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APPLICATION NUMBER:

210874Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA) / Supplemental NDA (sNDA)
Application Number(s)	NDA 210874 / NDA 209091/S-002
Priority or Standard	Standard
Submit Date(s)	July 2, 2018
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PDUFA Goal Date	May 2, 2019
Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	March 25, 2019
Established/Proper Name	Dapagliflozin + Saxagliptin + Metformin HCl Extended-Release / Dapagliflozin + Saxaglitpin HCl (b) (4)
(Proposed) Trade Name	QTERNMET XR / QTERN
Applicant	AstraZeneca
Dosage Form(s)	QTERNMET XR: The Applicant is seeking approval of film-coated tablets containing the following dapagliflozin/saxagliptin/metformin extended-release dosage strengths: 2.5 mg/2.5 mg/1000 mg; 5 mg/2.5 mg/1000 mg; 5 mg/5 mg/1000 mg; 10 mg/5 mg/1000 mg QTERN: Film-coated tablets containing 10 mg of dapagliflozin and 5 mg of saxagliptin are currently approved. The Applicant is seeking approval of a dapagliflozin 5 mg/saxagliptin 5 mg dosage strength.
Applicant Proposed Dosing Regimen(s)	QTERNMET XR: Once daily oral administration. QTERN: Once daily oral administration.
Applicant Proposed Indication(s)/Population(s)	QTERNMET XR: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) (b) (4) QTERN: 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.
Recommended Indication(s)/Population(s) (if applicable)	The recommended labeling change for Section 1 of QTERNMET XR and QTERN to include: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended labeling change for Section 2.2 to include: No dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m^2 and to contraindicate use with an eGFR below 45 mL/min/1.73 m^2.

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Glossary

4MSU	4-Month Safety Update
AACE	American Association of Clinical Endocrinologists
ABNL	Abnormal
AC	Advisory Committee
ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
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
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area-Under-the-Curve
AZ	AstraZeneca
β-cell	Beta-Cell
BE	Bioequivalence
BG	Blood Glucose
BILI	Bilirubin
BMD	Bone Mineral Density
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BW	Body Weight
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDS	Core Data Sheet
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval

CKD 3A	Chronic Kidney Disease Stage 3A
ClinRO	Clinician Reported Outcome
C_{max}	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Controls
CMQ	Custom MedDRA Query
COA	Clinical Outcome Assessment
COPD	Chronic Obstructive Lung Disease
C-Peptide	Connecting Peptide
CR	Complete Response
CRCL	Creatinine Clearance
CRF	Case Report Form
CRL	Complete Response Letter
CRO	Contract Research Organization
CRT	Clinical Review Template
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcomes Trial
CT	Computed Tomography
Dapa	Dapagliflozin
DB	Double-Blind
DBP	Diastolic Blood Pressure
D/C	Discontinuation
DCCT	Diabetes Control and Complication Trial
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
EASD	European Association for the Study of Diabetes
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End-Of-Study
EOT	End-Of-Treatment
ESRD	End Stage Renal Disease
ETMF	Electronic Trial Master File
EU	European Union
FAERS	FDA Adverse Event Reporting System
FAS	Full Analysis Set

FCDP	Fixed Combination Drug Product
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide 1
GM	Geometric Mean
GRand	Global Randomization
H	Hour
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HCl	Hydrochloride
HDL-C	High-Density Lipoprotein Cholesterol
HDPE	High-Density Polyethylene
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HX	History
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
iPSP	Initial Pediatric Study Plan
IQR	Interquartile Range
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LT	Long-term
LTSS	Long Term Stability Study
MACE	Major Adverse Cardiovascular Event
MAR	Missing at Random
MDRD	Modification in Diet and Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEDS	Medications
MET	Metformin
MTT	Mixed Meal Tolerance Test
MMRM	Mixed Effects Model with Repeated Measures

NAI	No Action Indicated
NDA	New Drug Application
NGSP	National Glycohemoglobin Standardization Program
NO	Number
NLR	Normal laboratory range
NYHA	New York Heart Association
OAI	Official Action Indicated
ObsRO	Observer Reported Outcome
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PDLC	Predefined Limits of Change
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PerfO	Performance Outcome
PIND	Pre-Investigational New Drug
PK	Pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PO	Orally ('per os')
PPG	Postprandial Glucose
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PT	Preferred Term
QD	Daily
R	Randomization
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAXA	Saxagliptin
SBP	Systolic Blood Pressure
Scr	Serum Creatinine
SGLT2	Sodium-Glucose Cotransporter 2
SLC	Safety Labeling Change
SMQ	System MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SPOOS	Significant Payments of Other Sorts
ST	Short-term
$T_{1/2}$	Elimination Half-Life
T1D	Type 1 Diabetes Mellitus

T2D	Type 2 Diabetes Mellitus
TBILI	Total Bilirubin
TC	Total Cholesterol
TG	Triglycerides
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
TID	Thrice Daily
T_{max}	Time to maximum plasma concentration
Total-C	Total Cholesterol
TSH	Thyroid-Stimulating Hormone
TSI	Tracked Safety Issue
UA	Uric Acid
UACR	Urine Albumin-To-Creatinine Ratio
UGE	Urinary Glucose Excretion
UGT1A9	UDP-glucuronosyltransferase 1A9
ULN	Upper Limit of Normal
US	United States
USA	United States of America
USPI	United States Package Insert
UKPDS	United Kingdom Prospective Diabetes Study
V	Visit
VAI	Voluntary Action Indicated
Wk	Week
WOCBP	Women of Childbearing Potential
XR	Extended-release
YR	Year

1. Executive Summary

1.1. Product Introduction

QTERNMET XR (dapagliflozin, saxaglip0tin and metformin HCl extended-release) is a new fixed combination drug product (FCDP) submitted for marketing approval by the AstraZeneca Pharmaceuticals LP (referred to as the Applicant throughout the remainder of this review) as a New Drug Application (NDA 210874) in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act[1] and Section 314 of Title 21 CFR 314.50.[2]

The components of QTERNMET XR are approved antihyperglycemic agents with an indication as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Dapagliflozin 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.[3] Saxagliptin 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 type 2 diabetes mellitus (T2D).[4] Metformin, a biguanide, improves glucose tolerance, decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5] The combination of an SGLT2 inhibitor with a DPP-4 inhibitor, added onto background metformin therapy[6-8] and the combination of an SGLT2 inhibitor[5,9-12] or a DPP-4 inhibitor[13-18] with metformin all provide complementary mechanisms of action to improve glycemic control.

The proposed indication for QTERNMET XR is as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) QTERNMET XR will be available as a film-coated tablet for once daily oral administration, and will contain the following dapagliflozin/saxagliptin/metformin extended-release dosage strengths: 2.5 mg/2.5 mg/1000 mg; 5 mg/2.5 mg/1000 mg; 5 mg/5 mg/1000 mg; 10 mg/5 mg/1000 mg.

QTERN (NDA 209091) is a dapagliflozin/saxagliptin FCDP approved on February 27, 2017.[19] This product is indicated 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.[6] QTERN is currently only available as a film-coated tablet for once daily oral administration, containing 10 mg of dapagliflozin and 5 mg of saxagliptin. The Applicant is seeking approval of a dapagliflozin 5 mg/saxagliptin 5 mg dosage strength, with an expanded indication as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) .

In the Applicant's proposed labeling for QTERNMET XR and revised labeling for QTERN, (b) (4) However, based on efficacy and safety data from study D1690C00024 (DERIVE), a dedicated moderate renal impairment clinical trial, the Agency recently approved (February 22, 2019) two supplemental NDAs (sNDAs)—one for FARXIGA (sNDA 202293-015; dapagliflozin) and a second for XIGDUO XR (sNDA 205649-009; dapagliflozin/metformin extended-release FCDP). Prescribing Information for each product was revised to reflect that no dose adjustment is needed for patients with an eGFR ≥45 mL/min/1.73 m^2. Considering these approvals, as well as the approved use of a saxagliptin 5 mg daily dose in patients with an eGFR ≥45 mL/min/1.73 m^2,[20] I recommend that the labeling of QTERNMET XR and QTERN state that no dose adjustment is necessary for patients with an eGFR ≥45 mL/min/1.73 m^2.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend an approval action for NDA 210874 (QTERNMET XR) and sNDA 209091-002 (QTERN), pending agreement on proposed labeling. In accordance with 21 CFR 314.126(a)(b),[21] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of these Applications.

To support the proposed indication for QTERNMET XR and revised indication for QTERN, the Applicant has provided clinical data from two pivotal clinical trials (i.e., D1683C00005 and CV181169) which evaluated the concomitant addition of dapagliflozin and saxagliptin to background metformin therapy (≥1500 mg per day) in adult T2D patients with inadequate glycemic control. Trial D1683C00005, a 24-week randomized, double-blind, active-controlled, parallel group Phase 3 clinical trial, compared the efficacy and safety of dapagliflozin 5 mg plus saxagliptin 5 mg plus metformin to dapagliflozin 5 mg plus metformin or saxagliptin 5 mg plus metformin. Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in hemoglobin A1c [HbA1c] from baseline to Week 24, using a return to baseline washout analytical approach for individuals with missing data), the triple therapy arm resulted in a modest but statistically significant HbA1c reduction compared to the dapagliflozin dual therapy arm (-0.40%; 95% confidence interval [CI], -0.55%, -0.24%) and the saxagliptin dual therapy arm (-0.32% [95% CI -0.48%, -0.17%]).

Trial CV181169, a 24-week randomized, double-blind, active-controlled, parallel group Phase 3 trial, compared the efficacy and safety of dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin (≥1500 mg per day) to dapagliflozin 10 mg plus metformin or saxagliptin 5 mg plus metformin. Again, using the Agency's preferred analysis, the triple therapy arm resulted in a statistically significant HbA1c reduction compared to the dapagliflozin dual therapy arm (-0.26% [95% CI -0.47%, -0.05%]) and the saxagliptin dual therapy arm (-0.49% [95% CI -0.70%, -0.27%]).

Efficacy and safety data from three additional Phase 3 trials (CV181168, CV181365, and CV181369) also were submitted to support the pivotal efficacy trials for these Applications. Trial CV181168 was a 24-week (with a 28-week long-term [LT] extension), randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial designed to evaluate the efficacy and safety of stepwise (sequential) addition of saxagliptin to dapagliflozin plus metformin compared with the addition of placebo to dapagliflozin plus metformin in subjects with T2D who had inadequate glycemic control on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). This trial was the pivotal Phase 3 trial used to support the approval of QTERN.[22] Trial CV181365, a 52-week randomized, double-blind, active-controlled, parallel-group study (with a blinded 104-week extension), compared the efficacy and safety of dapagliflozin 10 mg plus saxagliptin 5 mg as add-on therapy with metformin to glimepiride (up to 6 mg/day) plus metformin in T2D subjects with inadequate control on metformin monotherapy (≥1500 mg/day). Trial CV181369 is a noninferiority trial that compared the efficacy and safety of dapagliflozin plus saxagliptin as add-on therapy with metformin to insulin glargine plus metformin in adult T2D subjects with inadequate glycemic control on metformin therapy (≥1500 mg/day) with or without a sulfonylurea. The results of all three trials were supportive (i.e., triple therapy was noninferior to insulin plus metformin or resulted in statistically significant greater reductions in HbA1c from baseline vs. comparison arms).

In summary, the chemical and pharmacologic characteristics of dapagliflozin, saxagliptin and metformin are well-known, and there is extensive clinical experience with their use worldwide. Further, the established efficacy and safety profiles of these products, and the overall risk/benefit assessment of dapagliflozin plus saxagliptin as add-on metformin therapy in subjects with T2D who have inadequate glycemic control with metformin monotherapy supports approval of these Applications.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated 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). Therapies for T2D have focused on improving glycemic control as assessed by change in hemoglobin A1c (HbA1c). While there are multiple drug products approved both as individual drugs and as FCDPs, many patients are unable to achieve glucose targets. Thus, additional therapeutic options are needed to facilitate individualization of therapy.

QTERNMET XR is a combination of dapagliflozin, a SGLT2 inhibitor, saxagliptin 5 mg, a DPP-4 inhibitor, and metformin extended-release, a biguanide. The three active pharmaceutical ingredients are combined at a fixed dosage which allows for dosing of all three products via a single tablet formulation. The proposed dosage strengths of the dapagliflozin/saxagliptin/metformin tablets (i.e., 2.5mg/2.5 mg/1000 mg; 5 mg/2.5 mg/1000 mg; 5 mg/5 mg/1000 mg; and 10 mg/5 mg/1000 mg) are intended to support approved doses of dapagliflozin (5-10 mg/day),[23] saxagliptin (5 mg/day),[20] and metformin (1000-2000 mg/day).[24]

The contribution of the three components to the claimed effect has been demonstrated at the doses studied in the pivotal and supporting Phase 3 clinical trials. The results of these trials provide evidence that the combination of dapagliflozin and saxagliptin, added to maximum tolerated background metformin (≥1500 mg/day), is statistically superior to either of the individual components in reducing HbA1c at 24 weeks. It is notable that the labeled recommended starting dose of dapagliflozin is 5 mg once daily, which is subsequently titrated to 10 mg daily in patients tolerating the 5 mg dose should additional glycemic control be required.

The safety profiles of the QTERNMET XR and QTERN are reflective of individual components of these products. The most common adverse reactions (reported in >5% of subjects) were respiratory tract infections (13.6%), urinary tract infections (5.7%), and dyslipidemia (5.1%), which are also common to either saxagliptin and/or dapagliflozin separately. Although antihyperglycemic FCDPs have a potential for an increased risk of hypoglycemia compared to the individual components, the incidence of hypoglycemia (defined as blood glucose <54 mg/dL regardless of the presence or absence of symptoms) and severe hypoglycemia (events requiring assistance due to neuroglycopenia, characterized by altered mental and/or physical status) were 1% and 0.2%, respectively, and no subjects discontinued study medication due to hypoglycemia.

Elevations in serum creatine kinase (CK) constituted a unique safety finding observed at the time of approval of QTERN. In the pooled safety analysis, an imbalance in the number of subjects who experienced marked serum CK elevations >10x the upper limit of normal (a marker of muscle injury/necrosis) was observed in the dapagliflozin plus saxagliptin treatment arms. These marked laboratory changes were reported in five (1%) dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin treated subjects compared to one subject (0.3%) randomized to dapagliflozin plus metformin, and no subjects randomized to saxagliptin plus metformin. Although these laboratory abnormalities were typically asymptomatic, transient (approximately two weeks in duration), and did not require discontinuation of therapy, rhabdomyolysis was reported for one of the five subjects with CK elevations with no other obvious cause identified. Pre-existing comorbidities in this subject make the assessment of causality challenging. It is somewhat reassuring that no further cases of marked CK elevations were reported with the submission of safety data from four additional clinical trials with the current Applications.

In summary, the data suggests that each of the components of the FCDP contribute to improving glycemic control at the doses evaluated in the pivotal and supporting Phase 3 clinical trials. However, there remains some concern regarding the potential for an increased risk for muscle injury/necrosis incurred with the use of the FCDP over the use of the individual components alone. I believe that the overall benefit-risk for patients is favorable and that the musculoskeletal safety concern has been addressed through labeling and can continue to be evaluated with routine pharmacovigilance. Thus, I would recommend approval of QTERNMET XR and expanding the indication for QTERN.

Benefit-Risk Dimensions

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.[25-28] The Center for Disease Control (CDC) estimates that nearly 30 million people with T2D in the United States.[27,29]	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),[30-36] the United Kingdom Prospective Diabetes (UKPD) study,[28,37-40] and the Kumamoto Study,[41] 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.[42] 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.[42-45] • While all approved antihyperglycemic medications have been shown to improve glycemic control, data on the ability of many of these agents to improve clinical outcomes is generally limited or not available.	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
Benefit	• The results the five Phase 3 clinical trials demonstrate that the addition of dapagliflozin (5 mg or 10 mg) added to saxagliptin 5 mg plus metformin results in better glycemic control (i.e., greater HbA1c reductions) compared to the individual components or glimepiride plus metformin and is noninferior to insulin glargine plus metformin at the doses evaluated in the trials.	The two pivotal clinical trial (i.e., D1683C00005 and CV181169) have provided sufficient evidence to support efficacy of QTERNMET XR, as well as an expanded indication for QTERN. Additionally, these trials and the supporting Phase 3 clinical trials (i.e., CV181168, CV181365, and CV181369) provide support that dapagliflozin and saxagliptin added to metformin background antihyperglycemic therapy has added benefit on glycemic control over the individual components at the doses used in these studies. The benefit of the triple therapy product would be most relevant to the population of T2D patients with inadequate glycemic control despite maximum tolerated treatment with metformin (≥1500 mg/day), as this population was evaluated in the pivotal Phase 3 clinical trials. It is acknowledged that dual or triple FCDPs may limit flexibility in dose adjustments. However, based on usage data, the proposed dose formulations of QTERNMET XR and QTERN should be sufficient for dose adjustments in the majority of the intended patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The risk associated with these FCDPs are consistent with would be expected by combining the safety profile of the individual products. • The main safety issue was a numeric imbalance of marked laboratory elevations of creatinine kinase (i.e., >10 times the upper laboratory limits) occurring in the dapagliflozin plus saxagliptin plus metformin treatment arms, with one case of rhabdomyolysis reported. This marked laboratory abnormality was previously identified in the QTERN clinical program, and no new cases were reported with the current submission that included safety data from four additional clinical trials. This safety concern is already included in labeling for QTERN, and the Applicant proposes to include the same information in Section 6.1 (Clinical Trials Experience) of QTERNMET XR labeling. • No risk evaluation and mitigation strategy is recommended for this product.	The clinical risks associated with use of the dapagliflozin plus saxagliptin plus metformin are what would be expected with the use of these drugs individually. However, a numeric imbalance in the number of cases of marked elevations in serum CK concentrations was observed in subjects randomized to the dapagliflozin 10 mg/day plus saxagliptin 5 mg/day plus metformin (≥1500 mg/day) treatment arms. Although these marked laboratory changes were typically asymptomatic, transient in nature, and did not require discontinuation of investigational product, a case of rhabdomyolysis was previously reported in a patient with other comorbidities for which other obvious causes were not identified. This potential safety signal is addressed in proposed product labeling, and continued pharmacovigilance is recommended.

1.4. Patient Experience Data

Subject-reported changes from baseline in treatment satisfaction, quality of life scales, and barriers to medication adherence were reported for one of the supporting trials (CV1811369). These data were considered exploratory by the Applicant, were not included in a hierarchical testing procedure to adjust for multiple testing, and were not intended for product labeling. The data were not submitted or evaluated and will not be discussed further in this review.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

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 β-cell dysfunction and resistance to insulin activity with inadequate insulin production to maintain euglycemia).[46,47] According to the 2017 National Diabetes Statistics Report, diabetes affects an estimated 30.3 million people within the United States (U.S.),[29] of which T2D accounts for 90-95% of all diagnosed cases.[27,29] 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.[48]

Patients with T1D may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2D may present similarly but may also be asymptomatic. As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy)[25] and macrovascular (e.g., myocardial infarction, stroke) complications.[26,28] 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.[49] Diabetes remains a leading cause of kidney failure,[50] adult-onset blindness,[51,52] and non-traumatic lower limb amputations.[53,54] Additionally, people with diabetes are more than twice as likely to have cardiovascular disease (CVD) or stroke as nondiabetic individuals—and at an earlier age.[55,56] Several reports suggest that CVD may affect approximately 40% of T1D patients over 65 years of age and 32% of persons with T2D.[57] Diabetes was the seventh leading cause of death in 2015,[29] and CVD remains a major cause of death among diabetics. Additionally, between 2009 and 2015, an increase in diabetes-related lower extremity amputations was observed nationally, annual emergency department visits for hyperglycemic crisis almost doubled (i.e., from 16.2 to 29.4 per 1000), hospitalizations increased by 73% (from 15.3 to 24.2 per 1000), and deaths increased by 55% (from 15.7 to 24.2 per 1000).[58-60] Based on the results of the Diabetes Control and Complication Trial (DCCT),[30-36] the United Kingdom Prospective Diabetes Study (UKPDS),[28,37-40] and the Kumamoto Study,[41] 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 29, Appendix 13.3). 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.[44] 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.[61] The ADA/EASD report recommends initiating antihyperglycemic therapy for the management of T2D with metformin as monotherapy. According to a 2008-2015 Medical Expenditure Panel Survey, approximately 56% of adult diabetics in the U.S. used a single antihyperglycemic medication, of which 51% of these individuals used metformin.[62] 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, such as a glucagon-like peptide 1 (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.[44] Similar recommendations also have been published in the ADA's Standards of Medical Care in Diabetes–2019,[42] and suggested by the American College of Physicians (ACP),[63,64] and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE).[65] The AACE/ACE also recommends initiating metformin plus a second antihyperglycemic agent for patients presenting with an HbA1c >7.5%.[65] In a retrospective cohort study that included patients with an HbA1c ≥8% after at least three months of metformin therapy, earlier antihyperglycemic treatment intensification was associated with lower HbA1c concentrations.[66] Several studies also have reported advantages from adding a third noninsulin agent,[44,67-69] as well as triple therapy with both oral and injectable antihyperglycemic agents.[70-73] 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).[74] Additionally, three FCDPs that contain an SGLT2 inhibitor plus a DPP-4 inhibitor (i.e., empagliflozin/linagliptin,[75,76] dapagliflozin/saxagliptin,[6,19] and ertugliflozin/sitagliptin[7,77]) were approved primarily based on Phase 3 trials which demonstrated improved glycemic control as add-on therapy in combination with metformin (i.e., triple therapy).

Over time, due to progressive loss of β-cell function (i.e., decreased insulin secretion), many patients with T2D may require and benefit from the addition of insulin therapy.[42,78] Initiation of insulin therapy also may be considered earlier when hyperglycemia is severe (e.g., blood glucose is ≥300 mg/dL or hemoglobin A1c [HbA1c] >10%), hyperglycemic symptoms (e.g., polyuria or

polydipsia) are present, or there is evidence of increased catabolism (e.g., weight loss, hypertriglyceridemia, ketosis).[42]

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, Semaglutide
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, Ertugliflozin
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/.
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 Table 29, Appendix 13.3.

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.[79-81] Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations (please refer to Table 29).[42,64,65] 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, acute kidney injury and pancreatitis, and allergic reactions have been reported with DPP-4 inhibitors and GLP-1 receptor agonists. Additionally, metabolic acidosis has occurred with the use of metformin (lactic acidosis) and SGLT2 inhibitors (ketoacidosis). 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, difficulty with administering accurate doses). Additionally, insulin products often require patient self-monitoring of blood glucose and increase the risk of hypoglycemia in combination with other antihyperglycemic agents, while inhaled insulin (e.g., AFREZZA) is contraindicated in patients with chronic obstructive lung disease (COPD). More recently, the FDA issued Drug Safety Communications to warn the public of increased risks of lower extremity amputations[82,83] and Fournier's gangrene[84] with SGLT2 inhibitors.

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.[85] Nonadherence to oral antihyperglycemic agents has been reported in 7%-64% of patients with T2D,[86,87] and has been associated with poor glycemic control,[88,89] diabetes-related hospitalizations[90,91] and increased mortality.[90] For patients requiring combination antihyperglycemic therapy, adherence may improve with a reduction in pill burden through the use of FCDPs.[92-94] 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. Additionally, as noted above, antihyperglycemic therapy may need to be individualized based on comorbid medical conditions (see Appendix 13.3, Table 29).

Rationale for the Use of Dapagliflozin-Containing Products in T2D Patients with Moderate Renal Impairment (i.e., eGFR 45-60 mL/min/1.73 m^2):

Diabetic kidney disease occurs in 20-40% of patients with diabetes,[25] with approximately 22% of individuals with T2D having an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (i.e., CKD stage ≥3).[95] Further, diabetic kidney disease can progress to end-stage renal disease (ESRD) and is the leading cause of ESRD in the U.S.[25,96,97] In the UKPDS, 29% of T2D patients

developed renal impairment within 15 years of diagnosis.[98] The presence of CKD increases cardiovascular (CV) risk among patients with either T1D or T2D.[99] Additionally, progressive renal insufficiency may increase the risk of hypoglycemia due to decreases in renal elimination of insulin, incretins, and renally eliminated antihyperglycemic medications.[100] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glycemic control (i.e., target HbA1c <6%) was associated with an increased risk of hypoglycemia[101] and mortality[102] among T2D patients with kidney disease at baseline. However, intensive glucose control also has been associated with improved renal outcomes (e.g., end stage renal disease/dialysis/renal transplantation, renal death, eGFR and/or albuminuria) in patients with T1D[103,104] and T2D[105,106] after 10 and two years, respectively.

Some approved antihyperglycemic products are contraindicated or not recommended, require dosage adjustments, are associated with increased risk of hypoglycemia, or have not been adequately studied in patients with T2D and renal impairment (see Table 29, Appendix 13.3). Additionally, the SGLT2 inhibitors and GLP-1 agonists have labeled warnings of acute kidney injury and/or impairment of renal function. However, these antihyperglycemic medications also may have beneficial effects on long-term renal outcomes. The SGLT2 inhibitors have been reported to improve renal oxygenation and intra-renal inflammation, and are associated with reductions in renal tubular glucose reabsorption, glomerular hyperfiltration, body weight, blood pressure (BP), intraglomerular pressure, albuminuria, rate of decline in eGFR, and adverse renal outcomes.[107-121] The GLP-1 receptor agonists and DPP-4 inhibitors also have been reported to improve renal outcomes.[119,122-125]

As part of the original dapagliflozin clinical development program, the Applicant conducted a randomized, double-blind, placebo-controlled Phase 3 trial (i.e., MB102029) to compare glycemic efficacy and renal safety of dapagliflozin (5 mg/day and 10 mg/day) to placebo as add-on to standard of care in T2D subjects with moderate renal impairment (i.e., eGFR ≥30 to <60 mL/min/1.73 m^2).[(1)] In this trial, dapagliflozin did not improve glycemic control (i.e., the mean change in HbA1c from baseline to week 24 was not statistically different from placebo for either dapagliflozin treatment arm). Based on these results, product labeling of FARXIGA (dapagliflozin) at the time of approval stated that initiation is not recommended in patients with an eGFR <60 mL/min/1.73 m^2, and use is not recommended in patients with an eGFR persistently between 30 to <60 mL/min/1.73 m^2.[23] FARXIGA also was contraindicated in patients with an eGFR <30 mL/min/1.73 m^2. Similarly, XIGDUO XR (dapagliflozin/metformin extended-release) labeling recommended not to initiate or continue use if the eGFR is <60 mL/min/1.73 m^2, and this product also was contraindicated at this level of renal function.[5] It is noted that at the time of product approval (October 29, 2014) metformin also was contraindicated in patients with renal

[1] Applicant's MB102029 Clinical Study Report (dated November 24, 2010), available at: \\cdsesub1\evsprod\nda202293\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-ii-diabetes\5351-stud-rep-contr\mb102029\study-mb102029-csr-st-lt-up-to-data-cut-off.pdf

dysfunction (i.e., a serum creatinine concentration ≥1.5 mg/dL for men and ≥1.4 mg/dL women, or abnormal creatinine clearance).

In their post-hoc analyses of a subset of subjects with CKD 3A (eGFR ≥45 to <60 mL/min/1.73 m2) in Trial MB102029, the Applicant reported nonsignificant mean placebo-corrected reductions in HbA1c at week 24 for the dapagliflozin 5 mg and 10 mg treatment arms of -0.37% (95% confidence interval [CI, -0.83, 0.10]) and -0.33% (95% CI [-0.8, 0.14]), respectively.[126] The Applicant felt that the lack of statistical significance in glycemic efficacy could be at least partially attributable to the trial being underpowered (i.e., 40 subjects in the placebo arm; 35 subjects in the dapagliflozin 5 mg/day arm; and 32 subjects in the dapagliflozin 10 mg/day arm) and subject to type 2 error. They also conducted a meta-analysis of a pool of 9 Phase 2b/3 clinical trials from their original dapagliflozin submission. Based on the results of this analysis, the placebo-corrected adjusted mean reductions in HbA1c from baseline to week 24 were -0.23% (95% CI [-0.47, 0.02]) for the dapagliflozin 5 mg/day treatment arm and -0.39% (95% CI [-0.65, -0.14]) for the dapagliflozin 10 mg/day arm for the subset of subjects (n=359) with a baseline eGFR between 30 to <60 mL/min/1.73 m^2.(2) Seven of these trials were designed as combination or add-on to background antihyperglycemic therapy studies, and the placebo effect was relatively large (i.e., mean HbA1c change from baseline of -0.48%, 95% CI [-0.66, -0.30]).

Similarly, during the review of the Applicant's original NDA submission, Dr. Wei Liu, the statistical reviewer for this Application, conducted a meta-analysis of 13 Phase 2b/3 placebo-controlled trials from the dapagliflozin development program, which included Trial MB102029, to explore the effects of dapagliflozin 5 and 10 mg by baseline renal function. Based on this analysis, modest but statistically significant placebo-subtracted reductions in HbA1c from baseline to Week 24 were observed for both the dapagliflozin 5 mg (-0.23%, 95% CI [-0.44, -0.01]) and 10 mg (-0.32%, 95% CI [-0.47, -0.16]) treatment arms in subjects with a baseline eGFR ≥45 to <60 mL/min/1.73m^2. This analysis used a last observation carried forward (LOCF) approach to address missing data, which is no longer considered acceptable by the Division.

On April 23, 2018, the Applicant submitted efficacy supplements for FARXIGA (NDA 202293/S-015) and XIGDUO XR (NDA 205649/S-009) which provided results from a dedicated moderate renal impairment clinical trial (i.e., D1690C00024) intended to support a change to the United States Prescribing Information (USPI) of FARXIGA and XIGDUO XR to reflect that no dose adjustment is needed for T2D patients with an eGFR of ≥45 mL/min/1.73 m^2. This trial was a multicenter, double-blind, placebo-controlled, parallel group, randomized Phase 3 trial to evaluate the glycemic efficacy and renal safety of dapagliflozin in subjects with T2D and CKD 3A who have inadequate control on usual standard of care. Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to week 24) using an

[2] Applicant's Summary of Clinical Efficacy Appendices (dated November 22, 2010), labeled as Table A1.1.2.10, page 72 of 290, available at: \\cdsesub1\evsprod\nda202293\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-ii-diabetes\5353-rep-analys-data-more-one-stud\ise\appendices-for-2-7-3.pdf

intention-to-treat (ITT) estimand that included measurements obtained after glycemic rescue or discontinuation of investigational product (IP), the dapagliflozin treatment arm resulted in a modest but statistically significant HbA1c reduction compared to the placebo arm (-0.28% [95% CI -0.48%, -0.07%]) added to standard of care. The results for the key secondary endpoints, reduction in body weight (BW), fasting plasma glucose (FPG), and systolic blood pressure (SBP) were supportive. On February 22, 2019, the Agency approved both sNDAs.[127,128] It also is noted that several other SGLT2 inhibitors (i.e., canagliflozin-containing products[11,129] and empagliflozin-containing products[8-10,130]) are approved for use in T2D patients with CKD 3A renal insufficiency (i.e., an eGFR ≥45 mL/min/1.73 m^2), while initiation or continuation of ertugliflozin-containing products[7,12,131] are not recommended with an eGFR between 30 and <60 mL/min/1.73 m^2.

Based on these data, I recommend that the proposed labeling for QTERNMET XR and Qtern also state that no dose adjustment is necessary for patients with an eGFR ≥45 mL/min/1.73 m^2. However, these products should be contraindicated in patients with an eGFR <45 mL/min/1.73 m^2 as the approved and proposed dose formulations of these products do not allow for titration of the dapagliflozin component to the 10 mg maximum recommended dose while limiting saxagliptin exposure to 2.5 mg (i.e., the recommended dose for patients with an eGFR <45 mL/min/1.73 m^2).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

DAPAGLIFLOZIN-CONTAINING AND SAXAGLPITN-CONTAINING PRODUCTS: Dapagliflozin (FARXIGA); Saxagliptin (ONGLYZA); Dapagliflozin/Metformin Extended-Release (XIGDUO XR); Saxagliptin/Metformin Extended-Release (KOMBIGLYZE XR); and Dapagliflozin/Saxagliptin (QTERN)

Dapagliflozin (FARXIGA) belongs to the class of antihyperglycemic agents known as SGLT2 inhibitors and is administered orally once daily. This product was approved by the FDA in 2014 as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[132] Other FDA-approved SGLT2 inhibitors include canagliflozin (approved in 2013),[129] empagliflozin (approved in 2014),[130] and ertugliflozin (approved in 2017).[131] In 2014, XIGDUO XR, a FCDP containing dapagliflozin and extended-release metformin, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both dapagliflozin and metformin is appropriate.[133] In 2017, QTERN, a FCDP containing dapagliflozin and saxagliptin, was approved 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.[19]

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for much of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE).[134-136] In patients with T2D, these pharmacodynamics changes have been reported to be associated with excretion of approximately 70 grams of glucose in the urine per day, increases in urinary volume, lower HbA1c and fasting glucose concentrations, and reductions in body weight and SBP.[3,126,137-139] Due to dapagliflozin's dependency on glucose filtration at the glomerulus, patients with decreased renal function may have less response to the glycemic lowering effects of dapagliflozin.[126] However, for the subset of subjects with chronic kidney disease 3A (CKD 3A; eGFR 45 to <60 mL/min/1.73 m^2) in Trial MB102029, the median (interquartile range [IQR]) 24-hour (24-h) UGE at Week 52 was similar between the dapagliflozin 5 mg (44.20 g/24 h, IQR [31.50-57.60]) and 10 mg (42.65 g/24 h, IQR [24.43-59.68) treatment arms compared to the placebo arm (1.80 g/24 h, IQR [0.25-5.50]. These results are consistent with the median 24-h UGE at Week 24 in the dapagliflozin 10 mg (41.22 g/24 h, IQR [21.43-63.29]) and placebo (0.45 g/24 h, IQR [0.14-5.37) arms in Trial D1690C0024.(3)

Saxagliptin belongs to the class of antihyperglycemic agents known as DPP-4 inhibitors. In patients with T2D, DPP-4 enzyme activity is inhibited for a 24-hour period following oral administration of saxagliptin. 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 a meal.[4,140] As add-on therapy to metformin, the combination of dapagliflozin and saxagliptin is associated with improved glycemic control.[141-146]

Metformin improves glucose control in patients with T2D, lowering both basal and postprandial plasma glucose. Although the mechanisms of action of this drug have not been clearly elucidated, the pharmacodynamic effects are likely pleiotropic.[147] Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with T2D or in healthy subjects except in unusual circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.[148] The combination of dapagliflozin[138,139,143,149-155] and metformin is associated with improved glycemic control.

[3] Data derived from Trials D1690C0024 and MB102029 by Dr. Renu Singh, the Clinical Pharmacology reviewer for these sNDA.

However, XIGDUO XR product labeling includes a Boxed Warning of postmarketing cases of metformin-associated lactic acidosis resulting in death, hypothermia, hypotension and resistant bradyarrhythmias. These cases primarily occurred in patients with significant renal impairment.[5] At the time of the initial product approval (October 29, 2014), labeling of metformin-containing products strongly recommended against the use of metformin in some patients with abnormal renal function (elevated serum creatinine concentrations or reductions in creatinine clearance). However, on April 8, 2016, the Agency issued a Drug Safety Communication informing healthcare providers that manufacturers would be required to revise the labeling of metformin-containing drugs to indicate that these products may be safely used in patients with mild to moderate renal impairment.[156] In the revised labeling, metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2, and use is not recommended in patients with an eGFR between 30-45 mL/min/1.73 m^2. Additionally, labeling states that the benefits and risks of continued treatment with metformin should be assessed in patients whose eGFR falls below 45 mL/min/1.73 m^2, and it should be discontinued if the patient's eGFR falls below 30 mL/min/1.73 m^2.[156]

FARXIGA is formulated as film-coated tablets containing either 5 mg or 10 mg of dapagliflozin. The recommended starting dose is 5 mg orally once daily in the morning with or without food and can be increased to 10 mg once daily in patients tolerating this dose who require additional glycemic control. Use of FARXIGA is not recommended in patients with an eGFR <45 mL/min/1.73 m^2. FARXIGA is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.[23]

ONGLYZA is formulated as film-coated tablets containing either 2.5 mg or 5 mg of saxagliptin. The recommended starting dose is 2.5 mg or 5 mg orally once daily in the morning with or without food. In patients with an eGFR <45 mL/min/1.73 m^2, systemic exposure (i.e., the area-under-the curve [AUC]) of saxagliptin and its active metabolite (5-hydroxy saxagliptin) may increase by more than two-fold. Therefore, the recommended daily dose of saxagliptin is limited to 2.5 mg daily in this patient population.[20] The saxagliptin 2.5 mg dose also is recommended for patients taking strong cytochrome P450 3A4/5 inhibitors.

QTERN is formulated as a film-coated tablet containing 10 mg of dapagliflozin and 5 mg of saxagliptin. The recommended dose is 10 mg dapagliflozin/5 mg saxagliptin orally once daily in the morning with or without food. Initiation or continued use of QTERN is not recommended with an eGFR <60 mL/min/1.73 m^2, and this product is contraindicated in patients with moderate to severe renal impairment (eGFR <45 mL/min/1.73 m^2) or end-stage renal disease, or patients on dialysis.[6] With the current sNDA (i.e., NDA 209091/S-002), the Applicant did not request revisions for QTERN product labeling to include information from Trial D1690C00024, as this trial was under review at the time the current Applications were submitted. However, based on the results of this trial and revised labeling for FARXIGA[23] and XIGDUO XR,[5] revisions to the Dosage and Administration section to reflect that no dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m^2 will be considered and discussed during labeling negotiations for this

supplement, as well as NDA 210874 (QTERNMET XR). Additionally, a low-dapagliflozin dose QTERN formulation (i.e., a film-coated tablet containing 5 mg of dapagliflozin and 5 mg of saxagliptin) is being evaluated as part of this review.

XIGDUO XR is available as film-coated tablets containing either 2.5 mg of dapagliflozin with 1000 mg metformin hydrochloride (HCl) extended-release (2.5 mg/1000 mg), 5 mg of dapagliflozin with 500 mg metformin HCl extended-release (5 mg/500 mg), 5 mg dapagliflozin with 1000 mg metformin HCl extended-release (5 mg/1000 mg), 10 mg of dapagliflozin with 500 mg metformin HCl extended-release (10 mg/500 mg), or 10 mg of dapagliflozin with 1000 mg metformin HCl extended release (10 mg/1000 mg).[157] XIGDUO XR is administered orally once daily in the morning with food. The starting dose is individualized based on the patient's current treatment. For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg, and the maximum recommended daily dose for this product is 10 mg dapagliflozin/2000 mg metformin HCl extended-release. Use of XIGDUO XR is not recommended in patients with an eGFR <45 mL/min/1.73 m^2 and contraindicated with an eGFR <30 mL/min/1.73 m^2, ESRD or dialysis.[5]

KOMBIGLYZE XR is available as film-coated tablets containing either 2.5 mg of saxagliptin with 1000 mg metformin hydrochloride (HCl) extended-release (2.5 mg/1000 mg), 5 mg of saxagliptin with 500 mg metformin HCl extended-release (5 mg/500 mg), or 5 mg of saxagliptin with 1000 mg metformin HCl extended-release (5 mg/1000 mg). KOMBIGLYZE XR is administered orally once daily with the evening meal. The starting dose is individualized based on the patient's current treatment. The saxagliptin dose should be limited to 2.5 mg for patients taking strong cytochrome P450 3A4/5 inhibitors and individuals with an eGFR <45 mL/min/1.73 m^2.[13] Initiation of KOMBIGLYZE XR is not recommended in patients with an eGFR between 30-45 mL/min/1.73 m^2, and it is contraindicated with an eGFR <30 mL/min/1.73 m^2.[13]

3.2. Summary of Presubmission/Submission Regulatory Activity

The relevant regulatory history for the submitted Applications is summarized in Table 2 below. ONGLYZA (saxagliptin; NDA 22350), KOMBIGLYZE XR (saxagliptin/metformin extended-release FCDP; NDA 200678), FARXIGA (dapagliflozin; NDA 202293), XIGDUO XR (dapagliflozin/metformin extended-release FCDP; NDA 205679) and QTERN (dapagliflozin/saxagliptin FCDP; NDA 209091) all previously received marketing approval in the U.S. for the treatment of T2D in adult patients (please see Section 3.1 above). Of most relevance for the current submissions is the recent approval for the use of FARXIGA and XIGDUO XR in patients with CKD 3A (i.e., an eGFR ≥45 mL/min/1.73 m^2) and continued statistical advice from the Agency that the primary efficacy analysis should include all HbA1c data from all randomized subjects, regardless of treatment adherence and rescue status.

Table 2: Summary of Presubmission/Submission Regulatory History for NDA 210874 and NDA 209091/S-002

Date	Summary of Relevant Agency Interactions
July 31, 2009	NDA 22350 – FDA approves ONGLYZA (saxagliptin) once-daily treatment for adults with T2D.
November 5, 2010	NDA 200678 – FDA approves KOMBIGLYZE XR (saxagliptin/metformin extended-release) once-daily treatment for adults with T2D.
	(b) (4)
June 17, 2013	PIND 118840 – PIND meeting request was received, and FDA agreed to provide written responses to the Sponsor's questions.
June 25, 2013	PIND 118840 – Submission of Change in Sponsor Contact.
July 8, 2013	PIND 118840 – Submission of Pre-IND Briefing Document Question 1 – Design of LTSS Question 2 – proposal for tests included and excluded in the LTSS study Question 3 – proposed dissolution test method for use in the LTSS study Question 4 – biowaiver proposal for BE studies.
July 18, 2013	PIND 118840 – Submission of Amendment to the PIND Briefing Document – Dissolution Test Method and Sponsor questions.
August 5, 2013	PIND 118840 – FDA's written response to Questions #1, #2, and #4 in the July 8, 2013 Briefing Document and additional FDA comments.
August 19, 2013	PIND 118840 – Submission of Sponsor's clarification of FDA August 5, 2013 response on long-term stability testing + dissolution testing response (justification of dissolution method for saxagliptin/dapagliflozin film coated combination tablets, 2.5/5mg, 5/5mg, 2.5/10mg and 5/10mg).
September 16, 2013	PIND 118,840 – FDA's response to Sponsor's clarifying follow up questions submitted August 19, 2013 Question 1 (stability requirements) and Question 3 (dissolution testing).
November 22, 2013	PIND 118840 – FDA Advice/Information Request Letter - indicated which stability data should be included in the initial NDA submission.

Date	Summary of Relevant Agency Interactions
January 8, 2014	NDA 202293 – FDA approves FARXIGA (dapagliflozin) tablets for the treatment of adult patients with T2D.
January 22, 2014	IND 118840 – Submission of initial IND application for the saxagliptin/dapagliflozin FCDP (including submission of protocol for BE Study CV181341).
March 6, 2014	IND 118840 – FDA Non-hold comments on initial IND 118840 application of January 22, 2014, (i.e., serum amylase and lipase should be included in laboratory testing, and heart failure should be defined and prospectively adjudicated).
March 7, 2014	IND 118840 – Submission of transfer of ownership and regulatory responsibility for IND 118840 from BMS to AstraZeneca.
March 18, 2014	IND 118840 – Submission of Sponsor's response to March 6, 2014, FDA non-hold comments on IND 118840 application. The Sponsor agreed to monitor amylase/lipase and to prospectively assess events of heart failure and report them as SAEs.
April 16, 2014	IND 118840 – Saxagliptin/Dapagliflozin FCDP Tablet; submission of iPSP.
April 25, 2014	IND 118840 – Submission of Saxagliptin/Dapagliflozin FCDP Tablet: Request for Type B pre-NDA meeting.
April 30, 2014	IND 118840 – FDA letter received granting the pre-NDA meeting on June 23, 2014.
May 9, 2014	IND 118840 – Submission of Request for separate CMC-focused Type B pre-NDA meeting to discuss format and content of the CMC sections of the saxagliptin/dapagliflozin FCDP NDA.
May 23, 2014	IND 118840 – Submission of Pre-NDA briefing document for the June 23, 2014 pre-NDA meeting.
May 28, 2014	IND 118840 – FDA letter granting a separate CMC-focused pre-NDA meeting on July 2, 2014.
June 6, 2014	IND 118840 – Submission of CMC Pre-NDA meeting background document for the July 2, 2014 meeting.
June 16, 2014	IND 118840 – FDA issuance of pre-NDA Meeting Preliminary Comments. In the comments, FDA requested that the Sponsor address the potential for mutual drug interactions between existing therapy (e.g., metformin), dapagliflozin, and saxagliptin. It was agreed that if BE was demonstrated (b) (4) A dissolution method for both analytes of the drug product should be developed. FDA did not agree that study CV181169 by itself would be sufficient to support filing and approval of the saxagliptin/dapagliflozin FCDP, and at least 52 weeks of exposure would be required for review of safety. FDA requested that the information from study CV181168 and/or study MB102129 be submitted in the initial NDA and integrated with the data from CV181169 at the time of NDA submission.

Date	Summary of Relevant Agency Interactions
June 24, 2014	IND 118840 – FDA's Preliminary Meeting Comments for CMC pre-NDA meeting between FDA and the Sponsor. The Sponsor determined that the FDA's letter sufficiently addressed their questions, and the meeting scheduled for July 2, 2014 was cancelled.
June 27, 2014	IND 118840 – The Sponsor provided information on Study D1690C00010 to address the FDA's issue regarding duration of exposure for the safety review of the FCDP.
June 30, 2014	IND 118840 – Submission of Regulatory contact change from BMS to AstraZeneca.
July 14, 2014	IND 118840 FDA Correspondence recommending the Sponsor submit a revised iPSP requesting a waiver of pediatric studies.
July 23, 2014	IND 118840 – FDA official minutes of the June 23, 2014 Saxagliptin/Dapagliflozin pre-NDA meeting between FDA and the Sponsor. The FDA determined that clinical studies were required to support efficacy of the lower strength FCDP (i.e., saxagliptin 5 mg/dapagliflozin 5 mg) and that statistical or pharmacological modeling would not be acceptable.
July 30, 2014	IND 118840 – Submission of Request for Proprietary Name Review.
August 5, 2014	IND 118840 – Sponsor submission in follow up to pre-NDA meeting on June 23, 2014, addressing one of the issues requiring further discussion; support for the efficacy of all possible dose combinations.
August 14, 2014	IND 118840 – Sponsor submission in follow-up to FDA pre-NDA meeting on July 23, 2014, addressing one of the Issues Requiring Further Discussion; the duration of exposure for the safety review.
August 19, 2014	IND 118840 – FDA granted written response to the Sponsor's meeting request to discuss safety and efficacy issues relating to the IND.
September 12, 2014	IND 118840 – Submission of response to FDA request for information; consolidated List of Sponsor Questions for Request for FDA Feedback.
October 7, 2014	IND 118840 – Submission of revised iPSP following FDA advice (July 14, 2014) recommending that the Sponsor request a waiver of pediatric studies for all ages.
October 16, 2014	IND 118840 – FDA response to the Sponsor's correspondence, dated July 30, 2014, requesting review of the proposed proprietary name QTERN for saxagliptin/dapagliflozin FCDP; FDA completed its review and proprietary name was conditionally acceptable.

Date	Summary of Relevant Agency Interactions
October 23, 2014	IND 118840 – FDA Meeting Request – Written Responses. FDA response to Sponsor's questions in August 14, 2014, and September 12, 2014, background package. FDA felt that study CV181169 may be adequate for evaluation of efficacy of the high dose combination, and it would be acceptable to submit this study without additional study of the lower dose combination. Additional study of the lower dose combination may be required in the post-marketing setting if the higher dose combination is approved. The Sponsor made the decision to submit the NDA for only the dapagliflozin 10 mg /saxagliptin 5mg dosage strength of the FCDP, and this was determined to be acceptable by FDA.
October 29, 2014	NDA 205649 – FDA approves XIGDUO XR (dapagliflozin/metformin HCl extended-release) once-daily treatment for adults with T2D.
November 14, 2014	IND 118840 – FDA PeRC confirms agreement to the Sponsor's revised iPSP, including the waiver requested, with request for revisions to the final iPSP.
	(b) (4)

Date	Summary of Relevant Agency Interactions
(b) (4)	(b) (4)
April 27, 2016	NDA 209091 – The NDA for QTERN is submitted which included the completed Trials CV181168 (pivotal), CV11869 (supportive) and MB102129 (supportive) to support efficacy and safety of the FCDP. The proposed indication was: as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) .
August 25, 2016	PIND 131385 – The Sponsor requests a type B PIND meeting seeking FDA advice regarding the proposed BE study to open the IND and the overall BE and registration strategy to obtain marketing approval for QTERNMET XR.
September 22, 2016	PIND 131385 – The Sponsor submits a briefing package for a type B PIND meeting.
October 25, 2016	PIND 131385 – FDA provided written responses requesting that the Sponsor clearly outline how the proposed trials support NDA filing to demonstrate a contribution of each component to the claimed effect, why the proposed triple therapy FCDP is needed, and why this product addresses the need of a significant patient population with T2D requiring concurrent use. The Sponsor also was asked to provide support for the clinical utility of the proposed doses, justify why lower or intermediate doses of metformin would not be needed, and to address potential swallowability issues. FDA also noted that a waiver of in vivo testing requirements may be considered for the proposed 5 mg/2.5 mg/1000 mg and 5 mg/5 mg/1000 mg strengths.

Date	Summary of Relevant Agency Interactions
October 31, 2016	PIND 131385 – The Sponsor submitted follow-up questions regarding the adequacy of Trials D1683C0005 and CV181169 to meet 21 CFR 300.50 requirements for the proposed FCDP and asked whether the metformin contribution has to be individually studied as it will be used as background therapy for all subjects.
November 18, 2016	PIND 131385 – The Sponsor emails follow-up questions regarding the design of the BE study related to the lack of a reference for the 2.5 mg/2.5 mg/1000 mg FCDP strength.
December 23, 2016	PIND 131385 – FDA provided responses to the Applicant's October 31, 2016, follow-up questions, stating that should the Sponsor choose to submit only Trials D1683C0005 and CV181169, they would need to provide clear justification for why the contribution of metformin does not need to be studied. Alternatively, they could consider how other available data could be leveraged to support a conclusion that there is a contribution of metformin, or conduct a study demonstrating the contribution of each component of their three drug FCDP. In response to the Sponsor's November 18, 2016, follow-up question, FDA favored the evaluation of the intermediate 5 mg/2.5 mg/1000 mg strength and using the 2.5 mg saxagliptin and 5/1000 mg dapagliflozin/metformin XR tablets as the reference products.
February 27, 2017	NDA 209091 – QTERN is approved with the 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. Limitations of use include: 1) is not indicated for the treatment of T1D or DKA, and 2) should only be used in patients who tolerate 10 mg dapagliflozin.
March 15, 2017	IND 131385 – The Sponsor opens the IND with their Phase 1 BE study (D168AC00001).
April 20, 2017	IND 131385 – The Sponsor submits a request for review of the proposed propriety name, QTERNMET XR.
May 17, 2017	IND 131385 – A briefing document and request for a Type B pre-NDA meeting – written responses only for QTERNMET XR is submitted. The same clinical data package also will be used to support a sNDA for QTERN.
June 29, 2017	IND 131385 – The Sponsor submits an iPSP requesting a full waiver from conducting pediatric studies.
July 25, 2017	IND 131385 – FDA provides written responses for the Type B Pre-NDA meeting. FDA recommended that the Sponsor's 7-study pooled analyses include adjustments to address differences in the studies (e.g., stratifying by study and dose) to maintain reliability and validity of comparisons. Also, a 5-study pool in which dapagliflozin and saxagliptin were initiated simultaneously should be included, with appropriate adjustments to address differences in study designs. Comparisons of the previously submitted 3-study pool with the 7-study pool would be reasonable. The proposed content of the 4MSU was reasonable.

Date	Summary of Relevant Agency Interactions
August 25, 2017	IND 131385 – The Sponsor requested further clarification on the pooling strategy of safety data. They agreed to analyze the 5-study and 7-study pool similarly, with adjustments for treatment duration, dose, and study design. Trial CV181365 would remain blinded until the short-term study was completed.
September 11, 2017	IND 131385 – FDA provided an email response stating that the proposed pooling strategy was reasonable.
September 18, 2017	IND 131385 – FDA provided written responses to the iPSP acknowledging the Sponsors request to waive the requirement for pediatric assessments for all pediatric age groups, and requested that the Sponsor submit the Agreed iPSP within 90 days.
October 20, 2017	IND 131385 – FDA provided a Conditionally acceptable Letter to the Sponsor for the proposed propriety name QTERNMET XR.
November 17, 2017	IND 131385 – The Sponsor submits an Agreed iPSP for Qternmet XR, requesting a full waiver from conducting pediatric studies.
November 29, 2017	IND 131385 – The Sponsor submits the briefing document for a Type C meeting request regarding a potential color change for 2 of the 4 tablet strengths.
January 15, 2018	IND 131385 – FDA provided written responses to Type C meeting request. The proposed documentation and data package to support the potential color change in the outer film coat of two tablet strengths was considered acceptable. FDA requested that the dissolution profile data with the proposed dissolution method for the 5 mg/2.5 mg/1000 mg strength and the 10 mg/5 mg/1000 mg strength with the original color and the f2 comparison between them be submitted. FDA agreed with the proposal to submit 12-month ICH stability data on 4 tablet strengths (current tablet color) and that the Sponsor could submit stability data on tablets with the new tablet color within 30 days after receipt of the original NDA submission.
January 18, 2018	IND 131385 – FDA provided Agreement Letter for the Agreed iPSP.
July 2, 2018	NDA 210874 and NDA 209091/S-002 – The QTERNMET XR NDA and QTERN sNDA are submitted to the FDA for review.
February 22, 2019	NDA202293/S-015 and NDA 205649/S-009 – Farxiga and Xigduo XR sNDAs are approved with labeling reflecting that no dose adjustments are needed with an eGFR ≥45 mL/min/1.73 m^2.

Source: Adapted from the Applicant's Summary of Relevant FDA Interactions, available at:
\\cdsesub1\evsprod\nda210874\0001\m1\us\20180702-attachment-relevant-fda-interactions.pdf
\\cdsesub1\evsprod\nda209091\0027\m1\us\20180702-attachment-fda-interactions.pdf
Abbreviations: 4MSU, 4-Month Safety Update; BE, bioequivalence; BMS, Bristol-Myers Squibb; CFR, Code of Federal Regulations; CMC, Chemistry, Manufacturing, and Controls; CR, Complete Response; CR, Complete Response; CRL, Complete Response Letter; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FCDP, fixed combination drug product; FDA, Food and Drug Administration; IND, Investigational New Drug; iPSP, initial pediatric study plan; LTSS, long-term stability study; NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act; PeRC, Pediatric Review Committee; PIND, Pre-Investigational New Drug; SAEs, serious adverse events; sNDA, supplemental New Drug Application; T2D, type 2 diabetes mellitus; and XR, extended-release.

3.3. Foreign Regulatory Actions and Marketing History

Qternmet XR is not currently marketed in any country. As of January 14, 2019, QTERN is approved in 41 countries, and is under review in 10 additional countries. QTERN was first approved for marketing in the 28 European Union (EU) member countries plus Iceland, Liechtenstein and Norway. QTERN also is approved in Argentina, Australia, Canada, Mexico, Serbia, South Korea, Switzerland, Taiwan, Philippines and the United States of America (USA).

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

4.1. Office of Scientific Investigations (OSI)

In the original NDA for QTERN (b) (4) Dr. Cynthia Kleppinger, from the Office of Scientific Investigations (OSI), was asked to inspect five domestic clinical sites and the contract research organization (b) (4) for the supporting Phase 3 clinical trial, CV181169. Regulatory violations were noted for four sites inspected, and a Form FDA-483 was issued for each of the four respective clinical investigators. Dr. Kleppinger felt that the violations would not significantly impact primary safety and efficacy analyses, and that the "reliability of data from these sites was acceptable for use in support of the indication." For more detailed information, please refer to Dr. Kleppinger's review (b) (4)

With the resubmission of the QTERN application (NDA 209091), OSI was not re-consulted with a request to conduct additional audits/site inspections.

For the current Applications, Dr. Kleppinger was again consulted and asked to inspect three domestic clinical sites (Table 3), accounting for 61 of 1058 (5.8%) of subjects enrolled in Trial D1683C00005. The clinical site inspections primarily focused on review of informed consent forms (ICFs), 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. The rationale for the three selected inspections were primarily based on the following: higher subject enrollment, site risk ranking (identified through the site selection tool), or treatment responders; lack of previous OSI inspection; previous concern of fraud/scientific misconduct; low AEs with high discontinuation rate, and high rates of AEs and SAEs.

Following review of the full Establishment Inspection Reports and the documents submitted with that report, No Action Indicated (NAI) letters were issued to Drs. Dennis and Bueso, stating that the Agency did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance (i.e., the data from these sites were considered reliable). However, the classification for Dr. Altamirano was Voluntary Action Indicated (VAI). A Form FDA-483, Inspectional Observations, was issued for the following reasons: 1) failure to inform subjects of new unanticipated risks (i.e., warnings of acute kidney injury as requested by the IRB) for all randomized subjects; 2) failing to reconsent five subjects with the most current IRB approved ICF; 3) failure to meet the protocol specific window for rescue therapy safety laboratory retest (i.e., within 3-5 days) for four subjects, of which one was 34 days out of the protocol window; and 4) failure to print, review, and maintain safety labs for three subjects. In her review, Dr. Kleppinger stated that although regulatory violations were noted, these violations were unlikely to significantly impact the primary efficacy and safety analyses, and the data from this site is acceptable for use in support of the indication for this Application. I concur with Dr. Kleppinger's assessments.

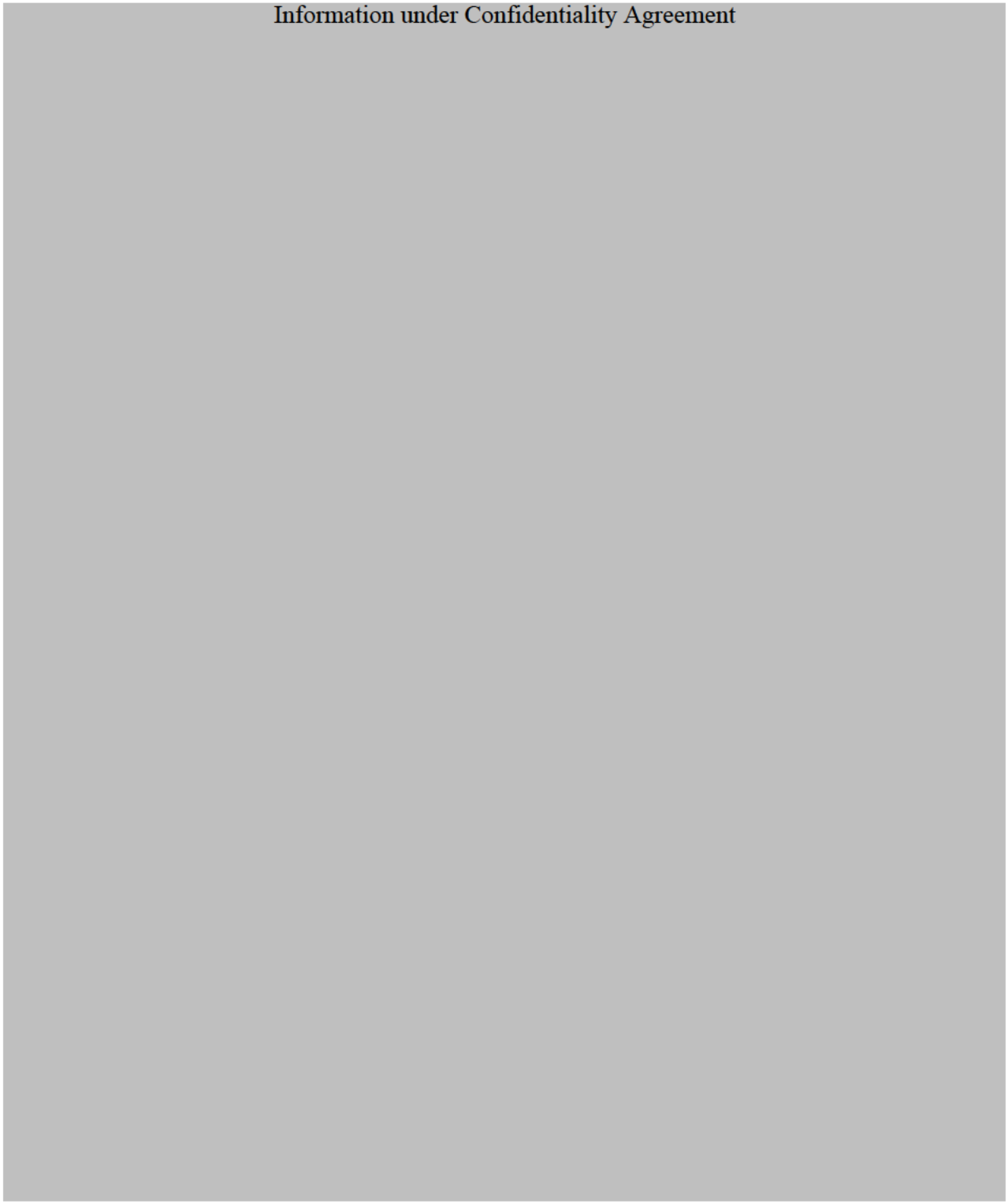
Table 3: Protocol/Site Identification

Investigator Location	Site #	Subjects Enrolled	Rationale for Site Selection	Classification (Inspection Dates)
Dario Altamirano, MD AGA Clinical Trials Hialeah, FL	7819	28	• Ranked #3 for site risk • Enrolled 28 subjects • High site-specific efficacy effect size • Complaint in 2011 (Sponsor closed site, OAI downgraded to VAI) • Site re-inspected in 2013 (NAI)	**VAI** Derivation(s) from Regulations
Gerardo Bueso, MD Endocrine Associates Houston, TX	7822	21	• Ranked #7 for site risk • Enrolled 21 subjects • Lower than average AEs • Higher than average D/C rate • Not previously inspected	**NAI** (11/5/2018 to 11/9/2018)
Patrick Dennis, MD DelRicht Research New Orleans, LA	7826	12	• Ranked #25 for site risk • Enrolled 12 subjects • Second highest safety number • Not previously inspected.	**NAI** (10/1/2018 to 10/4/2018)

Abbreviations: AEs, adverse events; D/C, discontinuation; NAI, No Action Indicated; OAI, Official Action Indicated (OAI); SAEs, serious adverse events; VAI, Voluntary Action Indicated.

In addition to FDA inspections done by the Office of Regulatory Affairs, the European Medicines Agency (EMA) has currently in house a marketing application for dapagliflozin/saxagliptin/

metformin (EU reference number EMEA/H/C/004910) and shared with OSI their Integrated Inspection Report dated March 1, 2019, of Study CV181168. The trial included 315 subjects



Information under Confidentiality Agreement

Information under Confidentiality Agreement After full review of the inspectional reports, the OSI reviewer was in agreement with the assessment.

4.2. Product Quality

The Quality Assessment was performed by the following members of the Quality Review Team: Dr. Christopher Galliford served as the Application Technical Lead and Drug Product reviewer; Dr. Ramsharan Mittal was the Drug Substance reviewer; Dr. Ted Chang was the Process and Facility reviewer, Dr. Sarah Ibrahim was the Biopharmaceutics reviewer, Dr. Anika Lalmansingh was the Regulatory Business Process Manager, and Dr. James Laurenson was the Environmental Assessment reviewer. Based on their review, the Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 210874 from a Chemistry and Manufacturing Controls (CMC) perspective, noting that there are no outstanding deficiencies and the manufacturing facilities have an approval recommendation. Please refer to the respective reviews for more detailed information.

Summary of Quality Provided by the Applicant

QTERNMET XR is a FCDP containing contain the active pharmaceutical ingredients dapagliflozin, saxagliptin and metformin hydrochloride extended-release as film coated tablets in the following dosage strengths: 2.5 mg/2.5 mg/1000 mg (2 tablets once daily), 5 mg/2.5 mg/1000 mg (2 tablets once daily), 5 mg/5 mg/1000 mg (1 tablet once daily) and 10 mg/5 mg/1000 mg (1 tablet once daily). (b) (4) This drug product is manufactured at the AstraZeneca LP facility at Mount Vernon, Indiana. The dapagliflozin drug substance is manufactured (b) (4) Saxagliptin drug substance is manufactured (b) (4). The Applicant requested that the Agency refer to the dapagliflozin and saxagliptin drug substance details in the dapagliflozin NDA 202293 and saxagliptin NDA 22350, respectively. Metformin

hydrochloride is sourced from (b) (4) The Applicant also requested that the Agency refer to the (b) (4) The Applicant claims that the excipients are compatible with drug substances. The rate and extent of absorption of dapagliflozin, saxagliptin and metformin from the FCDP are the same as each moiety coadministered as separate products. The film coating and a shape and size that is similar to XIGDUO XR support swallowability. The Applicant states that 12-month data for the QTERNMET XR tablets from the ongoing long-term stability study support a proposed 24-month shelf-life for the high-density polyethylene (HDPE) bottle with the following storage statement: "Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

Figure 1: Formulation Design of QTERNMET XR FCDP Tablet

(b) (4)

Source: Adapted from the Applicant's 0.1.1P QOS – Drug Product report, labelled as Figure 2, page 6 of 72, available at: \\cdsesub1\evsprod\nda210874\0001\m2\23-qos\drug-product.pdf

In his Executive Summary, Dr. Galliford noted that the drug substances in QTERNMET XR are the same dose and form as several of the Applicant's currently approved FCDPs (i.e., QTERN, KOMBIGLYZE XR, and XIGDUO XR). Additionally, it was acknowledged that long-term stability was demonstrated when the product is packaged in (b) (4) bottles intended for commercial distribution. He stated that a 24-month shelf-life will be granted through the approval letter based on stability data at intermediate storage conditions, and recommended that the product be stored below 30°C (86°F).

QTERN is a FCDP containing the active pharmaceutical ingredients dapagliflozin and saxagliptin as film coated tablets in the following dosage strengths: 5 mg/5 mg and 10 mg/5mg. This FCDP is comprised (b) (4) (Figure 2). The Applicant notes that the additional QTERN 5 mg/5 mg strength is based on the same formulation design principle as the approved 10 mg/5 mg strength. Excipients in the 5 mg/5 mg formulation also are the same as those presented in the 10 mg/5 mg formulation. (b) (4) The (b) (4) coating contains the same ingredients as those used for the approved strength. The manufacturing process, manufacturing site and commercial container closure

systems are identical for both formulations. The Applicant requested a biowaiver through dissolution, compositional similarity, and physiochemical and pharmacokinetic (PK) data to bridge the dapagliflozin 5 mg/saxagliptin 5 mg dose formulation to the dapagliflozin/saxagliptin 10 mg/5 mg and 5 mg/2.5 mg tablets for which BE to the monocomponents has been demonstrated. Based on the review of the biopharmaceutics data, Dr. Ho-Pi Lin, the Biopharmaceutics reviewer for NDA209091/S-002, felt that the proposed strength in this supplement was acceptable from a biopharmaceutics' perspective, and recommended approval. Additionally, Dr. Wei-Hua Emily Wu, the CMC reviewer, felt that the stability data on drug product packaged in HDPE bottles conform to acceptance criteria, and that the Applicant had submitted adequate information and data to support approval of this sNDA.

It is noted that the products used in the QTERNMET XR and QTERN clinical development programs, were not the same as the 'to be marketed' products. However, the BE study (D168C00001) was conducted to bridge the two pivotal Phase 3 trials (i.e., D1683C00005 and CV181169).

Figure 2: Formulation Design of QTERN FCDP Tablet

Source: Adapted from the Applicant's 0.1.1P QOS – Drug Product document, labeled as Figure 1, page 4 of 54, available at: \\cdsesub1\evsprod\nda209091\0027\m2\23-qos\drug-product-5-and-5-mg.pdf

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were conducted or submitted for these Applications. In his review, Dr. Jeffrey Quinn, the Pharmacology/Toxicology reviewer, stated that no additional nonclinical studies were needed, and recommended approval of these Applications. From the pharmacology/toxicology perspective, Dr. Quinn felt that the overall toxicology programs for approved dapagliflozin- and saxagliptin-containing products were adequate to support the

approval. Please refer to his review (dated March 19, 2019) for additional information on the nonclinical findings of these products.

4.5. Clinical Pharmacology

The Clinical Pharmacology reviewer for this Application, Dr. Mohammad Absar, evaluated the clinical pharmacology data for NDA 210874, and recommends approval of these Applications. Please refer to his review (dated March 27, 2019) for a detailed discussion of the Clinical Pharmacology issues relevant to this submission.

QTERNMET XR: To support approval of this triple FCDP, the Applicant submitted data from a bioequivalence study (D168AC0001) and two biowaiver requests. Study D168AC0001 compared the BE of QTERNMET XR (i.e., dapagliflozin 5 mg/saxagliptin 2.5 mg/metformin XR 1000 mg FCDP and dapagliflozin 10 mg/saxagliptin 5 mg/metformin XR 1000 mg FCDP) to the individual components (i.e., saxagliptin 2.5 mg or 5 mg plus dapagliflozin 5 mg/metformin XR 1000 mg FCDP or dapagliflozin 10 mg/metformin XR 1000 mg) in 84 healthy volunteers (42 in Cohort 1 [lower dose FCDP] and 42 in Cohort 2 [higher dose FCDP]).[(4)] This study was intended to bridge the data from the two pivotal trials (i.e., C1683C00005 and CV181169) that used the monocomponents (i.e., dapagliflozin, saxagliptin, and metformin) and not the to-be-marketed FCDP. This study used a 3-period, 3-treatment, single-dose, open-label, single-center crossover design. Overall, BE of dapagliflozin, saxagliptin and metformin were established between QTERNMET XR (5mg /2.5 mg/1000 mg and 10 mg/5 mg/1000 mg) relative to the reference products when administered in the fed state. The results indicate that switching from the individual components to QTERNMET XR tablets will produce similar systemic exposures to dapagliflozin, saxagliptin and metformin. Although the geometric mean ratio for the dapagliflozin maximum plasma concentration (C_{max}) was slightly above the upper bound of 125 (i.e., C_{max} 100.99, 128.48) in Cohort 1, the Applicant states that according to FDA guidance, if the differences in rate and extent of absorption do not meaningfully affect the safety and efficacy, bioequivalence may be considered met.[159] They note that urinary glucose excretion, the primary pharmacodynamic effect of dapagliflozin, is mainly driven by the area-under-the-curve (AUC), not C_{max}. For Cohort 2, all pairwise comparisons were within the 80 to 125 bioequivalence limits. No apparent food effect was observed on the overall exposure (i.e., AUC) of dapagliflozin, saxagliptin (and the 5-hydroxy saxagliptin metabolite), and metformin. The C_{max} for saxagliptin, 5-hydroxy saxagliptin and metformin were similar between fed and fasted states. However, the C_{max} for dapagliflozin was approximately 38% (geometric mean 61.81; 90% CI [54.80, 69.72]) lower under fed (42.27 ng/mL) vs. fasted (68.39 ng/mL) conditions. In his review, Dr. Absar noted that this difference is consistent with previous findings observed with dapagliflozin[5] and is not considered clinically meaningful. There were no deaths, SAEs or AEs leading to discontinuation of investigational product (IP) reported in this study.

[(4)] Applicant's CSR for Study D168AC001, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\d168ac00001\d168ac00001-clinical-study-report.pdf

4.5.1. Mechanism of Action

QTERNMET XR is a FCDP containing dapagliflozin, saxagliptin and metformin extended-release. QTERN is a FCDP composed of saxagliptin and dapagliflozin. Dapagliflozin is an SGLT2 inhibitor which prevents renal glucose reabsorption in the proximal renal tubules, thus increasing renal glucose excretion and improving glycemic control. The amount of glucose removed is dependent on the blood glucose concentration and the glomerular filtration rate.[3] Saxagliptin is a competitive DPP-4 inhibitor that slows inactivation of the incretin hormones which play a role in glucose-dependent insulin secretion and in reducing glucagon secretion. The net result of the presence of incretin hormones is improved glycemic control.[4] Metformin is a biguanide that decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5]

4.5.2. Pharmacodynamics

Dapagliflozin: Increases in the amount of glucose excreted in the urine are observed in both healthy subjects and T2D patients following oral administration of dapagliflozin. Dapagliflozin doses of 5 and 10 mg per day in patients with T2D results in excretion of approximately 70 grams/day of glucose in the urine. This urinary glucose excretion is associated with increases in urinary volume.[3]

Saxagliptin: Oral administration of saxagliptin 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), decreased glucagon concentrations, 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.[4] No clinically meaningful prolongations of the QTc interval were observed in healthy volunteers administered either eight times the recommended saxagliptin daily dose (i.e., 40 mg), or 50 times the recommended dapagliflozin daily dose (i.e., 500 mg).[3,4]

Metformin: Oral administration of metformin improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin does not produce hypoglycemia, except in unusual circumstances, and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.[5]

4.5.3. Pharmacokinetics

Dapagliflozin: Following oral administration of dapagliflozin in a fasted state, the C_{max} is typically achieved within two hours. Both C_{max} and AUC values increase proportionally with an increase in dose within the therapeutic range. The absolute oral bioavailability of dapagliflozin following the

administration of a 10 mg dose is approximately 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs the T_{max} by approximately 1 hour but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food. Dapagliflozin is approximately 91% protein bound, and protein binding is not altered with renal or hepatic impairment. The metabolism of dapagliflozin is primarily mediated by uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9), with minor metabolic clearance through CYP-mediated metabolism. Dapagliflozin is extensively metabolized, primarily to dapagliflozin 3-O-glucuronide, an inactive metabolite, accounting for approximately 61% of an administered dose. Dapagliflozin and related metabolites are primarily eliminated in the urine (75%, with 2% as parent drug) and feces (21%, with 15% as parent drug). The mean plasma terminal $t_{1/2}$ for dapagliflozin is approximately 12.9 hours.[3]

Saxagliptin: The PKs of saxagliptin and its active metabolite (i.e., 5-hydroxy saxagliptin) are similar in healthy subjects and patients with T2D. The C_{max} and AUC values of saxagliptin and active metabolite increase proportionally with doses ranging from 2.5 to 400 mg. Accumulation is not observed with repeated dosing. The median T_{max} is approximately two hours for saxagliptin and four hours for 5-hydroxy saxagliptin following a 5 mg oral dose. Saxagliptin may be administered with or without food. Protein binding is negligible, so therefore changes in blood protein levels with renal or hepatic impairment are not expected to alter the disposition of saxagliptin. The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The 5-hydroxy saxagliptin metabolite has approximately 50% of the DPP-4 inhibiting potency of the parent drug. Therefore, strong CYP3A4/5 inhibitors and inducers may alter the PKs of saxagliptin and its metabolite. Saxagliptin is eliminated by both renal (~75%) and hepatic pathways, with approximately 24% and 36% of a dose excreted in the urine as saxagliptin and 5-hydroxy saxagliptin, respectively. In subjects with moderate renal impairment with (eGFR 30 to less than 45 mL/min/1.73m^2), severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its active metabolite were >2 fold higher than AUC values in subjects with normal renal function. The mean plasma terminal elimination $t_{1/2}$ for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.[4]

Metformin: Following a single oral dose of metformin extended-release, the median T_{max} is approximately seven hours (range of 4 to 8 hours). The extent of absorption is increased by approximately 50% when administered with food. However, no food effects are observed on C_{max} or T_{max}. Metformin is negligibly bound to plasma proteins, does not undergo hepatic metabolism or biliary excretion, and is excreted in the urine unchanged. Renal clearance is approximately 3.5 times higher than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Approximately 90% of a dose is eliminated within the first 24 hours, and the plasma $t_{1/2}$ is approximately 6.2 hours (approximately 17.6 hours in blood, suggestive of distribution into erythrocytes).[5]

QTERN: With the original QTERN NDA, BE between the dapagliflozin 10 mg/saxagliptin 5 mg tablet formulation and the individual dapagliflozin 10 mg and saxagliptin 5 mg tablets was demonstrated following single dose administration in a fasted state in healthy volunteers (Study CV181341). Compared with the PKs of QTERN administered in a fasted state, administration with a high-fat meal resulted in a decrease in the dapagliflozin C_{max} by >40% and prolonged the time to T_{max} by approximately two hours. However, the AUC was not altered as compared with the fasted state. Similar food effects were observed with dapagliflozin, which were not considered to be clinically meaningful.[3] No food effect was observed for saxagliptin. A PK study (CV181191) submitted at that time also evaluated a potential drug-drug interaction between saxagliptin and dapagliflozin. The results of this study showed that there isn't a drug-drug interaction between dapagliflozin 10 mg and saxagliptin 5 mg.

With the current QTERN submission, no additional BE studies or drug-drug interaction studies were submitted to support the dapagliflozin 5 mg/saxagliptin 5 mg dose formulation. Instead, the Applicant compared *in vitro* dissolution profiles from dapagliflozin/saxagliptin 5 mg/5 mg and 10 mg/2.5 mg tablets to dissolution profiles for dapagliflozin/saxagliptin 5 mg/2.5 mg and 10 mg/5 mg tablets. They also compared dissolution profiles from dapagliflozin/saxagliptin 5 mg/2.5 mg, 10 mg/2.5 mg, 5 mg/5 mg, and 10 mg/5 mg tablets to FARXIGA tablets (10 mg and 5 mg) and ONGLYZA tablets (5 and 2.5 mg). Based on these data, a biowaiver was requested for the 5 mg dapagliflozin/5 mg saxagliptin FCDP dose strength. They felt that dissolution, compositional similarity, and physiochemical and PK data support a biowaiver to bridge the dapagliflozin 5 mg/saxagliptin 5 mg FCDP strength to the strengths (10 mg/5 mg and 5 mg/2.5 mg tablets) for which BE to the individual components has been demonstrated. The biowaiver request was considered acceptable by Dr. Ho-Pi Lin, and I concur with the Biopharmaceutics review team. It is noted that the Applicant did not provide a rationale for not requesting a dose formulation that includes a saxagliptin 2.5 mg component, which is the recommended dose for patients with an eGFR <45 mL/min/1.73 m^2. However, dapagliflozin is not recommended in patients with this level of renal impairment.

4.6. Devices and Companion Diagnostic Issues

Not applicable. These Applications do not involve a companion device or diagnostic product.

4.7. Consumer Study Reviews

Not applicable. This Application 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 QTERNMET XR for the proposed indication and QTERN for the revised indication, the Applicant has submitted data from eight Phase 3 clinical trials (Table 4). Trials D1683C00005 and CV181169 are the pivotal Phase 3 efficacy trials intended to support the following proposed indications:

1) QTERNMET XR: as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4)
2) QTERN: as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4).

Both trials compared dual add-on therapy (i.e., dapagliflozin plus saxagliptin) to the monocomponents (i.e., dapagliflozin or saxagliptin) when administered concomitantly with metformin therapy (≥1500 mg/day). Trials CV181168 (the pivotal trial used to support the approval of QTERN), CV181365, and CV181369 were submitted to support efficacy and safety. Additionally, the Applicant intends to include all five trials in Section 14 (Clinical Studies) of labeling. Trials CV181363, MB102129, and D168C00014 were submitted primarily to support safety.

Table 4: Listing of Clinical Trials Relevant to NDA 210874 and NDA 209091/S-002

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints*	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Pivotal Efficacy and Safety Trials							
D1683C00005[a] (Efficacy and Safety) **NCT02681094** **EudraCT Number 2015-005406-11** *Trial Initiation Date: February 26, 2016* *Trial Completion Date:* March 7, 2018	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 5 mg + Saxa 5 mg + OL Met ≥1500 mg • Saxa 5 mg + Met ≥1500 mg • Dapa 5 mg + OL Met ≥1500 mg PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • % Subjects HbA1c <7% • FPG • BW	24 wks	**883/832** Dapa + Saxa + Met 293/273 Saxa + Met 296/283 Dapa + Met 294/276	• ≥18 years old • T2D • HbA1c ≥7.5 to ≤10% • Met (≥1500 mg x ≥8 wks)	119 Sites 6 Countries
CV181169[b] (Efficacy and Safety) **NCT 016060007** **EudraCT Number 2012-000679-18** *Trial Initiation Date: June 5, 2012* *Trial Completion Date:* July 17, 2014	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter efficacy and safety trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met XR ≥1500 mg • Saxa 5 mg + OL Met XR ≥1500 mg • Dapa 10 mg + OL Met XR ≥1500 mg PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • 2-h PPG • FPG • % Subjects HbA1c <7% • BW	24 wks	**534/490** Dapa + Saxa + Met 179/169 Saxa + Met 176/161 Dapa + Met 179/160	• ≥18 years old • T2D • HbA1c ≥8 to ≤11.5% • Met (≥1500 mg x ≥8 wks)	145 Sites 8 Countries
Supporting Efficacy and Safety Trials							
CV181168[c] (Efficacy and Safety) **NCT01619059** **EudraCT Number 2011-006323-37** *Trial Initiation Date: June 29, 2012* *Trial Completion Date: ST: November 25, 2014*	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter efficacy and safety trial – Sequential add-on to Met (inadequate control on Dapa + Met)	• Saxa 5 mg + OL Dapa 10 mg + OL Met IR ≥1500 mg • Placebo + OL Dapa 10 mg + OL Met IR ≥1500 mg	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • 2-h PPG • FPG • % Subjects HbA1c <7%	ST: 24 wks ST+LT: 52 wks	**ST: 315/298** Saxa + Dapa + Met 153/142 Placebo + Dapa + Met 162/156 **ST+LT: 297/280** Saxa + Dapa + Met	• ≥18 years old • T2D • HbA1c ≥8 to ≤11.5% • Met (≥1500 mg x ≥8wks)	79 Sites 9 Countries

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints*	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
LT; May 18, 2015					142/133 Placebo + Dapa + Met 155/147		
CV181365[d] (Efficacy and Safety) **NCT02419612** **EudraCT Number 2014-003721-18** *Trial Initiation Date: August 14, 2015* *Trial Completion Date: ST: December 6, 2017* *LT: Ongoing*	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met ≥1500 mg • Glim 1-6 mg + OL Met ≥1500 mg PO daily	Change from BL to Wk 52: *Primary* • HbA1c *Secondary* • BW • % Subjects HbA1c <7% • SBP • Time to rescue • Percent rescued	ST: 52 wks ST+LT: 156 wks	**444/385** Dapa + Saxa + Met 227/197 Glim + Met 217/188	• ≥18 years old • T2D • HbA1c ≥7.5 to ≤10.5% • Met (≥1500 mg x ≥8 wks)	87 Sites 10 Countries
CV181369[e] (Efficacy and Safety) **NCT02551874** (b) (4) *Trial Initiation Date: October 20, 2015* *Trial Completion Date: ST: December 4, 2017* *LT: Ongoing*	Phase 3, randomized, OL, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + Met XR ≥1500 mg ± SU • Insulin glargine + OL Met XR ≥1500 mg ± SU PO daily	Change from BL to Wk 24: *Primary* • HbA1c (non-inferiority) *Secondary* • BW • % Hypoglycemia (≤70 mg/dL) • % Subjects HbA1c <7% with no hypoglycemia • 24-hour mean glucose at Wk 2 (CGM) • % Subjects HbA1c <7%	ST: 24 wks ST+LT: 52 wks	**650/584** Dapa + Saxa + Met XR ± SU 324/298 Insulin glargine + Met XR ± SU 326/286	• ≥18 years old • T2D • HbA1c ≥7.5 to ≤10.5% • Met (≥1500 mg x ≥8 wks) ± SU	112 Sites 11 Countries
Supporting Safety Trials							
MB102129[f] (Efficacy and Safety) **NCT01646320** **EudraCT Number 2011-006324-20** *Trial Initiation Date:*	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter efficacy and safety trial – Sequential add-on to Saxa + Met	• Dapa 10 mg + OL Saxa 5 mg + OL Met IR ≥1500 mg • Placebo + OL Saxa 5 mg + OL Met IR ≥1500 mg PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • FPG • 2-h PPG • BW	ST: 24 wks ST+LT: 52 wks	**ST: 320/301** Dapa + Saxa + Met IR 160/148 Placebo + Saxa + Met IR 160/153	• ≥18 years old • T2D ***Stratum A:*** • HbA1c ≥8 to ≤11.5% at screening ***Stratum B*** • HbA1c ≥7.5 to	64 Sites 8 Countries

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints*	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
September 21, 2012 *Trial Completion Date:* *ST: December 6, 2014* *LT: July 10, 2015*	(inadequate control on Saxa + Met)		• % Subjects HbA1c <7%		**ST+LT: 294/281** Dapa + Saxa + Met IR 147/141 Placebo + Saxa + Met IR 147/140	≤10.5% at screening ***Stratum C*** • HbA1c ≥7 to ≤10.5% prior randomization; Met (≥1500 mg x ≥8 wks	
D1689C00014[g] (Efficacy and Safety) **NCT 02471404** **EudraCT Number 2015-002376-24** *Trial Initiation Date: September 21, 2015* *Trial Completion Date: June 7, 2017*	Phase 4, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + OL Met IR ≥1500 mg • Dapa 10 mg + Saxa 5 mg + OL Met IR ≥1500 mg • Glim 1-6 mg + OL Met ≥1500 mg PO daily	Change from BL to Wk 52: *Primary* • HbA1c *Secondary* • Hypoglycemia (≤70 mg/dL) • BW • FPG • Time to rescue	52 wks	**939/867** Dapa + Met 314/281 Dapa + Saxa + Met 312/298 Glim + Met 313/288	• ≥18 years old • T2D • HbA1c ≥7.5 to ≤10.5% • Met (≥1500 mg x ≥8 wks) ± SU	250 Sites 5 Countries
CV181363[h] (Efficacy and Safety) **EudraCT Number 2014-001102-17** *Trial Initiation Date: December 22, 2014* *Trial Completion Date: ST: December 20, 2015* *LT: May 27, 2017*	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial – Add-on to Met (inadequate control on Met)	• Dapa 10 mg + Saxa 5 mg + OL Met ≥1500 • Sita 100 mg + OL Met ≥1500 mg PO daily	Change from BL to Wk 26: *Primary* • HbA1c *Secondary* • % Subjects HbA1c <7% • BW • FPG	ST: 26 wks ST+LT: 52 wks	**461/411** Dapa + Saxa + Met 232/213 Sita + Met 229/198	• ≥18 years old • T2D • HbA1c ≥8 to ≤10.5% • Met (≥1500 mg x ≥8 wks)	87 Sites 6 Countries
Biopharmaceutics Study							
D168AC00001[i] (Pivotal BE Study) **NCT03169959** *Trial Initiation Date: May 29, 2017* *Trial Completion Date:*	Phase 1, OL, randomized, 2 parallel cohorts, 3-treatment, 3-period, crossover BE study	**Cohort 1** • Saxa + Dapa + Met XR 2.5/5/1000 mg; Fed • Dapa + Saxa + Met XR 5/2.5/1000 mg; Fed • Daxa+Saxa+Met XR	***Primary*** • Dapa C_{max}, AUC_{0-T} and AUC_{INF} • Saxa C_{max}, AUC_{0-T} and AUC_{INF} • Met C_{max}, AUC_{0-T} and	Single dose	84/81	Fed and fasted healthy subjects	1 Site 1 Country

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints*	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
July 31, 2017		5/2.5/1000 mg; Fasted **Cohort 2** • Saxa + Dapa + Met XR 5/10/1000 mg; Fed • Daxa+Saxa+Met XR 10/5/1000 mg; Fed • Daxa+Saxa+Met XR 10/5/1000 mg; Fasted	AUC_{INF} ***Secondary*** • PK parameters for dapagliflozin, saxagliptin, 5-OH saxagliptin, and metformin				

Source: Adapted from the Applicants Tabular Listing of All Clinical Studies, available at: \\cdsesub1\evsprod\nda209091\0000\m5\52-tab-list\tabular-listing.pdf.
Abbreviations: 5-OH, 5-hydroxy; AUC, area-under-the-curve; BE, bioequivalence; BL, baseline; BW, body weight; CGM, continuous glucose monitoring; C_{max}, maximum plasma concentration; Dapa, dapagliflozin; DDI, drug-drug interaction; EudraCT, European Union Drug Regulating Authorities Clinical Trials; FCDP, fixed combination drug product; FPG, fasting plasma glucose; Glim, glimepiride; H, hour; HbA1c, hemoglobin A1c (glycosylated hemoglobin); INF, infinity; IR, immediate-release; LT, long-term treatment period; Met, metformin; NCT, National Clinical Trial identifier; OL, open-label; PK, pharmacokinetic; PO, oral; PPG, postprandial glucose; Saxa, saxagliptin; SBP, systolic blood pressure; Sita, sitagliptin; ST, short-term treatment period; SU, sulfonylurea; T2D, type 2 diabetes; wks, weeks; and XR, extended-release.
* Endpoints presented according to sequential testing procedure for the trials used to support efficacy (i.e., D1683C00005, CV181169, CV181168, CV181365, CV181369).
a. Applicant's CSR for Trial D168C00005, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\d1683c00005\d1683c00005-clinical-study-report.pdf
b. Applicant's CSR for Trial CV181169, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181169\cv181169-clinical-study-report.pdf
c. Applicant's CSR for Trial CV181168, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf
d. Applicant's CSR for Trial CV181365, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-365\cv181365-clinical-study-report.pdf
e. Applicant's CSR for Trial CV181369, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-369\cv181-369-clinical-study-report.pdf
f. Applicant's CSR for Trial MB102129, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\mb102129-st-lt\mb102129-st-lt-clinical-study-report.pdf
g. Applicant's CSR for Trial D1689c00014, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\d1689c00014\d1689c00014-clinical-study-report.pdf
h. Applicant's CSR for Trial CV181363, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-363\cv181363-clinical-study-report-st.pdf
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-363-st-lt\cv181363-clinical-study-report-st-lt.pdf
i. Applicant's CSR for Study D168AC00001, available at:
\\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\d168ac00001\d168ac00001-clinical-study-report.pdf

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 five Phase 3 clinical trials (i.e., Trials D1683C00005, CV181169, CV181168, CV181365, and CV181369) (b) (4) For a detailed discussion of the statistical analyses of these trials, please refer to the Statistical Review of Dr. Jennifer Clark (dated March 28, 2019), the primary statistical reviewer for these 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. Overview and Objectives

The following five Phase 3 clinical trials were used to support the efficacy of QTERNMET XR and QTERN for the proposed indications:

1. **Trial D1683C00005:** *A Multi-Center, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5 mg Co-administered with Dapagliflozin 5 mg compared to Saxagliptin 5 mg or Dapagliflozin 5 mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone*

   Primary Objective: To demonstrate the superiority of the change from baseline HbA1c achieved with the co-administered saxagliptin 5 mg and dapagliflozin 5 mg to either agent individually after 24 weeks.

   Trial D1683C0005 is one of the Applicant's two pivotal Phase 3 trials. This 24-week, randomized, double-blind, active-controlled, parallel-group, add-on to metformin trial compared the efficacy and safety of concomitant (dual) addition of dapagliflozin 5 mg plus saxagliptin 5 mg daily to the individual components (i.e., either dapagliflozin 5 mg/day or saxagliptin 5 mg/day) in adult T2D subjects who had inadequate glycemic control (i.e., HbA1c ≥7.5% and ≤10.0%) on a stable dose of metformin (≥1500 mg/day for at least eight weeks).

2. **Trial CV181169:** *A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in*

Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone

Primary Objective: To compare the mean change from baseline in HbA1c achieved with concurrent addition of saxagliptin and dapagliflozin to metformin vs. the addition of placebo and saxagliptin to metformin and vs. the addition of placebo plus dapagliflozin to metformin after 24 weeks of double-blind treatment.

This second pivotal trial was a 24-week randomized, double-blind, active-controlled, parallel-group, add-on to metformin trial that compared the efficacy and safety of concomitant addition of dapagliflozin 10 mg plus saxagliptin 5 mg daily to saxagliptin 5 mg/day and to dapagliflozin 10 mg/day in adult T2D subjects who had inadequate glycemic control (i.e., HbA1c ≥8.0% to ≤12.0%) on stable doses of metformin (≥1500 mg/day for at least eight weeks).

3. **Trial CV181168:** *Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin*

   Primary Objective: To compare the mean change from baseline in HbA1c achieved with saxagliptin added to dapagliflozin plus metformin vs. placebo added to dapagliflozin plus metformin after 24 weeks of short-term, double-blind treatment.

   Trial CV181168 was intended to provide supporting efficacy and safety data for NDA 210874 (QTERNMET XR). This trial was the pivotal trial for the original QTERN NDA and is included in approved product labeling. The Applicant also intends to include the data from this trial in Section 14 (CLINICAL STUDIES) of QTERNMET XR labeling. In this trial, efficacy and safety was evaluated based on the sequential (stepwise) addition of saxagliptin 5 mg/day or placebo in adult subjects with T2D who have inadequate glycemic control (i.e., HbA1c ≥7.0% to ≤10.5%) on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). The trial consisted of a 24-week, randomized, double-blind, placebo-controlled, short-term (ST) treatment period, followed by a 28-week long-term (LT) site- and subject-blind treatment period (i.e., 52-week total treatment duration).

4. **CV181365:** *A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone*

Primary Objective: To compare the mean change from baseline in HbA1c achieved with saxagliptin in coadministration with dapagliflozin added to current background therapy with metformin, compared with glimepiride added to current background therapy with metformin at Week 52.

Trial CV181365 was a 52-week randomized, double-blind, active-controlled, parallel group study with a blinded 104-week extension phase. This trial compared orally once daily dapagliflozin 10 mg and saxagliptin 5 mg coadministered in combination with metformin to once daily glimepiride (titrated from 1mg to 6 mg or highest tolerable dose over 12 weeks) plus placebo with metformin (≥1500 mg per day) in T2D subjects with inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) on a stable dose of metformin alone (≥1500 mg/day for at least eight weeks). The glimepiride/placebo dose was kept constant, except for down-titration in the event of hypoglycemia.

5. **Trial CV181369:** *A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin Compared to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy*

   Primary Objective: To examine whether the mean change from baseline in HbA1c with co-administered dapagliflozin 10 mg and saxagliptin 5 mg plus metformin with or without sulfonylurea is noninferior (using a noninferiority margin of 0.3%) to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

   Trial CV181369 was a 24-week randomized, open label, active-controlled, parallel group study with a 28-week extension period that compared orally once daily dapagliflozin 10 mg and saxagliptin 5 mg coadministered with metformin with or without a sulfonylurea to titrated subcutaneous insulin glargine coadministered with metformin with or without a sulfonylurea in adult T2D subjects with inadequate glycemic control (HbA1c ≥8.0% and ≤12.0%).

These trials were all multicenter, randomized, double-blinded, controlled trials, and met regulatory standards for adequate and well-controlled studies (21 CFR 314.126).[21] The objectives of these trials were to demonstrate superiority of the dapagliflozin plus saxagliptin plus metformin combination treatment arm to the individual components or to glimepiride, and to show noninferiority to insulin glargine.

6.1.2. Study Designs

The study designs for the five efficacy trials are presented in Appendix 13.4. The treatment approach used for Trials DV168C00005, CV181169, CV181369 and CV181365 was to administer dapagliflozin plus saxagliptin concomitantly (simultaneously) as add-on therapy to metformin (≥1500 mg/day) in subjects with inadequate glycemic control on metformin alone. This triple

therapy combination arm was compared to the individual components (i.e., dapagliflozin or saxagliptin using a factorial design in Trials D168C00005 and CV181169), to glimepiride in Trial CV181365, or to insulin glargine with/without a sulfonylurea (noninferiority analytical approach) in Trial CV181369, all as add-on therapy to metformin. A sequential add-on treatment approach was used for Trial CV181168, in which open-label dapagliflozin 10 mg/day was initially added to metformin for an eight-week treatment period, and subjects were then randomized to saxagliptin or placebo. Trial CV181369 used a noninferiority analytical approach to evaluate the primary endpoint (change from baseline in HbA1c). All other trials were designed to evaluate superiority of triple therapy to comparators for the primary endpoint.

Trials D168C00005, CV181169, and CV181168 used fixed doses for treatment and comparator arms, while Trials CV181365 and CV181369 included a 12-week titration phase for adjustments in the glimepiride (i.e., adjustments every 3 weeks up to 6 mg/day), and insulin glargine (i.e., titration to target with adjustments every 3 days based on the average of the previous average 3-day FPG concentrations) dosing, respectively.

Trials DV168C00005 and CV181169 were 24 weeks in duration, while Trials CV181168 and CV181369 included a 24-week double-blind treatment phase with a 28-week extension period, and Trial CV181365 used a 52-week double-blind treatment phase with a 104-week extension period. The extension phases were subject- and site-blinded. The extension phases for two of the trials (CV181365 and CV181369) were ongoing at the time these Applications were submitted. Consistent with other Phase 3 antihyperglycemic clinical development programs, the 24 to 52-week double-blind treatment durations were adequate to determine a treatment effect and assess durability of glycemic response.

6.1.3. Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria for the five Phase 3 trials are presented in Table 5. Generally, these trials enrolled relatively healthy adult subjects with T2D.

Table 5: Summary of Key Inclusion and Exclusion Criteria by Phase 3 Trial

Trials	D1683C00005	CV181169	CV181168	CV181365	CV181369
INCLUSION CRITERIA					
Age ≥18 years	X	X	X	X	X
T2D men/women	X	X	X	X	X
HbA1c ≥7 to ≤10.5%			X		
HbA1c ≥7.5 to ≤10%	X				
HbA1c ≥7.5 to ≤10.5%				X	
HbA1c ≥8 to ≤11.5%					
HbA1c ≥8 to ≤12%		X			X
FPG ≤270 mg/dL	X	X	X	X	X
C-peptide ≥ 1 ng/mL	X	X	X		X

Trials	D1683C00005	CV181169	CV181168	CV181365	CV181369
Background metformin ≥1500 mg/d for ≥8 wks	X	X	X	X	X
BMI ≤45 kg/m^2		X	X		X
BMI 20-45 kg/m^2	X			X	
EXCLUSION CRITERIA					
T1D, Hx of DKA, Secondary DM	X	X	X	X	X
Symptoms of poorly controlled T2D	X	X	X		
Prespecified cardiovascular/vascular disease within 3 months*	X	X	X	X	X
Prespecified renal/urologic diagnosis¶	X	X	X	X	X
Significant hepatic disease†	X	X	X	X	X
Pancreatic disease (current/acute/chronic pancreatitis)	X			X	X
Hematological/oncological disease‡	X	X	X	X	X
Hx of hypersensitivity/intolerance/contraindication to IPs	X	X	X	X	X
Prohibited antihyperglycemic agents	X	X	X	X	X
Bariatric surgery or in a weight loss program or medications¶	X	X	X	X	X
New/Chronic systemic corticosteroid therapy	X	X		X	X
Unstable or prespecified medical condition¶	X	X	X	X	X
Pregnant/breastfeeding	X	X	X	X	X
Clinically significant PE, ECG, or laboratory findings	X			X	X
Uncontrolled HTN (SBP ≥160 mmHg or DBP ≥100 mmHg)	X	X	X		
Abnormal clinical labs					
eGFR <60 mL/min/1.73 m^2		X	X		
CrCl <60 mL/min	X			X	X
SCr ≥1.5 mg/dL males/≥1.4 mg/dL females	X	X	X	X	X
ALT or AST >3x ULN	X	X	X	X	X
TBILI >2 to 2.5x ULN	X	X	X	X	X
Positive hepatitis serology	X	X	X	X	X
TSH outside of normal reference limits with abnormal FT4	X	X	X	X	X
Hemoglobin <11 g/dL (males) or <10 g/dL (females)	X	X	X	X	X
Hematuria	X	X	X	X	X

Source: Adapted from the Applicants' CSRs for Trials D1683C0005, CV181169, CV181168, CV181365, and CV181369, available at:
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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; 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.

* Myocardial infarction, cardiac surgery or revascularization, unstable angina, unstable CHF or EF ≤40%, TIA, arrhythmia.
¶ History of unstable or rapidly progressing renal disease, congenital glucosuria.
† Severe hepatic disease or positive hepatitis serology.
‡ Hemoglobinopathy, malignancy within 5 years, bladder cancer or history of irradiation to abdomen or pelvis, bone marrow transplantation, immunocompromised, blood transfusion or donation within 120 days.
ⴖ Endocrine, psychiatric or rheumatic disorder, volume depleted, alcohol or substance abuse, compulsorily detained for treatment of psychiatric or physical illness.

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 reviewed by the Division. Eligibility criteria also were consistent across trials (Table 5).

6.1.4. Study Treatments

Depending on the respective Phase 3 trial, IP was administered once daily in the morning (or twice daily for the administration of metformin IR tablets) and provided by the Applicant as follows:

- **D1683C00005:** Dapagliflozin 5 mg tablets and matching placebo tablets; and saxagliptin 5 mg tablets and matching placebo
- **CV181169:** Dapagliflozin 10 mg tablets and matching placebo tablets; saxagliptin 5 mg tablets and matching placebo; and metformin XR 500 mg tablets
- **CV181168:** Saxagliptin 5 mg tablets and matching placebo tablets; dapagliflozin 10 mg tablets; and metformin IR 500 mg tablets
- **CV181365:** Dapagliflozin 10 mg tablets and matching placebo tablets; saxagliptin 5 mg tablets and matching placebo; and glimepiride 1 mg, 2, mg, and 4 mg capsules and matching placebo capsules (titrated from Weeks 3-12)
- **CV181369:** Dapagliflozin 10 mg tablets; saxagliptin 5 mg tablets; and insulin glargine (titrated up to Week 12)

It is noted that while all subjects were required to receive open-label background therapy of metformin (≥1500 mg), and some also received open-label sulfonylureas (≥50% of the maximum recommended daily dose), these products were not always provided by the Applicant. Additionally, metformin IR was used in Trial CV181168, metformin XR was used in Trial CV181169, and metformin IR or XR were used in Trials D1683C00005, CV181365, and CV181369. However, investigators were asked to continue subjects on stable doses of these medications (except in the cases of down-titration for hypoglycemic events with sulfonylureas). Although it would have been better if the Applicant provided these products as study medications and used only

metformin XR for all trials, I think that this is acceptable and consistent with the use of background antihyperglycemic therapy in other antihyperglycemic clinical development programs.

Rationale for Dose Selection:

The dapagliflozin 5 mg dose was selected for Trial D1683C00005 since it is the recommended starting dose of dapagliflozin. The dapagliflozin 10 mg dose was chosen because it was the dose most widely studied in clinical development and is the approved maximum recommended dose. The Applicant also believes that this dose provides the most favorable benefit/risk profile. The saxagliptin 5 mg dose was selected for all studies as it is an approved dose, and drug utilization data suggests that this dose would encompass a significant patient population requiring concurrent therapy. Additionally, the 2.5 mg dose is typically recommended for moderate or severe renal impairment (eGFR <45 mL/min/1.73 m^2) and all five trials excluded subjects with a CrCl or eGFR of <60 mL/min/1.73 m^2. For trials that include 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/double dummy masking technique (e.g., matching placebo was provided in identical packaging as active treatment). Subjects, investigators, personnel or designees of the Applicant remained blinded throughout the double-blind treatment period with the exception of personnel generating the randomization scheme, the Applicant's Supply Chain Study Management and Global Pharmacovigilance (e.g., to unblind certain data for Expedited Safety Reports), and the clinical research organization (CRO) providing the IVRS/IWRS and involved with packaging and labeling of IPs. Subjects and trial site staff also remained blinded until completion of the LT extension periods for Trials CV181168 and CV181365.

Subjects were randomized into each study arm using a 1:1 or 1:1:1 treatment allocations (i.e., for two and three arm comparisons, respectively), stratified by site in Trials CV181169 and CV181365, and by current background use of metformin or metformin plus a sulfonylurea in Trial CV181369. Randomization was typically 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 Trials CV181365 and CV181369, which included a 12-week dose titration phase for the comparator arms (i.e., glimepiride and insulin glargine, respectively), dose titration of blinded

study medication was not permitted at any time during the trials. Additionally, open-label metformin doses were to remain unchanged during the double-blind treatment periods.

For Trial CV181365, subjects had site visits every three weeks to enable titration of glimepiride from Weeks 3-12. The glimepiride starting dose was 1 mg, which could be up-titrated in 1-2 mg increments to a maximum dose of 6 mg to achieve glycemic control (i.e., FPG concentration <110 mg/dL) or the highest tolerable daily dose. If titration was not medically indicated at Week 3, reassessment for up-titration also occurred at Weeks 6, 9, and 12. The dose could be down-titrated during the titration period if hypoglycemic events occurred and subsequently up-titrated once during the 12-week titration period.

For Trial CV181369, subjects received an initial dose of 2 units/kg body (BW) or at least 10 units of insulin glargine per day. The trial used a treat-to-target approach (target FPG of ≤100 mg/dL) in which subjects self-titration their insulin dose in 2-units increments every three days until Week 8 based on the average FPG during the previous three days (see Table 6). The titration was evaluated at each site visit, and the investigator could provide recommendation between Weeks 8 and 12 based on FPG concentrations measured at the (b) (4). Down-titration of insulin after Week 8 was allowed for hypoglycemia.

Table 6: Insulin Dose Titration Scheme (up to Week 8)

Average fasting blood glucose concentration	Dose of insulin for the next 3 days
≥100 mg/dL	Increase current dose by 2 Units
≥80 mg/dL **AND** < 100 mg/dL	Keep current dose the same
< 80 mg/dL	Decrease current dose by 2 Units

Source: Adapted from the Applicant's Clinical Study Protocol, page 104 of 224, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-369\cv181-369-12-1-01-protocol-and-protocol-amendments.pdf

The Applicant's treat-to-glycemic target approach, using FPG concentrations, to titrate basal insulin doses is acceptable.[160-166]

6.1.5. Administrative Structure of the QTERNMET XR and QTERN Development Program

The five trials used to support efficacy were conducted at approximately 529 clinical sites across 16 countries. The responsible parties for the administrative structure of each trial are presented in Table 7.

Table 7: Administrative Structure of the Phase 3 Efficacy Trials

Trials	D1683C00005	CV181169	CV181168	CV181365	CV181369
ACTIVITY					
Trial Sponsor	AZ	BMS	BMS	BMS transfer to AZ	BMS transfer to AZ
Monitoring	AZ	(b) (4)	BMS	(b) (4)	
IP Management/Supply	AZ	BMS	BMS		BMS/AZ
Management	AZ	BMS	BMS	BMS transfer to AZ	BMS transfer to AZ
HAC/CAC Committees	Yes	Yes	Yes	Yes	Yes
IVRS/IWRS service (b) (4) Glucometers					(b) (4)
CGM and ePRO reporting					(b) (4)
Project Management/ Clinical Monitoring			BMS	(b) (4)	BMS (b) (4)
Data Management/ Clinical Programing	(b) (4)	BMS, (b) (4) (b) (4)	BMS, (b) (4)	(b) (4)	(b) (4)
Statistical Analysis		BMS, (b) (4) (b) (4)	BMS		(b) (4)
Medical Writing		BMS	BMS	(b) (4)	

Source: Adapted from the Applicants' CSRs for Trials D1683C0005, CV181169, CV181168, CV181365, and CV181369, available at:
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Abbreviations: AZ, AstraZeneca; BMS, Bristol-Myers-Squibb; CAC, Cardiovascular Adjudication Committee; CGM, continuous glucose monitoring; CV, cardiovascular; ePRO, electronic patient reported outcomes; HAC, Hepatic Adjudication Committee; IP, investigational product; IVRS, Interactive Voice Response System; and IWRS, Interactive Web Response System.

For all trials, suspected serious CV and hepatic adverse events were adjudicated by a blinded, independent Clinical Event Committee (CEC), and a Hepatic Adjudication Committee, respectively. These committees conducted all their operations in accordance with International Conference on Harmonization (ICH) GCP guidelines. Adjudication was performed in a blinded fashion, and CEC members remained blinded to randomization codes throughout the adjudication process. All trials also included a (b) (4) for efficacy and safety laboratory assessments.

It is noted that during the conduct of several of the trials (CV181365 and CV181369), BMS transferred ownership and regulatory responsibility for IND 118840 (dapagliflozin/saxagliptin) to AZ, the Applicant. During the transition, BMS initiated these trials on behalf of AZ. I do not feel this transfer of ownership/responsibility altered the quality or validity of the data from these trials.

6.1.6. Protocol Procedures and Schedule

All five trials included a 2-week screening/enrollment period (see Appendix 13.4). The trials with 24-week primary efficacy assessments (D1683C00005, CV181169, CV181168 and CV181369) included scheduled study visits at baseline and Weeks 6, 12, and 24, with an additional visit at Week 18 in Trial CV181169, CV181168. For Trials CV181168 and CV181369, which included 28-week LT extension phases, visits were scheduled every 8- to 12-week during the LT treatment period. For Trial CV181365, study visits were usually scheduled every three weeks during for the 52-week ST treatment phase, and every 13 weeks thereafter for the LT extension period. Adverse event monitoring and assessments of vital signs, clinical laboratory parameters and adherence to IP were usually performed at study visits.

Dietary Restrictions/Instructions:

Subjects received counseling on dietary and life-style modifications (in accordance with the ADA or local medical standards of care for subjects with T2D) by a dietician or qualified healthcare professional at screening and throughout the trial. Investigational sites also reinforced diet and exercise counseling during the randomized treatment period. Additionally, investigators or designees ensured that subjects received an adequate daily intake of minerals and vitamins, in accordance with the National Academy of Sciences or similar local guidelines.

Concurrent Medications:

All five trials required the use of open-label background metformin therapy (≥1500 mg; Section 6.1.4). Additionally, for Trial CV181365, stable doses of a sulfonylurea (≥50% of the approved maximum recommended daily dose) were permitted. Other antihyperglycemic medications were not permitted except those prespecified for glycemic rescue therapy. Medications commonly used by diabetic patients or recommended as standard of medical care (e.g., antihyperlipidemics, antiplatelets, antihypertensives) were typically allowed. Use of medications that could affect body weight was not allowed for any of the trials (Table 5), 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 (usually

defined as ≥80% and ≤120% of that prescribed) was assessed through subject interview and tablet counts. During the trial, the importance of adherence to study medications was reinforced for all subjects who were <80% compliant following randomization.

Rescue Medication:

For Trials D1683C00005, CV181169, and CV181168, subjects with inadequate glycemic control during the double-blind treatment period were eligible to receive open-label rescue medication usually based on the criteria presented in Table 8. These criteria were usually based upon the [redacted] (b) (4) FPG and repeat confirmatory FPG (~3-5 days), and are consistent with the 2008 Diabetes Guidance.[167] Subjects who met any of the criteria were required to complete a rescue visit, and subsequently prescribed open-label antihyperglycemic rescue medication (except GLP-1 analogs, other DPP-4/SGLT inhibitors, or metformin) in accordance with local approved labeling/standard of care. For Trials CV181365 and CV181369, insulin was the preferred first line therapy, whereas in Trials CV181169 and CV181168, either insulin or other antihyperglycemic medications were acceptable. For Trial D1683C00005, dapagliflozin 10 mg/day plus saxagliptin 5 mg/day was considered first line therapy as subjects in this trial randomized to dapagliflozin arms only received the 5 mg/day dose. Subjects were asked to continue with the planned study visits and continued to receive blinded study medication. During the LT extension phases, subjects were eligible to receive open-label rescue therapy in addition to their study medication based on HbA1c criteria. These subjects also were required to complete a rescue visit and continue with their scheduled follow-up visits. Due to the 12-week insulin titration period in Trial CV181369, the use of rescue therapy was initiated after Week 12 using the criteria below (i.e., FPG >200 mg/dL from Weeks 12-24 and HbA1c >8% after Week 24).

Table 8: Criteria for Initiation of Antihyperglycemic Rescue Therapy

Study Visits	Rescue Laboratory Criteria [redacted] (b) (4)
Double-blind treatment period	
Week 6	FPG >270 mg/dL
After Week 6 to Week 12	FPG >240 mg/dL
Weeks 12-24	FPG >200 mg/dL
Long-term safety extension period	
After Week 24	HbA1c >8%

Source: Adapted from the Applicants' Clinical Protocols or CSRs for Trials D1683C00005, CV181169, CV181168, CV181365, and CV181369, labeled as Table 2, page 51 of 498; Table 3.5.1.1, page 733 of 3208; Table 3.1.1, page 52 of 3639 and Table 3.1.1 page 30 of 3270; and Table 5, page 56 of 1990, 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 (b) (4).

Rescue criteria for Trial CV181365 are presented in Table 9. Insulin was the recommended first-line rescue therapy as subjects were already taking dual or triple therapy. Rescue therapy did not include GLP-1 analogs, other DPP-4/SGLT inhibitors, or sulfonylureas. The procedures following rescue were similar to those described for the other trials above.

Table 9: Criteria for Initiation of Antihyperglycemic Rescue Therapy

Study Visits	Rescue Laboratory Criteria (b) (4)
Double-blind treatment period	
Week 9	FPG >270 mg/dL
After Week 9 to Week 16	FPG >240 mg/dL
After Week 16 to Week 28	FPG >220 mg/dL
After Week 28 to Week 52	FPG >200 mg/dL
Long-term safety extension period	
After Week 52	HbA1c >7.5%

Source: Adapted from the Applicants' CSR for Trials CV181365, labeled as Table 6, page 56 of 1707, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-365\cv181365-clinical-study-report.pdf

Overall, I felt that the above glycemic rescue criteria for all trials were adequate.

Subject Withdrawal/Discontinuation:

Subjects were usually discontinued from study medication for the following reasons:

- Withdrawal of informed consent

- Clinical adverse events (AEs), laboratory abnormalities, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation would not be in the best interest of the subject
- Incorrectly enrolled
- Pregnancy
- Termination of the trial
- Loss of ability to freely provide consent (e.g., incarceration)
- eGFR (or CrCl by Cockroft-Gault) <60 mL/min/1.73m^2 for 12-16 weeks
- ALT and/or AST >3x ULN and TB >2x ULN or ALT and/or AST >5x ULN for ≥14 days or ALT and/or AST ≥10x ULN
- Protocol-defined major hypoglycemia episode or recurrent hypoglycemia episodes (e.g., fingerstick blood glucose ≤54 mg/dL and/or hypoglycemia symptoms)

In cases where a decision was made to discontinue investigational product, subjects were to be followed until resolution/stabilization. Subjects would complete an early termination visit and be asked to continue in the study for the scheduled follow-up visits. Subjects prematurely discontinuing the trial could be contacted for collection of vital status information. The sample size estimates usually assumed that 3-5% of subjects would be nonevaluable (e.g., would not have a post-baseline HbA1c assessment), and therefore these subjects were not replaced.

6.1.7. Study Endpoints

Primary Efficacy Endpoint:

- Mean change from baseline in HbA1c (%) at Week 24 (or Week 52 for Trial CV181365)

The primary efficacy endpoint for all five 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.[168]
- 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%.[169,170]
- HbA1c has excellent reliability, predicts some of the diabetes-specific complications, and provides a basis for treatment decisions in patients with T2D.[171,172]
- Lowering HbA1c reduces microvascular complications[37,38,172,173] and may lower the risk of macrovascular complications[28,32] 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."[167] Scheduled measurements of HbA1c used for eligibility criteria, efficacy analyses, and need for glycemic rescue, were performed at a (b) (4).

Key Secondary 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 were assessed at Week 24 or Week 52 (CV1813650). The following secondary endpoints were included in the Applicant's hierarchical testing procedure:

- Proportion of subjects with an HbA1c <7%
- Proportion of subjects with confirmed (BG <70 mg/dL) hypoglycemia (CV181365 and CV181369)
- Proportion of subjects with an HbA1c <7% with no hypoglycemia (Trials CV181365 and CV181369)
- Mean change from baseline in:
    - Fasting plasma glucose (FPG; mg/dL)
    - 2-hour postprandial glucose (PPG; mg/dL) during a mixed meal tolerance test (MTT)
    - Body weight (BW; kg)
    - Sitting systolic blood pressure (SBP; mmHg)
    - Time to glycemic rescue
    - 24-hour mean blood glucose (BG) concentration (mg/dL) at Week 2 by continuous glucose monitoring (CGM)

To control for Type I error due to multiple testing, the above secondary efficacy endpoints were included in the Applicant's prespecified testing sequence. The hierarchy of statistical testing for these endpoints by trial is presented in Table 10.

Table 10: Sequential Testing Order for Key Secondary Endpoints by Trial

Trials	D1683C00005	CV181169	CV181168	CV181365	CV181369
SECONDARY ENDPOINTS	• HbA1c <7%* • FPG* • BW¶	• 2-h PPG • FPG • HbA1c <7% • BW¶	• 2-h PPG • FPG • HbA1c <7%	• BW • HbA1c <7% • SBP • Time to rescue	• BW • Hypoglycemia • HbA1c <7% w/o hypoglycemia • 24-h BG (substudy)

Source: Adapted from the Applicant's Clinical Summary of Efficacy, labeled as Table 8, page 37-38 of 123, available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-efficacy.pdf

Abbreviations: 2-h PPG; 2 hour postprandial glucose concentration; 24-h BG, mean 24-hour blood glucose concentration; BW, body weight; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure.
* Testing dapagliflozin + saxagliptin + metformin vs. saxagliptin + metformin, then vs. dapagliflozin + metformin.
¶ Testing dapagliflozin + saxagliptin + metformin vs. saxagliptin + metformin.

The glycemic endpoints (HbA1c <7%, FPG, and 2-hour PPG) are considered supportive measures of efficacy in Phase 3 trials,[167] and have been included in product labeling for other approved antihyperglycemic products. The analyses of these endpoints were based on measurements performed by a (b) (4). To control for Type I error due to multiple testing, the above secondary efficacy endpoints were included in the Applicant's prespecified testing sequence. However, it is noted that the clinical relevance of several of the key secondary endpoints (i.e., time to glycemic rescue, proportion of subjects with hypoglycemia, proportion of subjects with an HbA1c without hypoglycemia, and 24-hour mean glucose concentration) is uncertain, (b) (4)

Other Relevant Endpoints:

- Safety: Adverse events (AEs), and clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings

6.1.8. Statistical Analysis Plan

For the analysis of efficacy endpoints, the Applicant used a mixed model repeated measures (MMRM) analytical approach with an intention-to-treat (ITT) estimand for the analysis population in Trial D1683C00005 and an efficacy estimand for the other four trials. The MMRM model included terms for baseline value, treatment group, time, the interaction of treatment group and time, and the interaction of baseline value and time. Randomization was stratified by background antihyperglycemic treatment (i.e., metformin vs. metformin plus sulfonylurea) for Trial CV181369 and by site in Trials CV181169 and CV181365. The ITT estimand used all randomized subjects who had a baseline measurement and received at least one dose of IP. Data after glycemic rescue and premature discontinuation were used in the analysis. The efficacy estimand used all randomized subjects who received at least one dose of IP and excluded data after rescue or treatment discontinuation. For the secondary endpoint that compared the proportion of subjects achieving an HbA1c <7% between treatment arms, a logistic regression model was used.[174,175] A 2-sided, p-value of <0.05 was considered to indicate statistical significance for the primary (i.e., mean change in HbA1c from baseline to Week 24 or 52) and secondary efficacy analyses. The 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 secondary endpoint only if the two-sided p-value was <0.05 for all previous endpoint analyses).

Dr. Jennifer Clark was the Statistical Reviewer for these Applications. Since Trial CV181168 was previously reviewed by Dr. Anna Kettermann for the original QTERN NDA, Dr. Clark did not

reanalyze these data. For a detailed discussion of the statistical issues of this trial, please refer to Dr. Kettermann's review, dated January 4, 2017.

In Dr. Clark's review, she noted that the ITT estimand is consistent with the analytical approaches used for labeling of other antihyperglycemic products. However, she expressed concern with the exclusion of post-discontinuation data (e.g., after glycemic rescue therapy or early study termination) by the Applicant for their efficacy analyses, stating that it is inappropriate to represent missing data for those who do not adhere to therapy by the data from those on the same arm who adhere to the therapy. Results may not reflect the actual efficacy findings should all of the subjects who participated in the trial have been included in the analysis. She also noted that the MMRM analytical approach, used in all efficacy analyses, has a missing at random (MAR) assumption (i.e., missing data for those off-treatment is considered to be the same as that of observed data for those subjects who remained on treatment in the same arm) which is not consistent with current Agency recommendations. Therefore, to limit the potential for favorably increasing the benefit of the investigational arm, she reanalyzed the efficacy endpoints using all available data, including measurements collected after rescue or discontinuation, to impute outcomes for those with missing data (i.e., a retrieved dropout approach). If there were inadequate data post rescue/discontinuation, then she used a placebo washout analysis when a placebo or component of the experimental treatment (i.e., dapagliflozin or saxagliptin) is the control arm, and a return to baseline washout approach (i.e., baseline values for individuals with missing data are used for multiple imputations) otherwise. Additionally, the washout for the noninferiority trial (i.e., CV181369) included a penalty set by the noninferiority margin. In the previous review of Trial CV181168, Dr. Kettermann used a retrieved dropout analytical approach for handling missing data. For a more detailed discussion of the Statistical Analysis Plan (SAP) and the statistical approach used by Dr. Clark, please refer to her Statistical Review (dated March 28, 2019).

6.1.9. 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.

6.1.10. Study Results

Compliance with Good Clinical Practice:

The Applicant states that all studies in the clinical development program were conducted in accordance with GCP, as documented by the ICH and the FDA.

Financial Disclosure:

The Applicant submitted a Form FDA 3454 for each of the covered trials (i.e., Trials CV181017,

CV181168, CV181169, CV181191, CV181363, CV181365, CV181369, C1683C00005, D1689C00014, D168AC00001, and MB102129). They reported six investigators with positive financial disclosures, and 24 investigators for whom a signed Investigator Financial Interests and Disclosure Statement Form were never received. Based on review of these data and the relatively low numbers of randomized subjects at the respective trial sites, I do not feel that there was undue bias that would affect the efficacy findings of these trials. Please see Section 13.2 below for details.

Patient Disposition:

The disposition of subjects across the five trials relevant to the evaluation of efficacy is presented in Table 11. Approximately 86% to 96% of subjects completed the ST treatment phase (i.e., Week 24 or 52). The most common reasons for not completing the ST period included development of study-specific discontinuation criteria (Trial D1683C00005), lost to follow-up and/or subject withdrew consent (Trials CV181169, CV181168, and CV181369), AEs (Trial CV181365). Obvious differences in disposition between the triple therapy arm and the dual therapy arms containing two of the components were not apparent. Numerically higher numbers of subjects in the triple therapy arm discontinued IP due to AEs for both Trials CV181365 (n=4 subjects with either 'Blood creatinine increased' or 'Glomerular filtration rate decreased') and CV181369 (n=4 subjects with either 'Chronic kidney disease', 'Creatinine renal clearance decreased', or 'Glomerular filtration rate decreased'). It is noted that subjects with a reduction in eGFR to <60 mL/min/1.73 m^2 in these trials were withdrawn from IP.

Table 11: Subject Disposition for Phase 3 Efficacy Trials (Randomized Population)

Trial	D1683C00005			CV181169			CV181168		CV181365		CV181369	
Treatment Arm	Dapa 5 mg + Saxa 5 mg + Met	Dapa 5 mg + Met	Saxa 5 mg + Met	Dapa 10 mg + Saxa 5 mg + Met	Dapa 10 mg + Met	Saxa 5 mg + Met	Dapa 10 mg + Saxa 5 mg + Met	PLA + Dapa 10 mg + Met	Dapa 10 mg + Saxa 5 mg + Met	Glim + Met	Dapa 10 mg + Saxa 5 mg + Met	Insulin glargine + Met
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. Randomized	293	294	296	179	179	176	153	162	227	217	324	326
Complete ST Phase	256 (87.4)	255 (87.0)	243 (82.4)	169 (94.4)	160 (89.4)	161 (91.5)	142 (92.8)	156 (96.3)	197 (86.8)	188 (87.0)	298 (92.0)	286 (89.7)
Discontinuation of IP	37 (12.6)	38 (13.0)	52 (17.6)	10 (5.6)	19 (10.6)	15 (8.5)	11 (7.2)	6 (3.7)	30 (13.2)	28 (13.0)	26 (8.0)	33 (10.3)
Lack of efficacy	1 (0.3)	5 (1.7)	14 (4.7)	0	0	0	0	0	0	1 (0.5)	–	–
Adverse event	10 (3.4)	4 (1.4)	1 (0.3)	1 (0.6)	1 (0.6)	0	0	1 (0.6)	8 (3.5)	1 (0.5)	5 (1.5)	1 (0.3)
Subj request to D/C	7 (2.4)	10 (3.4)	9 (3.1)	1 (0.6)	2 (1.1)	0	1 (0.7)	0	–	–	–	–
Withdrew consent	0	0	0	1 (0.6)	6 (3.4)	8 (4.5)	4 (2.6)	2 (1.2)	–	–	–	–
Lost to follow-up	0	0	0	5 (2.8)	8 (4.5)	6 (3.4)	4 (2.6)	2 (1.2)	6 (2.6	6 (2.8)	8 (2.5)	11 (3.4)
Noncompliance	2 (0.7)	0	1 (0.3)	0	0	1	1 (0.7)	1 (0.6)	2 (0.9)	2 (0.9)	0	3 (0.9)
Pregnancy	0	0	0	1 (0.6	1 (0.6)	0	0	0	0	0	0	0
No longer eligible	11 (3.8)	13 (4.4)	20 (6.8)	0	0	0	1 (0.7)	0	0	1 (0.5)	4 (1.2)	0
Other	6 (2.0)	6 (2.0)	7 (2.4)	1 (0.6	1 (0.6)	0	0	0	–	–	0	1 (0.3)

Source: Adapted from the Applicant's Summary of Clinical Efficacy, labeled as Table 10, page 56 of 123, and the CSRs for Trials CV181168, CV181365, CV181369, available at:
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Abbreviations: Dapa, dapagliflozin; D/C, discontinue; Glim, glimepiride; IP, investigational product; Met, metformin; Saxa, saxagliptin; ST, short-term controlled phase; Subj, subject.

Protocol Violations/Deviations:

Relevant protocol deviations were defined as deviations that were likely to impact the primary efficacy analysis of trial results. Across the Phase 3 clinical program, major protocol deviations were reported in approximately 1.1% to 12.9% of subjects—9.4% (82 subjects) in Trial D1683C00005; 3.2% (17 subjects) in Trial CV181169; 6.0% (19 subjects) in Trial CV181168; 1.1% (5 subjects) in Trial CV181365; 12.9% (83 subjects) in Trial CV181369. The most common deviations for these trials in the triple therapy arms included overall treatment compliance <80% or >120% of the intended dose, and subjects who took no dose of dapagliflozin or a dose of dapagliflozin outside of dose range for ≥two consecutive weeks in the open-label or ST double-blind period. A review of the major deviations did not reveal any obvious/important trends or treatment differences across trial arms.

Table of Demographic Characteristics:

The baseline demographics (Table 12) and clinical characteristics (Table 13) of randomized subjects are summarized below. Within and across trials, treatment groups appeared to be well-balanced for demographics and clinical characteristics at baseline. Overall, the trial population was predominantly White, and relatively young (mean age approximately 55 years). A limited number of subjects were over 75 years of age. The trials were conducted worldwide; with the approximately 47% of randomized subjects residing in the North American region, with more than one-third of subjects randomized from the U.S. The mean body mass index (BMI) was >30 kg/m^2 across all trials. The mean baseline HbA1c concentrations ranged from 7.1% to 9.1%, and the average duration of diabetes was greater than seven years. Since subjects with an eGFR <60 $mL/min/1.73m^2$ were to be excluded from study participation, the mean eGFR was >90 $mL/min/1.72\ m^2$ in all trials.

Table 12: Baseline Demographics for Phase 3 Efficacy Trials (Randomized Population)*

Trial	D1683C00005			CV181169			CV181168		CV181365		CV181369	
Treatment Arm	**Dapa 5 mg + Saxa 5 mg + Met**	**Dapa 5 mg + Met**	**Saxa 5 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Dapa 10 mg + Met**	**Saxa 5 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**PLA + Dapa 10 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Glim + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Insulin glargine + Met**
DEMOGRAPHICS	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. Randomized — no. (%)	290	289	291	179	179	176	153	162	227	216	324	319
Age, mean ± SD — yr	57.2±10.68	55.9±10.94	57.0±9.94	53.4 (9.8)	53.5 (9.7)	54.6 (9.6)	54.7 ± 9.8	54.5 ± 9.3	56.1 ± 10.1	56.1 ± 9.2	55.7 ± 9.5	55.3 ± 9.6
<65 yr — no. (%)	212 (73.1)	219 (75.8)	221 (75.9)	160 (89.4)	158 (88.3)	148 (84.1)	132 (86.3)	140 (86.4)	182 (80.2)	171 (79.2)	265 (81.8)	260 (81.5)
≥65 yr — no. (%)	78 (26.9)	70 (24.2)	70 (24.1)	19 (10.6)	21 (11.7)	28 (15.9)	21 (13.7)	22 (13.6)	45 (19.8)	45 (20.8)	59 (18.2)	59 (18.5)
≥75 yr — no. (%)	16 (5.5)	9 (3.1)	12 (4.1)	2 (1.1)	1 (0.6)	0	2 (1.3)	3 (1.9)	2 (0.9)	3 (1.4)	4 (1.2)	5 (1.6)
Female sex — no. (%)	148 (51.0)	137 (47.4)	134 (46.0)	94 (52.5)	90 (50.3)	82 (46.6)	80 (52.3)	86 (53.1)	110 (48.5)	115 (53.2)	148 (45.7)	148 (46.4)
Race — no. (%)												
White	265 (91.4)	257 (88.9)	258 (88.7)	120 (67.0)	131 (73.2)	121 (68.8)	136 (88.9)	141 (87.0)	204 (89.9)	195 (90.3)	263 (81.2)	254 (79.6)
Black	10 (3.4)	17 (5.9)	24 (8.2)	22 (12.3)	16 (8.9)	22 (12.5)	11 (7.2)	9 (5.6)	4 (1.8)	5 (2.3)	28 (8.6)	35 (11.0)
Asian	9 (3.1)	9 (3.1)	6 (2.1)	12 (6.7)	10 (5.6)	11 (6.3)	5 (3.3)	8 (4.9)	—	—	12 (3.7)	12 (3.8)
Other	6 (2.1)	6 (2.1)	3 (1.0)	25 (14.0)	22 (12.3)	22 (12.5)	1 (0.7)	4 (2.5)	19 (8.4)	16 (7.4)	9 (2.8)	12 (3.8)
Ethnic Group												
Hispanic/Latino — no. (%)	99 (34.1)	95 (32.9)	99 (34.0)	52 (29.1)	52 (29.1)	51 (29.0)	40 (26.1)	42 (25.9)	76 (33.5)	73 (33.8)	124 (38.3)	131 (41.1)
Not Hispanic/Latino	191 (65.9)	194 (67.1)	192 (66.0)	35 (19.6)	41 (22.9)	40 (22.7)	44 (28.8)	51 (31.5)	138 (60.8)	131 (60.6)	170 (52.5)	156 (48.9)
Not Reported				92 (51.4)	86 (48.0)	85 (48.3)	69 (45.1)	69 (42.6)	13 (5.7)	12 (5.6)	30 (9.3)	32 (10.0)
Region — no. (%)												
North America	127 (43.8)	135 (46.7)	137 (47.1)	98 (54.7)	100 (55.9)	99 (56.3)	78 (51.0)	86 (53.1)	57 (25.1)	55 (25.5)	168 (51.9)	168 (52.7)
Europe	124 (42.8)	121 (41.9)	117 (40.2)	40 (22.3)	40 (22.3)	34 (19.3)	55 (35.9)	55 (34.0)	131 (57.7)	124 (57.4)	111 (34.3)	117 (36.7)
Latin America	39 (13.4)	33 (11.4)	37 (12.7)	39 (21.8)	38 (21.2)	40 (22.7)	20 (13.1)	21 (13.0)	39 (17.2)	37 (17.1)	45 (13.9)	34 (10.7)
Asia/Pacific	0	0	0	2 (1.1)	1 (0.6)	3 (1.7)	0	0	0	0	0	0
Country — no. (%)												
U.S.	88 (30.3)	103 (35.6)	108 (37.1)	87 (48.6)	93 (52.0)	90 (51.1)	62 (40.5)	67 (41.4)	57 (25.1)	55 (25.5)	168 (51.9)	168 (52.7)
Other	202 (69.7)	186 (64.4)	183 (62.9)	92 (51.4)	86 (48.0)	86 (48.9)	91 (59.5)	95 (58.6)	170 (74.9)	161 (74.5)	156 (48.1)	151 (47.3)

Source: Derived from the adsl.xpt dataset and adapted from the Applicant's Summary of Clinical Efficacy, labeled as Table 11, page 62 of 123, and the CSRs for Trials CV181168, CV181365, CV181369, available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-efficacy.pdf
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Abbreviations: Dapa, dapagliflozin; D/C, discontinued; Glim, glimepiride (1-6 mg/day); Met, metformin (≥1500 mg/day); no., number; Saxa, saxagliptin; SD, standard deviation; ST, short-term controlled phase (24 or 52 weeks); Subj, subject. US, United States; and yr, years. *All subjects randomized who received ≥1 dose of investigational product.

Table 13: Clinical Characteristics for Phase 3 Efficacy Trials (Randomized Population)*

Trial	D1683C00005			CV181169			CV181168		CV181365		CV181369	
Treatment Arm	**Dapa 5 mg+ Saxa 5 mg + Met**	**Dapa 5 mg + Met**	**Saxa 5 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Dapa 10 mg + Met**	**Saxa 5 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**PLA + Dapa 10 mg + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Glim + Met**	**Dapa 10 mg + Saxa 5 mg + Met**	**Insulin glargine + Met**
DEMOGRAPHICS	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. Randomized — no. (%)	290	289	291	179	179	176	153	162	227	216	324	319
BMI, mg/m^2 — mean ± SD	31.5 ± 5.5	31.8 ± 5.2	32.4 ± 5.5	31.8 ± 4.8	31.5 ± 5.3	31.8 ± 5.1	31.4 ± 5.2	31.3 ± 5.3	32.4 ± 5.3	32.2 ± 5.1	32.5 ± 5.3	32.0 ±5.4
T2D Duration, mean ± SD — yr	7.5 ± 6.3	7.6 ± 6.3	7.8 ± 5.8	7.1 ± 5.0	7.4 ± 5.4	8.2 ± 5.5	8.1 ± 7.0	7.4 ± 5.8	7.7 ± 6.4	7.9 ± 6.5	9.6 ± 6.5	9.3 ± 6.2
<3 yr — no. (%)	82 (28.3)	71 (24.6)	69 (23.7)	40 (22.3)	39 (21.8)	28 (15.9)	36 (23.5)	36 (22.2)	55 (24.2)	53 (24.5)	47 (14.5)	49 (15.4)
≥3 to ≤10 yr — no. (%)	123 (42.4)	133 (46.0)	134 (46.0)	86 (48.0)	90 (50.3)	92 (52.3)	72 (47.1)	78 (48.1)	106 (46.7)	105 (48.6)	137 (42.3)	145 (45.5)
>10 yr — no. (%)	85 (29.3)	84 (29.1)	88 (30.2)	51 (28.5)	50 (27.9)	56 (31.8)	45 (29.4)	48 (29.6)	66 (29.1)	58 (26.9)	140 (43.2)	125 (39.2)
Glycemic Status												
HbA1c% — mean ± SD	8.1 ± 0.9	8.2 ± 0.9	8.3 ± 1.0	7.1 ± 5.0	7.4 ± 5.4	8.2 ± 5.5	8.0 ± 0.8	7.9 ± 0.9	8.4 ± 0.8	8.5 ± 0.8	9.04 ± 1.0	9.05 ± 1.1
<8% — no. (%)	125 (43.1)	122 (42.2)	112 (38.5)	41 (22.9)	41 (22.9)	30 (17.0)	85 (55.6)	99 (61.1)	76 (33.5)	60 (27.8)	44 (13.6)	48 (15.0)
8 to <9% — no. (%)	116 (40.0)	105 (36.3)	107 (36.8)	59 (33.0)	61 (34.1)	62 (35.2)	50 (32.7)	42 (25.9)	94 (41.4)	90 (41.7)	124 38.3)	112 (35.1)
≥9% — no. (%)	49 (16.9)	62 (21.5)	72 (24.7)	79 (44.1)	77 (43.0)	84 (47.7)	18 (11.8)	21 (13.0)	57 (25.1)	66 (30.6)	156 (48.1)	159 (49.8)
2-h PPG, mg/dL — mean ± SD	—	—	—	215.3 ± 58.2	223.1 ± 58.0	232.5 ± 65.7	208.5 ± 50.1	206.4 ± 53.1	—	—	—	—
FPG, mg/dL — mean ± SD	171.3 ± 43.5	176.3 ± 45.8	179.6 ± 46.0	180.4 ± 45.5	185.0 ± 48.4	191.8 ± 45.3	163.9 ± 34.4	157.6 ± 34.6	172.9 ± 41.5	176.5 ± 42.4	189.5 ± 55.5	188.6 ± 53.8
eGFR, $mL/min/1.73m^2$ — mean ± SD	91.4 ± 21.7	93.4 ± 22.1	92.1 ± 20.6	96.6 ± 19.6	93.9 ± 19.9	92.5 ± 19.5	92.8 ± 21.6	93.9 ± 20.6	93.7 ± 23.0	93.0 ± 21.1	94.6 ± 23.6	97.3 ± 231.7

Source: Derived from the adsl.xpt dataset and adapted from the Applicant's Summary of Clinical Efficacy, labeled as Table 11, page 62 of 123, and the CSRs for Trials CV181168, CV181365, CV181369, available at:
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Abbreviations: Dapa, dapagliflozin; D/C, discontinued; Glim, glimepiride (1-6 mg/day); Met, metformin (≥1500 mg/day); no., number; Saxa, saxagliptin; SD, standard deviation; ST, short-term controlled phase; Subj, subject. US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigational product.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use:

In the five Phase 3 trials, subjects were generally considered to be compliant with their investigational treatment regimen if their adherence rates (based primarily on tablet counts) were between 80-120%. Adherence to oral antihyperglycemic therapy has been reported to range from 36-93% in patients remaining on treatment for six to 24 months.[86] Additionally, prospective electronic monitoring studies have documented that patients took 67-85% of their oral antihyperglycemic doses as prescribed.[86] Although there is no universally accepted definition for what constitutes adequate adherence, a compliance rate of >80% is reasonable.[90,91,176] During the ST, double-blind treatment period compliance rates with administration of IP were reported to be 91.7% in Trial D168C00005, 100% in Trial CV181169, 98.8% in Trial CV181168, 99.1% in Trial CV181365, and 99.4% in Trial CV181369. It is unlikely that this relatively low rate of nonadherence in these trials will affect the interpretation of the primary and key secondary efficacy finding.

Use of concomitant medications and allowed antihyperglycemic rescue therapy are discussed above (please refer to Section 6.1.6). Glycemic rescue or discontinuation of IP due to lack of efficacy was a secondary endpoint in Trial CV181365, and an exploratory endpoint for the other four trials. However as previously stated, the Applicant typically did not account for the data from subjects who received rescue therapy or discontinued the use of study medication prior to completion of the ST double-blind treatment period in their primary efficacy analyses. This could result in the evaluation of only those subjects who achieved a therapeutic response or tolerated therapy. In their reviews, Drs. Clark and Kettermann (i.e., for Trial CV181168) noted that data for the primary efficacy analysis (i.e., HbA1c at Weeks 24 or 52) were missing for 5.1% to 12.3% of subjects across the five trials. They reanalyzed the efficacy data using placebo washout and return to baseline washout analytical approaches. Please refer to their respective reviews for further discussion.

Efficacy Results – Primary Endpoint:

The results of the primary efficacy analyses (i.e., control-subtracted change in HbA1c from baseline to Weeks 24 or 52) performed using a MMRM approach by the Applicant, and the Agency's reanalysis of these data, are presented in Table 14 below. Compared to use of the individual components of the FCDP (i.e., dapagliflozin 5 mg or 10 mg plus metformin or saxagliptin 5 mg plus metformin) triple combination therapy with dapagliflozin (5 mg or 10 mg) plus saxagliptin (5 mg) plus metformin resulted in modest but statistically significant reductions in HbA1c. Additionally, the results remained significant regardless of exclusion (Applicant's analysis) or inclusion (Agency reanalysis) of HbA1c data collected after glycemic rescue/discontinuation. The triple therapy arm was also superior to glimepiride plus metformin and noninferior to insulin plus metformin with/without a sulfonylurea. (b) (4), Dr. Clark recommends that the ITT estimands be used (i.e., based on all available data, regardless of rescue or discontinuation), with either a placebo washout or baseline washout imputation approach for missing data.

Table 14: HbA1c Change from Baseline Analyses (Phase 3 Trials)

Analysis	Triple Therapy Arm	Comparator	Comparator
Trial D1683C00005 *(Add-on Therapy with Dapagliflozin 5 mg plus Saxagliptin 5 mg in Subjects on Metformin)*			
HbA1c (%)			
Applicant's Analysis (ITT Estimand)[a]	**Dapa 5mg + Saxa 5mg + Met**	**Dapa 5 mg + Met**	**Saxa 5 mg + Met**
Sample Size (N)[b]	290	289	291
Baseline (mean)	8.1	8.2	8.3
Change from baseline to Week 24 (95% CI)	−1.03 (−1.14, −0.92)	−0.63 (−0.74, −0.52)	−0.69 (−0.80, −0.58)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.40 (−0.55, −0.24)	−0.34 (−0.50, −0.19)
P-Value		P<0.0001	P<0.0001
FDA's Analysis (Control Arm Washout)[c,d]			
Change from baseline to Week 24	−1.02 (−1.13, −0.90)	−0.62 (−0.73, −0.51)	−0.69 (−0.80, −0.59)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		− 0.40 (−0.55, −0.24)	−0.32 (−0.48, −0.17)
P-Value		P<0.0001	P<0.0001
Trial CV181169 *(Add–on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg in Subjects on Metformin)*			
HbA1c (%)			
Applicant's Analysis (Efficacy Estimand)[a]	**Dapa 10mg + Saxa 5mg + Met**	**Dapa 10 mg + Met**	**Saxa 5 mg + Met**
Sample Size (N)[b]	179	179	176
Baseline (mean)	8.9	8.9	9.0
Change from baseline to Week 24 (95% CI)	−1.49 (−1.64, −1.34)	−1.22 (−1.37, −1.07)	−0.99 (−1.14, −0.84)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.27 (−0.48, −0.06)	−0.50 (−0.71, −0.29)
P-Value		P<0.0001	P<0.0001
FDA's Analysis (Control Arm Washout)[c,d]			
Change from baseline to Week 24	−1.49 (−1.64, −1.34)	−1.23 (−1.38, −1.08)	−1.00 (−1.15, −0.85)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.26 (−0.47, −0.05)	−0.49 (−0.70, −0.27)
P-Value		P=0.015	P<0.0001
Trial CV181168 *(Add-on Therapy with Saxagliptin in Subjects on Dapagliflozin plus Metformin)*			
HbA1c (%)			
Labeled Analysis (Control Arm Washout)[c,d]	**Saxa 5 mg + Dapa 10 mg/Met**	**Placebo + Dapa 10 mg/Met**	
Sample Size (N)[e]	153	162	
Baseline (mean)	8	7.9	
Change from baseline to Week 24 (95% CI)	−0.5 (−0.6, −0.4)	−0.2 (−0.3, −0.1)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.4 (−0.5, −0.2)	
P-Value		P<0.0001	

Analysis	Triple Therapy Arm	Comparator	Comparator
Trial CV181365 *(Add-on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg vs. Glimepiride in Subjects on Metformin)*			
HbA1c (%)			
Applicant's Analysis (Efficacy Estimand)[f]	**Dapa 10mg + Saxa 5mg + Met**	**Glim 1-6 mg + Met**	
Sample Size (N)[b]	227	216	
Baseline (mean)	8.4	8.5	
Change from baseline to Week 24 (95% CI)	−1.36 (−1.49, −1.22)	−0.97 (−1.1, −0.84)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.39 (−0.58, −0.20)	
P-Value		P<0.001	
FDA's Analysis (Baseline Washout)[c,g]			
Change from baseline to Week 52	−1.23 (−1.37, −1.09)	−0.94 (−1.09, −0.80)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.29 (−0.49, −0.08)	
P-Value		P=0.006	
Trial CV181369 *(Add-on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg vs. Insulin glargine in Subjects on Metformin ± SU)*			
HbA1c (%)			
Applicant's Analysis (Efficacy Estimand)f	**Dapa 10mg + Saxa 5mg + Met**	**Insulin glargine + Met**	
Sample Size (N)[b]	324	319	
Baseline (mean)	9.0	9.0	
Change from baseline to Week 24 (95% CI)	−1.68 (−1.81, −1.56)	−1.56 (−1.69, −1.44)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.12 (−0.30, 0.05)	
NIM (upper 95% CI bound <0.3%)		Noninferior	
FDA's Analysis (Retrieved Dropout)[c,h]			
Change from baseline to Week 24	−1.65 (−1.86, −1.43)	−1.49 (−1.63, −1.35)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.16 (−0.42, 0.09)	
NIM (upper 95% CI bound <0.3%)		Noninferior	

Source: Adapted from Dr. Jennifer Clark's Statistical Review (dated March 28, 2019), labeled as Table 10, page 24 of 35; Dr. Anna Kettermann's Statistical Review (dated January 4, 2017) labeled as Tables 7-8, pages 19-20 of 31; the Applicant's proposed product labeling and Summary of Clinical Efficacy, available at:
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Abbreviations: —, not applicable; ±, with or without; CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin (≥1500 mg/day); NIM, noninferiority margin; RTB, return to baseline; Saxa, saxagliptin; and SU, sulfonylurea (>50% maximum recommended dose).

[a] The ITT estimand analysis includes data regardless of rescue or treatment discontinuation.
[b] N includes all randomized, treated subjects who had a baseline and at least one post-baseline measurement of the outcome variable.
[c] Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation.
[d] Model estimates calculated using multiple imputation to model washout of the treatment effect using control arm data for all subjects having missing Week 24 data.
[e] N includes all randomized, treated subjects.
[f] Mixed model of repeated measure analysis regardless of rescue and treatment discontinuation.
[g] Model estimates calculated using multiple imputation to model washout of the treatment effect using baseline data for all subjects having missing Week 52 data.
[h] Model estimates calculated using a retrieved dropouts multiple imputation for all subjects having missing Week 24 data.

Data Quality and Integrity:

As noted in Section 4.1 above, OSI was consulted to conduct additional audits/site inspections for these NDAs. Based on these inspections, as well as the inspection of Trial CV181168 conducted by the EMA, the data were considered acceptable. Additionally, in her review, Dr. Clark noted that the data necessary for her review were provided in the submission. She also confirmed and reanalyzed the analyses performed by the Applicant. However, it is noted that during the conduct of Trial D1683C00005, serious potential GCP violations were found at site 7869 for which the Applicant questioned the validity of the data from this site. Consequently, they amended the SAP prior to database lock and unblinding, so that subjects from this site would be excluded from tables and figures, and a selected set of key tables would be run twice (both with and without subjects from this site) to assess the impact of this exclusion. The decision to exclude these data was reported to the Agency before database lock. The results were similar for both analyses. Based on the discussion of the above findings, I feel that the data quality for these submissions was acceptable.

Efficacy Results – Secondary and Other Relevant Endpoints:

Key secondary analyses performed by the Applicant are presented in Table 15. For this portion of the review, only the endpoints to be included in product labeling will be discussed. For more detailed information on the evaluation of secondary endpoints, please refer to Dr. Clark's review. The dapagliflozin + saxagliptin + metformin triple therapy arms generally resulted in higher proportions of subjects achieving an HbA1c of <7%, and modest reductions in body weight and SBP. Although these results are supportive, the long-term clinical relevance of the observed differences between arms is uncertain. Additionally, although some weight loss was consistently reported across trials, the magnitude of these reductions (approximately 1.5-3%) would not be sufficient to pursue a weight loss claim (i.e., would not meet the FDA guidance criteria for weight management).[177] In overweight individuals, especially those with comorbidities such as T2D, weight >5% may be associated with improvement in various metabolic and cardiovascular risk factors.[178,179]

For Trial CV181168, both the 2-hour PPG and FPG analyses failed to show a statistically significant difference between the triple therapy and dual therapy comparator arm. In accordance with the prespecified SAP, hierarchical significance testing for the other key secondary endpoints was stopped once the result of the 2-hour PPG analysis was found to be nonsignificant, and therefore formal statistical testing of these endpoints were not performed. At the time of approval, it was felt that the statistical test results in Section 14 of product labeling should be limited to the primary efficacy analysis. However, to be consistent with SGLT2/DPP-4 class labeling, inclusion of descriptive statistics to show the "known" proportion of subjects who achieve an HbA1c <7% (i.e., to indicate that formal statistical testing was not performed) was allowed.

Table 15: Secondary Endpoint Analyses (Phase 3 Trials)

Analysis	Triple Therapy Arm	Comparator	Comparator
Trial D1683C00005 *(Add-on Therapy with Dapagliflozin 5 mg plus Saxagliptin 5 mg in Subjects on Metformin)*			
Body Weight (kg)			
Applicant's Analysis (ITT Estimand)[a]	**Dapa 5mg + Saxa 5mg + Met**	**Dapa 5 mg + Met**	**Saxa 5 mg + Met**
Sample Size (N)[b]	290	289	291
Baseline (mean)	87.1	89.5	92.3
Change from baseline to Week 24 (95% CI)	−2.01 (−2.37, −1.65)	−2.14 (−2.50, −1.78)	−0.41 (−0.77, −1.09)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		0.13 (−0.38, 0.63)	−1.60 (−2.10, −0.06)
FDA's Analysis (Control Arm Washout)[c,d]			
Change from baseline to Week 24	−1.97 (−2.34, −1.60)	−2.12 (−2.47, −1.76)	−0.41 (−0.76, −0.05)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		0.14 (−0.37, −0.66)	−1.56 (−2.08, −1.05)
Subjects with HbA1c <7% [N (%)]	124 (42.8)	63 (21.8)*	83 (28.5)¶
Trial CV181169 *(Add–on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg in Subjects on Metformin)*			
Body Weight (kg)			
Applicant's Analysis (Efficacy Estimand)[a]	**Dapa 10mg + Saxa 5mg + Met**	**Dapa 10 mg + Met**	**Saxa 5 mg + Met**
Sample Size (N)[b]	179	179	176
Baseline (mean)	87.2	86.3	88.2
Change from baseline to Week 24 (95% CI)	−2.05 (−2.52, −1.58)	−2.39 (−2.87, −1.91)	0 (−0.48, 0.49)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		0.34 (−0.33, 1.02)†	−2.05 (−2.73, −1.37)†
FDA's Analysis (Control Arm Washout)[c,d]			
Change from baseline to Week 24	−2.03 (−2.50, −1.56)	−2.29 (−2.77, −1.82)	0 (−0.47,0.47)
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−0.26 (−0.40, 0.93)†	−2.03 (−2.69, −1.36)†
Subjects with HbA1c <7% [N (%)]	72 (40.2)†	38 (21.2)†	29 (16.5)†
Trial CV181168 *(Add-on Therapy with Saxagliptin in Subjects on Dapagliflozin plus Metformin)*			
	Dapa 10mg + Saxa 5mg + Met	**Dapa 10 mg + Met**	
Sample Size (N)[b]	153	162	
Subjects with HbA1c <7% [N (%)]	Adjusted (35.3)†	Adjusted (23.1)†	
Trial CV181365 *(Add-on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg vs. Glimepiride in Subjects on Metformin)*			
Body Weight (kg)			
Applicant's Analysis (Efficacy Estimand)[f]	**Dapa 10mg + Saxa 5mg + Met**	**Glim 1-6 mg + Met**	
Sample Size (N)[b]	227	216	
Baseline (mean)	91.0	88.4	
Change from baseline to Week 24 (95% CI)	−3.11 (−3.65, −2.57)	0.95 (0.38, 1.50)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−4.06 (−4.84, −3.28)	

Analysis	Triple Therapy Arm	Comparator	Comparator
FDA's Analysis (Baseline Washout)[c,g]			
Change from baseline to Week 52	−2.78 (−3.35, −2.21)	0.70 (0.11, 1.29)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−3.48 (−4.30, −2.66)	
Subjects with HbA1c <7% [N (%)]	109 (48.0)[‡]	80 (36.9)	
Systolic Blood Pressure (mmHg)	**Dapa 10mg + Saxa 5mg + Met**	**Glim 1-6 mg + Met**	
Applicant's Analysis (Efficacy Estimand)[f]			
Baseline (mean)	129.9	132.5	
Change from baseline to Week 24 (95% CI)	−2.61 (−4.43, −0.79)	1.02 (−0.88, 2.93)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−3.63 (−6.27, −0.99)	
FDA's Analysis (Baseline Washout)[c,g]			
Change from baseline to Week 52	−2.46 (−4.36, −0.56)	0.64 (−1.28, 2.57)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−3.11 (−5.81, −0.40)	
Trial CV181369 *(Add-on Therapy with Dapagliflozin 10 mg plus Saxagliptin 5 mg vs. Insulin glargine in Subjects on Metformin ± SU)*			
Body Weight (kg)			
Applicant's Analysis (Efficacy Estimand)[f]	**Dapa 10mg + Saxa 5mg + Met**	**Insulin glargine + Met**	
Sample Size (N)[b]	324	319	
Baseline (mean)	89.8	89.4	
Change from baseline to Week 24 (95% CI)	−1.50 (−1.89, −1.12)	2.14 (1.75, 2.54)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−3.64 (−4.20, −3.10)	
FDA's Analysis (Retrieved Dropout)[c,h]			
Change from baseline to Week 24	−1.43 (−1.99, −0.86)	2.02 (1.53, 2.50)	
Difference Dapa + Saxa + Met vs. comparator (95% CI)		−3.44 (−4.20, −2.69)	
Subjects with HbA1c <7% [N (%)]	116 (35.8)	113 (35.4)	

Source: Adapted from Dr. Jennifer Clark's Statistical Review (dated March 28, 2019); Dr. Anna Kettermann's Statistical Review (dated January 4, 2017); and the Applicant's proposed product labeling and Summary of Clinical Efficacy, available at:
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Abbreviations: —, not applicable; ±, with or without; CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin (≥1500 mg/day); NIM, noninferiority margin; NR, not reported; NS, nonsignificant; RTB, return to baseline; Saxa, saxagliptin; and SU, sulfonylurea (>50% maximum recommended dose).

*p-value <0.0001 vs. dapagliflozin and saxagliptin plus metformin.

¶ p-value = 0.0018 vs. dapagliflozin and saxagliptin plus metformin.

† Not formally tested because of failing to achieve a statistically significant difference in an endpoint that was earlier in the testing sequence.

‡ p-value = 0.03 vs. glimepiride plus metformin.

[a] The ITT estimand analysis includes data regardless of rescue or treatment discontinuation.

[b] N includes all randomized, treated subjects who had a baseline and at least one post-baseline measurement of the outcome variable.

[c] Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation.

[d] Model estimates calculated using multiple imputation to model washout of the treatment effect using control arm data for all subjects having missing Week 24 data.

[e] N includes all randomized, treated subjects.

[f] Mixed model of repeated measure analysis regardless of rescue and treatment discontinuation.
[g] Model estimates calculated using multiple imputation to model washout of the treatment effect using baseline data for all subjects having missing Week 52 data.
[h] Model estimates calculated using a retrieved dropouts multiple imputation for all subjects having missing Week 24 data.

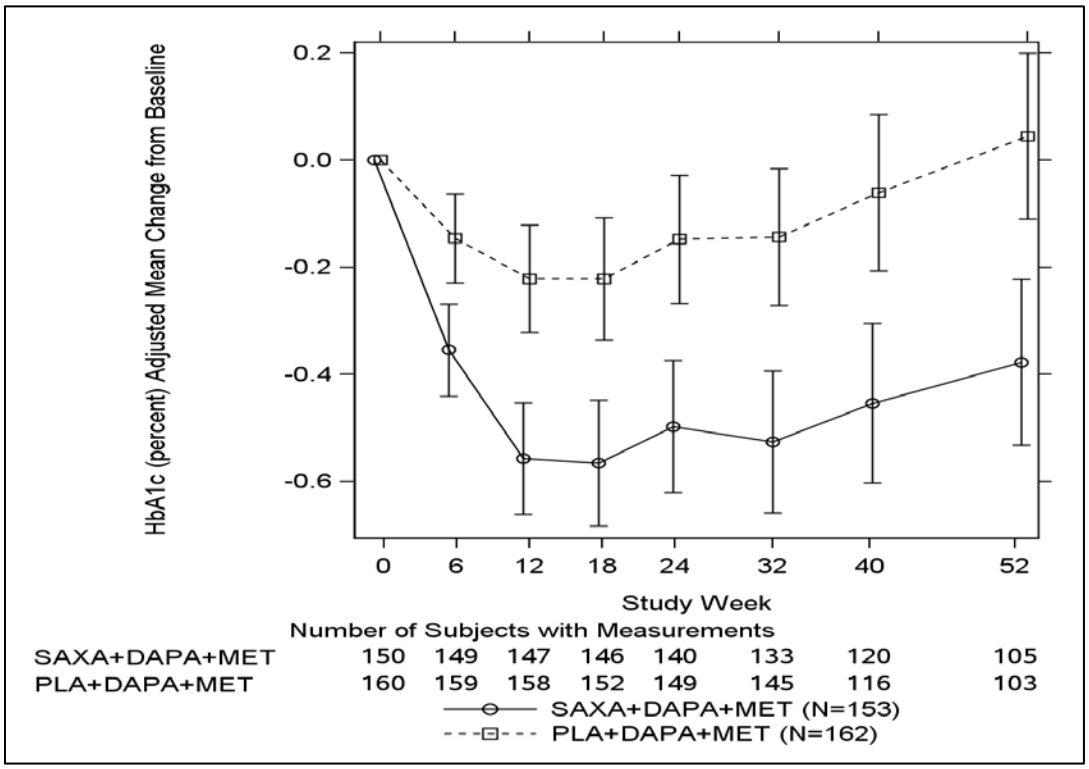
Dose/Dose Response:

Not applicable. Only Trial D1683C00005 evaluated the efficacy of triple combination therapy with the dapagliflozin 5 mg/day dose. All other trials used the 10 mg/day dose, and no single trial included both the 5 mg and 10 mg formulation. Additionally, the saxagliptin dose was fixed at 5 mg/day, and metformin was administered as background therapy at doses of ≥1500 mg daily.

Durability of Response:

Trial CV181365 (Figure 3), as well as efficacy findings from the LT controlled extension period of Trial CV181168 (data not shown), provide some support for the use of combination therapy with dapagliflozin, saxagliptin and metformin for 52 weeks. I feel that these data are supportive for showing a durability of glycemic response.

Figure 3: Change from Baseline to Week 52 in HbA1c Trial CV181365



Source: Reproduced from the Applicant's CSR for Trial CV181365, labeled as Figure 2, page 106 of 1707, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-365\cv181365-clinical-study-report.pdf

Persistence of Effect

Not applicable. No data were submitted to demonstrate a legacy effect (i.e., long-term benefit on prevention or reduction of diabetic complications) of triple therapy with dapagliflozin, saxagliptin and metformin following treatment discontinuation.

Additional Analyses Conducted on the Individual Trial:

The Applicant performed other secondary efficacy analyses (e.g., time to glycemic rescue, proportion of subjects with BG concentrations <70 mg/dL, proportion of subjects with an HbA1c <7% without BG concentrations <70 mg/dL, and 2-week 24-hour mean glucose concentration measured by CGM). The clinical relevance of these findings is uncertain, (b) (4)

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The Applicant intends to include efficacy findings for all five efficacy trials (D1683C00005, CV181169, CV181168, CV181365, and CV181369) (b) (4) (b) (4) The study designs for these trials were diverse (please refer to Appendix 13.4). Thus, an integrated analysis of the primary efficacy endpoint across the five Phase 3 trials was not performed. Nevertheless, to better understand the contribution of each of the individual components to these FCDPs; it is helpful to show 24- and 52-week HbA1c changes from baseline in each trial. Dr. Clark reanalyzed the data from four of the trials using the Agency's preferred analyses included data after rescue or discontinuation (Table 16). Based on her results, all trials achieved statistically significant HbA1c reductions. I also consider these differences to be clinically relevant. For completeness, the data from Dr. Kettermann's analysis of the primary efficacy data for trial CV181168 also are shown.

Table 16: Agency Analysis of Mean Change in HbA1c from Baseline to Week 24 or 52 for Phase 3 Trials to Support Efficacy (Data after Rescue/Discontinuation Included)

Trial	Saxa+Dapa+Met vs.	HbA1c Difference (95% CI)
D1683C00005	Dapagliflozin + Metformin	−0.40 (−0.55, −0.24)
	Saxagliptin + Metformin	−0.32 (−0.48, −0.17)
CV181169	Dapagliflozin + Metformin	−0.49 (−0.7, −0.27)
	Saxagliptin + Metformin	−0.26 (−0.47, −0.05)

Trial	Saxa+Dapa+Met vs.	HbA1c Difference (95% CI)
CV181168	Dapagliflozin + Metformin	−0.35 (−0.52, −0.18)
CV181365	Glimepiride + Metformin	−0.29 (−0.49, −0.08)
CV181369	Insulin glargine + Metformin	−0.15 (−0.40, 0.10)*

Source: Adapted from Dr. Clark's and Kettermann's Statistical Reviews (dated March 28, 2019 and January 4, 2017).
Abbreviations: CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin;
* The triple therapy combination was noninferior to insulin glargine (i.e., upper 95% CI bound <0.3%).

7.1.2. Secondary and Other Endpoints

The key secondary endpoints (b) (4) are presented above in Table 15. Also, please refer to Dr. Clark's review for additional information on the evaluation of secondary endpoints for each of the Phase 3 trials.

7.1.3. Subpopulations

Dr. Clark performed subgroup analyses of each Phase 3 trial. Please refer to her review for detailed information. Using a Bayesian hierarchical model, shrinkage estimates were derived to compare treatment effects among subgroups by age (<65 vs. ≥65 years old), gender, race, and geographical region (North America vs. other regions). Based on these analyses, she reported that shrinkage analyses showed no indication of differential treatment effects among subgroups.

7.1.4. Dose and Dose-Response

Please refer to Sections 6.1.4 and 6.1.10 for discussion of dose and dose-response, respectively.

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 weeks of antihyperglycemic therapy. All five Phase 3 clinical trials included a 24- or 52-week double-blind treatment period. Please refer to Section 6.1.10 above for discussion related to the duration and durability of glycemic efficacy related to Trials CV181168 and CV181365.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the Phase 3 clinical development programs, the trial populations included a limited number of subjects ≥75 years of age and the race was predominantly White. Overall, I believe that the clinical exposure from the individual dapagliflozin and saxagliptin clinical development programs, and extensive use of metformin worldwide, provide supporting safety and efficacy

data for the use of the monocomponents of the FCDP in these patient subsets. However, the therapeutic experience with the triple therapy combination is more limited at this time, making interpretation and generalizability of efficacy findings in these patient populations difficult.

7.2.2. Other Relevant Benefits

As discussed in more detail in Section 2.2 above, T2D affects more than 29 million people in the U.S., 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 29), and nonadherence or intolerance to the prescribed treatment regimen is common. Therefore, an oral, once-daily, FCDP that includes three pharmacologic antihyperglycemic drug classes with different mechanisms of action and a relatively low risk of hypoglycemia (e.g., DDP-4 plus SGLT2 plus biguanide) could be of benefit to patients and may improve adherence to prescribed therapy.

7.3. Integrated Assessment of Effectiveness

To demonstrate the efficacy of QTERNMET XR and a revised indication for QTERN, provided clinical data from two pivotal clinical trials (i.e., D1683C00005 and CV181169) which evaluated the concomitant addition of dapagliflozin and saxagliptin to background metformin therapy (≥1500 mg per day) in adult T2D patients with inadequate glycemic control. Trial D1683C00005, a 24-week randomized, double-blind, active-controlled, parallel group Phase 3 clinical trial, compared the efficacy and safety of dapagliflozin 5 mg plus saxagliptin 5 mg plus metformin to dapagliflozin 5 mg plus metformin or saxagliptin 5 mg plus metformin. Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in hemoglobin A1c [HbA1c] from baseline to Week 24, using a return to baseline washout analytical approach for individuals with missing data), the triple therapy arm resulted in a modest but statistically significant HbA1c reduction compared to the dapagliflozin dual therapy arm (-0.40%; 95% confidence interval [CI], -0.55%, -0.24%) and the saxagliptin dual therapy arm (-0.32% [95% CI -0.48%, -0.17%]).

Trial CV181169, a 24-week randomized, double-blind, active-controlled, parallel group Phase 3 trial, compared the efficacy and safety of dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin (≥1500 mg per day) to dapagliflozin 10 mg plus metformin or saxagliptin 5 mg plus metformin. Again, using the Agency's preferred analysis, the triple therapy arm resulted in a statistically significant HbA1c reduction compared to the dapagliflozin dual therapy arm (-0.26% [95% CI -0.47%, -0.05%]) and the saxagliptin dual therapy arm (-0.49% [95% CI -0.70%, -0.27%]).

Efficacy and safety data from three additional Phase 3 trials (CV181168, CV181365, and CV181369) also were submitted to support the pivotal efficacy trials for these Applications. Trial CV181168 was a 24-week (with a 28-week long-term [LT] extension), randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial designed to evaluate the efficacy and

safety of stepwise (sequential) addition of saxagliptin to dapagliflozin plus metformin compared with the addition of placebo to dapagliflozin plus metformin in subjects with T2D who had inadequate glycemic control on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). This trial was the pivotal Phase 3 trial used to support the approval of QTERN.[22] Trial CV181365, a 52-week randomized, double-blind, active-controlled, parallel-group study (with a blinded 104-week extension), compared the efficacy and safety of dapagliflozin 10 mg plus saxagliptin 5 mg as add-on therapy with metformin to glimepiride (up to 6 mg/day) plus metformin in T2D subjects with inadequate control on metformin monotherapy (≥1500 mg/day). Trial CV181369 is a noninferiority trial that compared the efficacy and safety of dapagliflozin plus saxagliptin as add-on therapy with metformin to insulin glargine plus metformin in adult T2D subjects with inadequate glycemic control on metformin monotherapy (≥1500 mg/day). The results of all three trials were supportive (i.e., triple therapy was noninferior to insulin plus metformin or resulted in statistically significant greater reductions in HbA1c from baseline vs. comparison arms).

Based on the totality of these data, and in accordance with 21 CFR 314.126(a)(b),[21] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of QTERNMET XR and an amended indication for QTERN.

8. Review of Safety

8.1. Safety Review Approach

The submission included eight Phase 3/4 clinical trials (i.e., Trials CV181168, CV181169, CV181363, CV181365, CV181369, D1683C00005, D1689C00014, and MB102129). The safety evaluation for these Applications was primarily based on the integrated safety data from the following three study pools:

1) **3-study pool:** Trials CV181168, CV181169, and MB102129
2) **5-study pool:** Trials CV181169, CV181363, CV181365, D1683C00005, and D1689C00014
3) **7-study pool:** Trials CV181168, CV181169, CV181363, CV181365, D1683C00005, D1689C00014, and MB102129

The 3-study pool was the safety pool used for approval of QTERN. However, the AEs were updated (recoded) from the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 to MedDRA version 20.0. Each of the three clinical trials used in this pool controlled for at least one of the monocomponents plus metformin (i.e., dapagliflozin 10 mg + metformin and/or saxagliptin 5 mg + metformin). For detailed discussion related to the safety from this study pool, please refer to the Clinical Review (dated February 21, 2017).

In response to a request from the Agency, the Applicant also created a 5-study pool to evaluate those trials in which dapagliflozin and saxagliptin were initiated simultaneously (concomitantly). The 7-study pool was the broadest pool and was intended to detect uncommon/rare AEs (e.g., deaths, malignancies) and to better assess the relatedness of treatment-emergent adverse events (TEAEs) with IP. The Applicant did not pool the sitagliptin + metformin treatment arm from Trial CV181363 or the glimepiride + metformin treatment arm from Trials CV181365 and D168C00014, stating that inclusion in the study pool would not be "interpretable or meaningful". Additionally, as Trial CV181369 was open-label and included a sulfonylurea as background therapy for some of the participants, the Applicant did not include this trial in the study pools. I concur with the exclusion of several of the treatment arms from Trials CV181363, CV181365 and D168C00014, as well as exclusion of Trial CV181369 from the study pools. Descriptions of the trial designs and study populations are provided in Table 4. Since two of the trials (i.e., the LT extension phases for Trial CV181365 and CV181369) were ongoing at the time of these submissions, safety data from the Four-Month Safety Update (4MSU) also were reviewed.

Based on the trial designs and use of the highest proposed doses, I believe that the 3-study pool remains the most relevant for inclusion in product labeling. This review will primarily focus on the safety findings associated with the additional safety data (i.e., the 5- and 7-study pools) submitted to these Applications. Summary information for the 3-study pool will be presented to

supplement the data from the larger safety pools when appropriate. For a more detailed review of safety for the 3-study pool, please refer to the Clinical Review of NDA 209091 (QTERN, dated February 21, 2017).

Pooled safety analyses were performed using a crude pooling approach. However, to account for differences in trial designs, the Applicant also used model-based adjustments (i.e., logistic regression model with treatment as a fixed effect and trial as a random effect) to estimate the probability of an event along with the 95% CI for select AE summary categories, common AEs, AESI (urinary tract infections [UTI], hypoglycemia, genital infections, renal impairment, and cardiac failure) and marked laboratory abnormalities (MAs, such as creatine kinase, creatinine, and platelet counts). The model assumes that the effect of trial is the same for all treatments (i.e., no interaction effects of treatment with trial) and that the adjusted estimate from the logistic regression corresponds to an estimate of the treatment effect for a "typical" trial within the pool. In cases where the event count was zero for a given treatment arm across all studies within the pool, the treatment arm was removed from the model. Only the crude rates were displayed for these treatments along with a Clopper Pearson confidence interval for the crude rate.[180]

The safety evaluation plan for this Application included routine assessments, as well as a focus on potential risks associated with SGLT2 inhibitors, DPP-4 inhibitors, and metformin (i.e., adverse events of special interest [AESI]). To identify AESI, the Applicant searched the AE databases using predefined lists of MedDRA preferred terms (PTs). AESI also were evaluated by treatment durations (≤6 months and >6 months) for five trials in the 7-study pool with a treatment duration of 52 weeks (CV 181168, CV181365, MB102129, D1689C00014, and CV181363). The Applicant also established two independent adjudication committees to evaluate hepatic 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 investigational product). A summary of the size of the safety population and duration of exposure to IPs in the 3-study pool is presented in Table 17, which included the same numbers and durations of exposures as the safety database used to support the original QTERN Application. Overall, 1169 subjects were randomized and treated, of which 492 received dapagliflozin 10 mg + saxagliptin 5 mg + metformin. The median duration of exposure was longer in this treatment arm (359 days) compared to the dapagliflozin 10 mg + metformin (176 days) and the saxagliptin 5 mg + metformin (176 days) treatment arms, with overall patient-years (p-y) of exposure of

370.2 p-y, 230.8 p-y and 227.6 p-y, respectively. On average, 86% (423/492) of subjects in the dapagliflozin + saxagliptin + metformin arm were exposed for at least 168 days (24 weeks), while approximately 48% were exposed for at least 360 days.

Table 17: Integrated Safety Population, Size and Duration of Exposure (3-study pool)

3-Study Pool	Dapa10+Saxa5+Met	Dapa10+Met	Saxa5+Met
Phase 3 Trials — no. (%)	**N=492**	**N=336**	**N=341**
CV181168	153 (31.1)	–	162 (47.5)
CV181169	179 (36.4)	176 (52.4)	179 (52.5)
MB102129	160 (32.5)	160 (47.6)	–
Dapagliflozin Exposure			
Mean (range) — days	274.5 (1, 396)	247.8 (1, 395)	247.4 (1, 404)
Median (IQR) — days	359.0 (169.0, 365.0)	175.5 (169.0, 364.0)	175.5 (169.0, 364.0)
Saxagliptin Exposure			
Mean (range) — days	274.6 (1, 396)	247.2 (1, 395)	248.1 (1, 404)
Median (IQR) — days	359.0 (169.0, 365.0)	176.0 (169.0, 364.0)	176.0 (169.0, 364.0

Source: Adapted from the Applicant's Summary of Clinical Efficacy (labeled as Table 3, page 40 of 143), available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-safety.pdf
Abbreviations: –, not applicable; Dapa10, dapagliflozin 10 mg/day; IQR, 25th and 75th interquartile range; Met, metformin; no., number; and Saxa5, saxagliptin 5 mg/day.

The 5-study pool included 2499 subjects, of which 950 received dapagliflozin 10 mg + saxagliptin 5 mg + metformin and 293 received dapagliflozin 5 mg + saxagliptin 5 mg + metformin. The median durations of exposures were 364 days and 268 days, respectively. Approximately 56% (536/950) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm were exposed for at least 360 days, while the median exposure for the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm was 168 days for all subjects. It is noted that Trials CV181169 and D168C00005 had 24-week treatment exposures, while the remaining trials had 52-week treatment durations.

Table 18: Integrated Safety Population, Size and Duration of Exposure (5-study pool)

5-Study Pool	Dapa10+Saxa5+ Met	Dapa10+Met	Saxa5+Met	Dapa5+Saxa5+ Met	Dapa5+Met
Phase 3 Trials — no. (%)	**N=950**	**N=492**	**N=471**	**N=293**	**N=293**
CV181169	179 (18.8)	179 (36.4)	176 (37.4)	–	–
CV181363	232 (24.4)	–	–	–	–
CV181365	227 (23.9)	–	–	–	–
D1683C00005	–	–	295 (62.6)	293 (100)	293 (100)
D1689C00014	312 (32.8)	313 (63.6)	–	–	–

5-Study Pool	Dapa10+Saxa5+ Met	Dapa10+Met	Saxa5+Met	Dapa5+Saxa5+ Met	Dapa5+Met
Dapagliflozin Exposure					
Mean (range) — days	303 (1, 412)	259.2 (1, 385)	–	156.2 (1, 206)	154.8 (1, 212)
Median (IQR) — days	363 (182, 365)	351 (169, 364)	–	168 (164, 170)	168 (164, 172)
Saxagliptin Exposure					
Mean (range) — days	303.3 (1, 412)	–	157.9 (1, 204)	156.2 (1, 206)	–
Median (IQR) — days	363 (182, 365)	–	168 (164, 170)	168 (164, 170)	–
Metformin Exposure					
Mean (range) — days	312.7 (1, 412)	282 (1, 395	204.4 (1, 404)	156.1 (1, 206)	154.8 (1, 212)
Median (IQR) — days	364 (351, 365)	357 (169, 364)	169 (166, 182)	168 (164, 170)	168 (164, 172)

Source: Adapted from the Applicant's Summary of Clinical Efficacy (labeled as Table 3, page 40 of 143), available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-safety.pdf
Abbreviations: –, not applicable; Dapa10, dapagliflozin 10 mg/day; IQR, 25th and 75th interquartile range; Met, metformin; no., number; and Saxa5, saxagliptin 5 mg/day.

The 7-study pool (Table 19) included 3134 subjects, 1263 received dapagliflozin 10 mg + saxagliptin 5 mg + metformin and 293 received dapagliflozin 5 mg + saxagliptin 5 mg + metformin. The median duration of exposure was longer in the arms that included dapagliflozin 10 mg compared to the other treatment arms. On average, 62% (780/1263) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm were exposed for at least 360 days. The exposure for the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm was the same for both the 5- and 7-study pools.

Table 19: Integrated Safety Population, Size and Duration of Exposure (7-study pool)

7-Study Pool	Dapa10+Saxa5+ Met	Dapa10+Met	Saxa5+Met	Dapa5+Saxa5+ Met	Dapa5+Met
Phase 3/4 Trials — no. (%)	**N=1263**	**N=654**	**N=631**	**N=293**	**N=293**
CV181168	153 (12.1)	–	162 (25.7)	–	–
CV181169	179 (14.2)	179 (27.4)	176 (27.9)	–	–
CV181363	232 (18.4)	–	–	–	–
CV181365	227 (18.0)	–	–	–	–
D1683C00005	–	–	295 (46.8)	293 (100)	293 (100)
D1689C00014	312 (24.7)	313 (47.9)	–	–	–
MB102129	160 (12.7)	160 (24.5)	–	–	–
Dapagliflozin Exposure					
Mean (range) — days	312.1 (1, 412)	281.2 (1, 395)	–	156.2 (1, 206)	154.8 (1, 212)
Median (IQR) — days	364 (350, 365)	357 (169, 364)	–	168 (164, 170)	168 (164, 172)
Saxagliptin Exposure					
Mean (range) — days	312.3 (1, 412)	–	204.6 (1, 404)	156.2 (1, 206)	–
Median (IQR) — days	364 (350, 365)	–	169 (167, 182)	168 (164, 170)	–

7-Study Pool	Dapa10+Saxa5+ Met	Dapa10+Met	Saxa5+Met	Dapa5+Saxa5+ Met	Dapa5+Met
Metformin Exposure					
Mean (range) — days	312.7 (1, 412)	282 (1, 395)	204.4 (1, 404)	156.1 (1, 206)	154.8 (1,212)
Median (IQR) — days	364 (351, 365)	357 (169, 364)	169 (166, 182)	168 (164, 170)	168 (164, 172)

Source: Adapted from the Applicant's Summary of Clinical Efficacy (labeled as Tables 3-4, page 40-42 of 143), available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-safety.pdf
Abbreviations: –, not applicable; Dapa5, dapagliflozin 5 mg/day; Dapa10, dapagliflozin 10 mg/day; IQR, 25th and 75th interquartile range; Met, metformin; no., number; and Saxa5, saxagliptin 5 mg/day.

For Trial CV181369, the median exposure was 169 days for both the dapagliflozin 10 mg + saxagliptin 5 mg + metformin and the insulin glargine + metformin treatment arms.

8.2.2. Relevant Characteristics of the Safety Population

The demographics and clinical characteristics for the 7-study pool are presented in Table 20. For this safety population, the baseline demographic and clinical characteristics appeared to be reasonably similar across the treatment arms and were consistent with those shown in Table 12 for the five Phase 3 trials used to support efficacy. There were relatively similar distributions of males and females, and U.S. and non-U.S. participants. The baseline HbA1c was approximately 8.3%, and the average duration of diabetes was 7.5 years. Overall, the population tended to be less than 65 years of age, were predominantly white, had a body mass index (BMI) above 30 kg/m^2, and normal renal function (i.e., eGFR >90 mL/min/1.73m^2). The majority of subjects received background metformin doses of at least 1500 mg/day, as prespecified in the respective protocols. In general, the demographics and clinical characteristics were consistent with other SGLT2 inhibitor and SGLT2 inhibitor FCDP development programs.

Table 20: Demographics and Clinical Characteristics (7-study pool)*

Demographics and Clinical Characteristics	Dapa 10 mg + Saxa 5 mg + Met (n=1263)	Dapa 10 mg + Met (n=654)	Saxa 5 mg + Met (n=631)	Dapa 5 mg + Saxa 5 mg + Met (n=293)	Dapa 5 mg + Met (n=293)
ENTERED LT TREATMENT PERIOD — NO. (%)	695 (55.0)	155 (23.7)	149 (23.6)	0	0
DEMOGRAPHICS					
Age, mean ± SD — yr	56.2 ± 9.3	55.6 ± 9.6	55.8 ± 9.8	57.2 ± 10.7	55.9 ± 10.9
<65 yr — no. (%)	1034 (81.9)	529 (80.9)	505 (80.0)	214 (73.0)	222 (75.8)
≥65 yr — no. (%)	229 (18.1)	125 (19.1)	126 (20.0)	79 (27.0)	71 (24.2)
≥75 yr — no. (%)	9 (0.7)	5 (0.8)	13 (2.1)	16 (5.5)	9 (3.1)
Female sex — no. (%)	628 (49.7)	288 (44.0)	302 (47.9)	149 (50.9)	138 (47.1)
Race — no. (%)					
White	1070 (84.7)	582 (89.0)	529 (83.8)	268 (91.5)	261 (89.1)
Black/African American	81 (6.4)	27 (4.1)	57 (9.0)	10 (3.4)	17 (5.8)
Asian	29 (2.3)	19 (2.9)	18 (2.9)	9 (3.1)	9 (3.1)
Other	83 (6.6)	26 (4.0)	27 (4.3)	6 (2.0)	6 (2.0)
Ethnicity — no. (%)					
Hispanic or Latino	271 (21.5)	96 (14.7)	175 (27.7)	102 (34.8)	96 (32.8)
Not Hispanic or Latino	649 (51.4)	403 (61.6)	287 (45.5)	191 (65.2)	197 (67.2)
Not reported	343 (27.2)	155 (23.7)	169 (26.8)	0	0

Demographics and Clinical Characteristics	Dapa 10 mg + Saxa 5 mg + Met (n=1263)	Dapa 10 mg + Met (n=654)	Saxa 5 mg + Met (n=631)	Dapa 5 mg + Saxa 5 mg + Met (n=293)	Dapa 5 mg + Met (n=293)
Region — no. (%)					
Europe	661 (52.3)	408 (62.4)	215 (34.1)	124 (42.3)	123 (42.0)
North America	402 (31.8)	186 (28.4)	287 (45.5)	130 (44.4)	137 (46.8)
Latin America	198 (15.7)	59 (9.0)	126 (20.0)	39 (13.3)	33 (11.3)
Asia/Pacific	2 (0.2)	1 (0.2)	3 (0.5)	0	0
Country — no. (%)					
United States	374 (29.6)	160 (24.5)	247 (39.1)	91 (31.1)	105 (35.8)
Mexico	198 (15.7)	59 (9.0)	126 (20.0)	39 (13.3)	33 (11.3)
Germany	151 (12.0)	162 (24.8)	21 (3.3)	22 (7.5)	22 (7.5)
Hungary	106 (8.4)	60 (9.2)	0	0	0
Poland	102 (8.1)	44 (6.7)	11 (1.7)	0	0
Romania	82 (6.5)	29 (4.4)	20 (3.2)	0	0
Russia	71 (5.6)	28 (4.3)	104 (16.5)	70 (23.9)	63 (21.5)
Slovakia	56 (4.4)	45 (6.9)	0	0	0
Czech Republic	48 (3.8)	26 (4.0)	39 (6.2)	32 (10.9)	38 (13.0)
South Africa	36 (2.9)	14 (2.1)	14 (2.2)	0	0
Canada	23 (1.8)	22 (3.4)	35 (5.5)	39 (13.3)	32 (10.9)
United Kingdom	8 (0.6)	0	6 (1.0)	0	0
Puerto Rico	5 (0.4)	4 (0.6)	5 (0.8)	0	0
Korea	2 (0.2)	1 (0.2)	3 (0.5)	0	0
Sweden	1 (0.1)	0	0	0	0
CLINICAL CHARACTERISTICS					
BMI, mg/m^2 — mean ± SD	32.2 ± 5.3	32.2 ± 5.3	32.2 ± 5.4	31.4 ± 5.5	32.0 ± 5.3
<25 mg/m^2 — no. (%)	88 (7.0)	45 (6.9)	52 (8.2)	27 (9.2)	15 (5.1)
25-30 mg/m^2 — no. (%)	390 (30.9)	189 (28.9)	184 (29.2)	104 (35.5)	108 (36.9)
≥30 mg/m^2 — no. (%)	785 (62.2)	420 (64.2)	395 (62.6)	162 (55.3)	170 (58.0)
Duration of T2D, mean ± SD — yr	7.5 ± 6.0	7.1 ± 5.4	7.9 ± 5.9	7.4 ± 6.3	7.6 ± 6.3
<3 yr — no. (%)	297 (23.5)	151 (23.1)	134 (21.2)	84 (28.7)	74 (25.3)
≥3 to ≤10 yr — no. (%)	618 (48.9)	336 (51.4)	305 (48.3)	124 (42.3)	133 (45.4)
>10 yr — no. (%)	346 (27.4)	167 (25.5)	192 (30.4)	85 (29.0)	85 (29.0)
Glycemic Status					
HbA1c% — mean ± SD	8.4 ± 0.9	8.3 ± 1.0	8.5 ± 1.1	8.1 ±0.9	8.2 ± 0.9
<8% — no. (%)	415 (32.9)	256 (39.1)	218 (34.5)	125 (42.7)	122 (41.6)
8 to <9% — no. (%)	514 (40.7)	250 (38.2)	221 (35.0)	116 (39.6)	105 (35.8)
≥9% — no. (%)	334 (26.4)	147 (22.5)	188 (29.8)	49 (16.7)	62 (21.2)
2-h PPG, mg/dL — mean ± SD	231.6 ±57.4	227.1 ± 59.7	249.8 ± 60.1	—	—
FPG, mg/dL — mean ± SD	177.3 ± 42.0	181.0 ± 44.0	182.6 ± 46.5	170.0 ± 79.3	176.2 ± 45.7
C-peptide, ng/mL — mean ± SD	1.6 ± 1.1	1.7 ± 1.1	2.4 ± 1.0	—	—
eGFR, mL/min/1.73m^2 — mean ± SD	92.3 ± 20.9	90.7 ± 20.1	92.1 ± 20.9	91.6 ± 21.9	93.3 ± 22.0
Metformin Dose, mg — no. (%)					
0 to <1500	15 (1.2)	11 (1.7)	0	1 (0.3)	0
1500 to <1701	316 (25.0)	193 (29.5)	185 (29.3)	102 (34.8)	73 (24.9)

Demographics and Clinical Characteristics	Dapa 10 mg + Saxa 5 mg + Met (n=1263)	Dapa 10 mg + Met (n=654)	Saxa 5 mg + Met (n=631)	Dapa 5 mg + Saxa 5 mg + Met (n=293)	Dapa 5 mg + Met (n=293)
1701 to <2500	589 (46.6)	355 (54.3)	332 (52.6)	126 (43.0)	154 (52.6)
≥2500	240 (19.0)	95 (14.5)	84 (13.3)	32 (10.9)	35 (11.9)

Source: Derived from the addm.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam -
Abbreviations: BMI, body mass index; C-peptide, connecting peptide; 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.

8.2.3. Adequacy of the safety database:

At the time of approval for QTERN, the Applicant provided safety database that included 370.2 p-y of exposure to triple combination therapy with dapagliflozin 10 mg + saxagliptin 5 mg + metformin. The database included a pool of three Phase 3 trials (i.e., CV181169, CV181168, and MB102129), and was considered adequate. With the current submissions, five additional Phase 3 trials (i.e., D1683C00005, CV181365, CV181363, CV181369, and D1689C00014) have been submitted, including one trial that had a dapagliflozin 5 mg + saxagliptin 5 mg + metformin treatment arm. These trials allow for comparisons of the dapagliflozin + saxagliptin + metformin triple therapy arms with dual therapy of the components, with insulin glargine, and with glimepiride. Additionally, larger safety pools (i.e., 5- and 7-study pools) were created to evaluate the less common AEs (please refer to Section 8.2.1 Overall Exposure. Based on the additional data, I feel that the exposure and safety data provided are 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 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 treatment periods was adequate to evaluate safety for these Applications. Additionally, many of the key safety findings reported in this Application were reproduced and confirmed using the integrated datasets. Based on these analyses, there were no obvious issues related to data quality.

8.3.2. Categorization of Adverse Events

The integrated analyses were conducted using the Randomized and Treated Subjects Dataset (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 double-blind treatment period. Adverse events in the CSR for the submitted trials were classified by System Organ Class (SOC) and/or Preferred Term (PT) and coded based on Medical Dictionary for Regulatory Activities (MedDRA) versions 20.0.

An AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an investigational (medicinal) product, and that did not necessarily have a causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs occurring from Day 1 of the ST treatment period up to 4 days and up to 30 days after the last dose of study medication during the ST+LT treatment period for non-serious AEs and SAEs, respectively. Adverse event occurrence 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, severe, or very severe), action taken, treatment required, outcome, and the Investigator's opinion regarding the relationship to study treatment. The intensity of AEs was graded using the following definitions:

- **Mild/Grade I:** Awareness of event but easily tolerated
- **Moderate/Grade II:** Discomfort enough to cause some interference with usual activity
- **Severe/Grade III:** Inability to carry out usual activity
- **Very Severe/Grade IV (for select trials):** Debilitating, significantly incapacitates subject despite symptomatic therapy

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

- 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 (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above)

All nonserious and serious AEs were to be followed until resolution or stabilization (e.g., as long as medically indicated).

The definitions, coding and cutoff dates for inclusion of TEAEs after discontinuing investigational product were acceptable. Also, comparisons were made between the verbatim terms (i.e., AE analysis datasets and select Case Report Form [CRF] text) provided by the investigators and the MedDRA PTs for which these AEs were coded. The classifications of these data appeared appropriate.

The Applicant also created Custom MedDRA Queries (CMQs) for identifying adverse events of special interest (AESI) from lists of prespecified PTs (identified prior to unblinding) or Standardized MedDRA Queries (SMQs). These AESI were primarily related to safety findings in the dapagliflozin, saxagliptin and metformin 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 biguanides. For the integrated safety assessment AESI included: genital infections, UTIs, hypoglycemia, renal impairment/failure, malignancies, fractures, cardiac failure, confirmed adjudicated CV events, decreased lymphocyte counts, decreased thrombocyte counts, pancreatitis, severe cutaneous adverse reactions, hypersensitivity reactions, liver injury/hepatic disorder, volume depletion (hypotension, dehydration, and hypovolemia), diabetic ketoacidosis, and lactic acidosis. For completeness, my safety evaluation also included 'Broad' Custom MedDRA Queries (CMQs) that were derived using existing SMQs and PTs for AESI from other SGLT2 inhibitor, DPP-4 inhibitor and metformin 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 13.5. Assessments for AESIs will be described in more detail in the relevant sections.

8.3.3. Routine Clinical Tests

The frequency of clinical laboratory safety assessments for each of the eight trials is described in the CSRs for the respective trials. Blood and urine samples were obtained for evaluation of standard safety laboratory panels (chemistry, hematology, and urinalysis) at screening and throughout the trial, typically at Weeks 0 (Day 1), 6, 12, 18, and 24 during the 24-week ST periods, every 8-13 weeks during LT extension periods, and at the end-of-trial (EOT), early termination or glycemic rescue visits. Laboratory assessments for the integrated safety datasets were also provided at these same time points. 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 (MAs). A listing of the MAs by relevant laboratory parameter, and the numbers/proportions (%) of subjects with these abnormalities, is discussed in more detail in Section 8.4.6. The safety laboratory panels and the frequency of assessments were adequate, based on the known toxicity profiles of dapagliflozin, saxagliptin and metformin, the patient population studied, and the proposed indications. Vital signs were evaluated based on changes from baseline at similar time points as described above. The normality or abnormality of ECG findings were determined by the investigator at baseline, and typically at Weeks 24 and/or 52.

8.4. Safety Results

A summary of the AEs reported in the integrated 5- and 7-study safety pools are presented in Table 21. Overall, more than 40% of subjects in all treatment arms in both the 5- and 7-study pools experienced at least one AE. Categories of events between these study pools were similar. As anticipated, subjects in the triple therapy dapagliflozin arms had higher numbers of subjects

with hypoglycemic events, including clinically significant hypoglycemia (i.e., BG <54 mg/dL). However, events of severe hypoglycemia (defined as neuroglycopenic symptoms requiring assistance of another person to actively administer carbohydrate or glucagon with prompt recovery, with a BG ≤70 mg/dL when measured) were limited, and no subjects in any treatment arm discontinued IP due to hypoglycemia. Additionally, higher proportions of SAEs were observed in the arms that included dapagliflozin, but no imbalances were observed between the triple or dual dapagliflozin combination therapy arms. The numbers of deaths were limited and are discussed further below (Section 8.4.1). Although numbers of events increased in the 5- and 7-study pools, the proportions of events (excluding hypoglycemia) were generally consistent with the 3-study pool (please refer to Appendix 13.6, Table 30).

As noted in Section 8.2.1, the safety data for the dapagliflozin + saxagliptin + metformin arm included longer treatment exposures than comparator arms, which should be considered when reviewing event counts for the respective study pools. Based on the Applicants model-adjusted analyses, the adjusted estimates (proportions) of events in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm were lower than the crude percentages for all adverse event categories in the 7-study pool.

Table 21: Summary of Adverse Events (Integrated 5- and 7-study pools Safety)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
EVENT — no. (%)										
At least one AE	521 (54.8)	275 (55.9)	209 (44.4)	121 (41.3)	123 (42.0)	716 (56.7)	369 (56.4)	323 (51.2)	121 (41.3)	123 (42.0)
Model-adjusted [%]*	[51.5]					[54.3]				
At least one hypoglycemia¶	90 (9.5)	11 (2.2)	13 (2.8)	19 (6.5)	9 (3.1)	99 (7.8)	18 (2.8)	16 (2.5)	19 (6.5)	9 (3.1)
Model-adjusted [%]*	[7.5]	[3.5]	[3.7]	[6.4]	[3.0]	[6.0]	[3.7]	[3.1]	[5.6]	[2.6]
Severe hypoglycemia†	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)
Clinically Significant‡	21 (2.2)	0	3 (0.6)	1 (0.3)	0	26 (2.1)	2 (0.3)	3 (0.5)	1 (0.3)	0
D/C due to hypoglycemia	0	0	0	0	0	0	0	0	0	0
Deaths	1 (0.1)	0	0	1 (0.3)	2 (0.7)	2 (0.2)	1 (0.2)	0	1 (0.3)	2 (0.7)
Model-adjusted [%]*	[0.1]					[0.1]				
At least one SAE	47 (4.9)	41 (8.3)	13 (2.8)	7 (2.4)	8 (2.7)	61 (4.8)	52 (8.0)	17 (2.7)	7 (2.4)	8 (2.7)
	[3.3]					[4.0]				
SAE leading to D/C of IP	2 (0.2)	13 (2.6)	1 (0.2)	1 (0.3)	2 (0.7	7 (0.6)	14 (2.1)	3 (0.5)	1 (0.3)	2 (0.7
Model-adjusted [%]*	[0.2]					[0.4]				
AE leading to D/C of IP	26 (2.7)	28 (5.7)	6 (1.3)	19 (6.5)	15 (5.1)	38 (3.0)	33 (5.0)	9 (1.4)	19 (6.5)	15 (5.1)
Model-adjusted [%]*	[2.1]					[2.5]				

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –, and adapted from the Applicant's ISS, pages 31-33, and 369-376 of 533, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\pooled-analysis-of-safety.pdf

Abbreviations: BG, blood glucose; Dapa, dapagliflozin; D/C, discontinuation; IP, investigational product; Met, metformin; and Saxa, saxagliptin.

*Adjusted estimate [%] using a logistic regression model adjusting for trial.

¶**Hypoglycemia:** all reported episodes of hypoglycemia on CRFs regardless of the self-monitoring blood glucose value and all episodes of FPG <70 mg/dL measured by the (b) (4) regardless of glycemic rescue.

†**Severe hypoglycemia:** neuroglycopenic symptoms requiring assistance of another person to actively administer carbohydrate or glucagon with prompt recovery, with BG ≤70 mg/dL (ADA Level 3).

‡**Clinically significant hypoglycemia**: BG <54 mg/dL (ADA Level 2).

8.4.1. Deaths

In the 3-study pool, there were only two deaths in subjects randomized to the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm, one due to acute myocardial infarction (MI; Subject MB102129 (b) (6)), and a second due to a gastric neoplasm (Subject CV181169- (b) (6)). In both cases, it was felt that a causal association with IP was unlikely. Please refer to the Clinical Review for NDA 209091 (QTERN, dated February 21, 2017) for further details of these cases.

With the current submissions, four additional deaths were reported in the 7-study pool, which included one subject (b) (6) in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm (pneumonia), one subject (b) (6) in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm (road traffic accident), and two in the dapagliflozin 5 mg + metformin group (MI and ventricular arrhythmia). Brief narrative summaries for the two cases in which subjects were randomized to dapagliflozin + saxagliptin + metformin arms are provided as follows:

- **Subject (b) (6):** a 68-year-old White male with T2D randomized to the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm in Trial CV181365, experienced a SAE of pneumonia on Day 70. The subject was hospitalized and died the following day. His medical history included obesity, hypertension, angina, coronary artery disease, congestive heart failure/hepatomegaly, dyslipidemia, hyperlipidemia, peripheral vascular disease, cerebral vascular disease, diabetic microvascular disease (retinopathy, neuropathy, and nephropathy), and past smoker. Concomitant medications included bisoprolol, spironolactone, perindopril, aspirin, and dabigatran. No other AEs were reported. The investigator considered the SAE of pneumonia to be unrelated to IP.

Given the age and comorbidities in this subject, I concur that it is difficult to establish a causal association of death with IP. Although DPP-4 inhibitors, including saxagliptin,[20] may be associated with a decrease in absolute lymphocyte count and possibly a predisposition to infections, several published reports did not find an association with their use and the risk of community acquired pneumonia.[181]

- **Subject (b) (6):** a 59-year-old Black male with T2D randomized to the dapagliflozin 5 mg + saxagliptin 5 mg + metformin treatment arm in Trial D1683C00005, had a motorcycle accident on Day 74, and died 49 days later. His medical history included peripheral neuropathy, chronic obstructive pulmonary disease (COPD), benign prostatic hyperplasia. Concomitant medications included salbutamol, finasteride, and gabapentin. No other AEs were reported. The investigator considered the event to be unrelated to IP.

I concur that a causal association of death with IP is unlikely. It is also acknowledged that gabapentin is associated with somnolence, dizziness, ataxia, nystagmus, and fatigue,[182] and therefore may have been a contributing factor for the road traffic accident involving this subject.

An additional death was reported in Trial CV181369 for a subject (b) (6) receiving dapagliflozin 10 mg + saxagliptin 5 mg + metformin + a sulfonylurea. The narrative is as follows:

- **Subject (b) (6):** a 72-year-old White female with T2D randomized to the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm in Trial CV181369, was admitted to the hospital on Day 112 for dyspnea and weight gain associated with bilateral pleural effusion, pulmonary edema, and SAEs of acute respiratory failure and congestive heart failure. An echocardiogram revealed normal left ventricular size and function with an ejection fraction of 72%. Left sided pleural effusion was shown by doppler. At the time of admission, her brain natriuretic peptide (BNP) was 221 pg/mL (normal reference limit [NRL] 0-101 pg/mL). On Day 124, she experienced AEs of acute kidney injury, leukocytosis, atelectasis, and pulmonary hypertension. The subject died on Day 129. Her medical history included obesity, hypertension, hyperlipidemia, cerebrovascular disease, COPD, and tobacco use (current smoker). Listed concomitant medications up to Day 112 included glimepiride, aspirin, lisinopril/hydrochlorothiazide, levothyroxine, triamterene/ hydrochlorothiazide, clopidogrel, verapamil, albuterol/ipratropium, levalbuterol, heparin, enoxaparin, ipratropium bromide, methylprednisolone, prednisone, furosemide, digoxin, insulin glargine, insulin aspart. After the data lock, the Cardiovascular Adjudication Committee had adjudicated the SAE of congestive heart failure. Other AEs reported included: musculoskeletal chest pain on Day 79; three episodes of falling (Days 79, 81, and 83), bradycardia, hypotension, blood potassium abnormal (5.8 mEq/L, NRL 3.3-5.1 mEq/L) and blood sodium decreased (128 mEq/L, NRL 135-147 mEq/L) on Day 84, pneumonia and chronic obstructive pulmonary disease (COPD) on Day 89 (IP withdrawn), pleural effusion and cardiomegaly on Day 93, atrial fibrillation on Day 94, arteriosclerosis coronary artery and emphysema on Day 95, peripheral edema on Day 101, and atrial fibrillation on Day 107. The investigator did not consider any of the above AEs to be related to IP.

Considering the subject's age and preexisting comorbidities it is difficult to determine a causal association between IP and the observed AEs. However, the possibility that saxagliptin may have contributed to heart failure or aggravated preexisting cardiac dysfunction[183-186] and that concomitant diuretic/angiotensin converting enzyme inhibitor (ACEI) use with an SGLT2 inhibitor may have further impaired renal function or predisposed this at-risk subject to hypotension/falling cannot be ruled out.

8.4.2. Serious Adverse Events

In the 3-study pool, the occurrences of SAEs were relatively limited (i.e., approximately 2-4% of subjects), with similar proportions of subjects experiencing these events across treatment arms. The SOC with the highest number of subjects with SAEs in the dapagliflozin 10 mg + saxagliptin + metformin treatment arm was cardiac disorders, which included four subjects; of which one subject (MB102129 (b) (6)) with an SAE of acute MI died. This treatment arm also included three neoplasms (i.e., hepatic cancer [CV181168 (b) (6), invasive ductal breast carcinoma [MB102129- (b) (6)], and gastric neoplasm [CV181169- (b) (6); resulted in death]), which all occurred during the ST treatment period; latencies between 59-137 days), and a single case each of rhabdomyolysis (CV181168 (b) (6); Day 280), thrombocytopenia (MB102129 (b) (6); Day 127), and pyelonephritis (CV181168- (b) (6); Day 307). These events were all previously reported during the original NDA review of NDA 209091, and will not be discussed further in this review.

Serious adverse events for the 5- and 7-study pools, sorted by the event rate in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin are presented in Table 22. For both study pools, higher proportions of SAEs were reported in the dapagliflozin 10 mg triple and dual therapy arms, of which higher proportions were observed in the dapagliflozin 10 mg + metformin arm. By MedDRA PT, SAEs occurring in more than one subject were limited. The SAEs occurring in ≥2 subjects in the 7-study pool receiving dapagliflozin 10 mg + saxagliptin 5 mg + metformin included 'Coronary artery disease', 'Acute myocardial infarction', 'Appendicitis', 'Cholelithiasis', 'Hypertensive crisis', 'Intervertebral disc protrusion', 'Osteoarthritis', 'Peripheral arterial occlusive disease', and 'Vertebrobasilar insufficiency'. Similar to the 3-study pool, the highest proportion of subjects with SAEs were coded to the cardiac disorders system organ class (SOC) for the 7-study pool (please see Appendix 13.7, Table 31). Review of events by MedDRA High Level Term (HLT) and High Level Group Term (HLGT), or by adjusting for trial also was not informative. In general, there were no apparent trends to suggest that the dapagliflozin + saxagliptin + metformin arms were associated an increased risk of specific SAEs over the individual components.

In Trial CV181369, SAEs were reported in 2.8% (9/324) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin ± sulfonylurea arm and 1.6% (5/319) of subjects in the insulin glargine + metformin ± sulfonylurea arm. Obvious trends in SAEs were not apparent in either treatment arm.

Table 22: Summary of Serious Adverse Events (Integrated 5- and 7-study pools Safety)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***SUBJECTS WITH* — no. (%)**	**47 (4.9)**	**41 (8.3)**	**13 (2.8)**	**7 (2.4)**	**8 (2.7)**	**61 (4.8)**	**52 (8.0)**	**17 (2.7)**	**7 (2.4)**	**8 (2.7)**
CORONARY ARTERY DISEASE	4 (0.4)	1 (0.2)	0	1 (0.3)	0	4 (0.3)	1 (0.2)	0	1 (0.3)	0
ACUTE MYOCARDIAL INFARCTION	2 (0.2)	0	0	0	0	3 (0.2)	0	0	0	0
APPENDICITIS	1 (0.1)	0	0	0	0	2 (0.2)	0	0	0	0
CHOLELITHIASIS	1 (0.1)	1 (0.2)	1 (0.2)	0	0	2 (0.2)	1 (0.2)	1 (0.2)	0	0
HYPERTENSIVE CRISIS	2 (0.2)	0	0	1 (0.3)	0	2 (0.2)	0	0	1 (0.3)	0
INTERVERTEBRAL DISC PROTRUSION	2 (0.2)	2 (0.4)	1 (0.2)	0	0	2 (0.2)	2 (0.3)	1 (0.2)	0	0
OSTEOARTHRITIS	2 (0.2)	1 (0.2)	0	0	0	2 (0.2)	1 (0.2)	0	0	0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0
VERTEBROBASILAR INSUFFICIENCY	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0
ABORTION SPONTANEOUS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ACOUSTIC NEUROMA	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ADENOCARCINOMA OF COLON	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ANAL FISTULA	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ANGINA PECTORIS	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.2)	0	0	0
ANGINA UNSTABLE	0	0	0	1 (0.3)	0	1 (0.1)	0	0	1 (0.3)	0
ATRIAL FIBRILLATION	0	0	0	0	0	1 (0.1)	1 (0.2)	0	0	0
CARDIAC FAILURE	0	0	0	0	0	1 (0.1)	0	0	0	0
CARDIAC FAILURE ACUTE	0	0	0	0	0	1 (0.1)	0	0	0	0
CEREBROVASCULAR ACCIDENT	1 (0.1)	2 (0.4)	0	0	2 (0.7)	1 (0.1)	2 (0.3)	0	0	2 (0.7)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0	0	0	1 (0.1)	0	0	0	0
DEPRESSION	1 (0.1)	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
DIABETIC FOOT	0	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
DYSFUNCTIONAL UTERINE BLEEDING	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ERYSIPELAS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
FEMORAL NECK FRACTURE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GANGRENE	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.2)	0	0
GASTRIC NEOPLASM	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GENERALISED TONIC-CLONIC SEIZURE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GOITRE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GUILLAIN-BARRE SYNDROME	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
HEADACHE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
HEPATIC CANCER	0	0	0	0	0	1 (0.1)	0	0	0	0
INVASIVE DUCTAL BREAST CARCINOMA	0	0	0	0	0	1 (0.1)	0	0	0	0
LARYNGITIS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
LUMBAR RADICULOPATHY	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
MENINGIOMA	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
MENTAL STATUS CHANGES	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
OVERDOSE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
PALPITATIONS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
PANCREATITIS CHRONIC	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
PERIPHERAL ARTERY THROMBOSIS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
PERIPHERAL VASCULAR DISORDER	0	0	0	0	0	1 (0.1)	0	0	0	0
PITUITARY TUMOUR BENIGN	0	0	0	0	0	1 (0.1)	0	0	0	0
PLANTAR FASCIITIS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
PNEUMONIA	1 (0.1)	1 (0.2)	1 (0.2)	0	0	1 (0.1)	1 (0.2)	1 (0.2)	0	0
POST LAMINECTOMY SYNDROME	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
POST PROCEDURAL COMPLICATION	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
POSTOPERATIVE WOUND INFECTION	0	0	0	0	0	1 (0.1)	0	0	0	0
PULMONARY EMBOLISM	0	0	1 (0.2)	0	0	1 (0.1)	0	1 (0.2)	0	0
PYELONEPHRITIS	0	0	0	0	1 (0.3)	1 (0.1)	0	0	0	1 (0.3)
RESPIRATORY FUME INHALATION DISORDER	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
RHABDOMYOLYSIS	0	0	0	0	0	1 (0.1)	0	0	0	0
RIB FRACTURE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
SEPSIS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
SKIN ULCER						1 (0.1)	0	0	0	0
SYNCOPE	0	0	0	0	0	1 (0.1)	0	0	0	0
THROMBOCYTOPENIA	0	0	0	0	0	1 (0.1)	0	0	0	0
THYROID MASS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
URINARY TRACT INFECTION	1 (0.1)	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
VENTRICULAR TACHYCARDIA	0	0	0	0	0	1 (0.1)	0	0	0	0
VOMITING	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ABSCESS LIMB	0	0	0	0	0	0	0	1 (0.2)	0	0
ABSCESS NECK	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ACQUIRED PHIMOSIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ADENOCARCINOMA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ANGIOEDEMA	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
ANKLE FRACTURE	0	0	1 (0.2)	0	0	0	0	2 (0.3)	0	0
ARTERITIS	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
ARTHRALGIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ARTHRITIS	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
ASTHMA	0	0	0	0	0	0	1 (0.2)	0	0	0
BACK PAIN	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
BASAL GANGLIA HAEMORRHAGE	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
BENIGN PROSTATIC HYPERPLASIA	0	1 (0.2)	1 (0.2)	0	0	0	1 (0.2)	1 (0.2)	0	0
BLADDER TRANSITIONAL CELL CARCINOMA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
BRADYARRHYTHMIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
BRAIN CONTUSION	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
BRAIN STEM INFARCTION	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
CATARACT	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
CHEST PAIN	0	0	1 (0.2)	0	0	0	1 (0.2)	1 (0.2)	0	0
COLITIS	0	0	0	0	0	0	1 (0.2)	0	0	0
CONSTIPATION	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
CONTUSION	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
CORONARY ARTERY OCCLUSION	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
DEEP VEIN THROMBOSIS	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
DIABETES MELLITUS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ENDOCARDITIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ENDOMETRIAL ADENOCARCINOMA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
FALL	0	0	0	0	0	0	1 (0.2)	0	0	0
FIBROMYALGIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
GASTRIC ULCER	0	0	0	0	0	0	0	1 (0.2)	0	0
GASTRITIS	0	1 (0.2)	0	0	0	0	2 (0.3)	0	0	0
HERNIA	0	0	0	0	0	0	1 (0.2)	0	0	0
HYPERKALAEMIA	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
HYPOKALAEMIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
LIVER FUNCTION TEST INCREASED	0	0	0	0	0	0	0	1 (0.2)	0	0
LUMBOSACRAL RADICULOPATHY	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
MALIGNANT MELANOMA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
MELANOMA RECURRENT	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
MICROCOCCUS INFECTION	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
MUSCLE RIGIDITY	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
MUSCULAR WEAKNESS	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
MYOCARDIAL INFARCTION	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0	1 (0.3)
MYOCARDIAL ISCHAEMIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
NEPHROLITHIASIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
NON-CARDIAC CHEST PAIN	0	0	0	0	0	0	1 (0.2)	0	0	0
OSTEOMYELITIS	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
PATELLA FRACTURE	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
RADIUS FRACTURE	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
REITER'S SYNDROME	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
RENAL IMPAIRMENT	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
RENAL NEOPLASM	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
RESTLESS LEGS SYNDROME	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
RETINAL DETACHMENT	0	0	0	0	0	0	1 (0.2)	0	0	0
ROAD TRAFFIC ACCIDENT	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
SCROTAL ABSCESS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
SMALL INTESTINAL OBSTRUCTION	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
STAPHYLOCOCCUS TEST POSITIVE	0	0	0	0	0	0	1 (0.2)	0	0	0
STERNAL FRACTURE	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
TACHYCARDIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
TENDON RUPTURE	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
TOOTH INFECTION	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
TRANSIENT ISCHAEMIC ATTACK	0	2 (0.4)	0	0	0	0	2 (0.3)	0	0	0
UMBILICAL HERNIA	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0
URETEROLITHIASIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
URETHRAL STENOSIS	0	2 (0.4)	0	0	0	0	2 (0.3)	0	0	0
URINARY INCONTINENCE	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
UTERINE HAEMORRHAGE	0	0	0	0	0	0	1 (0.2)	0	0	0
VENTRICULAR ARRHYTHMIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
VITRITIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; D/C, discontinuation; Met, metformin; and Saxa, saxagliptin.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs in the 3-study pool were few (<3%, data not shown). There were numerically more subjects who discontinued study medications due to AEs in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm with events related to renal function/impairment more common in this treatment group (i.e., glomerular filtration rate decreased, pollakiuria, renal impairment, and urine albumin/creatinine ratio increased).

In the 7-study pool, AEs leading to discontinuation of IP were reported in 3% of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm and in 6.5% of subjects receiving dapagliflozin 5 mg + saxagliptin 5 mg + metformin. These proportions were similar to the respective dapagliflozin + metformin treatment arms, and consistent with the events reported in the 5-study pool (Table 22). 'Creatinine renal clearance decreased' and 'Glomerular filtration rate decreased' were the more common MedDRA PTs reported for all arms that included dapagliflozin. 'Renal function analyses' was the most common HLT and 'Renal and urinary tract investigations and urinalyses' was the most common HLGT in these treatment arms. None of the renal impairment PTs were coded as serious, and no consistent trends were observed by SAEs.

The AEs resulting in discontinuation of IP in Trial CV181369 were limited (i.e., 2.9% [6/324] in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin ± sulfonylurea arm vs. 0.3% [1/319] in the insulin glargine + metformin ± sulfonylurea arm).

Table 23: Summary of Discontinuations Due to Adverse Events (Integrated 5- and 7-study pools Safety)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***SUBJECTS D/C IP DUE TO AES* — no. (%)**	**26 (2.7)**	**28 (5.7)**	**6 (1.3)**	**19 (6.5)**	**16 (5.5)**	**38 (3.0)**	**33 (5.0)**	**9 (1.4)**	**19 (6.5)**	**16 (5.5)**
CREATININE RENAL CLEARANCE DECREASED	6 (0.6)	9 (1.8)	0	0	0	6 (0.5)	9 (1.4)	0	0	0
GLOMERULAR FILTRATION RATE DECREASED	2 (0.2)	0	4 (0.8)	9 (3.1)	9 (3.1)	3 (0.2)	2 (0.3)	4 (0.6)	9 (3.1)	9 (3.1)
VULVOVAGINAL MYCOTIC INFECTION	2 (0.2)	1 (0.2)	0	0	0	3 (0.2)	1 (0.2)	0	0	0
HEADACHE	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0
URINARY TRACT INFECTION	0	0	0	0	0	2 (0.2)	0	0	0	0
ABDOMINAL DISCOMFORT	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ABDOMINAL PAIN	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ABDOMINAL PAIN UPPER	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ABORTION SPONTANEOUS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ANAL FUNGAL INFECTION	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ANGINA UNSTABLE	0	0	0	0	0	1 (0.1)	0	0	0	0
ASTHENIA	1 (0.1)	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
CARDIAC FAILURE	0	0	0	0	0	1 (0.1)	0	0	0	0
CHRONIC KIDNEY DISEASE	1 (0.1)	0	0	0	1 (0.3)	1 (0.1)	0	0	0	1 (0.3)
DENTAL CARIES	0	0	0	0	0	1 (0.1)	0	0	0	0
DEPRESSION	1 (0.1)	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
DERMATITIS ALLERGIC	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
DIABETIC NEPHROPATHY	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
DIZZINESS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
FOLLICULITIS	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
FUNGAL SKIN INFECTION	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
GASTROINTESTINAL HAEMORRHAGE	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
HEPATIC STEATOSIS	0	0	0	0	0	1 (0.1)	0	1 (0.2)	0	0

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
INVASIVE DUCTAL BREAST CARCINOMA	0	0	0	0	0	1 (0.1)	0	0	0	0
LOW DENSITY LIPOPROTEIN INCREASED	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
PLEURAL EFFUSION	0	0	0	0	0	1 (0.1)	0	0	0	0
PNEUMONIA	1 (0.1)	1 (0.2)	0	0	0	1 (0.1)	1 (0.2)	0	0	0
POLLAKIURIA	0	1 (0.2)	0	1 (0.3)	0	1 (0.1)	1 (0.2)	0	1 (0.3)	0
PYELONEPHRITIS	0	0	0	0	0	1 (0.1)	0	0	0	0
RENAL IMPAIRMENT	0	1 (0.2)	0	1 (0.3)	0	1 (0.1)	1 (0.2)	0	1 (0.3)	0
SKIN CANDIDA	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
SKIN INFECTION	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
THROMBOCYTOPENIA	0	0	0	0	0	1 (0.1)	0	0	0	0
TRANSAMINASES INCREASED	0	0	0	0	0	1 (0.1)	0	0	0	0
URINE ALBUMIN/CREATININE RATIO INCREASED	0	0	0	0	0	1 (0.1)	0	0	0	0
VAGINAL HAEMORRHAGE	0	0	0	0	0	1 (0.1)	0	0	0	0
VAGINAL INFECTION	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	0	0	0	1 (0.2)	0	0	0
ANKLE FRACTURE	0	0	0	0	0	0	0	1 (0.2)	0	0
ANXIETY	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ASCITES	0	0	0	0	0	0	1 (0.2)	0	0	0
BALANOPOSTHITIS	0	2 (0.4)	0	0	0	0	2 (0.3)	0	0	0
BLADDER TRANSITIONAL CELL CARCINOMA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
BRADYARRHYTHMIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
CEREBROVASCULAR ACCIDENT	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
CHRONIC MYELOID LEUKAEMIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
DECREASED APPETITE	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
DIARRHOEA	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
DRUG INTOLERANCE	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
DYSURIA	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
ENDOCARDITIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
GLOMERULAR FILTRATION RATE ABNORMAL	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
HEPATIC CIRRHOSIS	0	0	0	0	0	0	0	1 (0.2)	0	0
HYPERGLYCAEMIA	0	0	1 (0.2)	0	1 (0.3)	0	0	1 (0.2)	0	1 (0.3)
INTERVERTEBRAL DISC PROTRUSION	0	1 (0.2)	1 (0.2)	0	0	0	1 (0.2)	1 (0.2)	0	0
LIVER FUNCTION TEST INCREASED	0	0	0	0	0	0	0	1 (0.2)	0	0
MICROCOCCUS INFECTION	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
MYOCARDIAL INFARCTION	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0	1 (0.3)
MYOCARDIAL ISCHAEMIA	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
NAUSEA	0	0	0	1 (0.3)	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)
RENAL FAILURE	0	0	0	2 (0.7)	0	0	0	0	2 (0.7)	0
RENAL NEOPLASM	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
ROAD TRAFFIC ACCIDENT	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
SKIN EXFOLIATION	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
TRICUSPID VALVE INCOMPETENCE	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
URETHRAL STENOSIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0
URTICARIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
VENTRICULAR ARRHYTHMIA	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)
VISUAL IMPAIRMENT	0	0	0	1 (0.3)	0	0	0	0	1 (0.3)	0
VITRITIS	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	0

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; D/C, discontinuation; Met, metformin; and Saxa, saxagliptin.

8.4.4. Significant Adverse Events

Adverse events meeting the International Council for Harmonization (ICH) E3 definition of other significant adverse events 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

Based on the data from the 3-study pool, common AEs included in QTERN labeling and the proposed labeling for QTERNMET XR are upper respiratory tract infection, urinary tract infection, dyslipidemia, headache, diarrhea, back pain, genital infection and arthralgia.

The TEAEs reported in ≥2% of subjects in higher proportions of subjects in the dapagliflozin + saxagliptin + metformin arms for the 5- and 7-study pools are presented in Table 24. In the 7-study pool, common TEAEs in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm occurring in a higher proportion of subjects compared to the comparator arms included 'Upper respiratory tract infection' and 'arthralgia', while in the 5-study pool, 'Headache' was also included. In the 7-study pool, TEAE of 'Urinary tract infections', 'Pollakiuria', 'Nausea', and 'Glomerular filtration rate decreased' were more common in subjects receiving dapagliflozin 5 mg + saxagliptin 5 mg + metformin compared to dapagliflozin 10 mg + metformin.

Table 24: Summary of Common Treatment-Emergent Adverse Events (Integrated 5- and 7-study pools Safety)

	5-Study Pool					7-Study Pool				
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=950)**	**Dapa 10 mg + Met (n=492)**	**Saxa 5 mg + Met (n=471)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***SUBJECTS WITH TEAES* — no. (%)**	**521 (54.8)**	**275 (55.9)**	**209 (44.4)**	**123 (42.0)**	**121 (41.3)**	**716 (56.7)**	**369 (56.4)**	**323 (51.2)**	**121 (41.3)**	**123 (42.0)**
VIRAL UPPER RESPIRATORY TRACT INFECTION	63 (6.6)	35 (7.1)	13 (2.8)	9 (3.1)	5 (1.7)	74 (5.9)	42 (6.4)	20 (3.2)	5 (1.7)	9 (3.1)
URINARY TRACT INFECTION	31 (3.3)	20 (4.1)	13 (2.8)	3 (1.0)	7 (2.4)	57 (4.5)	31 (4.7)	29 (4.6)	7 (2.4)	3 (1.0)
HEADACHE	27 (2.8)	12 (2.4)	9 (1.9)	3 (1.0)	3 (1.0)	47 (3.7)	24 (3.7)	22 (3.5)	3 (1.0)	3 (1.0)
UPPER RESPIRATORY TRACT INFECTION	36 (3.8)	8 (1.6)	12 (2.5)	4 (1.4)	3 (1.0)	41 (3.2)	14 (2.1)	14 (2.2)	3 (1.0)	4 (1.4)
BACK PAIN	24 (2.5)	19 (3.9)	7 (1.5)	4 (1.4)	4 (1.4)	36 (2.9)	21 (3.2)	17 (2.7)	4 (1.4)	4 (1.4)
INFLUENZA	22 (2.3)	13 (2.6)	10 (2.1)	9 (3.1)	3 (1.0)	36 (2.9)	18 (2.8)	22 (3.5)	3 (1.0)	9 (3.1)
DIARRHOEA	17 (1.8)	10 (2.0)	8 (1.7)	2 (0.7)	3 (1.0)	32 (2.5)	16 (2.4)	17 (2.7)	2 (0.7)	3 (1.0)
BRONCHITIS	24 (2.5)	13 (2.6)	4 (0.8)	0	4 (1.4)	30 (2.4)	16 (2.4)	6 (1.0)	4 (1.4)	0
ARTHRALGIA	23 (2.4)	4 (0.8)	3 (0.6)	5 (1.7)	0	28 (2.2)	6 (0.9)	5 (0.8)	0	5 (1.7)
POLLAKIURIA	11 (1.2)	8 (1.6)	1 (0.2)	1 (0.3)	7 (2.4)	15 (1.2)	9 (1.4)	1 (0.2)	7 (2.4)	1 (0.3)
NAUSEA	8 (0.8)	6 (1.2)	6 (1.3)	5 (1.7)	6 (2.0)	14 (1.1)	8 (1.2)	14 (2.2)	6 (2.0)	5 (1.7)
GLOMERULAR FILTRATION RATE DECREASED	6 (0.6)	1 (0.2)	6 (1.3)	11 (3.8)	12 (4.1)	8 (0.6)	3 (0.5)	6 (1.0)	12 (4.1)	11 (3.8)

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; D/C, discontinuation; Met, metformin; and Saxa, saxagliptin.

8.4.6. Laboratory Findings

This section will primarily focus on prespecified marked laboratory abnormalities and observed changes from baseline in relevant laboratory tests.

Marked Laboratory Abnormalities

In the 3-study pool, CK elevations were the most clinically relevant MA reported at the time of the original review of NDA 209091 (QTERN), of which five subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm experienced CK elevations >10x ULN. Although these MAs were transient, typically normalized within two weeks even with continuation of therapy, one subject developed rhabdomyolysis for which an association with IP could not be completely ruled out. With the current submissions, no additional cases of rhabdomyolysis or CK elevations >10x ULN were reported for any treatment arm.

A summary table of prespecified marked laboratory abnormalities reported for the 7-study pool is presented in Table 25. Generally, the numbers of subjects with these laboratory changes were limited. However, compared to comparator arms, the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm included higher proportions of subjects with MAs of high hematocrit, serum creatinine, calcium, and creatine kinase, and low platelet counts and plasma glucose concentrations. Overall, review of the results from the 7-study pool did not identify any new safety signals or clinically meaningful laboratory changes beyond those known and labeled for approved dapagliflozin, saxagliptin and metformin products.

Mean Changes from baseline in Select Clinical Laboratory Parameters

Hematology: In the 7-study pool, small, but not clinically relevant, changes in hematology parameters from baseline to Week 52 were observed in hemoglobin (0.6 ± 0.82 g/dL) and hematocrit (1.8 ± 2.67%) for the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm, which were consistent with the observed changes in the dapagliflozin 10 mg + metformin arm (i.e., 0.5 ± 0.91 g/dL and 1.8 ± 2.67%, respectively). Changes in platelet and leukocyte counts were not meaningful.

Chemistry: In the 7-study pool, changes from baseline to Week 52 in serum chemistries for subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm included small changes in serum calcium (-0.05 ± 0.48 mg/dL), creatine kinase (-5 ± 94.6 U/L), creatinine (0.011 ± 0.12 mg/dL), eGFR (-1.38 ± 13.23 mL/min/1.73 m^2), magnesium (0.14 ± 0.15 mEq/L), and phosphate (0.06 ± 0.54 mg/dL), which again were not clinically meaningful. Additionally, the following mean percent changes in lipid parameters were reported: cholesterol (5.0 ± 21.2%); high-density lipoprotein cholesterol (HDL-C, 6.4 ± 16.8%); low-density lipoprotein cholesterol (LDL-C, 11.3 ± 44.6%), and triglycerides (2.5% ± 47.4%). It is noted that increases in LDL-C are/will be included in the Warnings and Precautions sections of both QTERN and QTERNMET XR.

Table 25: Summary of Marked Laboratory Abnormalities (Integrated 7-study pools Safety)

Lab Test Subgroup	Dapa 10 + Saxa 5 + Met (N=1253)			Dapa 10 + Met (N=654)			Saxa 5 + Met (N=631)			Dapa 5 + Saxa 5+ Met (N=293)			Dapa 5 + Met (N=293)		
Lab Test Description	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**
Erythrocyte/ Platelet Attributes															
Hemoglobin (<6 G/L, >18 G/dL)	1226	0	9 (0.7)	606	0	6 (1.0)	616	0	2 (0.3)	278	0	5 (1.8)	275	0	0
Hemoglobin (>20 G/dL)	1226	NA	0	606	NA	0	616	NA	0	278	NA	0	275	NA	0
Hematocrit (<20%, >55%)	1226	0	18 (1.5)	605	0	5 (0.8)	616	0	5 (0.8)	278	0	3 (1.1)	274	0	1 (0.4)
Hematocrit (>60%)	1226	NA	1 (0.1)	605	NA	0	616	NA	1 (0.2)	278	NA	0	274	NA	0
Platelets (<100 x 10^3/µL, >450 x 10^3/µL)	1221	7 (0.6)	14 (1.1)	605	0	10 (1.7)	616	2 (0.3)	6 (1.0)	277	2 (0.7)	3 (1.1)	274	1 (0.4)	3 (1.1)
Kidney function															
Creatinine (≥1.5 pre-Rx creatinine)	1246	NA	29 (2.3)	645	NA	10 (1.6)	622	NA	11 (1.8)	286	NA	8 (2.8)	279	NA	6 (2.2)
Creatinine (≥2.5 mg/dL)	1246	NA	2 (0.2)	645	NA	2 (0.3)	622	NA	1 (0.2)	286	NA	0	279	NA	0
Electrolytes															
Sodium, serum (<130 mEq/L, >150 mEq/L)	1218	3 (0.2)	16 (1.3)	604	0	11 (1.8)	622	1 (0.2)	10 (1.6)	284	1 (0.4)	0	278	0	0
Sodium, serum (<120 mEq/L)	1218	0	NA	604	0	NA	622	0	NA	284	0	NA	278	0	NA
Potassium, serum (≤2.5 mEq/L, ≥6.0 mEq/L)	1214	0	21 (1.7)	602	0	12 (2.0)	622	0	13 (2.1)	283	0	3 (1.1)	278	0	3 (1.1)

Lab Test Subgroup	Dapa 10 + Saxa 5 + Met (N=1253)			Dapa 10 + Met (N=654)			Saxa 5 + Met (N=631)			Dapa 5 + Saxa 5+ Met (N=293)			Dapa 5 + Met (N=293)		
Lab Test Description	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**	**N**	**Low n (%)**	**High n (%)**
Calcium, total[a]	1219	7 (0.6)	8 (0.7)	604	4 (0.7)	3 (0.5)	622	10 (1.6)	0	286	3 (1.0)	0	279	4 (1.4)	0
Phosphorus, inorganic[b]	1215	2 (0.2)	17 (1.4)	602	0	9 (1.5)	622	3 (0.5)	2 (0.3)	286	1 (0.3)	2 (0.7)	280	1 (0.4)	3 (1.1)
Magnesium, serum (<1 mEq/L, >4 mEq/L)	1219	0	0	604	0	0	622	3 (0.5)	0	284	0	0	277	0	0
Cardiac tests															
Creatine kinase (>5X	933	NA	6 (0.6)	334	NA	1 (0.3)	622	NA	2 (0.3)	286	NA	1 (0.3)	280	NA	1 (0.4)
Creatine kinase (>10X ULN)	933	NA	4 (0.4)	334	NA	1 (0.3)	622	NA	1 (0.2)	286	NA	0	280	NA	0
Glucose tests															
Plasma glucose unspecified (<54 mg/dL, >350 mg/dL)	1246	4 (0.3)	5 (0.4)	642	0	4 (0.6)	621	0	7 (1.1)	284	0	0	279	0	1 (0.4)
Protein tests															
Protein, total (>10 G/dL)	933	NA	0	334	NA	0	622	NA	0	286	NA	0	280	NA	0
Quantitative urine chemistry															
ACR (>1800 mg/G)	1229	NA	4 (0.3)	642	NA	3 (0.5)	619	NA	5 (0.8)	284	NA	3 (1.1)	280	NA	0

Source: Adapted from the Applicant's Summary of Clinical Safety, Labeled as Table 28, pages 123-125 of 143, available at: \\cdsesub1\evsprod\nda210874\0001\m2\27-clin-sum\summary-clin-safety.pdf
Abbreviations: ACR, albumin to creatinine ratio; Dapa, dapagliflozin; Met, metformin; NA, not applicable; pre-Rx, pretreatment; Saxa, saxagliptin; and ULN, upper limit of normal
[a] <7.5 mg/dL, ≥1 mg/dL from ULN and ≥0.5 mg/dL from pretreatment calcium; [b] Age 17-65: ≤1.8 mg/dL, ≥5.6 mg/dL, age ≥66: ≤2.1 mg/dL, ≥5.1 mg/dL

8.4.7. Vital Signs

The SGLT2 pharmacologic class, including dapagliflozin, has been associated with diuresis and volume depletion.[23,187 188] Therefore, assessments of vital signs were performed throughout the treatment periods of the respective trials. Reported mean changes from baseline to Week 52 in heart rate (-1.1 ± 8.4 beats per minute [bpm]), diastolic blood pressure (DBP, -1.4 ± 8.0 mmHg), and SBP (-3.3 ± 13.0 mmHg), were small in the 7-study pool for subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm. Additionally, changes from baseline in body weight an SBP were considered key secondary endpoints for several trials (please refer to Section 7.1.2). Baseline vital signs were similar across treatment arms in the respective trials, and reductions in body weight and SBP were modest (Table 15).

8.4.8. Electrocardiograms (ECGs)

The Applicant reported "no treatment-related clinically meaningful" safety findings related to ECGs. In the Integrated Summary of Safety (ISS), the following TEAEs were reported in the dapagliflozin + saxagliptin + metformin arms in the 7-study safety pool:

Dapagliflozin 10 mg/saxagliptin 5 mg/metformin arm:
Atrial fibrillation 0.6% (8/1263 subjects); Bradyarrhythmia <0.1% (1/1263); Bradycardia 0.2% (2/1263); Bundle branch block left 0.2% (3/1263); Electrocardiogram QT prolonged 0.1% (1/1263); Extrasystoles <0.1% (1/1263); Sinus bradycardia <0.1% (1/1263); Sinus tachycardia <0.1% (1/1263); Tachycardia <0.1% (1/1263); Ventricular arrhythmia <0.1% (1/1263); Ventricular extrasystole 0.3% (4/1263); and Ventricular tachycardia <0.1% (1/1263)

Dapagliflozin 5 mg/saxagliptin 5 mg/metformin arm:
Tachycardia 0.3% (1/293 subjects)

According to the CSRs for the 7-study safety pool, most subjects randomized to the dapagliflozin + saxagliptin + metformin treatment arm who had normal ECGs at baseline also had normal ECGs at Weeks 24 or 52. No clear imbalances were observed between treatment arms for abnormal ECG findings, and no trends in types of abnormalities were apparent. The additional safety data on ECG findings provided since the original QTERN NDA does not alter the known cardiovascular safety of QTERNMET XR or QTERN.

8.4.9. QT

Thorough QT (TQT) studies were not conducted for these Applications. In the 7-study safety pool, TEAEs of 'electrocardiogram QT prolonged' were reported for only one subject each in the dapagliflozin + saxagliptin + metformin (<0.1%) and the dapagliflozin/metformin (0.2%)

treatment arms. According to FARXIGA product labeling, dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended maximum dose) in a study of healthy subjects.[3] In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended maximum dose) of dapagliflozin in healthy subjects. Similarly, ONGLYZA product labeling states that once-daily, orally-administered saxagliptin in healthy subjects at doses up to 400 mg daily for two weeks (80 times the recommended maximum dose) had no clinically meaningful effect on QTc interval or heart rate.[4]

8.4.10. Immunogenicity

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

8.5. Analysis of Submission-Specific Safety Issues

The Applicant searched for AESI related to safety findings in the dapagliflozin, saxagliptin nonclinical and clinical programs, as well as known safety concerns associated with other SGLT2 inhibitors, DPP-4 inhibitors and metformin, and the respective FCDPs. These AESI included the following: genital infections, UTIs, hypoglycemia, renal impairment/failure, malignancies, fractures, cardiac failure, confirmed adjudicated CV events, decreased lymphocyte counts, decreased thrombocyte counts, pancreatitis, severe cutaneous adverse reactions, hypersensitivity reactions, liver injury/hepatic disorder, volume depletion (hypotension, dehydration, and hypovolemia), diabetic ketoacidosis, and lactic acidosis. Due to many of the AESI being relatively less common, the 7-study pool was the primary safety pool used to evaluate these events. In general, AESI occurred in higher proportions of subjects within the first six months, and, due to a longer exposure compared to the other treatment arms, the adjusted event rates for the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm were typically lower than the crude event rates.

8.5.1. 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.[189] Further, SGLT2 inhibitors appear to increase this risk,[190-192] possibly mediated through glucosuria. The risk of genital infections is included in both approved QTERN[6] and proposed QTERNMET XR labeling.

In the 7-study pool AEs of genital infection were reported in: 4% (50/1263) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg+ metformin arm; 6.9% (45/654) of subjects in the dapagliflozin 10 mg + metformin arm; 0.5% (3/631) of subjects in the saxagliptin 5 mg +

metformin arm; 3.4% (10/293) of subjects in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm; and 1.7% (5/293) of subjects in the dapagliflozin 5 mg + metformin arms. As anticipated, genital infections were more common in subjects receiving dapagliflozin, and, across the study population, in females (4.7% [71/3134] vs. 2.6% [42/1629] of males), with most subjects experiencing a single event. In the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm, the reported PTs included 'Vulvovaginal mycotic infection' (1.6%), 'Balanoposthitis' (1%), 'Vaginal infection' (0.6%), 'Genital infection fungal' (0.4%), 'Vulvovaginal candidiasis' (0.2%), 'Genital infection' (0.2%), and vulvovaginitis' (0.2%). The model-adjusted incidence rates were similar to the crude rates (data not shown). None of the events were coded as an SAE, but four subjects in the dapagliflozin 10 mg + saxagliptin + metformin arm (three due to vulvovaginal mycotic infection, and a fourth due to vaginal infection) discontinued IP. The results of the 7-study pool are consistent with the known risks for genital infections associated with SGLT2 inhibitors.

8.5.2. Urinary Tract Infections

Type 2 diabetic patients receiving SGLT2 inhibitors also are at increased risk for urinary tract infections (UTIs),[190,191] and warnings related to this risk are included in both approved QTERN[6] and proposed QTERNMET XR labeling.

In the 7-study pool AEs of urinary infection were reported in: 5.5% (70/1263) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm; 6.6% (43/654) of subjects in the dapagliflozin 10 mg + metformin arm; 5.8% (32/631) of subjects in the saxagliptin 5 mg + metformin arm; 3.1% (9/293) of subjects in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm; and 2.0% (6/293) of subjects in the dapagliflozin 5 mg + metformin arms. As with the risk of genital infections, AEs of UTI were again more common in females, affecting 7.9% [119/3134] across all treatment arms compared to 2.5% [41/1629] of male participants. Although three subjects, previously reported in the 3-study pool, who were receiving dapagliflozin 10 mg + saxagliptin 5 mg + metformin discontinued IP (i.e., two coded as UTI, and one associated with pyelonephritis), no additional cases of UTI led to treatment discontinuation. None of the remaining AEs of UTI for the dapagliflozin triple therapy arms were coded as SAEs. No additional safety concerns associated with the risk of UTIs were identified based on submission of the additional clinical trial data.

8.5.3. Hypoglycemia

For the Summary of Clinical Safety, the Applicant used the following definitions of hypoglycemic events (which were consistent with ADA criteria):

- Overall Hypoglycemia (ADA Level 1): Includes all reported episodes of hypoglycemia on the hypoglycemia CRF page(s) regardless of the self-monitoring blood glucose value and all episodes identified from (b) (4) FPG values ≤70 mg/dL.

- Clinically Significant Hypoglycemia (ADA Level 2): BG <54 mg/dL
- Severe Hypoglycemia (ADA Level 3): At least one episode of neuroglycopenic symptoms requiring third party help for neuroglycopenic recovery, prompt recovery, and a glucose value either not present or if glucose measured it must be ≤70 mg/dL

As anticipated based on the pharmacodynamics of the study medications and the patient population studied, the numbers of subjects experiencing at least one Level 1 hypoglycemic events in the 7-study pool (regardless of glycemic rescue therapy) were higher (6.5-7.8% vs. <3.1% for comparator arms) in the dapagliflozin triple therapy arms (please refer to Table 21). The reported Level 1 hypoglycemic events for subjects prior to glycemic rescue included the following: 7.5% (95/1263) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm; 2.6% (17/654) of subjects in the dapagliflozin 10 mg + metformin arm; 2.1% (13/631) of subjects in the saxagliptin 5 mg + metformin arm; 6.5% (19/293) of subjects in the dapagliflozin 5 mg + saxagliptin + metformin arm; and 3.1% (9/293) of subjects in the dapagliflozin 5 mg + metformin arms. Level 2 hypoglycemic events (i.e., BG <54 mg/dL) were more common in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm (2.1% [26/716] of subjects), compared to the other treatment arms (<0.5%). Level 3 events were limited to a single subject each in the dapagliflozin 10 mg and the dapagliflozin 5 mg triple therapy arms. No subjects in any treatment arm discontinued therapy due to hypoglycemia. It is acknowledged that the proportions of subjects with hypoglycemic events were lower for the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm in trials that included insulin (Trial CV181369) or sulfonylurea (Trials CV181365 and D1689C00014) comparator arms.

8.5.4. Renal Failure/Impairment

Sodium-glucose cotransport 2 inhibitors have been associated with postmarketing reports of acute kidney injury (AKI).[112] On June 14, 2016, the FDA strengthened the existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin.[193] 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.[194,195] Both QTERN[6] and proposed QTERNMET XR labeling include acute kidney injury and impairment of renal function in Section 5 (Warnings and Precautions).

In the 7-study pool, AEs of renal impairment/failure were reported in 2.2% of subjects in the dapagliflozin 10 mg + saxagliptin + metformin arm; 2.1% of subjects in the dapagliflozin 10 mg + metformin arm; 1.9% of subjects in the saxagliptin 5 mg + metformin arm; 5.5% of subjects in the dapagliflozin 5 mg + saxagliptin + metformin arm; and 4.1% of subjects in the dapagliflozin 5 mg + metformin arms (Table 26). Common MedDRA PTs included 'Glomerular filtration rate decreased' and 'Creatinine renal clearance decreased' for all treatment arms. In the dapagliflozin triple therapy arms, none of the AEs were coded as serious. No additional concerns related to renal safety were identified following review of the additional trial data.

Table 26: Summary of Renal Impairment/Failure AESI (7-study pool)

	7-Study Pool				
AESI Category	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***TOTAL EVENTS*— no. (%)**	**28 (2.2)**	**14 (2.1)**	**12 (1.9)**	**16 (5.5)**	**12 (4.1)**
Glomerular filtration rate decreased	8 (0.6)	3 (0.5)	6 (1.0)	12 (4.1)	11 (3.8)
Creatinine renal clearance decreased	7 (0.6)	9 (1.4)	0	0	0
Renal impairment	5 (0.4)	1 (0.2)	1 (0.2)	1 (0.3)	0
Blood creatinine increased	4 (0.3)	0	2 (0.3)	0	0
Acute kidney injury	2 (0.2)	0	0	0	0
Renal function test abnormal	1 (0.1)	0	0	0	0
Chronic kidney disease	1 (0.1)	0	3 (0.5)	0	1 (0.3)
Acute prerenal failure	1 (0.1)	0	0	0	0
Urine output decreased	1 (0.1)	0	0	0	0
Glomerular filtration rate abnormal	0	0	0	1 (0.3)	0
Renal failure	0	1 (0.2)	1 (0.2)	2 (0.7)	0

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; Met, metformin; and Saxa, saxagliptin.

8.5.5. Malignancies

Malignancies were reported in two subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm (i.e., invasive ductal breast carcinoma and pancreatic carcinoma), and one subject randomized to the dapagliflozin 10 mg + metformin treatment arm (bladder transitional cell carcinoma). The subject with breast carcinoma (MB102129 (b) (6) involving a 60-year-old White female) was previously reviewed and felt not to be associated with IP. The case involving pancreatic carcinoma is briefly summarized as follows:

- **Subject CV181168 (b) (6):** a 50-year-old White male with T2D randomized to the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm in Trial CV181168, experienced a SAE of hepatic cancer on Day 113 identified by abdominal ultrasound and confirmed by computed tomography (CT) scan on Day 128. A liver biopsy (Day 146) showed hepatic adenocarcinoma of biliary and pancreatic origin). His past medial history included dyslipidemia, hypertension, and obesity. His concomitant medications included bisoprolol, allopurinol (a history of gout not reported), hydrochlorothiazide, prazosin. No action was taken by the investigator and the subject remained on IP until Day 156. The subject subsequently received investigational antineoplastic (Day 189). The event was adjudicated as pancreatic carcinoma that metastasized to the liver and judged to be unrelated to IP.

Considering the onset of metastatic disease in this subject (i.e., approximately 3.8 months), I feel that it is unlikely to be related to investigational product.

8.5.6. Fractures

The SGLT2 inhibitors have been associated with small increases in parathyroid hormone concentrations, decreases in 1,25-dihydroxyvitamin D concentrations, and the potential for decreased bone mineral density, and fracture risk.[196] 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.[197]

In the 7-study pool, AEs of fracture were limited and occurred in 0.5% of subjects in the dapagliflozin 10 mg + saxagliptin + metformin arm; 0.5% of subjects in the dapagliflozin 10 mg + metformin arm; 1.3% of subjects in the saxagliptin 5 mg + metformin arm; 0.3% of subjects in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm; and 0.7% of subjects in the dapagliflozin 5 mg + metformin arms (Table 27). The fracture sites in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm included the ribs, femoral neck, humerus, patella, and foot. In the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm, one subject experienced two fractures (radius and sternum). For the seven subjects in these two arms, the mean age was 62 (50-67) years old and only two were females. Although one subject had an AE of 'Knee osteoarthritis' and 'Joint range of motion decrease', and a second had an AE of 'Low back pain', there were no AEs reported of falls or hypoglycemia. Based on the proportions of subjects with fractures and varied anatomic sites, I don't feel there is an increased risk of fracture with the dapagliflozin triple therapy combination over the individual components.

Table 27: Summary of Fractures (7-study pool)

	7-Study Pool				
AESI Category	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***TOTAL FRACTURES* — no. (%)**	**6 (0.5)**	**3 (0.5)**	**8 (1.3)**	**1 (0.3)**	**2 (0.7)**
Rib fracture	2 (0.2)	1 (0.2)	3 (0.5)	0	0
Femoral neck fracture	1 (0.1)	0	0	0	0
Patella fracture	1 (0.1)	0	1 (0.2)	0	0
Foot fracture	1 (0.1)	0	1 (0.2)	0	0
Humerus fracture	1 (0.1)	0	0	0	0
Hand fracture	0	1 (0.2)	0	0	0
Radius fracture	0	1 (0.2)	0	1 (0.3)	0
Sternal fracture	0	0	0	1 (0.3)	0
Ulna fracture	0	0	0	0	1 (0.3)
Forearm fracture	0	0	1 (0.2)	0	0
Ankle fracture	0	0	2 (0.3)	0	1 (0.3)

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; Met, metformin; and Saxa, saxagliptin.

8.5.7. Confirmed Adjudicated Cardiovascular Events

With the additional safety data submitted to these Applications, no additional CV events were adjudicated. The numbers of adjudicated CV events previously reported in the 3-study pool were few for all treatment arms, and consistent with the types of events expected in a T2D patient population.[198] In the saxagliptin cardiovascular outcomes trial (CVOT) (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; SAVOR), the Applicant reported that saxagliptin was not associated with an increase or decrease in the rate to first major adverse cardiovascular events (MACE), which included CV death, nonfatal myocardial infarction (MI), and/or nonfatal ischemic stroke.[4,199] Additionally, in a published meta-analysis report of the 21 Phase 2b/3 dapagliflozin clinical trials, dapagliflozin was not associated with an increase in CV risk.[200] The Applicant's recently published the findings of their dapagliflozin CVOT (i.e., Dapagliflozin Effect on CardiovascuLAR Events; DECLARE), the authors concluded that treatment with dapagliflozin in subjects with T2D who had or were at risk for atherosclerotic cardiovascular disease did not result in a higher or lower rate of MACE than placebo.[201] It is noted that this trial is currently under review, and these results have not been validated/confirmed.

In the SAVOR trial, an increase in the risk of hospitalization for heart failure was observed in the saxagliptin treatment arm (hazard ratio [HR] 1.27; 95% CI, 1.07, 1.51).[4,202] The Applicant assessed heart failure events as AESI in the QTERN and QTERNMET XR clinical programs. Based on their SMQ, events were limited, with possible heart failure AEs reported in 0.9% of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm; 0.8% in the dapagliflozin 10 mg + metformin arm, 1.3% in the saxagliptin 5 mg + metformin arm; 0.3% in the dapagliflozin 5 mg + metformin arm, and no subjects in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm (Table 28). Only two subjects, both in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm had heart failure events reported as serious, both were previously reported in the 3-study pool.

Table 28: Summary of Heart Failure Events (7-study pool)

	7-Study Pool				
AESI Category	**Dapa 10 mg + Saxa 5 mg + Met (n=1263)**	**Dapa 10 mg + Met (n=654)**	**Saxa 5 mg + Met (n=631)**	**Dapa 5 mg + Saxa 5 mg + Met (n=293)**	**Dapa 5 mg + Met (n=293)**
***TOTAL HEART FAILURE EVENTS* — no. (%)**	**11 (0.9)**	**5 (0.8)**	**8 (1.3)**	**0**	**1 (0.3)**
Oedema peripheral	6 (0.5)	2 (0.3)	5 (0.8)	0	1 (0.3)
Oedema	2 (0.2)	0	0	0	0
Orthopnoea	1 (0.1)	0	0	0	0
Cardiac failure	1 (0.1)	1 (0.2)	0	0	0
Cardiac failure acute	1 (0.1)	0	0	0	0
Peripheral swelling	1 (0.1)	1 (0.2)	3 (0.5)	0	0
Cardiac failure congestive	0	1 (0.2)	0	0	0
Cardiac failure chronic	0	1 (0.2)	0	0	0

Source: Derived from the adae.xpt dataset, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam –
Abbreviations: Dapa, dapagliflozin; Met, metformin; and Saxa, saxagliptin.

8.5.8. Confirmed Adjudicated Hepatic Events

Four subjects in the 7-study pool had an ALT or AST >3x ULN with total bilirubin >2x ULN within 14 days. Three of these subjects had received dapagliflozin 10 mg + saxagliptin 5 mg + metformin, and all were previously reviewed. No cases were reported in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm. Based on these data, no new cases were reported in the dapagliflozin triple therapy arms and no additional hepatic safety concerns were identified with these Applications.

8.5.9. Decreased Lymphocyte and Platelet Counts

In the 7-study pool, four subjects (0.3%) had an AESI related to decreased thrombocyte counts (0.3%) . One event (Subject MB102129 (b) (6)), previously reported in the 3-study pool, was considered serious. However, no new cases coded as serious by the investigators have been reported for the current submissions. No withdrawals or SAEs due to thrombocytopenia were reported in Trial CV18369.

8.5.10. Pancreatitis

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.[203] Subsequently, in the Applicant's saxagliptin CVOT (SAVOR), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) of subjects receiving saxagliptin compared to 9 of 8173 (0.1%) receiving placebo.[4,204] Both QTERNMET XR and the proposed Qtern labeling include pancreatitis in Section 5 (Warnings and Precautions).

At the time of approval of QTERN, a single SAE of chronic pancreatitis (Subject CV181169 (b) (6)) was reported, which was coded as mild in intensity. With the updated safety data, no additional cases of pancreatitis were reported for either the 7-study pool or for Trial CV181369.

8.5.11. Severe Cutaneous Adverse Reactions

Saxagliptin products include warnings of bullous pemphigoid and exfoliative skin conditions,[6,13,20] and are included in QTERN and proposed QTERNMET XR labeling. In the 7-study pool, cutaneous AEs were reported in 0.5% (6/1263) of subjects (n=4 'Conjunctivitis', and n=2 'Skin exfoliation' [scaling on feet], both reported previously in the 3-study pool) randomized to the dapagliflozin 10 mg + saxagliptin + metformin arm, and one subject ('Skin exfoliation') in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm. None of these events were coded as severe or serious. However, the subject from the dapagliflozin 5 mg triple therapy arm (b) (6) discontinued IP. A brief narrative is presented as follows:

- **Subject** (b) (6) a 58-year-old Black female with a 10-year history of T2D was randomized to the dapagliflozin 5 mg + saxagliptin 5 mg + metformin treatment arm in

Trial D16l83c00005. On Day 4, she developed skin exfoliation on her palms, reported as 'peeling of skin' and coded as mild in severity. Study medication was temporarily discontinued for one week (Days 5-11). Her medical history included rheumatoid arthritis, degenerative joint disease, hyperlipidemia, fatty liver disease, peripheral neuropathy and retinopathy, and her concomitant medications included aspirin, rosuvastatin, methylprednisolone (for rheumatoid arthritis), ketorolac, and gabapentin. When rechallenged, the subject again experienced skin exfoliation of the feet (Day 12), reported as mild in intensity, and IP was permanently discontinued (Day 14). The subject recovered from this second adverse cutaneious event on Day 24. Limited additional information was provided in the CRF or CSR. The event was considered related to IP by the investigator.

Since there was both a positive challenge, dechallenge and rechallenge associated with this case, I concur that the observed cutaneous AEs were treatment-related but feel that no additional changes need to be included in product labeling. It is acknowledged that gabapentin[205] and ketorolac[206] both carry warnings of severe cutaneous AEs (e.g., exfoliative dermatitis, erythema multiforme, Stevens-Johnson Syndrome, and/or toxic epidermal necrolysis). Their contributions to the observed skin reactions in this subject are uncertain.

No severe/serious cutaneous AEs were reported in Trial CV181369.

8.5.12. Severe Hypersensitivity Reactions

In the 7-study pool, no imbalances in hypersensitivity reactions between treatment arms were apparent. Approximately 2.1% (26/1263) of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm and 1.7% of subjects in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm reported hypersensitivity AEs. Of these subjects, a single subject experienced a serious hypersensitivity reaction of angioedema (b) (6), which is described as follows:

- **Subject (b) (6):** a 65-year-old White male with T2D was randomized to the dapagliflozin 5 mg + saxagliptin 5 mg + metformin treatment arm in Trial D16183C00005. On Day 142, he experienced 'Angioedema' (reported as angioneurotic oedema of the lip), reported as moderate in severity by the investigator. Study medication was not changed. Nine days later (Day 151), the subject had a second episode (reported as angioneurotic oedema of the tongue), followed by a third episode associated with a swollen right cheek (reported as angioneurotic oedema cheek) seven days later (Day 159), resulting in hospitalization. No relevant medical history was reported, and his concomitant medications included clopidogrel, ramipril, and atorvastatin/ezetimibe. Symptoms resolved, and the subject was discharged from the hospital on Day 160. The subject completed the trial on Day 162. The event was considered by the investigator to be related to ACEIs (ramipril).

Although I concur that angioedema is a well known allergic reaction associated with ACEIs,[207-209] including ramipril,[210] the limited information provided for this case make it difficult to rule out IP as a causal or contributing factor. However, proposed labeling adequately addresses this risk.

8.5.13. Volume Depletion

The SGLT2 inhibitors, including dapagliflozin, may be associated with osmotic diuresis and possible intravascular volume contraction, potentially predisposing patients to acute kidney injury, especially in at individuals with impaired renal function, heart failure, elderly patients, or patients receiving loop diuretics, ACEIs, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs).[23,193,211-213].

There were limited events of volume depletion reported in the 7-study pool, and no obvious imbalances were reported between treatment arms. Across all treatment arms, only a single event, occurring in the dapagliflozin 10 mg + saxagliptin + metformin arm, was coded as serious (i.e., Subject CV181168-(b) (6), previously reported for the 3-study pool). Proposed labeling adequately addresses the risk of volume depletion associated with QTERN and QTERNMET XR.

8.5.14. Metabolic Acidosis

Lactic acidosis is a boxed warning for metformin-containing products (e.g., KOMBIGLYZE and XIGDUO XR),[5,13] and diabetic ketoacidosis is a labeled warning for SGLT2 inhibitors, including dapagliflozin-containing products.[5,6,23] There were no events of lactic acidosis and limited events of diabetic ketoacidosis (DKA) reported in the 7-study pool. Potential events of DKA included only two subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm ('Blood ketone body increased', and 'Urine ketone body present'), and one subject in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm ('Urine ketone body present'). None of these AEs were serious or resulted in discontinuation of IP.

8.5.15. Myopathy/Rhabdomyolysis

No additional cases of either rhabdomyolysis or CK elevations >10x ULN have been reported since the review of NDA 209091 (QTERN). Please refer to Section 8.4.6.

8.5.16. Other Adverse Events Associated with SGLT2 Inhibitors, DPP-4 Inhibitors, and Metformin

Using broad CMQs, the AE datasets also were queried for other AESI associated with SGLT2 inhibitors, DPP-4 Inhibitors, and metformin, which included accidents and injury; acute kidney injury/chronic renal failure; arthropathies; bone and joint infections; bone disorders; bone fractures; bone, joint and vascular therapeutic procedures; dermal diabetic complications; diabetic microvascular complications; Fournier's gangrene; genital infections; heart failure/cardiomyopathy; hepatotoxicity; hypersensitivity/anaphylactic reaction/angioedema;

hypoglycemia; ketoacidosis; lactic acidosis; lymphopenia, malignancies and premalignant conditions; musculoskeletal and soft tissue investigations; myopathy/rhabdomyolysis; nephrolithiasis; opportunistic infections; osmotic diuresis; pancreatitis; peripheral artery disease; skin reactions; stomatitis/mouth ulcerations; thrombocytopenia; urinary tract infections; vascular insufficiency; venous thromboembolic events; volume depletion.

Based on the review of these data. event counts for many of the CMQs were limited/non-informative, and no trends were readily identified that suggested apparent imbalances between treatment arms for subjects with these AESI (Table 32).

It is noted that lower limb amputations were not recorded as AESI for both Applications. According to the Centers for Disease Control and Prevention (CDC), diabetes remains the leading cause of lower limb amputations,[214] resulting in approximately 108,000 hospitalizations for a lower-extremity amputation each year (i.e., 5 per 1000 persons with diabetes).[29] 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.[82,83,216-222] 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).[83] 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.[82] 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.[110,223] The highest absolute risk reported occurred in subjects with a history of peripheral vascular disease or prior amputation.

Besides canagliflozin-containing products, the risk of lower limb amputation also is listed in the Warnings and Precautions section of ertugliflozin-containing products.[7,12,213]

For the current Applications, the datasets, CSRs, and 4MSU were searched for the occurrence of amputations. Based on this review, there were no events identified in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin arm, and two events were reported for subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm (i.e., right toe amputation in a 58-year-old male associated with gangrene, and a right toe amputation due to a lawnmower accident in a 51-year-old male reported in the 4MSU). The event for the 58-year-old male is briefly discussed as follows:

- **Subject** (b) (6)**:** a 58-year-old White male with T2D was randomized to the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm in Trial CV181365. His medical history included hypertension, dyslipidemia, peripheral vascular disease, diabetic retinopathy, diabetic neuropathy, and angiopathy. On Day 70, he presented with cooling of lower extremities, heaviness in legs, and a weeping erythematous wound on the plantar side of his right foot. He was diagnosed with wet gangrene of the second right toe (considered to be a neuropathic form of diabetic foot). He had no tobacco history or prior diabetic ulcers. Ultrasound of pelvic and lower extremity arteries did not reveal stenosis, but there was some venous insufficiency noted on the left. The subject underwent a right toe amputation and necrectomy (Day 70). The event was assessed as moderate in intensity and unrelated to IP. Study drug was interrupted in response to event and again resumed on Study Day 99. The wound healed, without further complications.

Considering the preexisting comorbidities and limited information provided, it is difficult to establish a causal relationship with study medications. Whether IP may have been a contributing factor for the event in this at-risk subject cannot be ruled out.

During the clinical development programs for most SGLT2 inhibitors, including dapagliflozin, the occurrence of amputations often was not prespecified as an AESI, and these events were usually coded as procedures and not as AEs. Therefore, the potential for a class effect with all SGLT2 inhibitors remains uncertain. Additionally, since the eight clinical trials submitted to the current Applications included relatively young, healthy T2D patient populations and limited treatment exposures, there were few amputation events in the triple therapy arms. However, in the Applicants dapagliflozin CVOT (D1693C001; DECLARE), which included older subjects and longer treatment durations (median exposure of 48 months), the evaluation of amputation events was requested by the Agency. Although this trial is under review, an imbalance events between treatment arms was not apparent (i.e., 1.4% [123/8574] of subjects receiving dapagliflozin 10 mg vs. 1.3% [113/8569] of subjects in the placebo arm).[5]

[5] Applicant's Summary of Clinical Safety for NDA 202293, Trial D1693C001, labeled as Table 5, page 26 of 177, available at: \\cdsesub1\evsprod\nda202293\0461\m2\27-clin-sum\summary-clin-safety-declare.pdf

8.6. Safety Analyses by Demographic Subgroups

In general, there were no obvious imbalances between the dapagliflozin plus saxagliptin plus metformin triple therapy arms and comparators across age, gender or racial subgroups. However, it is acknowledged that the numbers of elderly subjects over age 75 years old were limited, the trial populations were predominantly White, and individuals with moderate to severe renal impairment (e.g., eGFR <60 mL/min/1.73 m2) were excluded from study participation. Therefore, it is difficult to generalize the safety findings to older, non-White, or renally impaired (e.g., CKD 3A) subpopulations. However, there is extensive use of the individual products alone and as combination antihyperglycemic therapy worldwide, including use in these subpopulations. Additionally, no apparent racial differences in safety or effectiveness were observed in the dapagliflozin, saxagliptin, or metformin development programs, and proposed (QTERNMET XR) and approved (QTERN) labeling for these products already caution prescribers on use in elderly patients and individuals with renal impairment.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No carcinogenicity or genotoxicity studies were performed for these Applications. Studies of the individual drugs were deemed to be adequate for assessment of the carcinogenicity and genotoxicity of the combination. However, an imbalance in newly diagnosed cases of bladder cancers was observed across 22 clinical trials in the dapagliflozin (FARXIGA) clinical program and is labeled as a Warnings and Precaution. For the current NDA, malignancy was reported for three subjects (i.e., gastric neoplasm, pancreatic cancer with hepatic metastases, and invasive ductal breast carcinoma) receiving the FCDP. The latency between exposure and diagnosis for all three cases was relatively short (i.e., 54 to 137 days). I do not believe that these cases are related to IP.

8.8.2. Human Reproduction and Pregnancy

Women who were pregnant or breastfeeding were excluded from study participation in all trials. For dapagliflozin- and saxagliptin-containing products, there is limited experience in pregnant or lactating females. In the QTERNMET XR and QTERN clinical treatment arms, there was a single pregnancy reported for a subject (b) (6) randomized to the dapagliflozin 10 mg/saxagliptin 5 mg/metformin triple therapy arm in Trial CV181169. The subject was a 41-year-old White female who had a positive pregnancy test on Day 14, withdrew from study (Day 15) and declined any additional follow-up (site contacted subject after the expected due date). An additional subject (b) (6), a 28-year-old White female randomized to the dapagliflozin 10 mg/saxagliptin 5

mg/metformin triple therapy arm in Trial CV181365, had a spontaneous abortion on Day 527 (163 days after the last dose of IP), requiring uterine curettage. Her relevant history included T2D duration of 2.6 years and limited current tobacco use. Due to the onset of miscarriage more than five months after discontinuing study medication, this event is not likely to be related to IP.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant is requesting that the Agency waive the pediatric assessment requirements for these Applications. They noted that use of FCDPs is reported to be very low, in part due to the need for frequent dose adjustments in this population. A survey of available databases indicates that between 0.3% (236 out of 77,840 patients; Pharmetrics database) and 2.0% (149 out of 7670 patients; GE Medical database) of all identified pediatric patients with T2D are treated with antihyperglycemic FCDPs approved for use in adult patients. Market research data also indicate that the average time for adaptation of dosing or adding additional therapy in adults with T2D is greater than two years. In the United States, metformin is used as single antihyperglycemic medication for an average of 24.4 months before a sulfonylurea is added. Assuming this sort of delay in treatment intensification is also true for pediatric patients, very few pediatric patients would receive triple combination therapy before reaching 18 years of age. Due to the relatively low prevalence of T2D in the pediatric population, coupled with anticipation that there will be a small number of pediatric patients for whom treatment with three drugs will be appropriate, it is considered to be impossible or highly impractical to conduct a clinical study to appropriately evaluate either their dual or triple antihyperglycemic FCDP product in this patient population.

On February 27, 2017, at the time of approval of QTERN (i.e., the dapagliflozin 10 mg/saxagliptin 5 mg tablet formulation) the Agency waived the pediatric study requirement on the basis that the necessary studies would be impossible or highly impracticable to complete because the number of available patients for whom participation in such studies would be appropriate is expected to be very small. The same would be true of the new dose formulation of QTERN and any triple therapy FCDP studies, as the study populations would be identical (i.e., the studies supporting the original QTERN application were conducted on a background of metformin, thereby constituting a triple combination of dapagliflozin + saxagliptin + metformin). Therefore, the Applicant is requesting a waiver of the PREA requirement to conduct a clinical trial investigating the use of the proposed triple drug FCDP in pediatric patients.

It also is noted that no pediatric subjects were enrolled in the QTERNMET XR or QTERN clinical development programs. Further, pediatric clinical trials and/or assessments on growth and development for either of the dapagliflozin or saxagliptin components of these products have not been completed.

On April 3, 2019, PeRC reviewed NDA 210874, and agreed for full waiver of pediatric assessments as studies are impossible or highly impracticable, and this should be annotated in the Agreed iPSP

as such (i.e., the reasons for waiving pediatric assessments should not include: "the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups").

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant states that there is no data available related to overdose of the combination of dapagliflozin + saxagliptin + metformin. Additionally, the FDA Adverse Event Reporting System (FAERS) database was searched using Empirical Signal™ and the following MedDRA PTs: 'Accidental overdose'; 'Drug abuse'; 'Intentional overdose'; 'Intentional product misuse'; 'Overdose'; and 'Prescribed overdose'. Two postmarketing case reports (Form FDA 3500) associated with SAEs of overdose were identified that included the combination of dapagliflozin, saxagliptin and metformin. Brief narrative summaries are provided:

Overdose – Dapagliflozin plus Saxagliptin plus Metformin:

Case #15658451: A report was submitted by the Health Authorities of Germany via the Federal Institute for Drugs and Medical Devices. The case involved a 72-years-old male patient who experienced the following: nausea, insulin hypoglycemia, diabetic coma, reduced general condition, diabetic coma, overdose accidental, hypoglycemia and vomiting, while he was treated with insulin glulisine, saxagliptin and insulin (product not specified). His past medical history included tuberculosis with sequelae (i.e., respiratory system and unspecified tuberculosis), diabetes mellitus, hyperlipidemia and mental disorder. Concomitant medications included simvastatin, vitamin B_{12}, aspirin, amitriptyline, salbutamol, fluticasone furoate, vilanterol trifenatate, zolpidem, bisoprolol, hydrochlorothiazide, dapagliflozin, metformin and omeprazole. On an unknown date, the patient started taking insulin glulisine (dosage unknown) SC, oral saxagliptin tablet 5 mg daily (which was increased on an unknown day) and SC insulin solution for injection at a dose of 12 units daily. No indications or batch numbers were reported for any of the medications. On an unknown day (unknown latency) after administration of suspect products, the patient developed nausea, hypoglycemia, diabetic coma, reduced general condition, diabetes with coma, overdose accidental, hypoglycemia and vomiting. The patient developed a serious insulin-related hypoglycemia (hyperinsulinemic hypoglycemia) and was hospitalized for this event. Relevant laboratory test results included a blood glucose of 16 mg/dL. Insulin glulisine and insulin were discontinued on an unknown date; and the dose increased for saxagliptin. It was not reported if the patient received a corrective treatment, and no outcomes for any of the events were reported.

Case #12308298: A report was received from a study investigator from the United States concerning a 38-year-old subject of unknown gender, enrolled in Trial CV181365. Information regarding the medical history of the subject was not provided. Concomitant medication included metformin. Study therapy started on (b) (6) for T2D. An event of overdose was reported on (b) (6). The subject had taken two tablets/day of saxagliptin 5 mg/placebo, two tablet/day of dapagliflozin 10 mg/placebo, and four tablets/day (two from each bottle) of glimeperide from (b) (6). The investigator reported that subject did not experience any side effects or symptoms other than blood glucose concentrations were slightly lower. IP was continued. The subject recovered from the event of overdose on (b) (6). The investigator assessed the event of overdose to be serious due to meeting the criterion of an important medical event, and reported the event as causally related to IP.

The information provided in the above expedited safety reports (possible accidental and intentional overdose) does not contain adequate detail to properly evaluate causal associations between the events and suspect products. I feel that these case reports do not alter the known risk-benefit profile the proposed either QTERNMET XR or QTERN. Additionally, the only narrative provided in the CSR for Trial CV181365 involved a 44-year-old White male (Subject (b) (6)) randomized to the dapagliflozin + saxagliptin + metformin treatment arm who had an SAE of overdose reported on Day 202. He took two pills (one day only) from the same glimepiride/placebo-labeled bottle. He reported sweating and vomiting, and his study glucometer showed a glucose concentration of 110 mg/dL (his personal glucometer read 80 mg/dL). Symptoms resolved within 30 minutes following ingestion of orange juice. A repeat blood glucose measurement following treatment was not reported. The event was coded as moderate in intensity and assessed as related to IP. No action was taken with IP.

Based on the known pharmacological properties of dapagliflozin, saxagliptin, or metformin, the potential for overdose, drug abuse, withdrawal, or rebound, is unlikely. However, approximately 12% of cases of spontaneous hypoglycemia referred for investigation may be factitious (i.e., due to intentional/surreptitious misuse of antihyperglycemic agents, such as sulfonylureas).[224,225] Additionally, a literature search revealed a single case of persistent hypoglycemia due to misuse of a sulfonylurea in combination with the DPP-4 inhibitor vildagliptin,[226] as well as reports of unintentional and intentional exposures to DPP-4 inhibitors.[227-229] In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite (i.e., 5-hydroxy saxagliptin) can be removed by hemodialysis (i.e., approximately 23% of the dose over four hours).[4] No published reports associated with dapagliflozin overdose, abuse or misuse were readily identified, and removal of dapagliflozin by hemodialysis has not been studied.[3] However, in the dapagliflozin clinical development program, single doses up to 500 mg (50x MRHD) and multiple doses of up to 100 mg/day (10x MRHD) for two weeks, did not result in obvious/clinically meaningful drug-related AEs or laboratory abnormalities. With extensive use of metformin worldwide since the 1950s, cases of metformin overdose have been published in the medical literature,[230-264] including in combination with a DPP-4 inhibitor.[235]

According to the most recent Periodic Benefit-Risk Evaluation Report (PBRER, dated March 15, 2019) for NDA 209091 (QTERN), there were no new cases of overdoses reported during the reporting period (i.e., July 15, 2018 to January 14, 2019). Cumulatively there have been a total of 29 case reports of overdoses for 29 subjects in the clinical development program; 2 out of the 29 cases were reported as SAEs. The Applicant states that they are not aware of any pattern of use (for example overdose, drug abuse, misuse or off-label use) of QTERN considered to be relevant for the interpretation of safety data.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The QTERNMET XR FCDP is not approved in any country, and there is no postmarketing experience with this product. While dapagliflozin, saxagliptin and metformin are approved, clinical experience with the use of the combination of the three components outside of the clinical trial setting is limited. Additionally, QTERN has marketing approval in 41 countries worldwide, and is under review in an additional 10 countries. In the most recent PBRER (dated March 15, 2019) for this FCDP, the following actions for safety reasons were taken during the reporting period (July 15, 2018, to January 14, 2019):

- *Diabetic Ketoacidosis:* The Applicant has updated the QTERN Core Data Sheet (CDS) to include results from their CVOT (D1693C001; DECLARE) and information on the risk of DKA.
- *Fournier's gangrene:* A labeling change sNDA which included the addition of necrotizing fasciitis of the perineum (Fournier's gangrene) in the Warnings and Precautions section of product labeling was approved by the Agency on October 2018. However, based on existing data from the dapagliflozin development program, the Applicant has chosen not to include this information in the CDS.

During the reporting period, approximately 2248 subjects have received dapagliflozin plus saxagliptin in the QTERN development program, and post-approval exposure worldwide was estimated to be approximately 9364 p-y (4886 p-y during the reporting period). Based on my review of the information reported in the PBRER, I do not feel that the cumulative efficacy and safety information (e.g., nonclinical data, clinical trial experience, literature) alter the known benefit-risk profile of this FCDP or warrant major labeling changes.

8.9.2. Expectations on Safety in the Postmarket Setting

QTERNMET XR is intended for patients with T2D who have not met their glycemic treatment goals with metformin. The recommended starting dose of dapagliflozin is 5 mg once daily, with up-titration to the 10 mg dose in patients who are tolerating therapy but require additional glycemic control.[3] With approval of QTERNMET, there is the potential that this FCDP could be prescribed for patients who are metformin-naïve and have a predisposition to dose-related AEs, such as volume depletion or acute kidney injury (e.g., elderly, hypovolemic, renal insufficiency, heart failure). However, the Limitations of Use section in proposed labeling states that QTERNMET XR is intended only for patients currently taking metformin, and the dosage formulations for this product allow for initiating therapy with the lower dapagliflozin 5 mg dose.

Additionally, older patients with T2D who require additional glycemic control may be placed on QTERNMET XR AND QTERN. As discussed above, there is scant data with saxagliptin plus dapagliflozin as combination add-on therapy to metformin in this population. However, there is some data

from the individual components to suggest what might be expected in terms of safety. The ONGLYZA (saxagliptin) product labeling[4] notes that no overall difference in safety was observed between subjects ≥65 years old (which included 1210 saxagliptin-treated subjects ≥75 years old) and younger subjects; while the FARXIGA labeling reports a higher proportion of adverse events of volume depletion and renal impairment or failure in dapagliflozin-treated subjects ≥65 years of age (which included 207 subjects ≥75 years old). As the current proposed population is one already treated with (and presumably tolerating) metformin, concern related to metformin use is less relevant.

The main safety concern originally observed in the QTERN development program was an imbalance in the number of subjects who experienced marked serum CK elevations reported in the dapagliflozin/saxagliptin combination therapy arms and the case of rhabdomyolysis without an obvious cause. Although these laboratory abnormalities were typically asymptomatic, transient, confounded by concomitant medications (e.g., statin and/or fibrate use) and other potential etiologies (e.g., exercise, syncope), and did not require discontinuation of therapy, the potential risk of muscle injury/necrosis remains unknown. Since the original review of the QTERN NDA (b) (4) there have been no additional cases of either rhabdomyolysis, or marked laboratory CK abnormalities submitted to the current Applications. There also were no additional cases reported in the Applicant's pharmacovigilance program. I believe that this safety signal is adequately addressed with proposed labeling and with routine pharmacovigilance.

In conclusion, no risk evaluation and mitigation strategy is recommended for this product.

8.9.3. Additional Safety Issues from Other Disciplines

At the time of this review, no additional safety issues were identified by the other review disciplines that would affect regulatory decision-making, product labeling, or postmarketing requirements.

8.10. Integrated Assessment of Safety

The safety profile of QTERNMET XR reflects the safety profile of its components, i.e., dapagliflozin, saxagliptin and metformin. The most common adverse reactions (reported in >2% of subjects) in the Applicant's 3-study safety pool were upper respiratory tract infections (13.6%), urinary tract infections (5.7%), dyslipidemia (5.1%), headache (4.3%), diarrhea (3.7%), backpain (3.3%), genital infection (3%), and arthralgia (2.4%). Antihyperglycemic FCDPs have the potential for an increased risk of hypoglycemia compared to the individual components. In the 3-study safety pool the adjusted incidence of Level 2 hypoglycemia (defined as a plasma glucose <54 mg/dL) and Level 3 hypoglycemia (defined as at least one episode of neuroglycopenic symptoms requiring assistance of another person to actively administer carbohydrate or glucagon with prompt recovery, with blood glucose ≤70 mg/dL when measured) for the triple therapy arm were relatively low (i.e., 1% [5/492 subjects] and 0.2% [1/492 subjects], respectively), while a single

subject (0.3% [1/341 subjects] in the dapagliflozin/metformin arm had Level 2 hypoglycemia and no subjects in either the dapagliflozin/metformin arm or saxagliptin/metformin arm had Level 3 hypoglycemia. No subjects in any of the arms discontinued study medication due to hypoglycemia.

A somewhat unique finding in the pooled safety analysis identified at the time of approval for the original QTERN NDA was an imbalance in the number of subjects who experienced markedly elevated serum CK concentrations >10x ULN (a marker of muscle injury/necrosis) in the dapagliflozin + saxagliptin + metformin treatment arms. These marked laboratory changes were reported in seven (1.4%) dapagliflozin + saxagliptin + metformin-treated subjects compared to one subject (0.3%) randomized to dapagliflozin/metformin arm, and no subjects randomized to saxagliptin/metformin arm. These laboratory abnormalities were typically asymptomatic, transient (approximately two weeks in duration), and did not require discontinuation of therapy. However, rhabdomyolysis was reported for one of the five subjects with CK elevations, for whom no other obvious cause was identified. While this safety finding was flagged as a concern at the time of approval, it is reassuring that no further cases were seen with the additional patient exposure in the updated safety database. Additionally, review of the integrated safety data from the eight clinical trials did not identify any new safety concerns other than those already included or proposed in product labeling.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee (AC) was held to discuss the two Applications which are the subject of this review.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed labeling for QTERNMET XR and QTERN 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

Labeling was reviewed for consistency with recently approved labeling for FARXIGA[23] and XIGDUO XR,[5] and to remove reassuring language that might imply safety (e.g., ADA Level 1 hypoglycemia comparisons with glimepiride) and efficacy (e.g., CGM 2-week data comparisons with insulin

glargine) claims. The relevant labeling issues that are the subject of this review include:

- **Section 1 Indications and Usage:** To revise the indication to "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus".

- **Section 2.2 Patients with Renal Impairment:** To state that no dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m^2 and that use of QTERNMET XR and QTERN are contraindicated if the eGFR is <45 mL/min/1.73 m^2.

- **Section 6.1 Clinical Trials Experience:** To include safety information from Trial D1690C0024 in the Impairment of Renal Function section, as well as additional renal safety information from the Applicant's pool of 12 placebo-controlled trials.

- **Section 8.6 Renal Impairment:** To include information from Trials D1690C0024 and MB102029, and information on the use of saxagliptin and metformin with renal impairment.

- **Section 11 Description:** To include information to describe the exact saxagliptin salt equivalency in labeling (b) (4)

- **Section 14 Clinical Studies:** To revise the Applicant's primary and key secondary efficacy findings based on the Agency's preferred analytical approach and include data from Trial D1690C0024. Additionally, the Division decided not to include the results of Trials 181365 and 181369 in Section 14 of labeling for both QTERN and QTERNMET XR for the following reasons:
    - These trials are not necessary for the safe and effective use of the respective products.
    - There is lack of precedent for including a comparison of an antihyperglycemic FCDP with a completely different product in antihyperglycemic product labeling.
    - For Trial 181365, comparison between dapagliflozin and saxagliptin plus metformin vs. glimepiride plus metformin is not a fair comparison (i.e., three drugs vs. two), and the glimepiride dose was not required to be titrated up to the maximum approved dose (i.e., 8 mg).
    - For Trial 181369, dapagliflozin and saxagliptin plus metformin vs. insulin glargine plus metformin also is an unfair comparison as limited titration was to occur past week 8 and the relatively slow titration of two units every three days make it less likely that patients would have reached insulin treatment goals (i.e., target FPG of ≤100 mg/dL) by Week 8. It is notable that the mean FPG in the insulin glargine arm remained ≥137 mg/dL from Weeks 8 through 24.

The Division has recently made the decision to simplify labeling of antihyperglycemic FCDPs with the indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus".[265,266] This language will be recommended for both Applications. Labeling negotiations are ongoing at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable for these submissions.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the known safety profiles of dapagliflozin, saxagliptin and metformin, and the extensive use of these products worldwide since approval, no additional risk management strategies are required or planned beyond the recommended labeling.

12. Postmarketing Requirements and Commitments

No postmarketing requirements (PMRs) or commitments (PMCs) will necessary for these Applications.

13.Appendices

13.1. References

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13.2. Financial Disclosure

The Applicant submitted a Form FDA 3454 for 11 covered trials. They report six investigators with positive financial disclosures, and 24 investigators for which a signed Investigator Financial Interests and Disclosure Statement Form was never received. The six investigators with financial interest to disclose included:

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:

- (b) (6), an investigator for Trial CV181369 (anticipated site randomization was (b) (6) subjects), received $175,736.57 for consulting services.
- (b) (6) an investigator for Trial D1689C00014 (anticipated site randomization was (b) (6) subjects) received in total $42,578.04 as honoraria, and financial reimbursement, research and development, and travel and expense costs.

Significant payments of other sorts:

- (b) (6) an investigator for Trial D1683C00005 (anticipated site randomization was (b) (6) subjects) received $76,081.72 for honoraria.
- (b) (6), and investigator for Trial D1683C00005 (anticipated site randomization was (b) (6) subjects) received $50,000 as a member of the Speaker Bureau.
- (b) (6), and investigator for Trials D1683C00005 (anticipated site randomization of (b) (6) subjects) and D1689C00014 (anticipated site randomization of (b) (6) subjects) received $223,773.60 as honoraria, and financial reimbursement, research and development, and travel and expense costs.

Significant equity interest held by investigator in Study Sponsor(s) (stock, stock options, or other financial interest):

- (b) (6) an investigator for Trial CV181365 (anticipated site randomization of (b) (6) subjects) holds (b) (6) shares of stock at a total monetary value of $54,232.80.

Based on review of these data and the relatively low numbers of randomized subjects at the respective trial sites, I do not feel that there was undue bias/influence that could affect the outcome of these trials.

Covered Clinical Study (Name and/or Number): CV181017, CV181168, CV181169, CV181191, CV181363, CV181365, D168AC00001, D1683C00005,

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 28 (6 with disclosable interests.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study Sponsor(s) (stock, stock options, or other financial interest) that exceeds $50,000.00 U.S. dollars: 1 Sponsor of covered study: CV181365, CV181369,		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 24		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Antihyperglycemic Products Approved in the United States

Table 29: 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	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.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			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 miglitol is not recommended.	**DISADVANTAGES:** • Generally modest HbA1c efficacy; gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[42,44]
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 because 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 tid) 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.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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; gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[42,44]
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 ($AUC_{0\text{-}INF}$) and peak (C_{max}) 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.

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 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 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; training requirements; and expense.[42,44]
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) 21591 (September 11, 2003)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older (product specific) 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.	• 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.	**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,

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 **GLUCOVANCE** (glyburide + metformin)	021178 (July 31, 2000)	• 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 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.	• 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 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.	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 m^2, known hypersensitivity to metformin (or components of combination product), metabolic acidosis, including diabetic ketoacidosis with or without coma. **WARNINGS AND PRECAUTIONS:** • Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. • Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required. **DISADVANTAGES:** • Gastrointestinal side effects (diarrhea, abdominal cramping); lactic acidosis risk (rare); vitamin B_{12} deficiency; multiple contraindications.[42,44]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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. The starting dose of glipizide/metformin should not exceed the daily doses of glipizide (or equivalent dose of another sulfonylurea) 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 in divided doses.		*Also, refer to Sulfonylureas for sulfonylurea-containing FCDPs and to DPP-4 inhibitors for DPP-4 inhibitor plus metformin-containing FCDPs.*
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	**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,

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			(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.	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 (e.g., fat-soluble vitamins). • Oral Suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet. **DISADVANTAGES:** • Generally modest HbA1c efficacy; constipation; increase in triglycerides; and may decrease the absorption of other medications.[44]
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)	**No dosage adjustments are provided in product labeling (has not been studied).** • 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

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				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 for other indications. **DISADVANTAGES:** Generally modest HbA1c efficacy; dizziness/syncope; nausea; fatigue; and rhinitis.[44]
DPP-4 Inhibitors				
JANUVIA (sitagliptin) *Combination Products* **JANUMET** (sitagliptin + metformin)	021995 (October 16, 2006) 022044 (March 30, 2007)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • 100 mg orally once daily. **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	**FOR SITAGLIPTIN MONOTHERAPY:** **eGFR >45 mL/min/1.73 m^2: No dosage adjustment necessary.** **eGFR ≥30 to <45 mL/min/1.73 m^2: 50 mg once daily.** **eGFR <30 mL/min/1.73 m^2: 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	**CONTRAINDICATIONS:** • History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to one of the product components. • Metabolic acidosis, including diabetic ketoacidosis (for JANUMET and JANUMET XR; Boxed Warning). **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.

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JANUMET XR (sitagliptin + metformin extended-release)	202270 (February 2, 2012)	receive an initial dose of sitagliptin 50 mg and metformin 1000 mg twice daily. **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.	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 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.*	• 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. • Metformin may lower Vitamin B12 levels (JANUMET and JANUMET XR). • 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. • 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

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				effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class.[42,44] *Also, refer to Biguanides for metformin-containing FCDPs.*
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	**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.**	**JUVISYNC CONTRAINDICATIONS:** • Concomitant administration of strong CYP3A4 inhibitors, gemfibrozil, cyclosporine, or danazole. • Active liver disease. • Pregnancy or nursing. *Also, refer to product labeling for simvastatin-containing products and SGLT2 Inhibitors for ertugliflozin-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 <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 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.	**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. • Metabolic acidosis, including diabetic ketoacidosis (for KAZANO; Boxed Warning). **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis. • Heart failure: consider the risks and benefits of NESINA prior to initiating

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			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.	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. • Dose-related edema may occur (for OSENI). • Increased incidence of fractures in female patients (for OSENI) • May increase the risk of bladder cancer (for OSENI). • Metformin may lower Vitamin B12 levels (for KAZANO). • 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.

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: 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.[42,44]
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.**	**KAZANO BOXED WARNING:** Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. *Also, refer to Biguanides for metformin-containing FCDPs.*
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.*	**OSENI BOXED WARNING:** .Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. **OSENI CONTRAINDICATION:** • Initiation in patients with established NYHA Class III or IV heart failure. *Also, refer to Thiazolidinediones for pioglitazone-containing FCDPs.*
ONGLYZA (saxagliptin)	022350 (July 31, 2009)	**INDICATION:**	**FOR SAXAGLIPTIN MONOTHERAPY:** **CrCl >50 mL/min: No dosage adjustment is recommended.**	**CONTRAINDICATIONS:** • eGFR <30 mL/min/1.73 m^2 (for KOMBIGLYZE XR).

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		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., ketoconazole.	**CrCl ≤50 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).** • 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 (N=8 per group) compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. The degree of renal impairment did not affect the Cmax of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of	• Metabolic acidosis, including diabetic ketoacidosis (for KOMBIGLYZE XR). • History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to saxagliptin or metformin (for KOMBIGLYZE XR). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (for KOMBIGLYZE XR). • Pancreatitis. • Heart failure: Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. • Vitamin B12 Deficiency (for KOMBIGLYZE). • 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.

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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.	saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than the AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal 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 <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 <45 mL/min/1.73 m^2.** **Limit the saxagliptin component to 2.5 mg daily if eGFR is <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*	• 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).[42,44] *Also, refer to Biguanides for metformin-containing FCDPs and to SGLT2 Inhibitors for dapagliflozin-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. • 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.	**CONTRAINDICATIONS:** • eGFR <30 mL/min/1.73 m^2 (for JENTADUETO and JENTADUETO XR). • Metabolic acidosis, including diabetic ketoacidosis (Boxed Warning for JENTADUETO and JENTADUETO XR). • History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperactivity, or to metformin for JENTADUETO and JENTADUETO XR). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (for JENTADUETO and JENTADUETO XR). • There have been postmarketing reports of acute pancreatitis, 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,
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.	**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.**	

JENTADUETO XR (linagliptin + metformin extended-release)	208026 (May 27, 2016)	• 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. **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.	**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.** *Also, refer to Biguanides for metformin-containing FCDPs and SGLT2 inhibitors for empagliflozin-containing FCDRs.*	angioedema, and exfoliative skin conditions. • Vitamin B_{12} deficiency. • 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.[42,44] *Also, refer to SGLT2 inhibitors for empagliflozin-containing FCDPs*

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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 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.	**FOR LIXISENATIDE MONOTHERAPY:** **eGFR ≥30 to 89 mL/min/1.73 m²: 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.** **eGFR 15 to 29 mL/min/1.73 m²: 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 m²: 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 m²) 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	**CONTRAINDICATIONS:** • During episodes of hypoglycemia (for SOLIQUA). • Hypersensitivity to lixisenatide or any product components or insulin glargine (for SOLIQUA). **WARNINGS AND PRECAUTIONS:** • Anaphylaxis and serious hypersensitivity reactions. • Pancreatitis. • Never share ADLYXIN or SOLIQUA pen between patients, even if the needle is changed. • Hypoglycemia with concomitant use of sulfonylurea or basal insulin. • Hyperglycemia or hypoglycemia with changes in SOLIQUA regimen. • Hypoglycemia: May be life-threatening (for SOLIQUA). • Overdose due to mediation errors (for SOLIQUA). • Acute kidney injury. • Immunogenicity. • Hypokalemia: May be life-threatening (for SOLIQUA). • Fluid retention and heart failure with use of thiazolidinediones (for SOLIQUA). **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea);
Combination Products **SOLIQUA** (insulin glargine + lixisenatide)	208673 (November 21, 2016)	**SOLIQUA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inject once a day within the hour prior to the first meal of the day. • SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. • Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). • Discontinue basal insulin or GLP-1 receptor agonist prior to initiation. • In patients naïve to basal insulin or to a GLP-1 receptor agonist, inadequately controlled on less than 30 units of basal insulin or on a GLP-1 receptor agonist, the starting dosage is 15 units (15 units insulin glargine/5 mcg		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		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 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.	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 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.	increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[42,44]
BYDUREON (exenatide extended-release) **BYDUREON BCISE** (exenatide extended-release)	022200 (January 27, 2012) 209210 (October 20, 2017)	**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.	**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	**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-

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BYETTA (exenatide)	021919 (October 30, 2009)	**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 more apart. • Initiate 5 mcg per dose twice daily; increase to 10 mcg twice daily after one month based on clinical response.	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 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.	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:** • 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 injury: May induce nausea and vomiting with transient hypovolemia and may worsen renal functions. Postmarketing increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation has been reported. Not recommended if patient with and eGFR <45 mL/min/1.73 m^2. • Gastrointestinal disease: Not recommended in patients with

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				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. • Acute gallbladder disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. **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.[42,44]
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.	**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	**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

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		• 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.	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.	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. • Acute kidney injury. **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.[42,44]
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.	**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	**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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• 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.	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.	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. • Acute kidney injury. **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.[42,44]
VICTOZA (liraglutide)	022341 (January 25, 2010)	**INDICATION:**	**No dosage adjustments are provided in product labeling; however, use with caution, due to reports of acute renal failure and exacerbation of chronic renal**	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is

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Combination Products **XULTOPHY** (insulin degludec/liraglutide)	208583 (November 21, 2016)	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 **XULTOPHY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Discontinue therapy with liraglutide or basal insulin prior to initiation of XULTOPHY 100/3.6. • Recommended starting dose in patients naïve to basal insulin or GLP-1 receptor agonist is 10 units (10 units of insulin degludec and 0.36 mg of liraglutide) given subcutaneously once-daily. • Recommended starting dose in patients currently on basal insulin or GLP-1 receptor agonists is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once-daily.	**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 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.	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:** • During episodes of hypoglycemia (for XULTOPHY). • 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 VICTOZA or XULTOPHY pen between patients, even if the needle is changed. • 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.

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		• 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. • 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.		• Hyper- or hypoglycemia with changes in XULTOPHY 100/3.6 regimen. • Overdose due to mediation errors (for XULTOPHY). • Hypoglycemia: May be life-threatening (for XULTOPHY). • Acute kidney injury: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. • Hypersensitivity and allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur). • Acute gallbladder disease: If cholelithiasis or cholecystitis are suspected gallbladder studies are indicated. • Hypokalemia: May be life-threatening. **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.[42,44]

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Insulins and Insulin Analogues				
Rapid-Acting Analogs **ADMELOG** (insulin lispro) **AFREZZA** (inhaled insulin human) **APIDRA** (insulin glulisine) **FIASP** (insulin aspart) **HUMALOG** (insulin lispro) **NOVOLOG** (insulin aspart) *Short-Acting* **HUMULIN R** (insulin human) **NOVOLIN R** (insulin human) *Intermediate-Acting* **HUMULIN N** (insulin isophane) **NOVOLIN N** (insulin isophane)	209196 (December 11, 2017) 022472 (June 27, 2014) 021629 (April 16, 2004) 208751 (September 29, 2017) 020563 (June 14, 1996) 020986 (June 7, 2000) 018780 (October 28, 1982) 019938 (June 25, 1991) 018781 (October 28, 1982) 19959 (July 1, 1991)	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 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.[42] ***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). Insulin aspart, insulin glulisine, insulin lispro, and regular	**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.** • In adults, the following adjustments have been previously suggested for insulin products:[267,268] — 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	**CONTRAINDICATIONS (AFREZZA):** • Patients with chronic lung disease (e.g., asthma, COPD) for AFREZZA. • During episodes of hypoglycemia. • Hypersensitivity to insulin product or one of the excipients. **WARNINGS AND PRECAUTIONS:** • Never share insulin pen injectors, syringes, or needles. • Acute bronchospasm (for AFREZZA). • Decline in pulmonary function (for AFREZZA). • Lung cancer (for AFREZZA). • Diabetic ketoacidosis (for AFREZZA). • Hyper- or hypoglycemia (e.g., with changes in insulin regimen). • Hypoglycemia: may be life-threatening. • Medication errors. • Hypersensitivity reactions. • Hypokalemia: may be life-threatening. • Fluid retention and heart failure with concomitant use of thiazolidinediones. **DISADVANTAGES:** Hypoglycemia, weight gain, uncertain mitogenic effects, injectable (except inhaled insulin), patient and provider reluctance, training requirements,

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Basal Analogs **BASAGLAR** (insulin glargine) **LANTUS** (insulin glargine) **LEVEMIR** (insulin detemir) **LUSDUNA** (insulin glargine) **TOUJEO** (insulin glargine) **TRESIBA** (insulin degludec) *Combination Products* **HUMALOG MIX** (insulin lispro protamine + insulin lispro) **NOVOLOG MIX** (insulin aspart protamine + insulin aspart) **RYZODEC** (insulin degludec + insulin aspart)	205692 (August 18, 2014) 021081 (April 20, 2000) 021536 (June 16, 2005) 208722 ***(Tentative Approval-July 19, 2017)*** 206538 (February 25, 2015) 203314 (September 25, 2015) 021017 (December 22, 1999) 021018 December 22, 1999 021172 (November 1, 2001) 203313 (September 25, 2015)	insulin also are labeled for intravenous (IV) administration. • **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 and ADMELOG:** Administer within 15 minutes before a meal or immediately after a meal. **NOVOLOG:** Administer within 5-10 minutes before a meal. • **For short-acting (SC):** **HUMULIN R and NOVOLIN R:** Administer approximately 30 minutes before a meal.	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.[269,270]	pulmonary toxicity (inhaled insulin).[42,44] May require a reduction in dose with renal or hepatic impairment. Spirometry (FEV_1) testing prior to and after starting inhaled insulin therapy. Hyperglycemia and ketoacidosis may occur due to insulin pump device malfunction.

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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.	**FOR PRANDIN MONOTHERAPY:** **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 (CrCl 20-40 mL/min).** • 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 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.	**CONTRAINDICATIONS:** • Metabolic acidosis, including diabetic ketoacidosis (for PRANDIMET). • Coadministration of gemfibrozil. • Known hypersensitivity to the drug or its inactive ingredients. • Severe renal impairment (eGFR <30 mL/min/1.73 m^2 for PRANDIMET). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (Boxed Warning for PRANDIMET). • Hypoglycemia. • Use with caution in patients with moderate to severe liver disease because such patients have not been studied. • Vitamin B12 deficiency (for PRANDIMET). • Serious cardiovascular adverse reactions with concomitant NPH insulin (for PRANDIMET). **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[42,44] *Also, refer to Biguanides for metformin-containing FCDPs.*

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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.	**For PRANDIMET:** **Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).** **Contraindicated in patients with eGFR <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.** *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 dose is 120 mg three times daily before meals. • The recommended dose is 60 mg three times daily before meals in patients who are near glycemic goal when treatment is initiated.	**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	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug or its inactive ingredients. **WARNINGS AND PRECAUTIONS:** • Not indicated for use in combination with NPH-insulin. • Hypoglycemia. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[42,44]

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			and patients with T2D, nateglinide plasma 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.	
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 ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR <45 mL/minute/1.73 m^2: Use is not recommended.** **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 of dapagliflozin 10 mg.	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to product or components. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis for FARXIGA and XIGDUO XR, and eGFR <45 mL/min/1.73 m^2 (for QTERN and QTERNMET XR). • Acute or chronic metabolic acidosis, including diabetic ketoacidosis (for XIGDUO XR and QTERNMET XR). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (Boxed Warning for XIGDUO XR and QTERNMET XR). • Pancreatitis (for QTERN and QTERNMET XR).

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			• 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 T2D with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.	• Heart failure (for QTERN and QTERNMET XR). • Hypotension: Before initiating dapagliflozin-containing products, 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.[271,272] • Acute kidney injury and impairment in renal function. • Urosepsis and pyelonephritis. • Hypoglycemia: In patients taking insulin or an insulin secretagogue with dapagliflozin-containing products, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. • Necrotizing fasciitis of the perineum (Fournier's gangrene). • Hypersensitivity reactions (e.g., urticaria, facial edema for QTERN). • Vitamin B_{12} deficiency (XIGDUO XR and QTERNMET XR). • Genital mycotic infections. • Increased LDL-C. • Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin-containing products should not be used in patients with active bladder

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				cancer and should be used with caution in patients with a prior history of bladder cancer. • Arthralgia: Severe disabling arthralgia has been reported in patients taking DPP-4 inhibitors (for QTERN and QTERNMET XR). • Bullous pemphigoid (for QTERN and QTERNMET XR). **DISADVANTAGES:** • Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[42,44] *Also, refer to DPP-4 inhibitors for saxagliptin-containing FCDPs and Biguanides for metformin-containing FCDPs.*
Combination Products **QTERN** (dapagliflozin + saxagliptin)	209091 (February 27, 2017)	**INDICATION (approval pending):** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Assess renal function before initiation of therapy and periodically thereafter. • Take once daily in the morning with or without food. • For patients not taking dapagliflozin, the recommended starting dose is 5 mg dapagliflozin/5 mg saxagliptin once daily.	**FOR QTERN (approval pending):** **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.**	

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Increase to 10 mg dapagliflozin/5 mg saxagliptin for patients tolerating 5 mg dapagliflozin/5 mg saxagliptin who require additional glycemic control. • Do not coadminister with strong cytochrome P450 3A4/5 inhibitors. • Swallow whole. Do not cut, crush or chew.		
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. • Assess renal function before initiating. Do not initiate or continue if eGFR is below 45 mL/min/1.73 m^2. • 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. • For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily. • Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release.	**FOR XIGDUO XR:** **eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR <45 mL/minute/1.73 m^2: Use is not recommended.** **eGFR <30 mL/minute/1.73 m^2, ESRD, or hemodialysis: Use is contraindicated.**	**XIGDUO XR BOXED WARNING:** • Lactic acidosis. *Also, refer to Biguanides for metformin-containing FCDPs.*

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• No dosage adjustment is indicated in patients with eGFR ≥45 mL/min/1.73 m^2. • XIGDUO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.		
QTERNMET XR (dapagliflozin + saxagliptin + metformin extended-release)	210874 (approval pending)	**INDICATION (approval pending):** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Assess renal function before initiation of therapy and periodically thereafter. • Individualize the starting total daily dose based on the patient's current regimen, effectiveness, and tolerability. • Take once daily in the morning with food. • For patients currently taking dapagliflozin, the recommended starting total daily dose is 5 mg dapagliflozin/5 mg saxagliptin/1000 mg or 2000 mg metformin once daily in the morning with food for patients not currently taking dapagliflozin. • The maximum recommended daily dose is 10 mg dapagliflozin/5 mg saxagliptin/metformin 2000 mg metformin. • Swallow whole. Do not cut, crush or chew.	**FOR QTERNMET XR (approval pending):** **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.**	**QTERNMET XR BOXED WARNING:** • Lactic acidosis. *Also, refer to Biguanides for metformin-containing FCDPs and DPP-4 Inhibitors for saxagliptin-containing FCDPs.*

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Discontinue at the time of, or prior to, an iodinated contrast imaging procedure. • Initiation is intended only for patients currently taking metformin.		
INVOKANA (canagliflozin)	204042 (March 29, 2013)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. • The recommended starting dose is 100 mg once daily, taken before the first meal of the day. • 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. • Assess renal function before initiating and periodically thereafter. • Limit the dose of INVOKANA to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 m^2. • Initiation or use is not recommended if eGFR is <45 mL/min/1.73 m^2.	**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.** **eGFR <45 mL/minute/1.73 m^2: Use not recommended when eGFR is persistently <45 mL/minute/1.73 m^2.** **Consider another antihyperglycemic agent in patients with an eGFR <45 to <60 mL/min/1.73 m2 receiving concurrent therapy with a UDP-glucuronosyl transferase (UGT) enzyme inducer.** **eGFR <30 mL/minute/1.73 m^2, ESRD or patients on dialysis: 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.	**INVOKANA/INVOKAMET /INVOKAMET 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 the leg. • Lactic acidosis (Boxed Warning for INVOKAMET and INVOKAMET XR). **CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to Product and components. • End-stage renal disease, dialysis or eGFR <30 mL/minute/1.73 m^2 (for INVOKANA) or <45 mL/min/1.73 m^2 (for INVOKAMET and INVOKAMET XR). • Metabolic acidosis, including diabetic ketoacidosis (for INVOKAMET and INVOKAMET XR). **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.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			• 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 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.	• Ketoacidosis.[271,272] • Acute kidney injury. • 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. • Necrotizing fasciitis of the perineum (Fournier's gangrene). • Genital mycotic infections. • Hypersensitivity reactions. • Bone fracture: Consider factors that contribute to fracture risk before initiating canagliflozin-containing products. • Vitamin B_{12} deficiency (for INVOKAMET and INVOKAMET XR). • Increased LDL-C. **DISADVANTAGES:** Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[42,44] *Also, refer to Biguanides for metformin-containing FCDPs.*
Combination Products **INVOKAMET** (canagliflozin + metformin)	204353 (August 8, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both	**FOR INVOKAMET AND INVOKAMET XR:** **Contraindicated in patients with an estimated eGFR <45 mL/min/1.73 m^2.**	**INVOKAMET BOXED WARNING:** • Lactic acidosis. *Also, refer to Biguanides for metformin-containing FCDPs.*

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		canagliflozin and metformin is appropriate. Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. • Assess renal function before initiating and periodically thereafter. • In patients with volume depletion not previously treated with canagliflozin, normalize volume status before initiating. • The starting dose is based on the patient's current regimen. • The recommended starting dose of canagliflozin is 50 mg twice daily and metformin HCl 500 mg twice daily. • Canagliflozin dose can be increased to 300 mg daily in patients tolerating canagliflozin 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 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.	**Limit the dose of canagliflozin component to 100 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.**	
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		**INVOKAMET XR BOXED WARNING:** • Lactic acidosis.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		canagliflozin and metformin is appropriate. Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. • Assess renal function before initiating and periodically thereafter. • Individualize based on the patient's current regimen. • Take two tablets once daily with the morning meal. Swallow whole. Never crush, cut, or chew. • 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 exceed a total daily canagliflozin dose of 300 mg.		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Gradually escalate metformin dose to reduce the gastrointestinal side effects while not exceeding a total daily dose of 2000 mg.		
JARDIANCE (empagliflozin)	204629 (August 1, 2014)	**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. • Assess renal function before initiating. • Do not initiate if eGFR is <45 mL/min/1.73 m^2. • 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.	FOR EMPAGLIFLOZIN MONOTHERAPY: **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, ESRD, or 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. • 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	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to product or components. • End-stage renal disease, dialysis or eGFR <30 mL/minute/1.73 m^2 (for JARDIANCE) and <45 mL/min/1.73 m2 (for SYNJARDY and SYNJARDY XR). • Metabolic acidosis, including diabetic ketoacidosis (for SYNJARDY and SYNJARDY XR). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (Boxed Warning for SYNJARDY and SYNJARDY XR). • Pancreatitis (for GLYXAMBI). • Heart failure (for GLYXAMBI). • Hypotension: Before initiating empagliflozin-containing products, assess and correct volume status in patients with renal impairment, the elderly, in patients with low SBP, and in patients on diuretics. • Ketoacidosis.[271,272] • 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			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. • Necrotizing fasciitis of the perineum (Fournier's gangrene). • Genital mycotic infections. • Hypersensitivity reactions. • Increased LDL-C. • Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors (for GLYXAMBI). • Bullous Pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors (for GLYXAMBI). • Vitamin B_{12} deficiency (for SYNJARDY and SYNJARDY XR). **DISADVANTAGES:** Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[42,44]
Combination Products **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 once	**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 DPP-4 inhibitors for linagliptin-containing FCDPs.*	

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, taken in the morning, with or without food. • Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily. • Assess renal function before initiating.		
SYNJARDY (empagliflozin + metformin)	206111 (August 26, 2015)	**SYNJARDY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and metformin is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • 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 gastrointestinal side effects due to metformin. • Assess renal function before initiating.	**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.** **May need to discontinue at time of, or prior to, iodinated contrast imaging procedures.** *Also, refer to Biguanides for metformin-containing FCDPs.*	**SYNJARDY BOXED WARNING:** • Lactic acidosis.
SYNJARDY XR (empagliflozin + metformin extended-release)	208658 (December 9, 2016)	**SYNJARDY XR INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and metformin is appropriate.	**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.**	**SYNJARDY XR BOXED WARNING:** • Lactic acidosis.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • Individualize the starting dose of based on the patient's current regimen. • The maximum recommended total daily dose is 25 mg empagliflozin/2000 mg metformin. • Take once daily with a meal in the morning, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin. • Assess renal function before initiating.	**May need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.** *Also, refer to Biguanides for metformin-containing FCDPs.*	
STEGLATRO (ertugliflozin)	209803 (December 19, 2017)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended dose is 5 mg once daily, taken in the morning, with or without food. • Dose may be increased to 15 mg once daily. • Assess renal function before initiating.	**FOR STEGLATRO, STEGLUJAN, AND SEGLURMET:** **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 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.** • In a Phase 1 clinical pharmacology study in patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg STEGLATRO, the mean increases in AUC of ertugliflozin were 1.6-, 1.7-, and 1.6-fold, respectively, for mild, moderate and severe renally impaired patients, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically meaningful. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment.	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to product or components. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. • Metabolic acidosis, including diabetic ketoacidosis (for SEGLUROMET). **WARNINGS AND PRECAUTIONS:** • Lactic acidosis (Boxed Warning for SEGLUROMET). • Pancreatitis (for STEGLUJAN). • Hypotension: Before initiating STEGLATRO, assess and correct volume status in patients with renal impairment, the elderly, and in patients on diuretics. • Ketoacidosis.[271,272]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			Also, refer to Biguanides for metformin-containing FCDPs and to DPP-4 inhibitors for linagliptin-containing FCDPs.	• Acute kidney injury and impairment in renal function. • Urosepsis and pyelonephritis. • Lower limb amputation. • Heart failure (for STEGLUJAN). • Necrotizing fasciitis of the perineum (Fournier's gangrene). • Hypoglycemia: Consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination. • Genital mycotic infections. • Hypersensitivity (for STEGLUJAN). • Vitamin B_{12} deficiency (for SEGLUROMET). • Increased LDL-C. • Pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors (for STEGLUJAN).
STEGLUJAN (ertugliflozin + sitagliptin)	209805 (December 19, 2017)	As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both ertugliflozin and sitagliptin is appropriate. • Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food.		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. • Assess renal function before initiating and periodically thereafter.		
SEGLUROMET (ertugliflozin + metformin)	209806 (December 19, 2017)	As an adjunct to diet and exercise to improve glycemic control in adults with T2D who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin. • Individualize the starting dose based on the patient's current regimen. • Maximum recommended dose is 7.5 mg ertugliflozin/1000 mg metformin twice daily. • Take twice daily with meals, with gradual dose escalation.		**SEGLUROMET BOXED WARNING:** • Lactic acidosis.
Sulfonylureas				
DIABINESE (chlorpropamide)	011641 (October 28, 1958; Discontinued)	**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.	**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.** **Alternate recommendations:** **eGFR >50 mL/min: Administer 50% of the recommended dose.[267]** **eGFR ≤50 mL/min, hemodialysis, peritoneal dialysis, or CRRT: Avoid use.[267]** • Chorpropamide undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as	**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, can produce severe hypoglycemia, which may result in coma, and may require hospitalization.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• 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).	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 affects 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.	• 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 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.[273] 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. Data to support this association are limited, and several studies, including a large

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				prospective trial (UKPDS, 1998)[38] have not supported an association. **DISADVANTAGES:** Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[44]
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. • Use 1 mg starting dose and titrate slowly in patients at increased risk for hypoglycemia (e.g., elderly, patients with renal impairment).	**FOR GLIMEPIRIDE MONOTHERAPY:** **The initial dose is 1 mg once daily with renal impairment; with careful titration based on FBG concentrations.** **May consider an alternative antihyperglycemic agent if eGFR <15 mL/min/1.73 m^2.[274]** • 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 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	**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). • 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. Data to support this association are limited, and several studies, including a large

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			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 that the elimination of the two major metabolites was reduced in patients with renal impairment. • *Also, refer to thiazolidinediones for TZD-containing FCDPs.*	prospective trial (UKPDS, 1998)[38] have not supported an association. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[42,44]
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.	**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.**	**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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• 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.	**A reduced dose may be necessary,[274] and a 50% reduction in dose has been suggested with an eGFR ≤50 mL/min.[267]** **Avoidance of the sustained-release formulation has also been suggested.[275]** • 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.*	increased CV mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce 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 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[44]
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. • 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		**GLUCOTROL XL CONTRAINDICATIONS:** • Known hypersensitivity to glipizide or any of the product's ingredients. • Hypersensitivity to sulfonamide derivatives. **GLUCOTROL XL WARNINGS AND 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.

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 lowest recommended dose, and observe patients for hypoglycemia.		• Hemolytic anemia: Can occur if G6PD deficient. • Cardiovascular mortality: Potential increased risk of cardiovascular mortality with sulfonylureas. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association.
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 not recommended.	**FOR GLYBURIDE MONOTHERAPY:** **There are no specific dosage adjustments provided in product labeling; however, use in patients with eGFR <60 mL/minute is not recommended.**[274] • 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. *Also, refer to Biguanides for metformin-containing FCDPs.*	**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. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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 delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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.		**DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[44] **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. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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, coumarins, 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**	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • DKA, with or without coma

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.	**are recommended because tolazamide is metabolized to active metabolites, which are eliminated in the urine.** • 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.	• 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. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce 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 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.

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				• 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.[44]
(Tolbutamide)	A086445† (April 10, 1979)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults 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	**There is no dosage adjustment provided in product labeling for patients with renal impairment; however, conservative initial and maintenance doses are recommended.** **Hemodialysis: Tolbutamide is not dialyzable (0% to 5%).** • Tolbutamide undergoes hepatic via CYP2C9 to hydroxymethyltolbutamide (mildly active) and carboxytolbutamide (inactive) and has an elimination	**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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		tolbutamide tablets should be done conservatively.	half-life of 4.5-6.5 hours. Approximately 75-85% is eliminated in the urine, primarily as metabolites.	plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[38] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce 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 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,

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[44]
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)	**ACTOS INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D in multiple clinical settings. • Initiate ACTOS at 15 mg or 30 mg once daily. Limit initial dose to 15 mg once daily in patients with NYHA Class I or II heart failure. If there is inadequate glycemic control, the dose can be increased in 15 mg increments up to a maximum of 45 mg once daily. Obtain liver tests before starting ACTOS. If abnormal, use caution when treating with ACTOS, investigate the probable	**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	**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.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		ause, treat (if possible) and follow appropriately.	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 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. Caution should also be advised with the use of pioglitazone in patients with underlying renal impairment who may already be at risk of volume overload. *Also, refer to Biguanides for metformin-containing FCDPs, DPP-4 inhibitors for alogliptin-containing FCDPs, and Sulfonylureas for glimepiride-containing FCDPs.*	**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 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.

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 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 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 or any other antidiabetic drug. **DISADVANTAGES:** Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[42,44]
AVANDIA (rosiglitazone) *Combination Products* **AVANDAMET** (rosiglitazone + metformin) **AVANDARYL** (rosiglitazone + glimepiride)	021071 (May 25, 1999) 021410 (October 10, 2002) 021700 (November 23, 2005)	**AVANDIA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. • Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention.	**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.	**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

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 initiate Avandia if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels.	• 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. Patients should be monitored for signs and symptoms of heart failure. Caution should also be advised with the use of rosiglitazone in patients with underlying renal impairment who may already be at risk of volume overload. 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.*	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:** • 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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. **DISADVANTAGES:** • Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[44]

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.

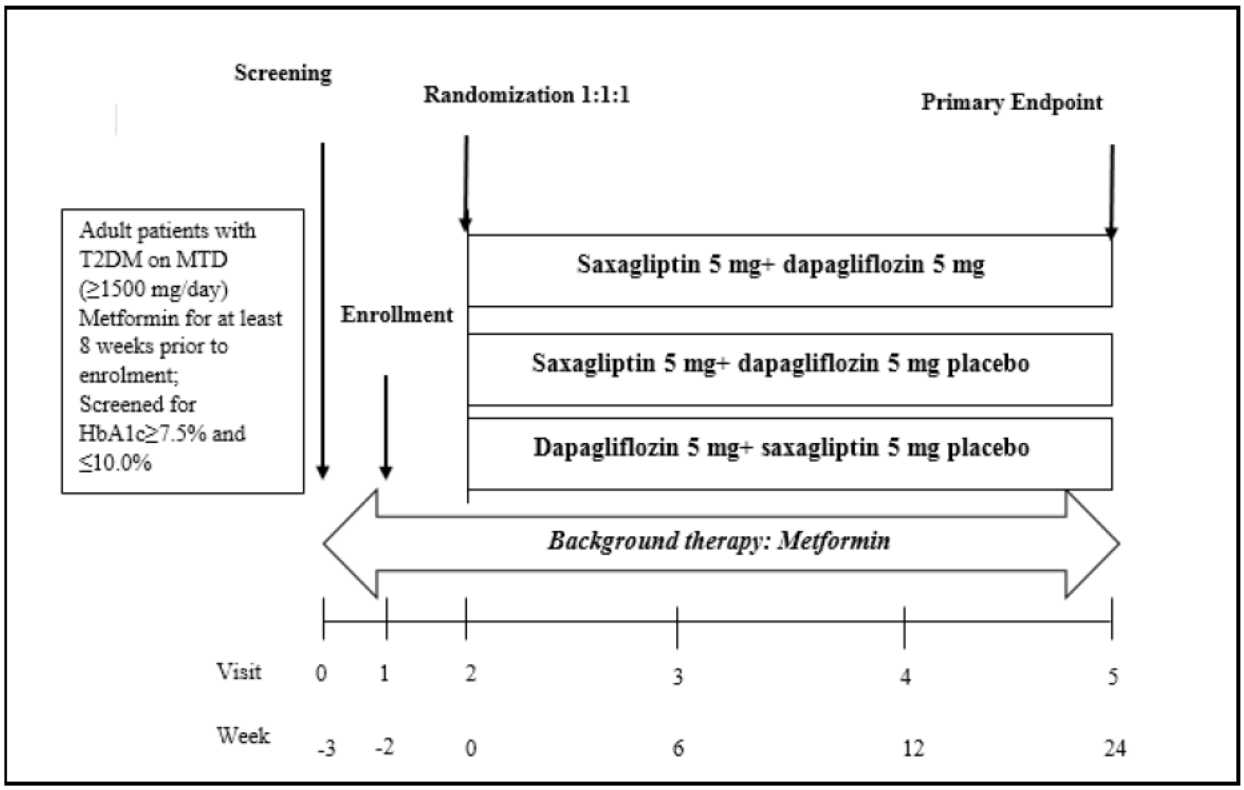
†Dosing guidelines for the mono-component of the FCDP, except in the case of JUVISYNC (sitagliptin + simvastatin).
¶Reference Listed Drug (RLD); approved under an Abbreviated New Drug Application (ANDA).
‡Contraindications and Warnings and Precautions relate to the mono-component of the FCDP unless specified otherwise

13.4. Study Designs for the Relevant Phase 3 Trials

The study designs for the five Phase 3 clinical trials relevant to the efficacy of NDA 210874 and NDA 209091/S-002 are presented below.

Trial D1683C00005: *A Multi-Center, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Saxagliptin 5 mg Co-administered with Dapagliflozin 5 mg compared to Saxagliptin 5 mg or Dapagliflozin 5 mg all given as Add-on therapy to Metformin in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin Alone*

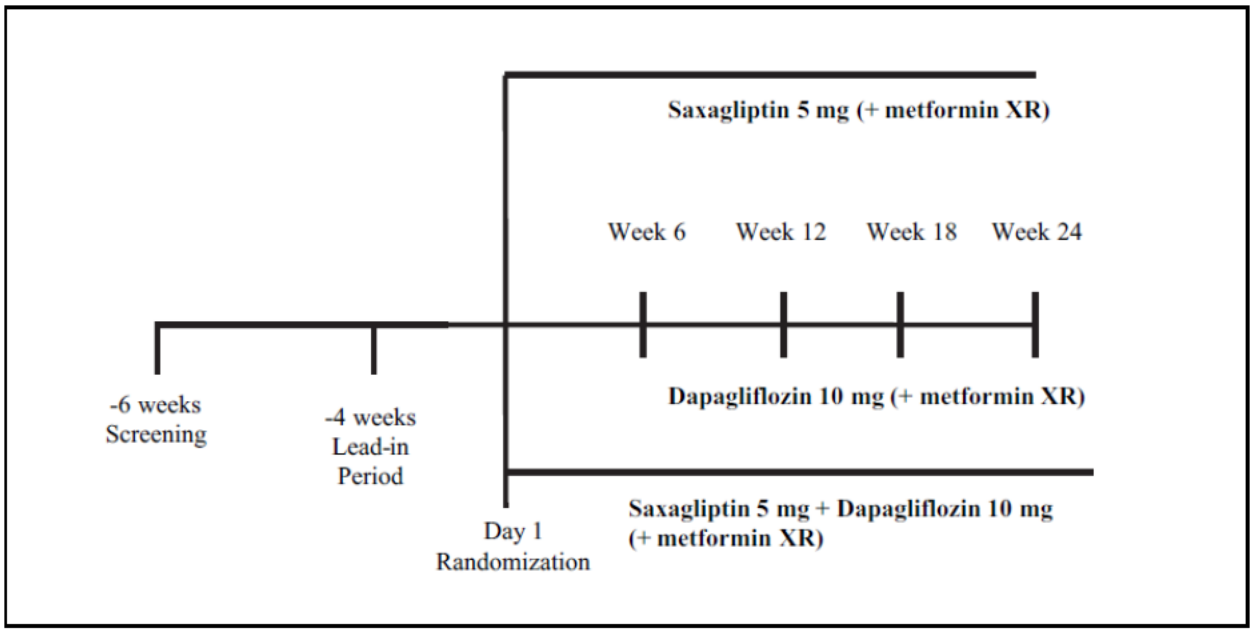
Figure 4: Study Design of Trial D1683C00005



Source: Reproduced from the Applicant's CSR for D1683C00005, labeled as Figure 1, page 22 of 1446, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\d1683c00005\d1683c00005-clinical-study-report.pdf

Trial CV181169: *A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone*

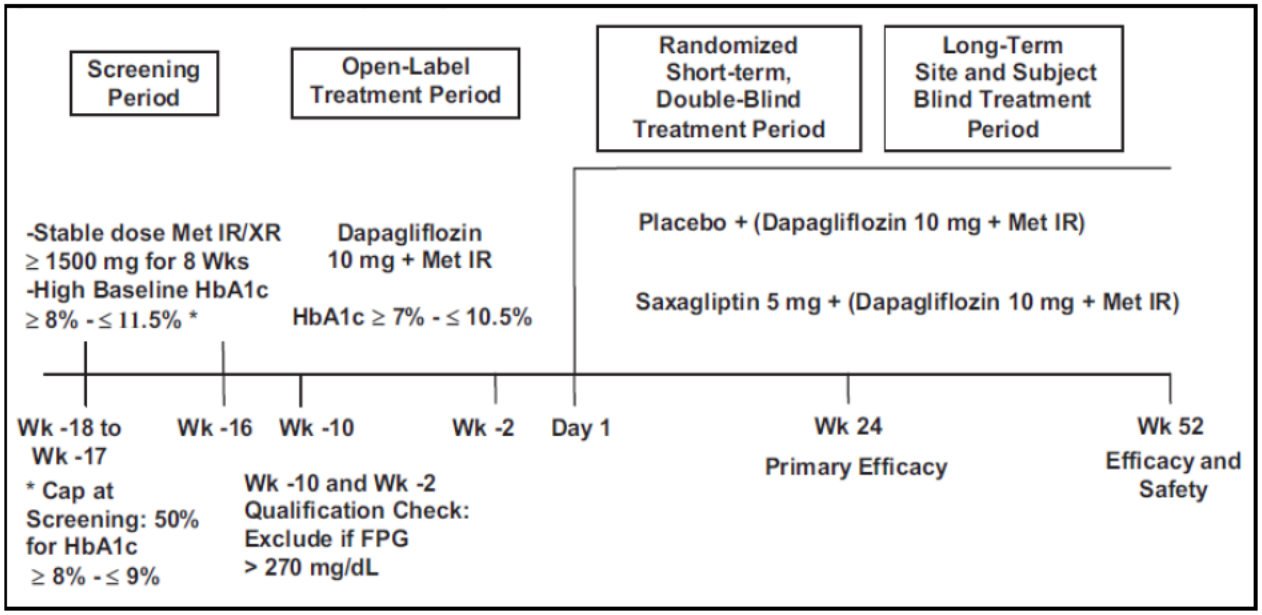
Figure 5: Study Design of Trial CV181169



Source: Reproduced from the Applicant's CSR for Trial CV181169, labeled as Figure 1, page 24 of 3208, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181169\cv181169-clinical-study-report.pdf

Trial CV181168: *Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin*

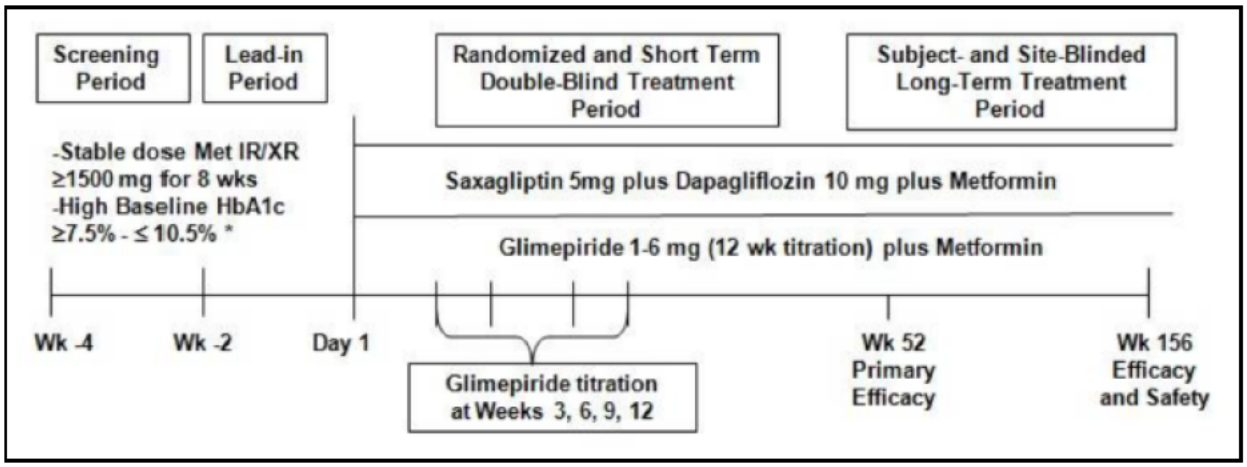
Figure 6: Study Design of Trial CV181168



Source: Reproduced from the Applicant's CSR for Trial CV181168, labeled as Figure 1, page 23 of 3639, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf

CV181365: *A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial with a Blinded 104-week Long-term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin in Combination with Metformin Compared to Glimepiride in Combination with Metformin in Adult Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone*

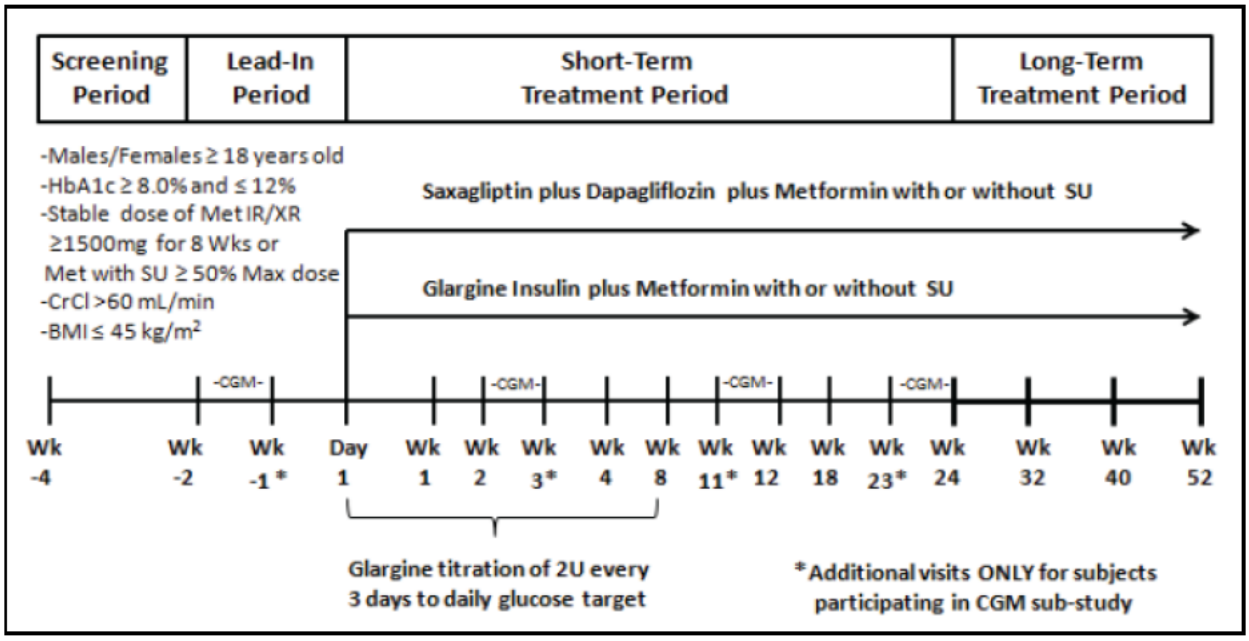
Figure 7: Study Design of Trial CV181365



Source: Reproduced from the Applicant's CSR for Trial CV181365, labeled as Figure 9-1, page 75 of 2209, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-365\cv181365-clinical-study-report.pdf

Trial CV181369: *A 24-week International, Multicenter, Randomized, Open-Label, Active-Controlled, Parallel Group, Phase 3b Trial with a 28-week Extension to Evaluate the Efficacy and Safety of Saxagliptin Co-administered with Dapagliflozin Compared to Insulin Glargine in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin with or without Sulfonylurea Therapy*

Figure 8: Study Design of Trial CV181369



Source: Reproduced from the Applicant's Clinical Study Report P005V01, labeled as Figure 9-1, page 90 of 2273, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181-369\cv181-369-clinical-study-report.pdf

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

Note: MedDRA v20 was used (i.e., latest version at the time of the database lock for which all AEs were coded) and SMQs/CMQs were derived from existing MedDRA SMQs and/or from SGLT2 inhibitor and/or Metformin Applications

ACCIDENTS AND INJURIES

MedDRA PTs: Abdomen crushing; Abdominal injury; Abdominal wall wound; Accident; Accident at home; Accident at work; Accidental death; Acetabulum fracture; Acoustic shock; Acrotrophodynia; Adrenal gland injury; Anal injury; Animal bite; Ankle fracture; Aortic injury; Aortic rupture; Aponeurosis contusion; Application site wound; Arterial injury; Arterial rupture; Atrial rupture; Atypical femur fracture; Atypical fracture; Avulsion fracture; Axillary nerve injury; Back injury; Bile duct stenosis traumatic; Bladder injury; Bladder perforation; Blast injury; Blindness traumatic; Bone contusion; Bone fissure; Bone fragmentation; Bowman's membrane injury; Brachial plexus injury; Brain contusion; Breast injury; Burn oral cavity; Burns first degree; Burns fourth degree; Burns second degree; Burns third degree; Bursa injury; Buttock injury; Cardiac contusion; Cartilage injury; Cataract traumatic; Cervical vertebral fracture; Cervix injury; Chance fracture; Chemical burn; Chemical burn of skin; Chemical burns of eye; Chemical eye injury; Chemical iritis; Chest crushing; Chest injury; Chillblains; Clavicle fracture; Closed globe injury; Cold exposure injury; Colon injury; Comminuted fracture; Commotio retinae; Complicated fracture; Compression fracture; Concussion; Conjunctival abrasion; Conjunctival laceration; Contusion; Corneal abrasion; Corneal perforation; Corrosive oropharyngeal injury; Costal cartilage fracture; Costochondral separation; Cranial nerve injury; Craniocerebral injury; Craniofacial fracture; Crush injury; Crush syndrome; Crushing injury of trunk; Deafness traumatic; Decapitation; Deep dissecting haematoma; Diaphragmatic injury; Diaphragmatic rupture; Diffuse axonal injury; Dislocation of sternum; Dislocation of vertebra; Drowning; Dural tear; Ear abrasion; Ear canal abrasion; Ear canal injury; Ear canal stenosis traumatic; Ear injury; Electric injury; Electric shock; Electrocution; Enophthalmos traumatic; Epidural haemorrhage; Epiphyseal fracture; Epiphyseal injury; Epiphysiolysis; Excoriation; External genitalia crushing; Extradural haematoma; Eye burns; Eye contusion; Eye injury; Eye luxation; Eyeball avulsion; Eyelash injury; Eyelid contusion; Eyelid haematoma; Eyelid injury; Face crushing; Face injury; Facial bones fracture; Facial nerve injury due to birth trauma; Fall; Femoral neck fracture; Femoral nerve injury; Femur fracture; Fibula fracture; First degree chemical burn of skin; Flail chest; Foot fracture; Forearm fracture; Foreign body aspiration; Foreign body in eye; Fourth degree chemical burn of skin; Fracture; Fracture displacement; Fracture of clavicle due to birth trauma; Fracture of penis; Fracture pain; Fractured coccyx; Fractured ischium; Fractured sacrum; Fractured skull depressed; Frostbite; Gallbladder injury; Gallbladder perforation; Gastrointestinal injury; Gastrointestinal organ contusion; Genital contusion; Genital injury; Gingival injury; Glaucoma traumatic; Greenstick fracture; Gun shot wound; Haematuria traumatic; Haemothorax; Hand fracture; Head injury; Heart injury; Heat cramps; Heat exhaustion; Heat stroke; Hepatic rupture; Hernia perforation; Hip fracture; Human bite; Humerus fracture; Hyperthermia; Hyphaema; Hypothermia; IIIrd nerve injury; Ilium fracture; Impacted fracture; Inguinal hernia perforation; Injury; Injury corneal; Injury to brachial plexus due to birth trauma; Internal injury; Intervertebral disc injury; Iris injury; IVth nerve injury; Jaw fracture; Joint dislocation; Joint hyperextension; Joint injury; Keratorhexis; Keraunoparalysis; Kidney contusion; Kidney rupture; Laceration; Laryngeal injury; Lens dislocation; Lenticular injury; Ligament injury; Ligament rupture; Ligament sprain; Limb crushing injury; Limb fracture; Limb injury; Limb reattachment surgery; Limb traumatic amputation; Lip injury; Lisfranc fracture; Liver contusion; Liver injury; Lower limb fracture; Lumbar vertebral fracture; Lumbosacral plexus injury; Lung perforation; Lymphatic duct injury; Median nerve injury; Meniscus cyst; Meniscus injury; Metallosis of globe; Mouth injury; Multiple fractures; Multiple injuries; Muscle contusion; Muscle injury; Muscle reattachment; Muscle rupture; Muscle strain; Musculocutaneous nerve injury; Musculoskeletal injury; Myocardial rupture; Nail avulsion; Nail injury; Nasal injury; Near drowning; Neck crushing; Neck injury; Nerve compression; Nerve injury; Nerve root injury; Nerve root injury cervical; Nerve root injury lumbar; Nerve root injury sacral; Nerve root injury thoracic; Oesophageal injury; Oesophageal rupture; Open fracture; Open globe injury; Optic nerve injury; Optic pathway injury; Oral contusion; Orbital compartment syndrome; Osteochondral fracture; Ovarian injury; Pancreatic contusion; Pancreatic duct rupture; Pancreatic injury; Paranasal sinus injury; Parasympathetic nerve injury; Patella fracture; Pellegrini Stieda disease; Pelvic fracture; Pelvic organ injury; Penetrating abdominal trauma; Penetrating eye injury repair; Penile contusion; Penis injury; Penis reattachment; Perforation bile duct; Perineal injury; Peripheral nerve injury; Peritoneal perforation; Peroneal nerve injury; Pharyngeal injury; Photoelectric

conjunctivitis; Pneumothorax traumatic; Post concussion syndrome; Posterior capsule rupture; Posterior tibial nerve injury; Post-traumatic headache; Post-traumatic neck syndrome; Post-traumatic osteoporosis; Post-traumatic pain; Prevertebral soft tissue swelling of cervical space; Product package associated injury; Pubis fracture; Pulmonary contusion; Radial head dislocation; Radial nerve injury; Radius fracture; Rectal injury; Renal injury; Repair of diaphragm injury; Retinal detachment; Retinal injury; Retinal tear; Rib fracture; Road traffic accident; Sacroiliac fracture; Scapula fracture; Scapulothoracic dissociation; Sciatic nerve injury; Scratch; Second degree chemical burn of skin; Shrapnel wound; Sinus tarsi syndrome; Skeletal injury; Skin abrasion; Skin injury; Skull fracture; Skull fractured base; Snake bite; Soft tissue injury; Spinal column injury; Spinal compression fracture; Spinal cord injury; Spinal cord injury cauda equina; Spinal cord injury cervical; Spinal cord injury lumbar; Spinal cord injury sacral; Spinal cord injury thoracic; Spinal epidural haematoma; Spinal epidural haemorrhage; Spinal fracture; Spinal fusion fracture; Spinal shock; Spinal subarachnoid haemorrhage; Spinal subdural haematoma; Spleen contusion; Splenic injury; Splenic rupture; Splenosis; Splinter; Spondylopathy traumatic; Sports injury; Stab wound; Sternal fracture; Sternal injury; Stress fracture; Struck by lightning; Subdural haematoma; Subdural haematoma evacuation; Subdural haemorrhage; Subretinal fluid; Sunburn; Superficial injury of eye; Sympathetic nerve injury; Synovial rupture; Tendon injury; Tendon rupture; Testicular injury; Testicular rupture; Thermal burn; Thermal burns of eye; Third degree chemical burn of skin; Thoracic vertebral fracture; Thyroid gland injury; Tibia fracture; Tongue injury; Tooth avulsion; Tooth fracture; Tooth injury; Torus fracture; Tracheal injury; Traumatic amputation; Traumatic anuria; Traumatic arthritis; Traumatic arthropathy; Traumatic arthrosis; Traumatic coma; Traumatic ear amputation; Traumatic fracture; Traumatic haematoma; Traumatic haemorrhage; Traumatic haemothorax; Traumatic intracranial haematoma; Traumatic intracranial haemorrhage; Traumatic iritis; Traumatic liver injury; Traumatic lung injury; Traumatic pancreatitis; Traumatic renal injury; Traumatic shock; Traumatic spinal cord compression; Traumatic torticollis; Traumatic ulcer; Traumatic ulcerative granuloma with stromal eosinophilia; Trench foot; Trunk injury; Tympanic membrane perforation; Ulna fracture; Ulnar nerve injury; Upper limb fracture; Ureteric injury; Ureteric perforation; Ureteric rupture; Urethral injury; Urethral perforation; Urethral stricture traumatic; Urinary bladder rupture; Urinary tract injury; Uveal prolapse; Vaginal laceration; Vaginal perforation; Vascular injury; Vascular rupture; Vena cava injury; Venous injury; Ventricle rupture; VIIIth nerve injury; VIIth nerve injury; VIth nerve injury; Vitreous detachment; Vitreous injury; Vitreous loss; Vitreous prolapse; Vth nerve injury; Vulval laceration; Vulvovaginal injury; Wound; Wrist fracture; XIIth nerve injury; XIth nerve injury

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; Chronic kidney disease-mineral and bone disorder; Coma uraemic; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Destructive spondyloarthropathy; 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; Foetal renal impairment; 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; Hyponatriuria; 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; Osteodystrophy; 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 papillary necrosis; Renal replacement therapy; Renal rickets; Renal transplant; Renal tubular atrophy; Renal tubular disorder; Renal tubular dysfunction; Renal tubular injury; 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

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; Musculoskeletal stiffness; Neck pain; Neuropathic arthropathy; Nodal osteoarthritis; Osteoarthritis; Osteoarthropathy; Palindromic rheumatism; Paraneoplastic arthritis; Patellofemoral pain syndrome; Periarthritis; Periarthritis calcarea; Periarticular disorder; 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; 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 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; Os trigonum syndrome; Osteitis; Osteitis condensans; Osteitis deformans; Osteolysis; Osteonecrosis; Osteonecrosis of external auditory canal; Osteonecrosis of jaw; Osteoradionecrosis; Osteorrhagia; Osteosclerosis; Osteosis; 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

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 maxilla elevation; Fractured sacrum; 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; Periprosthetic fracture; Pubis 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

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; 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; Vascular anastomosis; Vascular brachytherapy; Vascular catheterisation; Vascular graft; Vascular operation; Vascular stent insertion; Vasodilation procedure

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

Fournier's Gangrene

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; Penile erythema; Penile infection; Penile pain; Penile swelling; Penis disorder; Perineal abscess; Perineal infection; Perineal necrosis; Perineal pain; Scrotal abscess; Scrotal cyst; Scrotal inflammation; Scrotal pain; Scrotal swelling; Testicular cyst; Testicular pain; Vaginal abscess; Vaginal infection; Vulva cyst; Vulval abscess; Vulval cellulitis; Vulvitis; Vulvovaginal inflammation; Vulvovaginal swelling; Vulvovaginitis

Genital Infections

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

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 enlargement; 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 atrial enlargement; Left ventricular dilatation; Left ventricular dysfunction; Left ventricular end-diastolic pressure decreased; Left ventricular enlargement; 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; Refeeding syndrome; Restrictive cardiomyopathy; Right atrial dilatation; Right atrial enlargement; Right atrial pressure increased; Right ventricle outflow tract obstruction; Right ventricular dilatation; Right ventricular dysfunction; Right ventricular ejection fraction decreased; Right ventricular enlargement; 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; Surgical ventricular restoration; 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 enlargement; Ventricular failure; Ventricular hyperkinesia; Ventricular hypertrophy; Ventricular hypokinesia; Ventricular hypoplasia; Ventricular remodelling; Ventricular septal defect acquired; Viral cardiomyopathy; Viral myocarditis; Wall motion score index abnormal

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; Computerised tomogram liver abnormal; 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 colopathy; 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; White nipple sign; X-ray hepatobiliary abnormal; Yellow skin

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 hepatitis; Allergic keratitis; Allergic myocarditis; Allergic oedema; Allergic otitis externa; Allergic otitis media; Allergic pharyngitis; Allergic reaction to excipient; Allergic respiratory disease; Allergic respiratory symptom; Allergic sinusitis; 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 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 photosensitivity reaction; 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; Blister rupture; Blood immunoglobulin 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; Blood pressure diastolic decreased; Blood pressure systolic decreased; Breast oedema; Breast swelling; 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; Chest discomfort; 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; Conjunctival oedema; Conjunctivitis; Conjunctivitis allergic; Contact stomatitis; Contrast media allergy; Contrast media reaction; Corneal exfoliation; Corneal

oedema; Cough; 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 granulomatosis with polyangiitis; 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 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; Irregular breathing; 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; Mucocutaneous ulceration; Mucosa vesicle; Mucosal erosion; Mucosal exfoliation; Mucosal necrosis; Mucosal ulceration; Multiple allergies; Nasal crease; 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 oedema; 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; Perinephric oedema; Periorbital oedema; Peripheral oedema neonatal; 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; Soft tissue swelling; 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; Symmetrical drug-related intertriginous and flexural exanthema; 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; Hyperinsulinaemia; Hyperinsulinism; Hypoglycaemia; Hypoglycaemia neonatal; Hypoglycaemia unawareness; Hypoglycaemic coma; Hypoglycaemic encephalopathy; Hypoglycaemic seizure; Hypoglycaemic unconsciousness; Neuroglycopenia; Shock hypoglycaemic

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 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 increase

Lactic Acidosis

MedDRA PTs: Acetonaemia; 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

Lymphopenia

MedDRA PTs: A 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

Malignancies & Premalignant Conditions

MedDRA PTs: 5q minus syndrome; 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 promyelocytic leukaemia differentiation syndrome; 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; Allogenic bone marrow transplantation therapy; Alpha 1 foetoprotein abnormal; Alpha 1 foetoprotein increased; Alpha interferon therapy; Alpha-L-fucosidase increased; 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; Aplastic anaemia; Apocrine breast carcinoma; Appendix cancer; APUDoma; Arsenical keratosis; Aspiration bone marrow abnormal; Astroblastoma; 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 depletion therapy; 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; Bicytopenia; 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 gallbladder 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 disorder; Bone marrow failure; Bone marrow infiltration; Bone marrow leukaemic cell infiltration; Bone marrow metamyelocyte count increased; Bone marrow myelogram abnormal; Bone marrow reticulin fibrosis; Bone marrow transplant; 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; Breast tumour excision; 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; Computerised tomogram liver abnormal; Congenital fibrosarcoma; Congenital malignant neoplasm; Congenital melanocytic naevus; Congenital neoplasm; 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; Cytopenia; Dedifferentiated liposarcoma; Dermatofibrosarcoma protuberans; Dermatofibrosarcoma protuberans metastatic; Desmoplastic melanoma; Desmoplastic mesothelioma; Desmoplastic small round cell tumour; Diaphragm neoplasm; Differential white blood cell count abnormal; 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; Diffuse uveal melanocytic proliferation; 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 positive mucocutaneous ulcer; Epstein-Barr virus associated lymphoma; Epstein-Barr virus associated lymphoproliferative disorder; Erythraemic myelosis (in remission); Erythroblast count increased; Erythroblast morphology abnormal; 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; Granulocytes maturation arrest; Granulosa cell tumour of the testis; 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; Hyperleukocytosis; 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; Hypoplastic anaemia; Hysterectomy; Hysterosalpingectomy; Hysterosalpingo-oophorectomy; IDH differentiation syndrome; 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; Joint neoplasm; 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; Langerhans cell sarcoma; 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; Leptomeningeal myelomatosis; 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; Leukoerythroblastic anaemia; Leukoerythroblastosis; 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 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 joint neoplasm; 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 polyp; Malignant psoas syndrome; 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; Marrow hyperplasia; Mastectomy; Mastocytic leukaemia; Mastoidectomy; Mature B-cell type acute leukaemia; Maxillofacial sinus neoplasm; Mean platelet volume abnormal; Mean platelet volume decreased; Mediastinal biopsy abnormal; Mediastinum neoplasm; Medullary carcinoma of breast; Medullary thyroid cancer; Medulloblastoma; Medulloblastoma recurrent; Megakaryocytes abnormal; Megaloblasts increased; Meigs' syndrome; Melanoma recurrent; Melanoplakia oral; Meningeal neoplasm; Meningioma malignant; Mesenteric neoplasm; Mesothelioma; Mesothelioma malignant; Mesothelioma malignant recurrent; Metamyelocyte count increased; Metamyelocyte percentage increased; 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 spinal cord; 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; Mismatched donor bone marrow transplantation therapy; Mixed adenoneuroendocrine carcinoma; Mixed hepatocellular cholangiocarcinoma; Mixed-type liposarcoma; Modified radical mastectomy; Monoblast count increased; Monoclonal gammopathy; Monocytic leukaemia in remission; Mononuclear cell count abnormal; 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; Myeloblast count increased; Myeloblast percentage increased; Myeloblast present; Myeloblastoma; Myelocyte count increased; Myelocyte percentage increased; Myelocytosis; Myelodysplastic syndrome; Myelodysplastic syndrome transformation; Myelodysplastic syndrome unclassifiable; Myelofibrosis; Myeloid leukaemia; Myeloid leukaemia in remission; Myeloid maturation arrest; Myeloid metaplasia; Myeloma cast nephropathy; Myeloproliferative neoplasm; Myxofibrosarcoma; Myxoid liposarcoma; Naevoid melanoma; Nasal cavity cancer; Nasal neoplasm; Nasal sinus cancer; Nasopharyngeal cancer; Nasopharyngeal cancer metastatic; 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 bladder; Neuroendocrine carcinoma of the skin; Neuroendocrine tumour; Neuroendocrine tumour of the lung; Neuroendocrine tumour of the lung metastatic; Neuroendoscopy; Neurofibrosarcoma; Neurofibrosarcoma metastatic; Neurofibrosarcoma recurrent; Neuromyotonia; Neurotensinoma; Nipple neoplasm; Nipple resection; NMP22 test abnormal; 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; NUT midline carcinoma; Ocular cancer metastatic; Ocular haemangiopericytoma; Ocular lymphoma; Ocular neoplasm; Oesophageal adenocarcinoma; 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 polypectomy; Oesophageal prosthesis insertion; 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; Orchidotomy; 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; Packed red blood cell transfusion; 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; Pancytopenia; Panmyelopathy; Papillary renal cell carcinoma; 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 dermatosis; 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; Platelet maturation arrest; Platelet production decreased; 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 breast therapy pain syndrome; 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 gastrointestinal follicular 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; Proerythroblast count increased; Progesterone receptor assay positive; Prolactin-producing pituitary tumour; Prolymphocytic leukaemia; Promyelocyte count increased; 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; Red blood cell morphology abnormal; Red blood cell siderocytes

present; Red cell distribution width abnormal; 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 cell dysplasia; 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; Sideroblastic anaemia; 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; 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 breast carcinoma; 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; Tracheal resection; Transcatheter arterial chemoembolisation; Transcranial electrical motor evoked potential monitoring abnormal; Transformation to acute myeloid leukaemia; 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 inflammation; 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 pancreas abnormal; Ultrasound scan abnormal; Ultrasound scan vagina abnormal; Undifferentiated carcinoma of colon; Undifferentiated nasopharyngeal carcinoma; Undifferentiated sarcoma; Unrelated donor bone marrow transplantation therapy; 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; White blood cell analysis abnormal; 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; Creatine urine; Creatine urine abnormal; Creatine urine increased; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Diaphragm muscle weakness; Electromyogram abnormal; End stage renal disease; Flank pain; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Hypercreatinaemia; Hypercreatininaemia; 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

Nephrolithiasis

MedDRA PTs: Calculus urinary; Hydronephrosis; Nephrolithiasis; Pyelocaliectasis; Renal colic; Ureterolithiasis; Urinary sediment abnormal; Urinary sediment present

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; 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; Faecal elastase concentration abnormal; Faecal elastase concentration decreased; Fat necrosis; 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 failure; Pancreatic fibrosis; Pancreatic haemorrhage; Pancreatic injury; 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

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; Foot amputation; Iliac artery occlusion; Iliac vein occlusion; Intermittent claudication; Ischaemic limb pain; Ischaemic neuropathy; Leg amputation; Peripheral arterial occlusive disease; Peripheral arterial reocclusion; Peripheral artery angioplasty; Peripheral artery bypass; Peripheral artery occlusion; Peripheral artery restenosis; Peripheral artery stenosis; Peripheral artery stent insertion; Peripheral ischaemia; Peripheral revascularisation; Poor peripheral circulation; Toe amputation

Skin Reaction

MedDRA PTs: Acquired epidermolysis bullosa; Acute focal bacterial nephritis; 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 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 Ulcerations

MedDRA PTs: Allergic pharyngitis; Aphthous ulcer; Atrophic pharyngitis; 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 erythema; Pharyngeal exudate; Pharyngeal fistula; Pharyngeal haematoma; Pharyngeal haemorrhage; Pharyngeal inflammation; Pharyngeal injury; Pharyngeal lesion; Pharyngeal necrosis; Pharyngeal oedema; 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

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: Arterial bypass stenosis; Arterial insufficiency; Arterial occlusive disease; Arterial restenosis; Arterial spasm; Arterial stenosis; Arteriosclerosis; Arteriosclerosis Moenckeberg-type; Arteriosclerotic gangrene; 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; Fibromuscular dysplasia; Gangrene; Gangrene neonatal; Gas gangrene; Gastrointestinal ischaemia; Graft ischaemia; Haemorrhagic infarction; Hand-arm vibration syndrome; Iliac artery disease; Iliac artery occlusion; Iliac vein occlusion; Incision site vessel occlusion; Infarction; Intermittent claudication; Intestinal ischaemia; 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 occlusion; Peripheral artery restenosis; Peripheral artery stenosis; Peripheral coldness; Peripheral ischaemia; Peripheral vascular disorder; Peripheral venous disease; Phlebosclerosis; Plaque shift; Poor peripheral circulation; Popliteal artery entrapment syndrome; Post angioplasty restenosis; 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

Venous Thromboembolic Events

MedDRA PTs: Axillary vein thrombosis; Brachiocephalic vein occlusion; Budd-Chiari syndrome; Catheterisation venous; Cavernous sinus thrombosis; Central venous catheterisation; Cerebral venous thrombosis; Compression garment 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 in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal; Visceral venous thrombosis

Volume Depletion

MedDRA PTs: Acute prerenal failure; Anuria; 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; Neonatal anuria; Orthostatic heart rate response increased; Orthostatic hypotension; Orthostatic intolerance; Peripheral circulatory failure; Postural orthostatic tachycardia syndrome; Prerenal failure; 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

13.6. Adverse Event Summary (3-study pool)

Table 30: Summary of Adverse Events (Integrated 3-study pool)

	3-Study Pool		
Adverse Event Category	**Dapa 10 mg + Saxa 5 mg + Met (n=492)**	**Dapa 10 mg + Met (n=341)**	**Saxa 5 mg + Met (n=336)**
EVENT — no. (%)			
At least one AE	521 (54.8)	275 (55.9)	209 (44.4)
At least one hypoglycemia¶	11 (2.2)	9 (2.6)	5 (1.5)
Severe hypoglycemia†	1 (0.2)	0	0
Clinically Significant‡	5 (1.0)	2 (0.6)	0
D/C due to hypoglycemia	0	0	0
Deaths	1 (0.2)	1 (0.3)	0
At least one SAE	16 (3.3)	13 (3.8)	10 (3.0)
SAE leading to D/C of IP	5 (1.0)	1 (0.3)	2 (0.6)
AE leading to D/C of IP	13 (2.6)	6 (1.8)	3 (0.9)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam – and adapted from the Applicant's ISS, pages 33, and 386-389 of 533, available at: \\cdsesub1\evsprod\nda210874\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\iss\pooled-analysis-of-safety.pdf

Abbreviations: BG, blood glucose; Dapa, dapagliflozin; D/C, discontinuation; IP, investigational product; Met, metformin; and Saxa, saxagliptin.

* Adjusted estimate [%] using a logistic regression model adjusting for trial.

¶ **Hypoglycemia:** all reported episodes of hypoglycemia on CRFs regardless of the self-monitoring blood glucose value and all episodes of FPG <70 mg/dL measured by the (b) (4).

† **Severe hypoglycemia:** neuroglycopenic symptoms requiring assistance of another person to actively administer carbohydrate or glucagon with prompt recovery, with BG ≤70 mg/dL (ADA Level 3).

‡ **Clinically significant hypoglycemia**: BG <54 mg/dL (ADA Level 2).

13.7. Serious Adverse Events by System Organ Class (7-study pool)

Table 31: Summary of Serious Adverse Events by SOC (7-study pool)

System Organ Class	Dapa 10 mg + Saxa 5 mg + Met (n=1263)	Dapa 10 mg + Met (n=654)	Saxa 5 mg + Met (n=631)	Dapa 5 mg + Saxa 5 mg + Met (n=293)	Dapa 5 mg + Met (n=293)
TOTAL SUBJECTS WITH SAES— NO. (%)	**61 (4.8)**	**52 (8.0)**	**17 (2.7)**	**7 (2.4)**	**8 (2.7)**
Cardiac disorders	11 (0.9)	7 (1.1)	0	2 (0.7)	3 (1.0)
Infections and infestations	9 (0.7)	6 (0.9)	4 (0.6)	0	1 (0.3)
Nervous system disorders	8 (0.6)	5 (0.8)	1 (0.2)	0	3 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.6)	6 (0.9)	0	0	0
Injury, poisoning and procedural complications	6 (0.5)	2 (0.3)	4 (0.6)	2 (0.7)	1 (0.3)
Vascular disorders	6 (0.5)	0	1 (0.2)	2 (0.7)	0
Musculoskeletal and connective tissue disorders	5 (0.4)	8 (1.2)	2 (0.3)	0	1 (0.3)
Gastrointestinal disorders	4 (0.3)	2 (0.3)	3 (0.5)	0	1 (0.3)
Hepatobiliary disorders	2 (0.2)	1 (0.2)	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.2)	1 (0.2)	1 (0.2)	0	0
Endocrine disorders	2 (0.2)	0	0	0	0
Psychiatric disorders	2 (0.2)	1 (0.2)	0	0	0
Skin and subcutaneous tissue disorders	2 (0.2)	1 (0.2)	0	1 (0.3)	0
Reproductive system and breast disorders	1 (0.1)	3 (0.5)	1 (0.2)	0	0
Blood and lymphatic system disorders	1 (0.1)	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0	0	0	0
Investigations	0	1 (0.2)	1 (0.2)	0	0
Renal and urinary disorders	0	6 (0.9)	0	0	0
General disorders and administration site conditions	0	3 (0.5)	1 (0.2)	0	0
Metabolism and nutrition disorders	0	1 (0.2)	1 (0.2)	0	1 (0.3)
Eye disorders	0	2 (0.3)	0	1 (0.3)	0

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam -
Abbreviations: Dapa, dapagliflozin, Met, metformin; and Saxa, saxagliptin.

13.8. Adverse Events of Special Interest (7-study pool, Broad CMQs)

Table 32: Summary of AESI by Custom MedDRA Query (7-study pool)

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
MYOPATHY / RHABDOMYOLYSIS	**122 (9.7)**	**61 (9.3)**	**61 (9.7)**	**27 (9.2)**	**24 (8.2)**
BACK PAIN	47 (3.7)	25 (3.8)	21 (3.3)	5 (1.7)	4 (1.4)
MUSCULOSKELETAL PAIN	14 (1.1)	2 (0.3)	8 (1.3)	0	1 (0.3)
PAIN IN EXTREMITY	14 (1.1)	8 (1.2)	7 (1.1)	1 (0.3)	1 (0.3)
MYALGIA	9 (0.7)	5 (0.8)	3 (0.5)	2 (0.7)	1 (0.3)
BLOOD CREATINE PHOSPHOKINASE INCREASED	9 (0.7)	1 (0.2)	4 (0.6)	2 (0.7)	1 (0.3)
GLOMERULAR FILTRATION RATE DECREASED	8 (0.6)	3 (0.5)	7 (1.1)	12 (4.1)	11 (3.8)
CREATININE RENAL CLEARANCE DECREASED	7 (0.6)	9 (1.4)	0	0	0
RENAL IMPAIRMENT	6 (0.5)	1 (0.2)	1 (0.2)	1 (0.3)	0
MUSCLE SPASMS	6 (0.5)	6 (0.9)	11 (1.7)	1 (0.3)	3 (1.0)
BLOOD CREATININE INCREASED	4 (0.3)	0	4 (0.6)	0	0
ACUTE KIDNEY INJURY	2 (0.2)	0	0	0	0
FLANK PAIN	2 (0.2)	0	0	0	1 (0.3)
CHRONIC KIDNEY DISEASE	1 (0.1)	0	3 (0.5)	0	1 (0.3)
RHABDOMYOLYSIS	1 (0.1)	0	0	0	0
ACUTE PRERENAL FAILURE	1 (0.1)	0	0	0	0
MUSCULOSKELETAL CHEST PAIN	1 (0.1)	2 (0.3)	0	0	1 (0.3)
MUSCLE FATIGUE	1 (0.1)	0	0	0	0
NON-CARDIAC CHEST PAIN	0	2 (0.3)	1 (0.2)	0	0
CHROMATURIA	0	1 (0.2)	0	0	0
RENAL FAILURE	0	1 (0.2)	1 (0.2)	2 (0.7)	0
MYOSITIS	0	1 (0.2)	0	0	0
MUSCLE RUPTURE	0	1 (0.2)	0	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
BLOOD CALCIUM DECREASED	0	1 (0.2)	0	0	0
HYPOCALCAEMIA	0	1 (0.2)	0	0	0
MUSCULOSKELETAL STIFFNESS	0	1 (0.2)	0	0	0
MUSCULAR WEAKNESS	0	0	0	0	1 (0.3)
GLOMERULAR FILTRATION RATE ABNORMAL	0	0	0	1 (0.3)	0
MYOPATHY	0	0	1 (0.2)	0	0
URINARY TRACT INFECTIONS	**95 (7.5)**	**54 (8.3)**	**40 (6.3)**	**12 (4.1)**	**10 (3.4)**
URINARY TRACT INFECTION	68 (5.4)	35 (5.4)	33 (5.2)	8 (2.7)	6 (2.0)
DYSURIA	14 (1.1)	8 (1.2)	3 (0.5)	2 (0.7)	0
CYSTITIS	8 (0.6)	12 (1.8)	3 (0.5)	2 (0.7)	0
URETHRITIS	2 (0.2)	0	0	0	0
PROSTATITIS	2 (0.2)	1 (0.2)	0	0	0
ASYMPTOMATIC BACTERIURIA	2 (0.2)	0	0	0	0
URINARY TRACT INFECTION FUNGAL	1 (0.1)	1 (0.2)	2 (0.3)	0	1 (0.3)
PYELONEPHRITIS	1 (0.1)	0	0	0	2 (0.7)
LEUKOCYTURIA	1 (0.1)	1 (0.2)	1 (0.2)	0	1 (0.3)
ESCHERICHIA URINARY TRACT INFECTION	1 (0.1)	0	0	0	0
WHITE BLOOD CELLS URINE POSITIVE	0	2 (0.3)	1 (0.2)	0	0
BACTERIURIA	0	1 (0.2)	0	0	1 (0.3)
UROGENITAL INFECTION FUNGAL	0	1 (0.2)	0	0	0
URINARY TRACT INFLAMMATION	0	1 (0.2)	0	0	0
HYPERSENSITIVITY REACTIONS	**85 (6.7)**	**35 (5.4)**	**51 (8.1)**	**10 (3.4)**	**15 (5.1)**
COUGH	18 (1.4)	11 (1.7)	10 (1.6)	2 (0.7)	6 (2.0)
OEDEMA PERIPHERAL	8 (0.6)	2 (0.3)	7 (1.1)	0	1 (0.3)
RASH	7 (0.6)	2 (0.3)	6 (1.0)	1 (0.3)	0
SEASONAL ALLERGY	5 (0.4)	1 (0.2)	1 (0.2)	2 (0.7)	0
DERMATITIS ALLERGIC	4 (0.3)	1 (0.2)	2 (0.3)	1 (0.3)	0
CONJUNCTIVITIS	4 (0.3)	2 (0.3)	4 (0.6)	0	1 (0.3)
RHINITIS ALLERGIC	4 (0.3)	2 (0.3)	4 (0.6)	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
PRURITUS	4 (0.3)	1 (0.2)	4 (0.6)	0	0
DERMATITIS	3 (0.2)	2 (0.3)	1 (0.2)	1 (0.3)	1 (0.3)
DERMATITIS CONTACT	3 (0.2)	0	0	0	0
CONJUNCTIVITIS ALLERGIC	3 (0.2)	0	0	0	0
DYSPNOEA	3 (0.2)	0	1 (0.2)	0	0
ECZEMA	3 (0.2)	0	0	1 (0.3)	0
OEDEMA	2 (0.2)	0	0	0	0
HYPOTENSION	2 (0.2)	3 (0.5)	0	1 (0.3)	1 (0.3)
PERIPHERAL SWELLING	2 (0.2)	1 (0.2)	3 (0.5)	0	0
ERYTHEMA	2 (0.2)	1 (0.2)	2 (0.3)	0	2 (0.7)
EOSINOPHILIA	2 (0.2)	1 (0.2)	1 (0.2)	0	0
PRURITUS GENERALISED	2 (0.2)	0	1 (0.2)	0	0
SKIN EXFOLIATION	2 (0.2)	1 (0.2)	1 (0.2)	1 (0.3)	0
URTICARIA	1 (0.1)	0	0	1 (0.3)	1 (0.3)
SWELLING FACE	1 (0.1)	0	0	0	0
RESPIRATORY FAILURE	1 (0.1)	0	0	0	0
RASH MACULAR	1 (0.1)	0	0	0	0
PHOTOSENSITIVITY REACTION	1 (0.1)	0	0	0	0
APPLICATION SITE HYPERSENSITIVITY	1 (0.1)	0	0	0	0
EYE OEDEMA	1 (0.1)	0	0	0	0
URTICARIA CHRONIC	1 (0.1)	0	0	0	0
ANGIOEDEMA	1 (0.1)	0	0	1 (0.3)	0
HYPERSENSITIVITY	0	3 (0.5)	0	0	0
ASTHMA	0	3 (0.5)	2 (0.3)	0	2 (0.7)
LOCAL SWELLING	0	1 (0.2)	0	0	0
EYE PRURITUS	0	1 (0.2)	0	0	0
CIRCULATORY COLLAPSE	0	1 (0.2)	0	0	0
EOSINOPHIL COUNT INCREASED	0	1 (0.2)	0	0	0
RASH GENERALISED	0	1 (0.2)	0	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
DRUG HYPERSENSITIVITY	0	0	0	0	1 (0.3)
STOMATITIS	0	0	1 (0.2)	0	0
SWELLING	0	0	1 (0.2)	0	0
DERMATITIS ATOPIC	0	0	1 (0.2)	0	0
EOSINOPHILIC OESOPHAGITIS	0	0	1 (0.2)	0	0
LIP SWELLING	0	0	1 (0.2)	0	0
NASAL OBSTRUCTION	0	0	1 (0.2)	0	0
NEURODERMATITIS	0	0	1 (0.2)	0	0
ALLERGIC COUGH	0	0	1 (0.2)	0	0
BLISTER	0	0	1 (0.2)	0	0
ARTHROPATHIES	**76 (6.0)**	**21 (3.2)**	**19 (3.0)**	**6 (2.0)**	**9 (3.1)**
ARTHRALGIA	30 (2.4)	7 (1.1)	7 (1.1)	0	5 (1.7)
OSTEOARTHRITIS	14 (1.1)	2 (0.3)	3 (0.5)	2 (0.7)	3 (1.0)
SPINAL OSTEOARTHRITIS	8 (0.6)	0	0	1 (0.3)	0
ARTHRITIS	7 (0.6)	1 (0.2)	1 (0.2)	2 (0.7)	0
SPINAL PAIN	6 (0.5)	2 (0.3)	0	0	1 (0.3)
NECK PAIN	6 (0.5)	5 (0.8)	6 (1.0)	2 (0.7)	0
PERIARTHRITIS	5 (0.4)	1 (0.2)	0	0	0
GOUT	2 (0.2)	3 (0.5)	2 (0.3)	0	0
SPONDYLITIS	2 (0.2)	0	0	0	0
JOINT RANGE OF MOTION DECREASED	1 (0.1)	0	0	0	0
POLYARTHRITIS	1 (0.1)	0	0	0	0
MUSCULOSKELETAL STIFFNESS	0	1 (0.2)	0	0	0
REITER'S SYNDROME	0	1 (0.2)	0	0	0
JOINT SWELLING	0	0	1 (0.2)	0	0
PATELLOFEMORAL PAIN SYNDROME	0	0	1 (0.2)	0	0
GENITAL INFECTIONS	**70 (5.5)**	**64 (9.8)**	**5 (0.8)**	**14 (4.8)**	**6 (2.0)**
VULVOVAGINAL MYCOTIC INFECTION	21 (1.7)	17 (2.6)	1 (0.2)	2 (0.7)	1 (0.3)
BALANOPOSTHITIS	13 (1.0)	14 (2.1)	0	3 (1.0)	2 (0.7)

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
VAGINAL INFECTION	8 (0.6)	3 (0.5)	1 (0.2)	1 (0.3)	0
VULVOVAGINAL PRURITUS	8 (0.6)	4 (0.6)	0	2 (0.7)	1 (0.3)
GENITAL INFECTION FUNGAL	5 (0.4)	7 (1.1)	0	2 (0.7)	1 (0.3)
PRURITUS GENITAL	3 (0.2)	4 (0.6)	0	1 (0.3)	1 (0.3)
VULVOVAGINAL CANDIDIASIS	3 (0.2)	3 (0.5)	0	0	0
GENITAL INFECTION	2 (0.2)	1 (0.2)	0	1 (0.3)	0
PROSTATITIS	2 (0.2)	1 (0.2)	0	0	0
ACQUIRED PHIMOSIS	2 (0.2)	3 (0.5)	0	0	0
VAGINAL HAEMORRHAGE	2 (0.2)	2 (0.3)	1 (0.2)	0	0
VULVOVAGINITIS	2 (0.2)	0	0	0	0
PHIMOSIS	1 (0.1)	0	0	0	1 (0.3)
BACTERIAL VULVOVAGINITIS	1 (0.1)	0	0	0	0
VAGINAL DISCHARGE	1 (0.1)	2 (0.3)	0	1 (0.3)	0
BALANITIS CANDIDA	0	2 (0.3)	0	0	0
BACTERIAL VAGINOSIS	0	2 (0.3)	0	0	0
GENITAL CANDIDIASIS	0	1 (0.2)	1 (0.2)	0	1 (0.3)
VAGINAL ABSCESS	0	1 (0.2)	0	0	0
UROGENITAL INFECTION FUNGAL	0	1 (0.2)	0	0	0
VULVOVAGINAL INFLAMMATION	0	1 (0.2)	0	0	0
VULVAL ABSCESS	0	1 (0.2)	0	0	0
SCROTAL ABSCESS	0	1 (0.2)	0	0	0
BARTHOLINITIS	0	0	0	1 (0.3)	0
ENDOMETRIOSIS	0	0	1 (0.2)	0	0
PANCREATITIS	**60 (4.8)**	**26 (4.0)**	**33 (5.2)**	**8 (2.7)**	**5 (1.7)**
ABDOMINAL PAIN	24 (1.9)	5 (0.8)	5 (0.8)	1 (0.3)	0
NAUSEA	15 (1.2)	11 (1.7)	17 (2.7)	6 (2.0)	5 (1.7)
VOMITING	14 (1.1)	8 (1.2)	10 (1.6)	0	2 (0.7)
ABDOMINAL PAIN UPPER	8 (0.6)	4 (0.6)	4 (0.6)	1 (0.3)	0
ABDOMINAL DISTENSION	4 (0.3)	1 (0.2)	1 (0.2)	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
PANCREATITIS CHRONIC	1 (0.1)	0	1 (0.2)	0	0
LIPASE INCREASED	1 (0.1)	0	0	0	0
BLOOD BILIRUBIN INCREASED	1 (0.1)	0	2 (0.3)	0	0
GASTROINTESTINAL PAIN	1 (0.1)	0	0	0	0
ASCITES	0	1 (0.2)	0	0	0
HYPERBILIRUBINAEMIA	0	0	1 (0.2)	0	0
ABDOMINAL TENDERNESS	0	0	1 (0.2)	0	0
ACCIDENTS AND INJURIES	**50 (4.0)**	**31 (4.7)**	**37 (5.9)**	**7 (2.4)**	**7 (2.4)**
LIMB INJURY	6 (0.5)	2 (0.3)	1 (0.2)	0	1 (0.3)
CONTUSION	6 (0.5)	4 (0.6)	9 (1.4)	1 (0.3)	1 (0.3)
LIGAMENT SPRAIN	4 (0.3)	4 (0.6)	5 (0.8)	0	1 (0.3)
WOUND	3 (0.2)	3 (0.5)	2 (0.3)	0	0
RIB FRACTURE	2 (0.2)	1 (0.2)	3 (0.5)	0	0
LACERATION	2 (0.2)	3 (0.5)	3 (0.5)	1 (0.3)	1 (0.3)
THERMAL BURN	2 (0.2)	2 (0.3)	0	0	0
FOOT FRACTURE	2 (0.2)	1 (0.2)	1 (0.2)	0	0
FALL	2 (0.2)	2 (0.3)	5 (0.8)	0	0
MENISCUS INJURY	2 (0.2)	1 (0.2)	1 (0.2)	0	0
TOOTH FRACTURE	2 (0.2)	1 (0.2)	1 (0.2)	0	0
JOINT INJURY	2 (0.2)	0	1 (0.2)	0	0
SKIN ABRASION	1 (0.1)	0	2 (0.3)	0	0
ROAD TRAFFIC ACCIDENT	1 (0.1)	1 (0.2)	1 (0.2)	1 (0.3)	0
MULTIPLE FRACTURES	1 (0.1)	0	0	0	0
POST-TRAUMATIC PAIN	1 (0.1)	0	0	0	0
TIBIA FRACTURE	1 (0.1)	0	0	0	0
NERVE COMPRESSION	1 (0.1)	0	0	0	0
THORACIC VERTEBRAL FRACTURE	1 (0.1)	0	0	0	0
LIGAMENT RUPTURE	1 (0.1)	0	0	0	0
TENDON RUPTURE	1 (0.1)	0	0	0	1 (0.3)

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
SPLINTER	1 (0.1)	0	0	0	0
JOINT DISLOCATION	1 (0.1)	1 (0.2)	1 (0.2)	0	0
HUMERUS FRACTURE	1 (0.1)	1 (0.2)	0	0	0
SOFT TISSUE INJURY	1 (0.1)	0	0	0	0
FEMORAL NECK FRACTURE	1 (0.1)	0	0	0	0
SKELETAL INJURY	1 (0.1)	0	0	0	0
CORNEAL ABRASION	1 (0.1)	0	0	0	0
PATELLA FRACTURE	1 (0.1)	0	1 (0.2)	0	0
CARTILAGE INJURY	1 (0.1)	0	0	0	0
BURNS SECOND DEGREE	1 (0.1)	0	0	0	0
BRAIN CONTUSION	1 (0.1)	1 (0.2)	0	0	0
ANIMAL BITE	1 (0.1)	0	1 (0.2)	0	1 (0.3)
RETINAL DETACHMENT	0	2 (0.3)	0	2 (0.7)	0
MUSCLE RUPTURE	0	1 (0.2)	0	0	0
RADIUS FRACTURE	0	1 (0.2)	0	1 (0.3)	0
MUSCLE STRAIN	0	1 (0.2)	1 (0.2)	1 (0.3)	0
HAND FRACTURE	0	1 (0.2)	1 (0.2)	1 (0.3)	0
NERVE INJURY	0	1 (0.2)	0	0	0
SKIN INJURY	0	1 (0.2)	0	0	0
ANKLE FRACTURE	0	0	2 (0.3)	0	1 (0.3)
ULNA FRACTURE	0	0	0	0	1 (0.3)
STERNAL FRACTURE	0	0	0	1 (0.3)	0
BURNS FIRST DEGREE	0	0	1 (0.2)	0	0
TENDON INJURY	0	0	1 (0.2)	0	0
HYPERTHERMIA	0	0	1 (0.2)	0	0
FOREARM FRACTURE	0	0	1 (0.2)	0	0
ACUTE KIDNEY INJURY/CHRONIC RENAL FAILURE	**42 (3.3)**	**28 (4.3)**	**32 (5.1)**	**16 (5.5)**	**18 (6.1)**
GLOMERULAR FILTRATION RATE DECREASED	8 (0.6)	3 (0.5)	7 (1.1)	12 (4.1)	11 (3.8)
CREATININE RENAL CLEARANCE DECREASED	7 (0.6)	9 (1.4)	0	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
RENAL IMPAIRMENT	6 (0.5)	1 (0.2)	1 (0.2)	1 (0.3)	0
HYPERKALAEMIA	4 (0.3)	4 (0.6)	2 (0.3)	0	0
BLOOD CREATININE INCREASED	4 (0.3)	0	4 (0.6)	0	0
MICROALBUMINURIA	3 (0.2)	2 (0.3)	8 (1.3)	0	2 (0.7)
BLOOD POTASSIUM INCREASED	3 (0.2)	1 (0.2)	1 (0.2)	0	0
URINE ALBUMIN/CREATININE RATIO INCREASED	2 (0.2)	0	1 (0.2)	0	2 (0.7)
DIABETIC NEPHROPATHY	2 (0.2)	0	1 (0.2)	0	3 (1.0)
ACUTE KIDNEY INJURY	2 (0.2)	0	0	0	0
ACUTE PRERENAL FAILURE	1 (0.1)	0	0	0	0
CHRONIC KIDNEY DISEASE	1 (0.1)	0	3 (0.5)	0	1 (0.3)
URINARY CASTS PRESENT	1 (0.1)	0	0	0	0
PROTEINURIA	1 (0.1)	0	0	0	0
RED BLOOD CELLS URINE POSITIVE	1 (0.1)	0	1 (0.2)	0	0
RENAL FUNCTION TEST ABNORMAL	1 (0.1)	0	0	0	0
LEUKOCYTURIA	1 (0.1)	1 (0.2)	1 (0.2)	0	1 (0.3)
HYPERPHOSPHATAEMIA	1 (0.1)	1 (0.2)	0	0	0
URINE OUTPUT DECREASED	1 (0.1)	0	0	0	0
NORMOCHROMIC NORMOCYTIC ANAEMIA	1 (0.1)	0	0	0	0
WHITE BLOOD CELLS URINE POSITIVE	0	2 (0.3)	1 (0.2)	0	0
ALBUMINURIA	0	2 (0.3)	0	0	0
RENAL FAILURE	0	1 (0.2)	1 (0.2)	2 (0.7)	0
BLOOD CALCIUM DECREASED	0	1 (0.2)	0	0	0
HYPOCALCAEMIA	0	1 (0.2)	0	0	0
NEPHROPATHY	0	1 (0.2)	0	0	1 (0.3)
GLOMERULAR FILTRATION RATE ABNORMAL	0	0	0	1 (0.3)	0
BLOOD BICARBONATE DECREASED	0	0	1 (0.2)	0	0
OSMOTIC DIURESIS	**35 (2.8)**	**17 (2.6)**	**6 (1.0)**	**8 (2.7)**	**3 (1.0)**
POLLAKIURIA	20 (1.6)	10 (1.5)	1 (0.2)	7 (2.4)	1 (0.3)
POLYURIA	9 (0.7)	5 (0.8)	2 (0.3)	1 (0.3)	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
DRY MOUTH	4 (0.3)	4 (0.6)	2 (0.3)	0	0
MICTURITION URGENCY	3 (0.2)	0	0	0	1 (0.3)
THIRST	2 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.3)
NOCTURIA	1 (0.1)	0	1 (0.2)	0	1 (0.3)
POLYDIPSIA	0	3 (0.5)	0	1 (0.3)	0
HEART FAILURE/CARDIOMYOPATHY	**31 (2.5)**	**15 (2.3)**	**19 (3.0)**	**4 (1.4)**	**6 (2.0)**
OEDEMA PERIPHERAL	8 (0.6)	2 (0.3)	7 (1.1)	0	1 (0.3)
PALPITATIONS	5 (0.4)	2 (0.3)	1 (0.2)	0	1 (0.3)
CHEST PAIN	3 (0.2)	3 (0.5)	5 (0.8)	0	0
DYSPNOEA	3 (0.2)	0	1 (0.2)	0	0
SYNCOPE	2 (0.2)	2 (0.3)	0	0	0
OEDEMA	2 (0.2)	0	0	0	0
HEPATOMEGALY	2 (0.2)	0	0	2 (0.7)	0
PERIPHERAL SWELLING	2 (0.2)	1 (0.2)	3 (0.5)	0	0
VENTRICULAR ARRHYTHMIA	1 (0.1)	0	0	0	1 (0.3)
CARDIAC FAILURE	1 (0.1)	1 (0.2)	0	0	0
MENTAL STATUS CHANGES	1 (0.1)	0	0	0	0
NOCTURIA	1 (0.1)	0	1 (0.2)	0	1 (0.3)
ORTHOPNOEA	1 (0.1)	0	0	0	0
CARDIAC FAILURE ACUTE	1 (0.1)	0	0	0	0
ARRHYTHMIA	1 (0.1)	0	0	0	0
CARDIAC FAILURE CONGESTIVE	0	2 (0.3)	0	0	0
ELECTROCARDIOGRAM ABNORMAL	0	1 (0.2)	0	0	0
CARDIAC FAILURE CHRONIC	0	1 (0.2)	0	0	0
ASCITES	0	1 (0.2)	0	0	0
CONGESTIVE CARDIOMYOPATHY	0	1 (0.2)	0	0	0
BLOOD PRESSURE DIASTOLIC INCREASED	0	0	0	0	1 (0.3)
ORTHOSTATIC HYPOTENSION	0	0	0	1 (0.3)	1 (0.3)
CARDIOVASCULAR DISORDER	0	0	0	1 (0.3)	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
BLOOD PRESSURE INADEQUATELY CONTROLLED	0	0	2 (0.3)	0	0
DIABETIC MICROVASCULAR COMPLICATIONS	**29 (2.3)**	**9 (1.4)**	**17 (2.7)**	**2 (0.7)**	**7 (2.4)**
DIABETIC NEUROPATHY	16 (1.3)	2 (0.3)	4 (0.6)	1 (0.3)	1 (0.3)
MICROALBUMINURIA	3 (0.2)	2 (0.3)	8 (1.3)	0	2 (0.7)
DIABETIC RETINOPATHY	3 (0.2)	4 (0.6)	0	0	0
DIABETIC NEPHROPATHY	2 (0.2)	0	1 (0.2)	0	3 (1.0)
DIABETIC FOOT	2 (0.2)	2 (0.3)	1 (0.2)	0	0
RETINOPATHY	1 (0.1)	0	0	0	0
DEMYELINATING POLYNEUROPATHY	1 (0.1)	0	0	0	0
CHRONIC KIDNEY DISEASE	1 (0.1)	0	3 (0.5)	0	1 (0.3)
PROTEINURIA	1 (0.1)	0	0	0	0
RETINOPATHY PROLIFERATIVE	0	0	0	1 (0.3)	0
DIABETIC FOOT INFECTION	0	0	1 (0.2)	0	0
HEPATOTOXICITY	**19 (1.5)**	**8 (1.2)**	**19 (3.0)**	**3 (1.0)**	**1 (0.3)**
HEPATIC STEATOSIS	9 (0.7)	3 (0.5)	8 (1.3)	1 (0.3)	0
ALANINE AMINOTRANSFERASE INCREASED	4 (0.3)	3 (0.5)	6 (1.0)	0	1 (0.3)
TRANSAMINASES INCREASED	2 (0.2)	0	1 (0.2)	0	0
HEPATOMEGALY	2 (0.2)	0	0	2 (0.7)	0
LIVER FUNCTION TEST INCREASED	2 (0.2)	0	3 (0.5)	0	0
HEPATIC MASS	1 (0.1)	0	0	0	0
HEPATIC ENZYME INCREASED	1 (0.1)	1 (0.2)	0	1 (0.3)	0
HEPATIC CANCER	1 (0.1)	0	0	0	0
BLOOD BILIRUBIN INCREASED	1 (0.1)	0	2 (0.3)	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.1)	2 (0.3)	3 (0.5)	0	1 (0.3)
HEPATIC LESION	1 (0.1)	1 (0.2)	0	0	0
LIVER DISORDER	0	1 (0.2)	0	0	0
ASCITES	0	1 (0.2)	0	0	0
HYPERBILIRUBINAEMIA	0	0	1 (0.2)	0	0
HEPATIC CIRRHOSIS	0	0	1 (0.2)	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
VASCULAR INSUFFICIENCY	**18 (1.4)**	**5 (0.8)**	**6 (1.0)**	**1 (0.3)**	**0**
SKIN ULCER	5 (0.4)	2 (0.3)	2 (0.3)	0	0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	5 (0.4)	0	2 (0.3)	0	0
PERIPHERAL VENOUS DISEASE	3 (0.2)	1 (0.2)	1 (0.2)	1 (0.3)	0
DIABETIC FOOT	2 (0.2)	2 (0.3)	1 (0.2)	0	0
PERIPHERAL VASCULAR DISORDER	2 (0.2)	0	0	0	0
GANGRENE	2 (0.2)	0	1 (0.2)	0	0
PERIPHERAL COLDNESS	1 (0.1)	0	0	0	0
INTERMITTENT CLAUDICATION	1 (0.1)	0	0	0	0
DIABETIC FOOT INFECTION	0	0	1 (0.2)	0	0
MALIGNANCIES/PREMALIGNANT CONDITIONS	**16 (1.3)**	**14 (2.1)**	**0**	**0**	**2 (0.7)**
RECTAL POLYP	3 (0.2)	0	0	0	0
LARGE INTESTINE POLYP	3 (0.2)	5 (0.8)	0	0	0
ACTINIC KERATOSIS	1 (0.1)	0	0	0	0
INFECTED NEOPLASM	1 (0.1)	0	0	0	0
INVASIVE DUCTAL BREAST CARCINOMA	1 (0.1)	0	0	0	0
ADENOCARCINOMA OF COLON	1 (0.1)	0	0	0	0
NEOPLASM	1 (0.1)	0	0	0	0
HEPATIC CANCER	1 (0.1)	0	0	0	0
BASAL CELL CARCINOMA	1 (0.1)	0	0	0	1 (0.3)
RENAL NEOPLASM	1 (0.1)	1 (0.2)	0	0	0
ADRENAL NEOPLASM	1 (0.1)	0	0	0	0
SQUAMOUS CELL CARCINOMA OF SKIN	1 (0.1)	0	0	0	0
GASTRIC NEOPLASM	1 (0.1)	0	0	0	0
BLADDER TRANSITIONAL CELL CARCINOMA	0	1 (0.2)	0	0	0
BARRETT'S OESOPHAGUS	0	1 (0.2)	0	0	0
ADENOCARCINOMA	0	1 (0.2)	0	0	0
CROHN'S DISEASE	0	1 (0.2)	0	0	0
MALIGNANT MELANOMA	0	1 (0.2)	0	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
MELANOMA RECURRENT	0	1 (0.2)	0	0	0
LEUKOSTASIS SYNDROME	0	1 (0.2)	0	0	0
ENDOMETRIAL ADENOCARCINOMA	0	1 (0.2)	0	0	0
CHRONIC MYELOID LEUKAEMIA	0	0	0	0	1 (0.3)
BONE DISORDERS	**11 (0.9)**	**5 (0.8)**	**4 (0.6)**	**0**	**1 (0.3)**
SPINAL PAIN	6 (0.5)	2 (0.3)	0	0	1 (0.3)
EXOSTOSIS	2 (0.2)	0	0	0	0
SKELETAL INJURY	1 (0.1)	0	0	0	0
PERIOSTITIS	1 (0.1)	0	0	0	0
PAIN IN JAW	1 (0.1)	1 (0.2)	0	0	0
COCCYDYNIA	1 (0.1)	0	0	0	0
BONE FISTULA	0	1 (0.2)	0	0	0
HYPERPHOSPHATASAEMIA	0	1 (0.2)	0	0	0
METATARSALGIA	0	0	2 (0.3)	0	0
BONE PAIN	0	0	1 (0.2)	0	0
BONE MARROW OEDEMA	0	0	1 (0.2)	0	0
SKIN REACTION	**11 (0.9)**	**5 (0.8)**	**9 (1.4)**	**1 (0.3)**	**1 (0.3)**
SKIN ULCER	5 (0.4)	2 (0.3)	2 (0.3)	0	0
CONJUNCTIVITIS	4 (0.3)	2 (0.3)	4 (0.6)	0	1 (0.3)
SKIN EXFOLIATION	2 (0.2)	1 (0.2)	1 (0.2)	1 (0.3)	0
STOMATITIS	0	0	1 (0.2)	0	0
BLISTER	0	0	1 (0.2)	0	0
STOMATITIS/MOUTH ULCERS	**10 (0.8)**	**6 (0.9)**	**6 (1.0)**	**1 (0.3)**	**3 (1.0)**
OROPHARYNGEAL PAIN	7 (0.6)	6 (0.9)	2 (0.3)	1 (0.3)	3 (1.0)
ODYNOPHAGIA	1 (0.1)	0	0	0	0
APHTHOUS ULCER	1 (0.1)	0	0	0	0
PHARYNGEAL INFLAMMATION	1 (0.1)	0	0	0	0
UVULITIS	0	0	1 (0.2)	0	0
TONGUE DISCOMFORT	0	0	1 (0.2)	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
STOMATITIS	0	0	1 (0.2)	0	0
LIP SWELLING	0	0	1 (0.2)	0	0
FOURNIER'S GANGRENE	**9 (0.7)**	**7 (1.1)**	**1 (0.2)**	**1 (0.3)**	**0**
VAGINAL INFECTION	8 (0.6)	3 (0.5)	1 (0.2)	1 (0.3)	0
VULVOVAGINITIS	2 (0.2)	0	0	0	0
VAGINAL ABSCESS	0	1 (0.2)	0	0	0
SCROTAL ABSCESS	0	1 (0.2)	0	0	0
VULVOVAGINAL INFLAMMATION	0	1 (0.2)	0	0	0
VULVAL ABSCESS	0	1 (0.2)	0	0	0
BONE FRACTURES	**9 (0.7)**	**4 (0.6)**	**9 (1.4)**	**2 (0.7)**	**2 (0.7)**
FOOT FRACTURE	2 (0.2)	1 (0.2)	1 (0.2)	0	0
RIB FRACTURE	2 (0.2)	1 (0.2)	3 (0.5)	0	0
FEMORAL NECK FRACTURE	1 (0.1)	0	0	0	0
MULTIPLE FRACTURES	1 (0.1)	0	0	0	0
THORACIC VERTEBRAL FRACTURE	1 (0.1)	0	0	0	0
TIBIA FRACTURE	1 (0.1)	0	0	0	0
HUMERUS FRACTURE	1 (0.1)	1 (0.2)	0	0	0
PATELLA FRACTURE	1 (0.1)	0	1 (0.2)	0	0
RADIUS FRACTURE	0	1 (0.2)	0	1 (0.3)	0
HAND FRACTURE	0	1 (0.2)	1 (0.2)	1 (0.3)	0
ANKLE FRACTURE	0	0	2 (0.3)	0	1 (0.3)
ULNA FRACTURE	0	0	0	0	1 (0.3)
STERNAL FRACTURE	0	0	0	1 (0.3)	0
FOREARM FRACTURE	0	0	1 (0.2)	0	0
VOLUME DEPLETION	**8 (0.6)**	**6 (0.9)**	**0**	**2 (0.7)**	**2 (0.7)**
SYNCOPE	2 (0.2)	2 (0.3)	0	0	0
HYPOTENSION	2 (0.2)	3 (0.5)	0	1 (0.3)	1 (0.3)
PRESYNCOPE	1 (0.1)	0	0	0	0
URINE OUTPUT DECREASED	1 (0.1)	0	0	0	0

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
ACUTE PRERENAL FAILURE	1 (0.1)	0	0	0	0
DIZZINESS POSTURAL	1 (0.1)	1 (0.2)	0	0	0
CIRCULATORY COLLAPSE	0	1 (0.2)	0	0	0
ORTHOSTATIC HYPOTENSION	0	0	0	1 (0.3)	1 (0.3)
PERIPHERAL ARTERY DISEASE	**7 (0.6)**	**2 (0.3)**	**3 (0.5)**	**0**	**0**
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	5 (0.4)	0	2 (0.3)	0	0
DIABETIC FOOT	2 (0.2)	2 (0.3)	1 (0.2)	0	0
INTERMITTENT CLAUDICATION	1 (0.1)	0	0	0	0
DERMAL DIABETIC COMPLICATIONS	**6 (0.5)**	**4 (0.6)**	**3 (0.5)**	**0**	**0**
SKIN ULCER	5 (0.4)	2 (0.3)	2 (0.3)	0	0
DIABETIC FOOT	2 (0.2)	2 (0.3)	1 (0.2)	0	0
DIABETIC FOOT INFECTION	0	0	1 (0.2)	0	0
NEPHROLITHIASIS	**5 (0.4)**	**5 (0.8)**	**4 (0.6)**	**0**	**0**
NEPHROLITHIASIS	3 (0.2)	3 (0.5)	3 (0.5)	0	0
CALCULUS URINARY	1 (0.1)	0	0	0	0
RENAL COLIC	1 (0.1)	0	0	0	0
URETEROLITHIASIS	0	1 (0.2)	1 (0.2)	0	0
URINARY SEDIMENT ABNORMAL	0	1 (0.2)	0	0	0
THROMBOCYTOPENIA	**4 (0.3)**	**0**	**2 (0.3)**	**0**	**0**
THROMBOCYTOPENIA	3 (0.2)	0	1 (0.2)	0	0
PLATELET COUNT DECREASED	1 (0.1)	0	1 (0.2)	0	0
HYPOGLYCEMIA	**3 (0.2)**	**0**	**0**	**0**	**0**
HYPOGLYCAEMIA	3 (0.2)	0	0	0	0
Venous Thromboembolic Event	**2 (0.2)**	**1 (0.2)**	**1 (0.2)**	**0**	**0**
DEEP VEIN THROMBOSIS	1 (0.1)	0	1 (0.2)	0	0
PULMONARY EMBOLISM	1 (0.1)	0	1 (0.2)	0	0
THROMBOPHLEBITIS SUPERFICIAL	0	1 (0.2)	0	0	0
KETOACIDOSIS	**2 (0.2)**	**0**	**1 (0.2)**	**1 (0.3)**	**2 (0.7)**
URINE KETONE BODY PRESENT	1 (0.1)	0	0	1 (0.3)	2 (0.7)

CMQs	Dapa 10 mg + Saxa 5 mg + Met n=1263	Dapa 10 mg + Met n=654	Saxa 5 mg + Met n=631	Dapa 5 mg + Saxa 5 mg + Met n=293	Dapa 5 mg + Met n=293
BLOOD KETONE BODY INCREASED	1 (0.1)	0	0	0	0
KETONURIA	0	0	0	0	1 (0.3)
BLOOD BICARBONATE DECREASED	0	0	1 (0.2)	0	0
BONE AND JOINT INFECTIONS	**0**	**1 (0.2)**	**1 (0.2)**	**0**	**0**
OSTEOMYELITIS	0	1 (0.2)	1 (0.2)	0	0
LACTIC ACIDOSIS	**0**	**0**	**1 (0.2)**	**0**	**0**
BLOOD BICARBONATE DECREASED	0	0	1 (0.2)	0	0

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: Application 210874 - Sequence 0001 - Analysis Dataset Adam -
Abbreviations: Dapa, dapagliflozin, Met, metformin; and Saxa, saxagliptin.

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/s/

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