirus urinary tract infection; Cytomegalovirus viraemia; Disseminated cryptococcosis; Disseminated cytomegaloviral infection; Disseminated tuberculosis; Ear tuberculosis; Encephalitis cytomegalovirus; Encephalitis fungal; Endocarditis candida; Endocarditis histoplasma; Enterocolitis fungal; Epididymitis tuberculous; Extrapulmonary tuberculosis; Eye infection toxoplasmal; Female genital tract tuberculosis; Fungal abscess central nervous system;

Fungal cystitis; Fungal endocarditis; Fungal oesophagitis; Fungal peritonitis; Fungal retinitis; Fungal rhinitis; Fungal sepsis; Gastritis fungal; Gastroenteritis cryptococcal; Gastroenteritis cryptosporidial; Gastrointestinal fungal infection; Hepatic candidiasis; Hepatic infection fungal; Hepatitis toxoplasmal; Herpes oesophagitis; Herpes sepsis; Herpes simplex hepatitis; Herpes simplex visceral; Herpes zoster cutaneous disseminated; Herpes zoster disseminated; Herpes zoster infection neurological; Histoplasmosis; Histoplasmosis cutaneous; Histoplasmosis disseminated; Isosporiasis; JC virus infection; Joint tuberculosis; Listeria encephalitis; Listeria sepsis; Listeriosis; Lower respiratory tract infection fungal; Lymph node tuberculosis; Lymphadenitis fungal; Male genital tract tuberculosis; Meningitis candida; Meningitis coccidioides; Meningitis cryptococcal; Meningitis fungal; Meningitis herpes; Meningitis histoplasma; Meningitis listeria; Meningitis toxoplasmal; Meningitis tuberculous; Mycobacterial infection; Mycobacterium abscessus infection; Mycobacterium avium complex immune restoration disease; Mycobacterium avium complex infection; Mycobacterium chelonae infection; Mycobacterium fortuitum infection; Mycobacterium kansasii infection; Mycobacterium marinum infection; Mycobacterium tuberculosis complex test positive; Mycobacterium ulcerans infection; Myocarditis toxoplasmal; Necrotising fasciitis fungal; Neurocryptococcosis; Oesophageal candidiasis; Oesophageal tuberculosis; Opportunistic infection; Osteomyelitis fungal; Pancreatitis fungal; Pericarditis fungal; Pericarditis histoplasma; Pericarditis tuberculous; Peritoneal tuberculosis; Pneumocystis jirovecii infection; Pneumocystis jirovecii pneumonia; Pneumonia cryptococcal; Pneumonia cytomegaloviral; Pneumonia fungal; Pneumonia toxoplasmal; Presumed ocular histoplasmosis syndrome; Progressive multifocal leukoencephalopathy; Prostatitis tuberculous; Pulmonary tuberculoma; Pulmonary tuberculosis; Pyelonephritis fungal; Renal tuberculosis; Retinitis histoplasma; Salmonella bacteraemia; Salmonella sepsis; Salpingitis tuberculous; Silicotuberculosis; Sinusitis fungal; Spleen tuberculosis; Splenic infection fungal; Systemic candida; Thyroid tuberculosis; Toxoplasmosis; Tuberculoma of central nervous system; Tuberculosis; Tuberculosis bladder; Tuberculosis gastrointestinal; Tuberculosis liver; Tuberculosis of central nervous system; Tuberculosis of eye; Tuberculosis of genitourinary system; Tuberculosis of intrathoracic lymph nodes; Tuberculosis of peripheral lymph nodes; Tuberculosis ureter; Tuberculous abscess central nervous system; Tuberculous laryngitis; Tuberculous pleurisy; Tuberculous tenosynovitis; Tubo-ovarian abscess

Osmotic Diuresis

MedDRA PTs: Dry mouth; Dry throat; Micturition disorder; Micturition urgency; Nocturia; Pollakiuria; Polydipsia; Polyuria; Thirst; Tongue dry; Urine output increased

Pancreatitis

MedDRA PTs: Abdominal compartment syndrome; Abdominal distension; Abdominal pain; Abdominal pain upper; Abdominal rebound tenderness; Abdominal rigidity; Abdominal tenderness; Abdominal X-ray; Acute abdomen; Amylase abnormal; Amylase creatinine clearance ratio abnormal; Amylase increased; Ascites; Autoimmune pancreatitis; Bilirubin conjugated abnormal; Blood bilirubin increased; Blood trypsin increased; Computerised tomogram abdomen; Computerised tomogram abdomen abnormal; Cullen's sign; Cytomegalovirus pancreatitis; Endocrine pancreatic disorder; Endoscopic retrograde cholangiopancreatography; Endoscopic retrograde cholangiopancreatography abnormal; Endoscopic ultrasound; Endoscopic ultrasound abnormal; Exocrine pancreatic function test; Exocrine pancreatic function test abnormal; Fat necrosis; Faecal elastase concentration abnormal; Faecal elastase concentration decreased; Gastrointestinal pain; Gastrointestinal sounds abnormal; Grey Turner's sign; Haemorrhagic ascites; Haemorrhagic necrotic pancreatitis; Hereditary pancreatitis; Hyperamylasaemia; Hyperbilirubinaemia; Hyperlipasaemia; Ileus paralytic; Intra-abdominal pressure increased; Ischaemic pancreatitis; Jaundice; Lipase abnormal; Lipase increased; Lipase urine increased; Lung infiltration; Lupus pancreatitis; Magnetic resonance cholangiopancreatography; Nausea; Nuclear magnetic resonance imaging abdominal; Nuclear magnetic resonance imaging abdominal abnormal; Oedematous pancreatitis; Pancreatic abscess; Pancreatic calcification; Pancreatic duct rupture; Pancreatic enzyme abnormality; Pancreatic enzymes abnormal; Pancreatic enzymes increased; Pancreatic fibrosis; Pancreatic haemorrhage; Pancreatic injury; Pancreatic insufficiency; Pancreatic necrosis; Pancreatic phlegmon; Pancreatic pseudocyst; Pancreatic pseudocyst drainage; Pancreatitis; Pancreatitis acute; Pancreatitis bacterial; Pancreatitis chronic; Pancreatitis fungal; Pancreatitis haemorrhagic; Pancreatitis helminthic; Pancreatitis mumps; Pancreatitis necrotising; Pancreatitis relapsing; Pancreatitis viral; Pancreatorenal syndrome; Peripancreatic fluid collection; Premenstrual cramps; Secretin test; Secretin test increased; Steatorrhoea; Traumatic pancreatitis; Vomiting; Vomiting projectile

Relevant Clinical Laboratory Changes: Serum amylase >3x ULN; serum lipase >3x ULN.

Peripheral Artery Disease

MedDRA PTs: Acute focal bacterial nephritis; Diabetic foot; Diabetic gangrene; Diabetic macroangiopathy; Diabetic microangiopathy; Diabetic ulcer; Diabetic vascular disorder; Extremity necrosis; Extrinsic iliac vein compression; Femoral artery occlusion; Ischaemic limb pain; Ischaemic neuropathy; Foot amputation; Iliac artery occlusion; Iliac vein occlusion; Intermittent claudication; Leg amputation; Peripheral artery angioplasty; Peripheral artery bypass; Peripheral artery occlusion; Peripheral artery stent insertion; Peripheral arterial occlusive disease; Peripheral arterial reocclusion; Peripheral artery restenosis; Peripheral artery stenosis; Peripheral ischaemia; Peripheral revascularisation; Poor peripheral circulation; Toe amputation

Skin Reaction

MedDRA PTs: Acute focal bacterial nephritis; Acquired epidermolysis bullosa; Acute generalised exanthematous pustulosis; Anal ulcer; Anal ulcer haemorrhage; Anorectal ulcer; Auditory meatus external erosion; Blister; Blister rupture; Bullous impetigo; Conjunctivitis; Corneal exfoliation; Cutaneous vasculitis; Dermatitis bullous; Dermatitis exfoliative; Dermatitis exfoliative generalised; Diabetic neuropathic ulcer; Diabetic ulcer; Drug eruption; Drug reaction with eosinophilia and systemic symptoms; Epidermal necrosis; Epidermolysis; Epidermolysis bullosa; Erythema multiforme; Exfoliative rash; Eyelid erosion; Fixed drug eruption; Fungating wound; Genital erosion; Genital ulceration; Herpes gestationis; HLA-B*1502 assay positive; HLA-B*5801 assay positive; Hypopharyngeal synechiae; Infected skin ulcer; Lip erosion; Lip exfoliation; Lip ulceration; Mouth ulceration; Mucocutaneous ulceration; Mucosa vesicle; Mucosal erosion; Mucosal exfoliation; Mucosal necrosis; Mucosal ulceration; Nasal necrosis; Nasal septum ulceration; Nasal ulcer; Neuropathic ulcer; Nikolsky's sign; Noninfective conjunctivitis; Ocular pemphigoid; Oculomucocutaneous syndrome; Oral mucosal blistering; Oral mucosal exfoliation; Oral papule; Oropharyngeal blistering; Pemphigoid; Pemphigus; Penile exfoliation; Penile necrosis; Penile ulceration; Scab; Scrotal ulcer; Skin erosion; Skin exfoliation; Skin necrosis; Skin ulcer; Skin ulcer excision; Skin ulcer haemorrhage; Staphylococcal scalded skin syndrome; Stevens-Johnson syndrome; Stomatitis; Testicular necrosis; Tongue exfoliation; Toxic epidermal necrolysis; Toxic skin eruption; Vaginal exfoliation; Vaginal ulceration; Vulval ulceration; Vulvar erosion; Vulvovaginal rash; Vulvovaginal ulceration

Stomatitis/Mouth Ulceration

MedDRA PTs: Allergic pharyngitis; Aphthous ulcer; Behcet's syndrome; Bovine pustular stomatitis virus infection; Burning mouth syndrome; Contact stomatitis; Epiglottic erythema; Epiglottic oedema; Epiglottis ulcer; Gingival oedema; Gingival swelling; Glossodynia; Laryngeal discomfort; Laryngeal pain; Lip disorder; Lip erosion; Lip exfoliation; Lip haematoma; Lip haemorrhage; Lip injury; Lip swelling; Lip ulceration; Mouth haemorrhage; Mouth injury; Mouth swelling; Mouth ulceration; Mucocutaneous ulceration; Mucosal erosion; Mucosal excoriation; Mucosal exfoliation; Mucosal haemorrhage; Mucosal hyperaemia; Mucosal inflammation; Mucosal necrosis; Mucosal pain; Mucosal toxicity; Mucosal ulceration; Mucositis management; Necrotising ulcerative gingivostomatitis; Nicotinic stomatitis; Odynophagia; Oedema mouth; Oesophageal ulcer; Oesophageal ulcer haemorrhage; Oesophageal ulcer perforation; Oesophagitis ulcerative; Oral cavity fistula; Oral discomfort; Oral disorder; Oral dysaesthesia; Oral hyperaesthesia; Oral leukoedema; Oral lichen planus; Oral mucosa atrophy; Oral mucosa erosion; Oral mucosa haematoma; Oral mucosal blistering; Oral mucosal discolouration; Oral mucosal eruption; Oral mucosal erythema; Oral mucosal exfoliation; Oral pain; Oral papule; Oral submucosal fibrosis; Oral toxicity; Oropharyngeal blistering; Oropharyngeal cobble stone mucosa; Oropharyngeal discomfort; Oropharyngeal pain; Oropharyngeal plaque; Oropharyngeal scar; Oropharyngeal swelling; Palatal disorder; Palatal dysplasia; Palatal oedema; Palatal swelling; Palatal ulcer; Parotid gland haemorrhage; PFAPA syndrome; Pharyngeal disorder; Pharyngeal dyskinesia; Pharyngeal enanthema; Pharyngeal erosion; Pharyngeal oedema; Pharyngeal ulceration; Pyostomatitis vegetans; Pharyngeal erythema; Pharyngeal exudate; Pharyngeal fistula; Pharyngeal haematoma; Pharyngeal haemorrhage; Pharyngeal inflammation; Pharyngeal injury; Pharyngeal lesion; Pharyngeal mucosa atrophy; Pharyngeal necrosis; Pharyngeal ulceration; Plicated tongue; Pyostomatitis vegetans; Radiation mucositis; Ranula; Salivary duct inflammation; Salivary gland cyst; Salivary gland disorder; Salivary gland fistula; Salivary gland induration; Salivary gland mass; Salivary gland mucocoele; Salivary gland pain; Scalloped tongue; Sialectasia; Sialocele; Sialometaplasia; Sjogren's syndrome; Stevens-Johnson syndrome; Stomatitis; Stomatitis haemorrhagic; Stomatitis necrotising; Stomatitis radiation; Swollen tongue; Throat irritation; Throat lesion; Throat

tightness; Tongue atrophy; Tongue blistering; Tongue coated; Tongue discolouration; Tongue discomfort; Tongue disorder; Tongue eruption; Tongue exfoliation; Tongue geographic; Tongue haematoma; Tongue haemorrhage; Tongue infarction; Tongue injury; Tongue necrosis; Tongue oedema; Tongue pigmentation; Tongue ulceration; Tonsillar disorder; Tonsillar haemorrhage; Tonsillar ulcer; Toxic epidermal necrolysis; Traumatic ulcerative granuloma with stromal eosinophilia; Uvulitis

Thrombocytopenia

MedDRA PTs: Acquired amegakaryocytic thrombocytopenia; Haemolytic uraemic syndrome; Heparin-induced thrombocytopenia; Immune thrombocytopenic purpura; Megakaryocytes abnormal; Megakaryocytes decreased; Platelet count abnormal; Platelet count decreased; Platelet destruction increased; Platelet disorder; Platelet maturation arrest; Platelet production decreased; Platelet toxicity; Plateletcrit abnormal; Plateletcrit decreased; Thrombocytopenia; Thrombocytopenia neonatal; Thrombocytopenic purpura; Thrombotic thrombocytopenic purpura

Relevant Clinical Laboratory Changes: Thrombocyte (platelet) count <50 x 10^9 c/L; thrombocyte count decrease ≥25% and value <LLN.

Urinary Tract Infections

MedDRA PTs: Acute focal bacterial nephritis; Adenoviral haemorrhagic cystitis; Asymptomatic bacteriuria; Bacterial prostatitis; Bacterial pyelonephritis; Bacteriuria; Bacteriuria in pregnancy; Bladder candidiasis; Bladder diverticulitis; Candiduria; Costovertebral angle tenderness; Culture urine positive; Cystitis; Cystitis bacterial; Cystitis erosive; Cystitis escherichia; Cystitis glandularis; Cystitis gonococcal; Cystitis haemorrhagic; Cystitis helminthic; Cystitis interstitial; Cystitis klebsiella; Cystitis pseudomonal; Cystitis ulcerative; Cystitis viral; Cystitis-like symptom; Cytomegalovirus urinary tract infection; Dysuria; Emphysematous cystitis; Emphysematous pyelonephritis; Escherichia pyelonephritis; Escherichia urinary tract infection; Fungal cystitis; Genitourinary chlamydia infection; Genitourinary tract gonococcal infection; Genitourinary tract infection; HIV associated nephropathy; Kidney infection; Leukocyturia; Malacoplakia vesicae; Mycoplasma genitalium infection; Nephritis; Nitrite urine present; Nitrituria; Perinephric abscess; Perinephritis; Polyomavirus-associated nephropathy; Prostatic abscess; Prostatitis; Prostatovesiculitis; Pyelocystitis; Pyelonephritis; Pyelonephritis acute; Pyelonephritis chronic; Pyelonephritis fungal; Pyelonephritis mycoplasmal; Pyelonephritis viral; Pyonephrosis; Pyuria; Renal abscess; Renal cyst infection; Renal syphilis; Renal tuberculosis; Streptococcal urinary tract infection; Trigonitis; Tuberculosis bladder; Tuberculosis of genitourinary system; Tuberculosis ureter; Urachal abscess; Ureter abscess; Ureteritis; Urethral abscess; Urethral carbuncle; Urethral papilloma; Urethral stricture post infection; Urethritis; Urethritis chlamydial; Urethritis gonococcal; Urethritis mycoplasmal; Urethritis trichomonal; Urethritis ureaplasmal; Urinary bladder abscess; Urinary tract abscess; Urinary tract infection; Urinary tract infection bacterial; Urinary tract infection enterococcal; Urinary tract infection fungal; Urinary tract infection neonatal; Urinary tract infection pseudomonal; Urinary tract infection staphylococcal; Urinary tract infection viral; Urinary tract inflammation; Urine leukocyte esterase positive; Urogenital infection bacterial; Urogenital infection fungal; Urogenital trichomoniasis; Urosepsis; Viral haemorrhagic cystitis; White blood cells urine positive

Vascular Insufficiency

MedDRA PTs: Arteriosclerotic gangrene; Arterial insufficiency; Arterial occlusive disease; Arterial restenosis; Arterial spasm; Arterial stenosis; Arteriosclerosis; Arteriosclerosis Moenckeberg-type; Atherosclerotic plaque rupture; Atrophie blanche; Bone infarction; Brachial artery entrapment syndrome; Chest wall necrosis; Chillblains; Choroidal sclerosis; Claudication of jaw muscles; Compartment syndrome; Dependent rubor; Diabetic foot; Diabetic foot infection; Diabetic gangrene; Diabetic macroangiopathy; Diabetic microangiopathy; Diabetic ulcer; Diabetic vascular disorder; Digital pitting scar; Dry gangrene; Extremity necrosis; Extrinsic iliac vein compression; Femoral artery occlusion; Fibromuscular dysplasia; Gangrene; Gangrene neonatal; Gas gangrene; Graft ischaemia; Hand-arm vibration syndrome; Haemorrhagic infarction; Iliac artery disease; Iliac artery occlusion; Iliac vein occlusion; Incision site vessel occlusion; Infarction; Intermittent claudication; Ischaemia; Ischaemic limb pain; Ischaemic neuropathy; Ischaemic ulcer; Malignant atrophic papulosis; Malnutrition-inflammation-atherosclerosis syndrome; Man-in-the-barrel syndrome; May-Thurner syndrome; Mucocutaneous flap necrosis; Muscle hypoxia; Necrosis; Necrosis ischaemic; Necrosis of artery; Osteonecrosis; Osteonecrosis of external auditory canal; Osteonecrosis of jaw; Osteoradionecrosis; Peripheral arterial occlusive disease; Peripheral

arterial reocclusion; Peripheral artery bypass graft stenosis; Peripheral artery occlusion; Peripheral artery restenosis; Peripheral artery stenosis; Peripheral coldness; Peripheral ischaemia; Peripheral venous disease; Peripheral vascular disorder; Phlebosclerosis; Plaque shift; Post angioplasty restenosis; Poor peripheral circulation; Popliteal artery entrapment syndrome; Purple glove syndrome; Raynaud's phenomenon; Scleroderma associated digital ulcer; Scrotal gangrene; Septic necrosis; Skin flap necrosis; Skin ulcer; Soft tissue necrosis; Spontaneous amputation; Steal syndrome; Stoma site ischaemia; Strangulated hernia; Subclavian artery occlusion; Subclavian artery stenosis; Subclavian coronary steal syndrome; Subclavian vein stenosis; Tumour necrosis; Vascular compression; Vascular graft occlusion; Vascular graft restenosis; Vascular graft stenosis; Vascular insufficiency; Vascular occlusion; Vascular stenosis; Vascular stent occlusion; Vascular stent restenosis; Vascular stent stenosis; Vascular stent thrombosis; Vasoconstriction; Vasospasm; Venous occlusion; Venous stenosis; Venous ulcer pain; Visceral arterial ischaemia

Venous Embolic-Thrombotic Event

MedDRA PTs: Axillary vein thrombosis; Brachiocephalic vein occlusion; Budd-Chiari syndrome; Catheterisation venous; Cavernous sinus thrombosis; Central venous catheterisation; Cerebral venous thrombosis; Compression stockings application; Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Hepatic vein occlusion; Hepatic vein thrombosis; Homans' sign positive; Iliac vein occlusion; Inferior vena cava syndrome; Inferior vena caval occlusion; Intracranial venous sinus thrombosis; Jugular vein occlusion; Jugular vein thrombosis; Mahler sign; May-Thurner syndrome; Mesenteric vein thrombosis; Mesenteric venous occlusion; Obstetrical pulmonary embolism; Obstructive shock; Ophthalmic vein thrombosis; Ovarian vein thrombosis; Paget-Schroetter syndrome; Pelvic venous thrombosis; Penile vein thrombosis; Phlebectomy; Portal vein cavernous transformation; Portal vein occlusion; Portal vein thrombosis; Portosplenomesenteric venous thrombosis; Post procedural pulmonary embolism; Post thrombotic syndrome; Postoperative thrombosis; Postpartum venous thrombosis; Pulmonary embolism; Pulmonary infarction; Pulmonary microemboli; Pulmonary oil microembolism; Pulmonary thrombosis; Pulmonary vein occlusion; Pulmonary veno-occlusive disease; Pulmonary venous thrombosis; Renal vein embolism; Renal vein occlusion; Renal vein thrombosis; Retinal vein occlusion; Retinal vein thrombosis; SI QIII TIII pattern; Splenic vein occlusion; Splenic vein thrombosis; Subclavian vein thrombosis; Superior sagittal sinus thrombosis; Superior vena cava occlusion; Superior vena cava syndrome; Thrombophlebitis; Thrombophlebitis migrans; Thrombophlebitis neonatal; Thrombophlebitis superficial; Thrombosed varicose vein; Thrombosis; Thrombosis corpora cavernosa; Transverse sinus thrombosis; Vascular graft; Vena cava embolism; Vena cava filter insertion; Vena cava filter removal; Vena cava thrombosis; Venogram abnormal; Venoocclusive disease; Venoocclusive liver disease; Venous angioplasty; Venous occlusion; Venous operation; Venous recanalisation; Venous repair; Venous stent insertion; Venous thrombosis; Venous thrombosis neonatal; Venous thrombosis in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal; Visceral venous thrombosis

Volume Depletion

MedDRA PTs: Blood osmolarity increased; Blood pressure ambulatory decreased; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure immeasurable; Blood pressure orthostatic abnormal; Blood pressure orthostatic decreased; Blood pressure systolic decreased; Blood pressure systolic inspiratory decreased; Blood urea nitrogen/creatinine ratio increased; Capillary nail refill test abnormal; Central venous pressure decreased; Circulatory collapse; Decreased ventricular preload; Dehydration; Diastolic hypotension; Dizziness postural; Femoral pulse decreased; Hypoperfusion; Hypotension; Hypovolaemia; Hypovolaemic shock; Left ventricular end-diastolic pressure decreased; Mean arterial pressure decreased; Orthostatic heart rate response increased; Orthostatic hypotension; Orthostatic intolerance; Peripheral circulatory failure; Postural orthostatic tachycardia syndrome; Presyncope; Pulmonary arterial pressure decreased; Pulmonary arterial wedge pressure decreased; Pulse volume decreased; Radial pulse decreased; Renal ischaemia; Shock; Syncope; Urine flow decreased; Urine output decreased; Venous pressure decreased; Venous pressure jugular decreased; Volume blood decreased

Relevant Clinical Laboratory Changes: Hemoglobin >18 g/dL; Hemoglobin >20 g/dL; Hemoglobin increase >2.0 g/dL; Hemoglobin increase >2.0 g/dL and >ULN; Hematocrit >55%; Hematocrit >60%; effective serum osmolality ([2x sodium mEq/L + [glucose mg/dL/18]) >320 mOsm/kg; SBP drop ≥20 mmHg sitting to standing; DBP drop ≥10 mmHg sitting to standing; increase in heart rate of >30 bpm sitting to standing; SBP <90 mmHg; DBP <60 mmHg

13.5. Custom Query of AEs/Laboratory Assessments of Renal Impairment

The AE (aerpt.xpt and aeplus.xpt) and laboratory datasets (adlb.xpt) from the Placebo and Broad Pools were searched using a Custom Query (see Appendix 13.4) to identify renal-related AEs (e.g., acute renal failure and chronic kidney disease SMQs) and laboratory results potentially associated with renal impairment reported during exposure to IP (Table 43). Based on these searches, there appeared to be a modest dose-response and treatment effect, with higher proportions of ertugliflozin-treated subjects meeting these criteria (please refer to Section 8.4.6 for a detailed summary of renal function tests and renal-related AEs).

Table 43: Renal Impairment AEs and Laboratory Assessments (Placebo and Broad Pools)

Renal Impairment AEs and Laboratory Criteria	Placebo Pool			Broad Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
SUBJECTS WITH AEs OR ABNL. LABS	**136 (26.4*)**	**174 (33.5*)**	**192 (37.6*)**	**539 (37.2*)**	**762 (44.4*)**	**775 (45.8*)**
SUBJECTS WITH AEs—no. (%)	**6 (1.2)**	**9 (1.7)**	**7 (1.4)**	**61 (4.2)**	**73 (4.3)**	**87 (5.1)**
Glomerular filtration rate decreased	0	0	1 (0.2)	6 (0.4)	9 (0.5)	20 (1.2)
Hyperkalaemia	3 (0.6)	1 (0.2	2 (0.4)	12 (0.8)	17 (1.0)	15 (0.9)
Blood creatinine increased	0	1 (0.2)	1 (0.2)	3 (0.2)	8 (0.5)	14 (0.8)
Blood potassium increased	1 (0.2)	1 (0.2)	1 (0.2)	12 (0.8)	6 (0.3)	11 (0.6)
Renal impairment	2 (0.4)	1 (0.2)	0	4 (0.3)	3 (0.2)	7 (0.4)
Acute kidney injury	0	0	0	2 (0.1)	6 (0.3)	5 (0.3)
Microalbuminuria	0	0	0	6 (0.4)	7 (0.4)	4 (0.2)
Leukocyturia	0	0	0	2 (0.1)	0	3 (0.2)
Hypocalcaemia	0	0	0	1 (0.1)	4 (0.2)	3 (0.2)
Hyponatraemia	0	0	0	0	3 (0.2)	3 (0.2)
Blood urea increased	0	0	0	2 (0.1)	6 (0.3)	3 (0.2)
Proteinuria	0	1 (0.2)	0	4 (0.3)	3 (0.2)	3 (0.2)
Metabolic acidosis	0	0	0	0	1 (0.1)	2 (0.1)
Renal failure	0	1 (0.2)	1 (0.2)	0	1 (0.1)	2 (0.1)
Diabetic nephropathy	0	0	1 (0.2)	2 (0.1)	0	2 (0.1)
Blood phosphorus increased	0	1 (0.2)	0	0	1 (0.1)	2 (0.1)
Chronic kidney disease	0	0	0	4 (0.3)	6 (0.3)	2 (0.1)
Hypercreatininaemia	0	0	0	0	0	1 (0.1)
Urine albumin/creatinine ratio increased	0	0	0	2 (0.1)	0	1 (0.1)
Encephalopathy	0	0	0	0	0	1 (0.1)
Nephrosclerosis	0	0	0	0	0	1 (0.1)
Nephritis	0	0	0	0	0	1 (0.1)
Nephrogenic anaemia	0	0	0	0	0	1 (0.1)
Normochromic normocytic anaemia	0	0	0	0	0	1 (0.1)
Nephropathy	0	0	0	0	1 (0.1)	1 (0.1)
Pericarditis	0	0	0	0	0	1 (0.1)
Acute prerenal failure	0	0	0	0	1 (0.1)	0
White blood cells urine positive	0	0	0	3 (0.2)	1 (0.1)	0

Renal Impairment AEs and Laboratory Criteria	Placebo Pool			Broad Pool		
	Placebo (n=515)	Ertugliflozin 5 mg (n=519)	Ertugliflozin 15 mg (n=510)	Non-Ertugliflozin (n=1450)	Ertugliflozin 5 mg (n=1716)	Ertugliflozin 15 mg (n=1693)
Blood calcium decreased	0	0	0	1 (0.1)	0	0
Blood parathyroid hormone increased	0	0	0	1 (0.1)	1 (0.1)	0
Creatinine renal clearance decreased	0	0	0	1 (0.1)	0	0
Hypertensive nephropathy	0	0	0	1 (0.1)	0	0
Blood sodium decreased	0	0	0	0	1 (0.1)	0
Albuminuria	0	0	0	1 (0.1)	0	0
Hyperphosphataemia	0	2 (0.4)	0	1 (0.1)	2 (0.1)	0
SUBJECTS WITH ABNL. LABS—no. (%)	**135 (26.2*)**	**171 (32.9*)**	**190 (37.3*)**	**525 (36.2*)**	**741 (43.2*)**	**750 (44.3*)**
eGFR (mL/min/1.73m²) Abnl.	**115/498 (23.1)**	**141/504 (28.0)**	**159/497 (32.0)**	**425/1411 (30.1)**	**579/1674 (34.6)**	**602/1645 (36.6)**
Shift from ≥90 to 60-89 (CKD Stage 1 to 2)	95/498 (19.1)	96/504 (19.0)	106/497 (21.3)	263/1411 (18.6)	351/1674 (21.0)	343/1645 (20.9)
Shift from ≥90 to 45-59 (CKD Stage 1 to 3A)	1/498 (0.2)	2/504 (0.4)	2/497 (0.4)	7/1411 (0.5)	3/1674 (0.2)	10/1645 (0.6)
Shift from ≥90 to 30-44 (CKD Stage 1 to 3B)	1/498 (0.2)	0/504	0/497	2/1411 (0.1)	0/1674	2/1645 (0.1)
Shift from 60-89 to 45-59 (CKD Stage 2 to 3A)	19/498 (3.8)	44/504 (8.7)	48/497 (9.7)	98/1411 (7.0)	141/1674 (8.4)	176/1645 (10.7)
Shift from 60-89 to 30-44 (CKD Stage 2 to 3B)	0/498	0/504	0/497	10/1411 (0.7)	11/1674 (0.7)	12/1645 (0.7)
Shift from 60-89 to 15-29 (CKD Stage 2 to 3B)	0/498	0/504	0/497	1/1411 (0.1)	0/1674	1/1645 (0.1)
Shift from 45-59 to 30-44 (CKD Stage 3A to 3B)	0/498	0/504	2/497 (0.4)	51/1411 (3.6)	74/1674 (4.4)	66/1645 (4.0)
Shift from 45-59 to 15-29 (CKD Stage 3A to 4)	0/498	0/504	0/497	2/1411 (0.1)	4/1674 (0.2)	1/1645 (0.1)
Shift from 30-44 to <15 (CKD Stage 3B to 5)	0/498	0/504	0/497	0/1411	0/1674	1/1645 (0.1)
>30% ↓ from baseline	14/498 (2.8)	13/504 (2.6)	14/497 (2.8)	73/1411 (5.2)	95/1674 (5.7)	101/1645 (6.1)
>40% ↓ from baseline	4/498 (0.8)	4/504 (0.8)	4/497 (0.8)	22/1411 (1.6)	16/1674 (1.0)	27/1645 (1.6)
>50% ↓ from baseline	1/498 (0.2)	0/504	1/497 (0.2)	8/1411 (0.6)	2/1674 (0.1)	9/1645 (0.5)
eGFR <15 mL/min/1.73 m²	0/498	0/504	0/497	1/1411 (0.1)	0/1674	0/1645
Serum creatinine (mg/dL) Abnl.	**8/498 (1.6)**	**14/504 (2.8)**	**14/497 (2.8)**	**86/1411 (6.1)**	**125/1674 (7.5)**	**133/1645 (8.1)**
↑ ≥0.3 mg/dL from baseline	8/498 (1.6)	13/504 (2.6)	13/497 (2.6)	86/1411 (6.1)	123/1676 (7.3)	130/1645 (7.9)
↑ ≥1 mg/dL from baseline	0/498	0/504	0/497	3/1411 (0.2)	2/1676 (0.1)	4/1645 (0.2)
≥ 2.5 mg/dL	0/498	0/504	0/497	5/1411 (0.4)	9/1676 (0.5)	5/1645 (0.3)
≥1.5 x baseline	3/498 (0.6)	6/504 (1.2)	7/497 (1.4)	27/1411 (1.9)	26/1676 (1.6)	39/1645 (2.4)
≥2 x baseline	1/498 (0.2)	0/504	0/497	4/1411 (0.3)	1/1676 (0.1)	5/1645 (0.3)
Blood Urea Nitrogen (mg/dL) Abnl.	**25 (5.1)**	**39/496 (7.9)**	**48/489 (9.8)**	**135/1383 (9.8)**	**225/1639 (13.7)**	**253/1620 (15.6)**
>60 mg/dL	0/491	0/496	0/489	0/1383	0/1639	0/1620
≥50% ↑from baseline & >ULN	25/491 (5.1)	39 /496 (7.9)	48/489 (9.8)	135/1383 (9.8)	225/1639 (13.7)	253/1620 (15.6)
Serum potassium (mEq/L) Abnl.	**10/498 (2.0)**	**6/505 (1.2)**	**7/497 (1.4)**	**55/1411 (3.9)**	**61/1676 (3.6)**	**52/1644 (3.2)**
≥6 mEq/L	10/498 (2.0)	6/505 (1.2)	7/497 (1.4)	55/1411 (3.9)	61/1676 (3.6)	52/1644 (3.2)

Source: Derived from the iss and iss-broad adsl.xpt, aerpt.xpt and aeplus.xpt, adlb.xpt datasets, available at:
Application 209803 - Sequence 0000 - Analysis Dataset Legacy –; Application 209803 - Sequence 0000 - Analysis Dataset Legacy -
Abbreviations: ↓, decrease; ↑, increase; Abnl, abnormal; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease [MDRD] equation); Lab, clinical laboratory parameter; and ULN, upper limit of normal.
***Note:** The percentages for the pooled search were derived from the entire population, and does not account for missing laboratory values.

13.6. Hypoglycemic Events in the Phase 3 Clinical Program

Table 44: Documented and Severe Hypoglycemia in Individual Phase 3 Trials

Hypoglycemia*	Comparator	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Trial P001/1016 (Moderate Renal Impairment Trial)			
Treatment Arm	Placebo + AHA	Ertu 5 mg + AHA	Ertu 15 mg + AHA
Sample Size	N=154	N=158	N=155
Documented – n (%)	51 (33.1)	54 (34.2)	39 (25.2)
Symptomatic – n (%)	27 (17.5)	33 (20.9)	26 (16.8)
Severe – n (%)	3 (1.9)	5 (3.2)	3 (1.9)
Subjects receiving insulins, sulfonylureas, or meglitinides			
Sample Size	N=133	N=148	N=143
Documented – n (%)	48 (36.1)	53 (35.8)	39 (27.3)
Symptomatic – n (%)	27 (20.3)	33 (22.3)	26 (18.2)
Severe – n (%)	3 (2.3)	5 (3.2)	3 (1.9)
Trial P003/1022 (Placebo-Controlled Monotherapy Trial)			
Treatment Arm	Placebo	Ertu 5 mg	Ertu 15 mg
Sample Size	N=153	N=156	N=152
Documented – n (%)	1 (0.7)¶	4 (2.6)	4 (2.6)
Symptomatic – n (%)	2 (1.3)	2 (1.3)	4 (2.6)
Severe – No. (%)	0	0	2 (1.3)
Trial P007/1017 (Placebo-Controlled Trial in Combination with Metformin)			
Treatment Arm	Placebo + Met	Ertu 5 mg + Met	Ertu 15 mg + Met
Sample Size	N=209	N=207	N=205
Documented – n (%)	9 (4.3)	15 (7.2)	16 (7.8)
Symptomatic – n (%)	4 (1.9)	7 (3.4)	7 (3.4)
Severe – n (%)	1 (0.5)	1 (0.5)	0
Trial P002/1013 (Active-Controlled Trial Comparing Ertugliflozin to Glimepiride as Add-on to Metformin)			
Treatment Arm	Glimepiride + Met	Ertu 5 mg + Met	Ertu 15 mg + Met
Sample Size	N=437	N=448	N=440
Documented – n (%)	119 (27.2)	25 (5.6)	36 (8.2)
Symptomatic – n (%)	84 (19.2)	14 (3.1)	23 (5.2)
Severe – n (%)	10 (2.3)	1 (0.2)	1 (0.2)
Trial P006/1015 (Add-on Trial in Combination with Metformin and Sitagliptin)			
Treatment Arm	Placebo + Met + Sita	Ertu 5 mg + Met + Sita	Ertu 15 mg + Met + Sita
Sample Size	N=153	N=156	N=153
Documented – n (%)	5 (3.3)	7 (4.5)	3 (2.0)
Symptomatic – n (%)	4 (2.6)	6 (3.8)	1 (0.7)
Severe – n (%)	1 (0.7)	1 (0.6)	0

Hypoglycemia*	Comparator	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Trial P017/1047 (Initial Combination Therapy of Ertugliflozin and Sitagliptin)			
Treatment Arm	**Placebo**	**Ertu 5 mg + Sita 100 mg**	**Ertu 15 mg + Sita 100 mg**
Sample Size	N=97	N=98	N=96
Documented – n (%)	1 (1.0)	6 (6.1)	3 (3.1)
Symptomatic – n (%)	1 (1.0)	3 (3.1)	3 (3.1)
Severe – n (%)	0	0	2 (2.1)

Trial P005/1019 (Factorial Trial with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin)					
Treatment Regimen	**Sita 100 mg + Met**	**Ertu 5 mg + Met**	**Ertu 15 mg + Met**	**Ertu 5 mg + Sita 100 mg + Met**	**Ertu 15 mg + Sita 100 mg + Met**
Sample Size	N=247	N=250	N=248	N=243	N=244
Documented – n (%)	9 (3.6)	14 (5.6)	13 (5.2)	13 (5.3)	22 (9.0)
Symptomatic – n (%)	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.5)	12 (4.9)
Severe – n (%)	0	0	1 (0.4)	0	1 (0.4)

Source: Adapted from the Applicant's Clinical Summary of Safety, labeled as Tables 56 and 57, pages 202-203 of 372, available at: \\cdsesub1\evsprod\nda209803\0000\m2\27-clin-sum\summary-clin-safety.pdf
and the p001v01 Clinical Study Report, labeled as Table 14.3.2.1.7.2, page 1149 of 2401, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p001v01\p001v01.pdf

Abbreviations: +, plus; AHA, antihyperglycemic agents; Ertu, ertugliflozin; Met, metformin; n, number of subjects with ≥1 event; N, number of subjects; and Sita, sitagliptin.

Definitions: ***Documented***, measured blood glucose ≤70 mg/dL regardless of symptoms (i.e., asymptomatic or symptomatic); ***Symptomatic***, hypoglycemic episodes with clinical symptoms reported by the investigator; and ***Severe***, episodes that required assistance, either medical or non-medical (episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure were classified as having required medical assistance).

* **Phase A, Excluding glycemic rescue approach.**

¶ Two subjects with documented hypoglycemia reported in the p003v01 Clinical Study Report, labeled as Table 44, page 203 of 3191, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\p003v01\p003v01.pdf

13.7. Case Definitions of Ketoacidosis

For a 'certain', 'probable', or 'possible' diagnosis of ketoacidosis to be made, laboratory criteria for both acidosis and ketones had to be met (highest case definition selected if event met >1 case definition), and the clinical situation had to suggest that ketoacidosis was the primary explanation for these data. If a case meets criteria for a definition of certain, probable, or possible ketoacidosis, yet the committee member believes that the overall clinical situation is not consistent with ketoacidosis as the primary explanation for the data, then the committee member may instead choose to classify the case as unlikely to represent ketoacidosis.

Table 45: Case Definitions for the Diagnosis of Ketoacidosis

	ACIDOSIS	KETONES	COMMENTS
CERTAIN	Arterial or venous pH ≤7.30	Serum ketones positive	Ketoacidosis must be considered the primary explanation for the data. If possible, exclude other primary causes of acidosis (e.g., lactic acid, respiratory acidosis)
PROBABLE	Arterial or venous pH ≤7.30	Urine ketones positive*	Ketoacidosis must be considered the primary explanation for the data. If possible, exclude other primary causes of acidosis (e.g., lactic acid, respiratory acidosis)
POSSIBLE	Serum bicarbonate <18 mEq/L	Serum or urine ketones positive*	
UNLIKELY	Not Applicable	Not Applicable	Lab data defining acidosis and ketones are available but do not meet above criteria or ketoacidosis is not considered the primary explanation for the data; there may be evidence of another cause of metabolic acidosis (e.g., lactic acidosis, respiratory acidosis)
UNCLASSIFIABLE	Not Available	Not Available	Lab data defining acidosis and ketones are not available

Source: Adapted from the Applicant's Charter for the Clinical Case Review of Ketoacidosis, labeled as Appendix E, page 22 of 29, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04jbr6\04jbr6.pdf

13.8. Subjects with Lower Limb Amputations

Table 46: Amputations (4-MSU): n=11 Ertugliflozin vs. n=1 Non-Ertugliflozin

SUBJID	Arm	Age	Sex	Race	Day of Last Exposure	Amputation	Day of Procedure	Relevant Medical Hx	Relevant Con Meds	Tobacco Use	Hx Amput./ Revasc.	Prior SAE	SAE Day
0200351	**Non-Ertugliflozin** (Glimepiride)	54	Male	Asian	651	Toe amputation (I, great toe) in left foot	298	Atherosclerosis, Cellulitis of toe, Diabetic neuropathy, Duration of diabetes 1 year, Hyperlipidaemia	(-)	(+) Ex-smoker (32 pack-years)	(-)	Diabetic vascular disorder ("diabetic peripheral angiopathy") Diabetic gangrene	283 283
0200632	**Ertugliflozin** (5 mg)	72	Male	White	638	Toe amputation ("due to cellulitis")	577	Duration of diabetes 8 years	(-)	(+) Ex-smoker (40 pack-years)	(-)	Gangrene ("toe gangrene")	550
0600812	**Ertugliflozin** (5 mg)	52	Male	White	365	Toe amputation ("right toe amputation surgery")	188	Diabetic retinopathy, Erectile dysfunction, Duration of diabetes 5 years, Hypertension, Neuropathy peripheral, Skin ulcer (right foot ulcer)	(-)	(-)	(-)	Osteomyelitis ("osteomyelitis of right toe")	186
0710151	**Ertugliflozin** (5 mg)	58	Male	White	475	Foot amputation ("distal Syme amputation of the right second toe")	559	Duration of diabetes 28 years, Abscess limb (Abscess left and right foot 2014), Abscess limb (Abscess R foot), Cellulitis of left foot and right leg (2014), Foot operation (Foot surgery 2014), Peripheral venous disease (Venous insufficiency)	(-)	(+) Ex-smoker (7 pack-years)	(-)	Osteomyelitis acute (acute osteomyelitis of left foot) Osteomyelitis ("osteomyelitis R leg")	476 556
0101246	**Ertugliflozin** (15 mg)	73	Male	White	363	Limb amputation ("amputation of the left lower limb")	184	Chronic kidney disease, Dyslipidaemia, Hypertension, Nephropathy, Neuropathy peripheral	Furosemide 20 mg/d	(+) Ex-smoker (22.5 pack-years)	(-)	Diabetic foot infection Peripheral arterial occlusion	81 174

SUBJID	Arm	Age	Sex	Race	Day of Last Exposure	Amputation	Day of Procedure	Relevant Medical Hx	Relevant Con Meds	Tobacco Use	Hx Amput./ Revasc.	Prior SAE	SAE Day
0102405	**Ertugliflozin** (15 mg)	70	Male	White	364	Toe amputation ("amputation of the distal phalanx in right toe")	352	Cardiac catheterization, Chronic kidney disease, Coronary artery disease, Diabetic nephropathy, Diabetic neuropathy, Duration of diabetes 23 years, Dyslipidaemia, Hypertension	(-)	(-)	(-)	Cellulitis (cellulitis of right great toe")	352
0102476	**Ertugliflozin** (15 mg)	74	Female	White	98	Toe amputation (amputation of II, III, IV toes of right leg procedure)	101	Cardiac failure chronic, Chronic kidney disease, Diabetic neuropathy, Diabetic retinopathy, Duration of diabetes 12 years, Dyslipidaemia, Hypertension, Myocardial ischaemia, Peripheral venous disease	Indapamide 1.5 mg/d	(-)	(-)	Peripheral arterial occlusive disease ("right lower limb ischemia, Stage IV peripheral arterial disease")	73
0102483	**Ertugliflozin** (15 mg)	64	Male	White	28	Toe amputation	36	Angina pectoris, Chronic kidney disease, Diabetic neuropathy, Diabetic retinopathy, Duration of diabetes 23 years, Hyperlipidaemia, Hypertension, Peripheral arterial occlusive disease, Stent placement	(-)	(-)	(-)	Cellulitis ("Phlegmon of toe")	30
0201036	**Ertugliflozin** (15 mg)	53	Male	White	372	Toe amputation ("amputation of 2nd digit on left foot") Peripheral artery bypass ("distal left femoral-popliteal autovenous bypass")	252 252	Aortic disorder, Duration of diabetes 1 year, Dyslipidaemia, Hepatic steatosis, Myocardial infarction, Myocardial ischaemia, Peripheral artery bypass (2014), Peripheral ischaemia (2008), Peripheral venous disease (1993), Polyneuropathy, toe operation, Stent placement, Toe	(-)	(+) 18 cigarettes/d (11.4 pack-years)	(-)	Peripheral ischaemia ("progression of ischemic disease of lower extremities")	250

SUBJID	Arm	Age	Sex	Race	Day of Last Exposure	Amputation	Day of Procedure	Relevant Medical Hx	Relevant Con Meds	Tobacco Use	Hx Amput./ Revasc.	Prior SAE	SAE Day
								operation					
0500303	**Ertugliflozin** (15 mg)	58	Male	White	318	Toe amputation ("amputation of 2nd toe of left foot")	166	Diabetic neuropathy, Diabetic retinopathy, Diabetic vascular disorder (angiopathy of lower extremities), Duration of diabetes 3 years Hypertension, Peripheral arterial occlusive disease,	(-)	(+) Ex-smoker (36 pack-years)	(-)	Gangrene ('gangrene of the second toe of the left foot")	155
0710088	**Ertugliflozin** (15 mg)	56	Male	White	637	Toe amputation ("amputation left 2nd toe")	228	Dyslipidaemia, Duration of diabetes 7 years, Hypertension	(-)	(+) Ex-smoker (21 pack-years)	(-)	Peripheral ischaemia ("critical ischemia left foot	211
						Toe amputation	407					Cellulitis ("cellulitis with third metatarsal head")	398
0710319	**Ertugliflozin** (15 mg)	63	Male	White	342	Leg amputation ("amputation femoris – left leg amputation")	342	Atrial fibrillation, Congestive cardiomyopathy, Coronary artery disease, Diabetic retinopathy, Embolism (thromboembolism of popliteal; postsurgical in 2005), Hyperlipidemia, Hypertension, Ischaemic stroke, Peripheral artery aneurysm (popliteal 2005), Diabetic retinopathy, Coronary artery disease, Ischaemic stroke, Duration of diabetes 28 years	Indapamide 1.5 mg/d	(-)	(-)	Peripheral ischaemia ("critical limb ischemia of left leg")	334

Source: Adapted from the Applicant's Integrated Summary of Safety, labeled as Tables 254 and 255, pages 2098-2104 of 9829, and the Summary of Clinical Safety, labeled as Table 2.7.4:69, page 427-428 of 486.
Abbreviations: Amput, amputation; Hx, history; Revasc, peripheral revascularization procedure; Con Meds, concomitant medications; and SAE, serious adverse event.

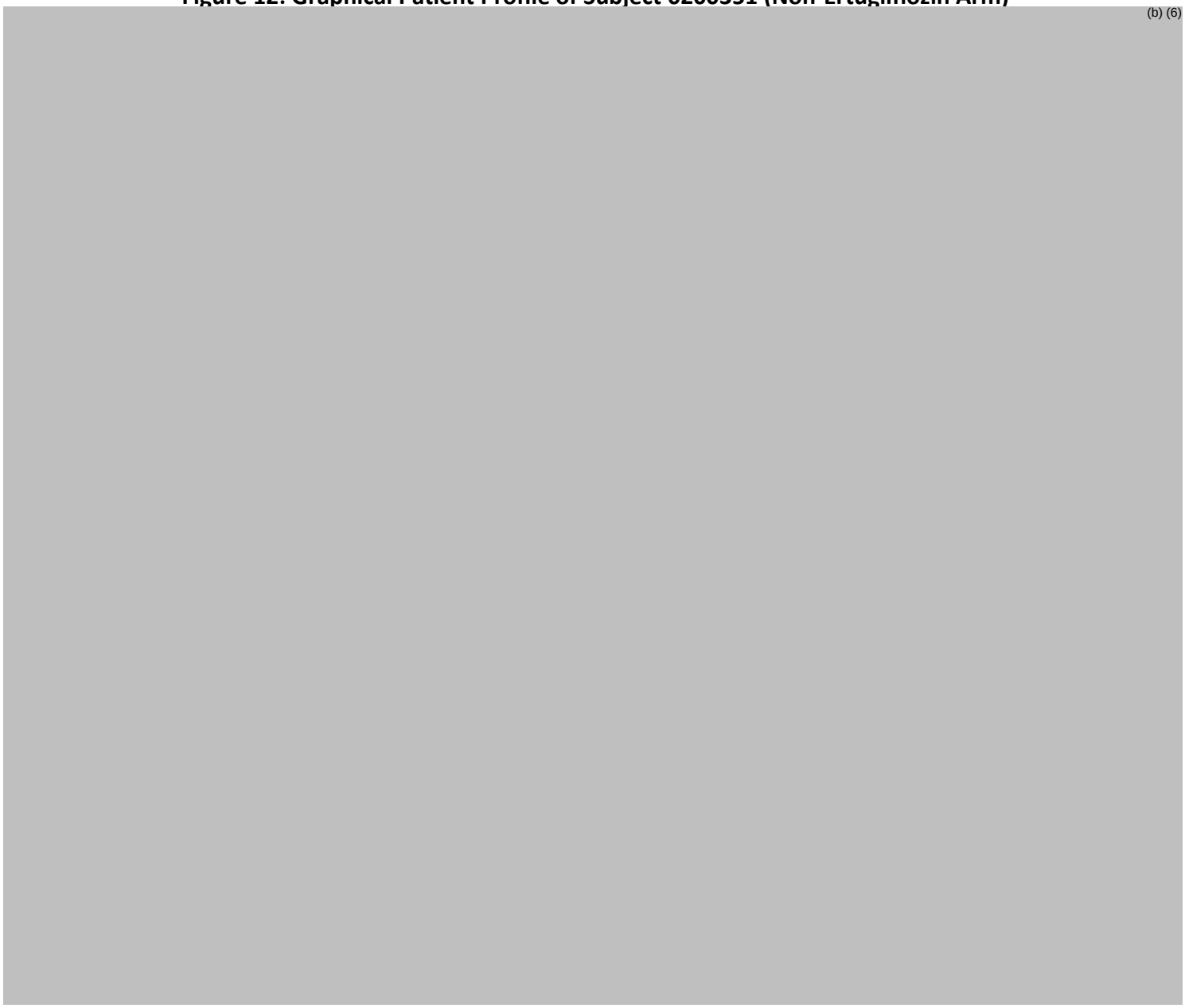
13.9. Narrative Summaries and Graphical Profiles of Subjects with Amputations

NON-ERTUGLIFLOZIN ARM (GLIMEPIRIDE)

Subject 0200351: 54-year-old Asian male with T2D for approximately 1 year was randomized to the non-ertugliflozin arm (i.e., glimepiride) in Trial P002/1013. Relevant past medical history included atherosclerosis, cellulitis of toe, diabetic neuropathy, folliculitis, hidradenitis, hyperlipidemia, and ex-smoker (32 pack-years). Relevant prior medication at the time of randomization included metformin (1700 mg/day), atorvastatin, pregabalin, clopidogrel, and aspirin. On Day 283, the subject experienced SAEs of diabetic vascular disorder (diabetic peripheral angiopathy) and diabetic gangrene (diabetic gangrene). These events were considered serious because hospitalization was required. The subject's left great toe had changed color, with no improvement on Days 295-296. On Day 297, the subject was hospitalized and diagnosed with diabetic peripheral angiopathy and diabetic gangrene. The subject's red blood cell sedimentation rate was 37 mm/hr (reference range: 0 to 10 mm/hr) and white blood cell count was 14.2 × 10^3/µl (reference range: 4-10 × 10^3/µl). An X-ray showed a soft tissue ulcer in the subject's left great toe, which was amputated on Day 298. On Day 299, a blood culture showed coagulase negative staphylococci. On Day 301, blood cultures were negative. A CT scan of the subject's left foot showed vascular calcification and reduced blood flow. On Day 303, skin incision and drainage were performed. Blood cultures were negative on Day 310 but showed coagulase-negative staphylococci on Days 315 and 322. The wound was sutured on Day 324. On Day 332, the subject's white blood cell count was 4.01 × 10^3/µL. The subject was treated with alprostadil 2 mL daily from Day 297 through 324, ceftriaxone 2 g daily from Day 297 through 326, thioctic acid 600 mg daily from Day 297 through 351, silver sulfadiazine 450 mL on Day 299, beraprost 0.12 mg daily from Day 325 through 410, vancomycin hydrochloride 2 g daily from Day 326 through 333, 0.75 g on Day 334, and 2.25 g daily from Day 335 to 347, linezolid 1200 mg daily from Day 347 to 351, rifampin 600 mg daily from Day 347 to 357, ciprofloxacin 1000 mg daily from Day 351 to 357, and cilostazol 200 mg daily from Day 351 to 410. He was discharged on Day 348. The subject was treated with beraprost sodium 4 tablets daily for diabetic peripheral vascular disease from Day 556. The study medication was not changed due to the events. The events of diabetic vascular disorder and diabetic gangrene resolved on Day 410. The subject completed Phase A of the study and entered Phase B on Day 378.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 3580-3645 of 10826, available at:
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-a.pdf

Figure 12: Graphical Patient Profile of Subject 0200351 (Non-Ertugliflozin Arm)



Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 5 MG ARM

Subject 0200632: 72-year-old white male with T2D for approximately 8 years was randomized to the ertugliflozin 5 mg arm in Trial P002/1013. He was receiving metformin 2000 mg daily when randomized. The subject was a former smoker (40 pack-years), but had no other relevant past medical history or medications. On Day 550, he experienced a SAE of gangrene (toe gangrene-first digit of right foot). The event was considered serious because hospitalization was required. Signs and symptoms included inflammation, swollen leg, hyperemia, and ulcers, which appeared on that same day. On Day 552, the subject was hospitalized, and his C-reactive protein (CRP) was 171.1 mg/L (reference range: 0.1-5.0 mg/dL). An X-ray of the toe showed no sign of osteomyelitis and no abnormalities were detected, and the physical examination revealed ruptured, livid toe without any pus. His white blood cell (WBC) count was 10.6×10^3/µL (reference range: 4-9.5×10^3/µL and his blood glucose was 142.2 mg/dL (reference range: 72-108 mg/dL). The subject was treated with diclofenac 50 mg daily, sulodexide 600 U_2 daily, and dipyrone 500 mg daily from Day 552 through 559. On Day 555, his uric acid was 8.1 mg/dL (reference range: 3.5-7.2 mg/dL). Despite conservative therapy, necrotic skin appeared on the right toe. The subject was discharged on Day 559 and readmitted on Day 574 due to right toe gangrene. The subject was treated with sodium chloride 500 mL daily, sulodexide 600 U_2 daily, and pentoxifylline 200 mg daily from Day 574 through 581. On Day 576, the erythrocyte sedimentation rate was 69 mm/h (reference range: 3- 12 mm/h), and WBC was 7.9×10^3/µL. On Day 577, an interphalangeal amputation at the first toe of the right foot was done. On Day 581, the subject was discharged from the hospital in good condition, and regular wound dressing was done. The study medication was not changed due to the event. The subject completed Phase A of the study and entered Phase B on Day 364. His last dose of study medication was on Day 638.

Source: Adapted from the Applicant's 04lmn3.pdf, SUR Table 7. Narratives for Amputations, pages 1053-1111 of 4600, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-a.pdf

Figure 13: Graphical Patient Profile of Subject 0200632 (Ertugliflozin 5 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 5 MG ARM

Subject 0600812: 52-year-old white male with T2D for approximately 5 years was randomized to the ertugliflozin 5 mg arm in Trial P006/1015. He was receiving metformin 2000 mg daily and sitagliptin 100 mg daily. No other relevant prior medications were recorded. The subject's past medical history included skin ulcer (right foot ulcer), peripheral neuropathy, vitamin D deficiency, hypertension, diabetic retinopathy and cervical vertebral fracture (C1-C2 fracture). The subject had no smoking history. On Day 186, the subject experienced a SAE of osteomyelitis of the right toe. This event was considered serious because hospitalization was required. Prior to study participation, the subject was being treated as an outpatient for a non-healing ulcer of the right great toe ulcer. His podiatrist suspected that the wound had developed into osteomyelitis, and on Day 185, an X-ray of the right toe was suggestive of osteomyelitis. The subject was hospitalized on Day 186. A wound culture revealed *Staphylococcus aureus*, and ceftriaxone was initiated. On Day 188, the subject underwent amputation of the right hallux with partial resection of the first metatarsal. On Day 190, the subject was discharged. He was treated with ceftriaxone 2 g daily from Day 186 through 232. The study medication was not changed due to the event. The event of osteomyelitis resolved on Day 232. The subject completed Phase A of the study and entered Phase B on Day 183; he completed Phase B on Day 366. `

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 8177-8215 of 10826, available at:
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-a.pdf

Figure 14: Graphical Patient Profile of Subject 0600812 (Ertugliflozin 5 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 5 MG ARM

Subject 0710151: 58-year-old white male with T2D for approximately 28 years was randomized to the ertugliflozin 5 mg arm in Trial P007/1017. He was receiving metformin 1700 mg/day at randomization. Relevant medical history included abscess and cellulitis of the left and right foot (2014), foot surgery (2014), knee replacement, knee surgery, and Achilles repair. The subject was a former smoker (7 pack-years). There was no other relevant medication at the time of randomization. On Day 425, the subject experienced a SAE of acute osteomyelitis of the left foot that was considered by the investigator to be of severe intensity. On Day 475, the subject presented to emergency room (ER) with complaint of infected left foot, foul, gangrenous smell, and low grade fever. His WBC count was $13.8\times10^3/\mu L$ (reference range: $4.1\text{-}12.3\times10^3/\mu L$). On the same day, he was hospitalized. It was reported that the subject's foot was operated on previously and had no issue, but 3.5 weeks prior to the ER visit the subject's foot had become painful with skin breakdown on the heel. On examination, the subject was diagnosed with multiple foot abscesses, and acute and chronic osteomyelitis. On Day 476, the subject underwent an incision and sharp excisional debridement procedure on left foot (left lateral heel) without resection of bone and on Day 483, another incision and sharp excisional debridement on left foot (left lateral heel) without resection of bone. On Day 486, the subject was transferred to the transitional care unit for intravenous (IV) antibiotic therapy. The plan was for discharge after 7 days of IV antibiotics. The subject insisted on discharge 1 day early. The study medication was withdrawn due to the event (Day 475). The SAE resolved on Day 525 and the subject was discharged from the hospital on oral antibiotics the same day. On Day 556, the subject experienced an SAE of acute osteomyelitis of the right leg that was considered by the investigator to be of severe intensity. His WBC count was $15.4\times10^3/\mu L$ (reference range: $4.1\text{-}12.3\times10^3/\mu L$). On the same day, the subject was hospitalized. It was observed that the subject was "not in good shape" and was referred to ER for worsening infection of right leg, which was noticeably swollen. On Day 559, the subject underwent foot amputation (distal Syme amputation of the right second toe). No gangrene was reported, but the right second toe was noted to have a neuropathic ulcer (Wagner Stage III). On Day 560, incisional drainage deep debridement was done, which was normal with no complication. The subject was to remain in the hospital for approximately 8 weeks and would continue to receive antibiotic treatment for infection. The SAE was reported ongoing at the time of this report and no other information was available regarding the subject's discharge from the hospital.

Source: Adapted from the Applicant's 04lmn3.pdf, SUR Table 7. Narratives for Amputations, pages 2251-2363 of 4600, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-a.pdf

Figure 15: Graphical Patient Profile of Subject 0710151 (Ertugliflozin 5 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0101246: 73-year-old white male with T2D for approximately 19 years and chronic kidney disease was randomized to the ertugliflozin 15 mg arm in Trial P001/1016. He was receiving metformin 1000 mg daily and insulin glargine 15_2 daily. Other relevant past medical history included diabetic foot infection, hypertension, dyslipidemia, and ex-smoker (22.5 pack-years). Relevant prior medication at the time of randomization included bezafibrate 200 mg daily, enalapril 10 mg daily, and furosemide 20 mg daily. On Day 81, the subject had an infected ulcer on his left foot with discoloration of toes, and was hospitalized for treatment. On Day 121, an eco-Doppler scan of the subject's legs showed plaques with at least 7% stenosis of the proximal left anterior tibial artery and a maximum of 46% stenosis of the left pedal artery. The subject was treated for peripheral arterial occlusive disease with aspirin 300 mg daily, ongoing from Day 127. A culture of the ulcer on Day 168 was negative. On that day, the subject had pain in his left leg with discoloration of the first and second toes, was hospitalized with a working diagnosis of soft tissue infection, and was treated with ceftriaxone, metronidazole, and dipyrone. A Doppler ultrasound scan of the subject's left leg on Day 168 showed signs of vascular compromise at the level of the popliteal artery. On Day 174, the subject experienced a serious adverse event of peripheral artery occlusion (peripheral arterial occlusion). This event was considered serious because hospitalization was required or prolonged, and because persistent or significant disability or incapacity was involved. Linezolid was begun (dose and dates not provided). On Day 184, the subject underwent supracondylar amputation of the left leg, and on Day 188 he was discharged. At discharge, the stump of the left leg was clean and bandaged, the sutures were well apposed with no blood or exudate, and the skin was pink. The subject was afebrile and stated that his symptoms had improved. His leukocyte count was normal. At the time of discharge, he was prescribed diclofenac and acetaminophen (doses and dates not provided). The study medication was not changed due to the event. The investigator considered the AE to be severe in intensity. The event of peripheral arterial occlusive disease resolved, with a sequela of walking disability, on Day 184. The subject completed Phase A of the study and entered Phase B, and the subject completed Phase B on Day 364.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 1177-1229 of 10826, available at:
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Figure 16: Graphical Patient Profile of Subject 0101246 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0102405: 70-year-old white male with T2D for approximately 23 years and chronic kidney disease was randomized to the ertugliflozin 15 mg arm in Trial P001/1016. He was receiving 144 IU daily insulin aspart and 40 IU daily insulin glargine when randomized. Other relevant past medical history included diabetic neuropathy, coronary artery disease, cardiac catheterization, hypertension and dyslipidemia. The subject had no smoking history. Relevant prior medication at the time of randomization included pregabalin 150 mg daily, aspirin 81 mg daily, lisinopril 10 mg daily and amlodipine 2.5 mg daily. On Day 352, the subject experienced a serious adverse event of cellulitis of right great toe. The event was considered serious because hospitalization was required. On Day 352, the subject injured his right great toe causing redness and some bleeding. The condition of his toe worsened and he visited the emergency room. At presentation, the subject's right great toe was noted to be red and swollen, warm and fluctuant at the tip, with a lymphatic streak up the foot. The subject had absent protective and epicritic sensation in the lower extremities, with dorsalis pedis and posterior pulses faintly palpable bilaterally. An X-ray showed no acute fracture or dislocation, but vascular calcifications were noted. There were no relevant abnormal laboratory results. The subject was admitted to the hospital with cellulitis and treated with intravenous piperacillin/tazobactam and clindamycin. On Day 353, a nuclear magnetic resonance imaging suggested early osteomyelitis in the distal phalanx of the first digit. There was no drainable fluid collection, and soft tissue swelling was noted around the forefoot. An evaluation of the lower extremity arterial system was performed bilaterally using Doppler ultrasonography revealing scattered atherosclerotic disease with peripheral vascular disease of the lower extremities. The anterior tibial, posterior tibial, and peroneal arteries were monophasic to the ankle. Systolic blood pressure on the right side ranged from 107 mmHg to 122 mmHg. On Day 357, the subject underwent incision and drainage of the right great toe. During the procedure, pus was found to be draining from the distal tuft of the right first distal phalanx. The nail was removed as the skin underneath the nail bed was non-viable. A phalangectomy was performed and the entire bone was revealed to be completely eroded and osteomyelitic with pus emanating from the medullary canal of the bone. The subject was treated post operatively with antibiotic, anti-inflammatory, and analgesic medications during hospitalization (medications, study days, and doses unknown). The event of cellulitis resolved on Day 358, and the subject was discharged from hospital on Day 359. The action taken with the study medication was not applicable. The investigator considered the AE to be moderate in intensity. The subject completed Phase A of the study and entered Phase B on Day 183. The subject completed Phase B on Day 365.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 1342-1399 of 10826, available at:
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Figure 17: Graphical Patient Profile of Subject 0102405 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0102476: 74-year-old white female with T2D for approximately 12 years and chronic kidney disease was randomized to the ertugliflozin 15 mg arm in Trial P001/1016. He was receiving 56 IU daily insulin lispro (+) insulin lispro protamine when randomized. Other relevant past medical history includes cardiac failure chronic, dyslipidemia, hypertension, myocardial ischemia, peripheral venous disease, and diabetic neuropathy. The subject had no smoking history. Relevant prior medication included rosuvastatin 10 mg daily, carvedilol 13 mg daily, amlodipine (+) valsartan 5/160 mg daily, rilmenidine 1 mg daily, and indapamide 1.5 mg daily. The subject's blood pressure and heart rate (sitting, supine, standing, respectively) on Day 1 were 156/86 mmHg and 88 beats/min, 148/86 mmHg and 84 beats/min, and 150/88 mmHg and 90 beats/min. The electrocardiogram (ECG) was normal and showed heart rate 92 beats/min. On Day 73, the subject experienced a SAE of peripheral arterial occlusive disease (right lower limb ischemia [Stage IV peripheral arterial disease]). This event was considered serious due to requiring hospitalization. On Day 99, the subject was hospitalized for peripheral ischemia, when she presented with ulcer, edema and pain on the lower right limb, with the onset of conditions starting on Day 73 as an infected wound on the third right toe (non-serious AE wound infection [infected wound toe III right leg]; moderate intensity). The wound was treated with antibiotics and local care but the condition worsened to stage IV peripheral arterial disease and right lower limb ischemia. Toes II, III and IV were diagnosed with wet gangrene. She was recommended to undergo right lower extremity amputation which she declined. She ultimately underwent amputation of Toes II, III and IV on Day 101. The subject was treated with ciprofloxacin 400 mg daily from Day 120 ongoing for prophylaxis of infection. The study medication was not changed due to the event. The investigator considered the AE to be severe in intensity. The event resolved with sequelae of persistent pain of the right leg on Day 127. During hospitalization on Day 120, the subject experienced a serious adverse event of cardiac failure chronic (Heart Failure NYHA III), and she was transferred from the surgery department to the cardiology department. This event was considered serious due to prolonging hospitalization. On the same day, the subject also experienced a non-serious AE of atrial fibrillation, mitral valve incompetence (stage III mitral regurgitation), tricuspid valve incompetence, secondary pulmonary hypertension, pleurisy, normochromic normocytic anemia, and hypokalemia that were all assessed as mild in intensity. Physical examination at the time revealed blood pressure of 200/120 mmHg, heart rate of 100 bpm, arrhythmic cardiac sounds, bilateral subcrepitant rales, absent peripheral pulse of tibial and periosa arteries, and right foot gangrene. Hypokalemia by dilution was considered a sign of the subject's cardiac failure. ECG showed atrial fibrillation and left ventricular hypertrophy; sinus rhythm 70/min and rare supraventricular extrasystoles. Echocardiography revealed stage 3 mitral regurgitation, stage 2 tricuspid regurgitation, and moderate secondary pulmonary hypertension. Based on chest X-ray, and thoracic surgery consultation, left pleurisy was present, and left thoracentesis was performed. The worsening of cardiac failure was considered to be caused by the toe amputation on Day 101. The subject was treated with spironolactone 50 mg daily from Day 120 ongoing and furosemide 40 mg daily from Day 120 ongoing. The subject was also treated with candesartan 32 mg daily, metoprolol 12.5 mg daily, and amlodipine 5 mg daily from Day 120 ongoing for arterial hypertension; enoxaparin 1.6 mL daily from Day 120 to 127 for prophylaxis of thrombotic events; and pantoprazole 40 mg daily from Day 120 to ongoing for gastric protection. The heart failure symptoms improved. The study medication was not changed due to the event of cardiac failure chronic. The investigator considered the AE to be severe in intensity. The event of cardiac failure chronic resolved on Day 127. The subject was discharged from the hospital on Day 127. On Day 83, the subject experienced a non-serious AE of glomerular filtration rate decreased. At baseline, the subject's eGFR was 85 mL/min/1.73 m^2 (upper limit of normal: >60 mL/min/1.73 m^2) but decreased to 48 mL/min/1.73 m^2 on Day 45. On Day 83, the subject's eGFR was 42 mL/min/1.73 m^2. No medication treatment for the event of glomerular filtration rate decreased was indicated. The study medication was not changed due to the event. The investigator considered the AE to be mild in intensity. The outcome of the event of glomerular filtration rate decreased was unknown on Day 161. Of note, the subject's eGFR at Day -43 was 54 mL/min/1.73m2 and on Day -13 was 50 mL/min/1.73m2. The subject's last dose of study medication was taken on Day 98.

Source: Adapted from the Applicant's 04hcs5-b.pdf, Table 3 - Narratives for Non-Fatal Adjudicated Events, pages 858-896 of 4595, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-b.pdf

Figure 18: Graphical Patient Profile of Subject 0102476 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0102483: 64-year-old white male with T2D for approximately 25 years and chronic kidney disease was randomized to the ertugliflozin 15 mg arm in Trial P001/1016. He was receiving 68 IU daily insulin glulisine and 40 IU daily insulin glargine when randomized. His relevant medical history included anemia, angina pectoris/stent placement, peripheral arterial occlusive disease, diabetic neuropathy, foot deformity, hyperlipidemia, hypertension/hypertensive heart disease, and diabetic retinopathy. Relevant medications included rosuvastatin, nebivolol, isosorbide mononitrate, calcium dobesilate, ticlopidine, pentoxifylline, furosemide, and indapamide. The subject had no smoking history. On Day 30, he experienced a SAE of cellulitis (phlegmon of toe) leading to discontinuation of the study medication. This event was considered a SAE due to requiring hospitalization. The condition was treated with clindamycin and amoxicillin/clavulanic acid from Day 30 through 58 (dose, unit and frequency not available), betahistine, and bandaged with betadine. On Day 36, the subject's toe was amputated. The relevant course of hospitalization and medical consultations were not available. On Day 58, the subject was discharged from the hospital. The study medication was discontinued due to the event. The investigator considered the AE to be severe in intensity. The event of cellulitis resolved with sequelae on Day 36. The subject's last dose of study medication was taken on Day 28.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 1786-1813 of 10826, available at:
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Figure 19: Graphical Patient Profile of Subject 0102483 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0201036: 53-year-old white male with T2D for approximately 1 year was randomized to the ertugliflozin 15 mg arm in Trial P002/1013. He was receiving metformin 2250 mg daily when randomized. Other relevant past medical history included aortic disorder, polyneuropathy, spinal pain, dyslipidemia, myocardial infarction, peripheral artery bypass, peripheral ischemia, toe operation, peripheral venous disease, and current smoking habit of 18 cigarettes per day (11.4 pack-years). Relevant prior medication at the time of randomization included metoprolol, sulodexide, nafronyl oxalate, diosmin (+) hesperidin, and aspirin. On Day 223, the subject experienced a non-serious AE of peripheral ischaemia. A CT angiogram of the arteries in the lower extremities was normal, and the peripheral ischemia was deemed mild. On Day 250, the subject experienced a SAE of peripheral ischemia (progression of ischemic disease of lower extremities). This event was considered serious because it required hospitalization. On Day 250, the subject presented with pain of the lower extremities and was hospitalized. Upon hospitalization, the subject's physical examination showed symmetrical carotid pulses, no bruit differentiated, no elevated jugular venous pressure, no signs of inflammation or swelling of the lower extremities, no psoriatic lesions or pigmentation in lower legs, pulses were palpable in the left lower extremity only in the common femoral artery and the popliteal artery, and positive for bilateral bruits and bilateral varicose veins. The second digit on the left lower extremity was perfused with skin trophic disorder and a reddening in the instep, no fluctuation. The subject was treated with clopidogrel bisulfate 75 mg daily and pentoxifylline 800 mg daily from Day 250 until ongoing and clindamycin 900 mg daily from Day 250 through 266. On Day 251, a percutaneous transluminal angioplasty was performed. On Day 252, a distal left femoral-popliteal bypass of the left lower extremity was performed, and the second toe of the left lower extremity was amputated. The subject had a chronic obstruction of bilateral superficial femoral artery, and there was significant stenosis of the popliteal artery over 70% and gangrene on the second toe of the left lower extremity. The gangrene was related to progression of ischemic disease of the lower extremity resulting in the amputation. On Day 259, relevant lab values included osmolality 292 mmol/kg, BUN 11.5 mg/dL, creatinine 0.62 mg/dL, and estimated glomerular filtration rate 109.8 mL/min/1.73 m^2. On Day 260, the event of peripheral ischaemia resolved, and the subject was discharged from the hospital. The study medication was not changed due to the event. The investigator considered the AE to be mild in intensity on Day 223, progressing to severe on Day 250 (due to hospitalization). The subject completed Phase A of the study and entered Phase B, and discontinued from Phase B due to a reason of 'other' on Day 373. The subject's last dose of study medication was on Day 372.

Source: Adapted from the Applicant's 04hcs5-b.pdf, Table 3 - Narratives for Non-Fatal Adjudicated Events, pages 2474-2529 of 4595, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-b.pdf

Figure 20: Graphical Patient Profile of Subject 0201036 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0500303: 58-year-old white male with T2D for approximately 3 years was randomized to the ertugliflozin 15 mg arm in Trial P005/1019. He was receiving metformin 2000 mg daily when randomized. Other relevant past medical history included diabetic polyneuropathy, diabetic angiopathy of lower extremities, peripheral artery disease, and ex-smoker (36 pack-years). Relevant medication at the time of randomization included atorvastatin, nebivolol, and aspirin. On Day 155, the subject experienced a SAE of gangrene of the second toe of the left foot. This event was considered serious because hospitalization was required. On Day 155, the subject experienced aching in his left foot and was hospitalized. On presentation at the hospital, physical examination showed swelling and redness of the left foot and blackening of the second toe on the left foot with localized hyperthermia. Blood and wound cultures were not performed. On Day 166, the subject underwent amputation of the second toe of his left foot. The subject was treated with ceftriaxone 1 g IM twice daily for 5 days, ornidazole 100 mg IV twice daily for 5 days, pentosan polysulfate 1.0 mL IM daily for10 days, deproteinated bovine blood 25.0 mL IV daily for 20 days, Plastazole 50 mg orally twice daily, alfa lipoic acid 600 mg orally twice daily, and arginine hydrochloride 1 spoonful orally 3 times daily (further information not provided). The subject's condition improved after treatment; the post-operative wound was covered in granulating tissue. On Day 175, the subject was discharged from the hospital in stable condition. The study medication was not changed due to the event. The investigator considered the SAE to be severe in intensity. The event of gangrene resolved on Day 166. On Day 318, the subject experienced a serious adverse event of ischemic stroke. The event was considered serious because it was fatal. On Day 318, the subject had a headache and lost consciousness at home. The subject's wife called an ambulance and the emergency doctor identified the event as ischemic stroke. The subject died at home on Day 318. An autopsy was performed, but the results were not available. The event of ischaemic stroke lasted for 1 hour and was fatal. The subject completed Phase A of the study and entered Phase B on Day 190. The subject's last dose of study medication was on Day 318.

Source: Adapted from the Applicant's 04hcs5.pdf, Table 1 – Death Narratives, pages 907-949 of 1107, available at: \\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5.pdf

Figure 21: Graphical Patient Profile of Subject 0500303 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0710088: 56-year-old white male with T2D for approximately 7 years was randomized to the ertugliflozin 15 mg arm in Trial P007/1017. He was receiving metformin at randomization. Relevant medical history included dyslipidemia, hypertension and ex-smoker (21 pack-years). Relevant medication at the time of randomization included atorvastatin, enalapril, and amlodipine. On Day 211, the subject experienced a SAE of peripheral ischaemia (critical ischemia left foot) that was considered by the investigator to be of severe intensity. Prior to the event (Day 194), the subject experienced cellulitis of the left foot that despite antibiotic treatment worsened to critical ischemia. The subject was hospitalized on Day 227 and on Day 228 underwent amputation of the left second toe. The subject received ciprofloxacin, metronidazole, moxifloxacin hydrochloride, acetaminophen (+) tramadol hydrochloride for the events. Follow-up on Day 274 revealed no sepsis and good wound healing. No action was taken with the study medication due to the events. The SAE of peripheral ischemia resolved on Day 230 and the subject was discharged from the hospital on the same day. The AE of cellulitis resolved on Day 236. On Day 398, the subject experienced an SAE of cellulitis of the third metatarsal head that was considered by the investigator to be of moderate intensity. On the same day, the subject also experienced a non-SAE of possible osteitis of the third metatarsal head that was considered by the investigator to be of moderate intensity. The subject was hospitalized on Day 405 and on Day 406, an X-ray of the limb revealed thickening of the third proximal phalanx, soft tissue swelling, and suspected chronic osteomyelitis. On Day 407, an amputation was done on the left third toe. The subject received sulfamethoxazole (+) trimethoprim and moxifloxacin hydrochloride for the event. No action was taken with the study medication due to the events. The SAE of cellulitis and the AE of osteitis both resolved with sequelae on Day 409, and the subject was discharged from the hospital on the same day. The subject continued participation in the 104-week study on study medication.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 8974-9022 of 10826, available at:
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Figure 22: Graphical Patient Profile of Subject 0710088 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

ERTUGLIFLOZIN 15 MG ARM

Subject 0710319: 63-year-old white male with T2D for approximately 28 years was randomized to the ertugliflozin 15 mg arm in Trial P007/1017. He was receiving metformin 3000 mg daily at randomization. Relevant medical history included embolism (thromboembolism of popliteal; postsurgical), hypertension, hyperlipidemia, atrial fibrillation, congestive cardiomyopathy, coronary artery disease, ischaemic stroke, peripheral artery aneurysm (popliteal), and diabetic retinopathy. The subject had no smoking history. Relevant medication at the time of randomization included indapamide (+) perindopril arginine, atorvastatin, carvedilol, aspirin (+) bisoprolol fumarate, piracetam, pentoxifylline, and acenocoumarol. On Day 334, the subject experienced a SAE of peripheral ischaemia (critical limb ischemia of left leg) that was considered by the investigator to be of severe intensity. On Day 339, the subject's laboratory tests results were CRP 218.5 mg/L (normal range: 0 - 10 mg/L), international normalized ratio (INR) 4.93 (normal range: 2-3), blood glucose: 14.6 mmol/L (normal range: 3.6 - 6.1 mmol/L), and white blood cell: 16.33 x 109/L (normal range: 4.5-11 x 109/L). The subject was hospitalized on Day 340 and underwent left femoral amputation on Day 342. The subject received pharmacological treatment for the SAE. The SAE resolved on Day 342. During hospitalization, the subject also experienced an SAE of pulmonary embolism on Day 352 and an SAE of cardiac failure (cardiac decompensation) on Day 354 both were considered by the investigator to be of severe intensity. On Day 354, chest CT scan revealed pulmonary embolism, hydrothorax and pericardial fluid; abdominal CT revealed ascites, expanded colon, atherosclerotic aorta and prostate hyperplasia. On Day 355, laboratory tests results were: INR: 1.22 (normal range: 0.8-1.2), activated partial thromboplastin time 34.6 sec (normal range: 26.4-37.5 sec), fibrin D-dimer 4.73 µg/mL (normal range: not specified), prothrombin time 13.2 sec (normal range: 9.7-11.8 sec). The subject received enoxaparin sodium for the SAE of pulmonary embolism. The subject experienced adverse events of ileus, hypokalemia, atrial fibrillation, hypotension, metabolic acidosis (arterial blood gas results were not available; blood pH on Day 360 was 7.5), dyspnoea and anxiety during hospitalization. The SAE of pulmonary embolism resolved on Day 360 and SAE of cardiac failure resolved on Day 366, when the subject was discharged from intensive care unit. The subject was discharged from the hospital on Day 472. The subject discontinued study medication on Day 342 due to the SAE of peripheral ischaemia and continued to be followed post-treatment.

Source: Adapted from the Applicant's 04hcs5-a.pdf, Table 2 - Narratives for Serious Adverse Events Not Meeting Criteria for CV Adjudication, pages 9384-9429 of 10826, available at:
\\cdsesub1\evsprod\nda209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04hcs5\04hcs5-a.pdf

Figure 23: Graphical Patient Profile of Subject 0710319 (Ertugliflozin 15 mg Arm)

Source: Derived in JReview using the adsl.xpt, mhplus.xpt, aeplus.xpt, prplus.xpt, and adlb.xpt
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AHA, American Heart Association; BUN, blood urea nitrogen; CREAT, creatinine; eGFR, estimated glomerular filtration rate; MHDECODE, medical history decode; PRDECOD, procedure decode; PRDURDD, procedure duration; PRRELSAE, procedure related to an SAE; and PRRESULT, procedure result; and SGLT2 Inhib, sodium-glucose cotransporter 2 inhibitor.

13.10. Follow-Up-Adjusted Incidence Rate of Amputations (Trial P004/1021)

Table 47: Subjects with Amputations (All Post-Randomization Follow-up*)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2744		2746		2747		5493		8237	
with one or more Amputations	**19**	**(0.7)**	**31**	**(1.1)**	**22**	**(0.8)**	**53**	**(1.0)**	**72**	**(0.9)**
with no Amputations	2725	(99.3)	2715	(98.9)	2725	(99.2)	5440	(99.0)	8165	(99.1)
Surgical and medical procedures										
Toe amputation	10	(0.4)	21	(0.8)	10	(0.4)	31	(0.6)	41	(0.5)
Leg amputation	7	(0.3)	6	(0.2)	7	(0.3)	13	(0.2)	20	(0.2)
Foot amputation	6	(0.2)	4	(0.1)	4	(0.1)	8	(0.1)	14	(0.2)
Amputation	0		1	(<0.1)	1	(<0.1)	2	(<0.1)	2	(<0.1)
Finger amputation	0		2	(0.1)	0		2	(<0.1)	1	(<0.1)
Limb amputation	1	(<0.1)	0		1	(<0.1)	1	(<0.1)	2	(<0.1)
Metatarsal excision	1	(<0.1)	0		0		0		1	(<0.1)
Events/Subject-Years Follow-up Time (1000-Subject-Years Incidence Rate)	**19/4242.4 (4.5)**		**31/4256.3 (7.3)**		**22/4231.6 (5.2)**					

Source: Adapted from the Applicant's CVOT amputation rates – multi-module-info-amendment-12oct2017, labeled as Tables 10.012 and 14.3.1.1.11, pages 1-2 of 4, available at: \\CDSESUB1\evsprod\NDA209803\0037\m1\us\multi-module-info-amendment-12oct2017.pdf

Note: Every subject was counted a single time for each applicable row and column. Three subjects (i.e., Ertugliflozin 5 mg arm with a toe amputation; ertugliflozin 15 mg arm with a leg amputation; and placebo arm with a ray amputation) had amputations identified via SAE comment text search and are not represented in the table. Queries have been sent to investigators to enter these procedures into the procedures database. Two finger amputations (one due to squamous cell carcinoma and a second due to osteomyelitis) subjects in the ertugliflozin 5 mg arm were included in this table.

* Surgical procedures between the first dose of treatment and last follow-up visit, regardless of last date of dosing with study medication, including events after initiation of glycemic rescue medication (i.e., on-study events).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK PUCINO
12/01/2017

WILLIAM H CHONG
12/04/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number(s): 209803, 209805, 209806 **Applicant:** Merck **Stamp Date:** December 19, 2016

Drug Name(s): **NDA/BLA Type:** Standard

STEGLATRO (Ertugliflozin)
STEGLUJAN (Ertugliflozin/Sitagliptin) Fixed Combination Drug Product (FCDP)
SEGLUROMET (Ertugliflozin/Metformin) FCDP

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	√			These Applications were submitted using eCTD format.
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	√			The labels conforms to the final rule governing the "Requirements On Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 18, 2006.
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
10.	Has the applicant submitted a benefit-risk analysis for the product?	√			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1) new molecular entity (NME; NDA 209803), FCDP with non-new molecular entities (NDA 209805 and NDA 209806). NDA 209806 is a 505(b)(2)

	Content Parameter	Yes	No	NA	Comment
					Application. The Applicant has provided Drug Master Files Letters of Authorization for metformin (b) (4) and will use GLUCOPHAGE (metformin hydrochloride) as the listed drug product.
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				GLUCOPHAGE (NDA 020357; metformin)
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	√			
14.	Describe the scientific bridge (e.g., BA/BE studies)				The Applicant has conducted bioequivalence studies (P027/1041 and P050/1058) to demonstrate bioequivalence of the FCDP to the individual components.
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:	√			Single ertugliflozin doses up to 300 mg and multiple doses up to 100 mg daily x 2 weeks, and 25 mg daily x 12 weeks have been studied.
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **NDA 209803** **Indication:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). **NDA 209805** **Indication:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) when treatment with both ertugliflozin and sitagliptin is appropriate. **NDA 209806** **Indication:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	√			All trials were submitted to NDA 209803. NDA 209805 will be supported by Trials P005/1019 (factorial design); P005/1019 co-administration with sitagliptin); P017/1047 (co-administration with sitagliptin); and P006/1015 (add-on to metformin and sitagliptin). NDA 209806 will be

	Content Parameter	Yes	No	NA	Comment
	(T2D) (b) (4) **Trial #1 (P003/1022):** Monotherapy; 52 weeks (26-week, double-blind, placebo-controlled, 26-week active-controlled); placebo vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg. **Trial #2 (P007/1017):** Combination therapy with metformin; 104 weeks (26-week, double-blind, placebo-controlled, 78-week active-controlled); placebo vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg. **Trial #3 (P002/1013):** Combination therapy with metformin; 104 weeks (52-week, double-blind, active comparator-controlled, 52-week, double-blind, active comparator-controlled); glimepiride vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg. **Trial #4 (P005/1019):** Combination therapy with metformin; 52 weeks (26-week, double-blind, active-controlled, 26-week active-controlled); ertugliflozin 5 mg + sitagliptin 100 mg vs. ertugliflozin 15 mg + sitagliptin 100 mg vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg vs. sitagliptin 100 mg. **Trial #5 (P006/1015):** Combination therapy with metformin and sitagliptin; 52 weeks (26-week, double-blind, placebo-controlled, 26-week, double-blind, placebo-controlled); placebo vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg **Trial #6 (P017/1047):** Combination therapy; 26-week, double-blind, placebo-controlled; placebo vs. ertugliflozin 5 mg + sitagliptin 100 mg vs. ertugliflozin 15 mg + sitagliptin 100 mg **Trial #7 (P001/1016; moderate renal impairment):** Special Population; non-metformin antihyperglycemic agents allowed; 52 weeks (26-week, double-blind, placebo-controlled, 26-week, double-blind, placebo-controlled); placebo vs. ertugliflozin 5 mg vs. ertugliflozin 15 mg				supported by Trials P007/1017 (add-on to metformin); P002/1013 (add-on to metformin); P006/1015 (add-on to metformin and sitagliptin); and P005/1019 (add-on to metformin).
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of			√	Between 20-67% of the all subjects treated

	Content Parameter	Yes	No	NA	Comment
	medicine in the submission?				populations (i.e., ~37%) from the seven Phase 3 trials were from North America (excluding Central America).
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	√			The Definitive QTc Study submitted to the Applications was P1010/1025.
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			√	These products are not currently marketed anywhere in the world. However, the Applicant has evaluated safety based on the known toxicity profiles of approved products in the respective pharmacologic class.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	√			In the all subjects as treated population, 3409 subjects were exposed to ertugliflozin, of which 553 were exposed for 25-50 weeks, 2204 for 50-76 weeks and 337 for 76-102 weeks.
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			Adverse events were coded using MedDRA version 19.0
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			Please refer to #22 above.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			√	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			For NDA 209803, the Applicant is requesting a waiver for pediatric subjects 0-<10 years, and we agreed on a deferral of a study in pediatric subjects 10 to <18 years until completion of the adult core Phase 3 glycemic efficacy studies confirming efficacy and safety (iPSP, August 26, 2013). For (b) (4) (NDA 209805 (b) (4) , we agreed to a waiver for all pediatric populations.
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	√			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
37.	Are all datasets to support the critical safety analyses available and complete?	√			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not Applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

From a clinical perspective, there were no major review issues identified at this time.

Frank Pucino, PharmD, MPH — January 29, 2017
Reviewing Medical Officer — Date

William Chong, MD — February 16, 2017
Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK PUCINO
02/16/2017

WILLIAM H CHONG
02/16/2017