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APPLICATION NUMBER:

212614Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	NDA 212614
Priority or Standard	Standard
Submit Date(s)	March 27, 2019
Received Date(s)	March 27, 2019
PDUFA Goal Date	January 27, 2020
Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	January 17, 2020
Established/Proper Name	Empagliflozin + Linagliptin + Metformin hydrochloride (HCl) Extended-Release
(Proposed) Trade Name	TRIJARDY XR
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage Form(s)	The Applicant is seeking approval of film-coated tablets containing the following empagliflozin/linagliptin/metformin extended-release dosage strengths: 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg
Applicant Proposed Dosing Regimen(s)	Once daily oral administration with a meal.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) (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 TRIJARDY XR to include: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The primary recommended labeling changes for Section 2.2 include: No dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m^2, and do not initiate or continue if eGFR is below 45 mL/min/1.73 mL/min/1.73 m^2. The recommended labeling change for Section 4 is to contraindicate use with an eGFR below 30 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
ATL	Application Technical Lead
AUC	Area-Under-the-Curve
β-cell	Beta-Cell
BA	Bioavailability
BE	Bioequivalence
BG	Blood Glucose
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim Customized MedDRA Queries
BILI	Bilirubin
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BW	Body Weight
CAD	Coronary Artery Disease
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDS	Core Data Sheet
CEC	Clinical Event Committee
CECP	Clinical Event Committee for Adjudicating Pancreatic Events
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
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
COPD	Chronic Obstructive Lung Disease
C-Peptide	Connecting Peptide
CRCL	Creatinine Clearance
CRF	Case Report Form
CRO	Clinical 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
DB	Double-Blind
DBP	Diastolic Blood Pressure
D/C	Discontinuation
DCCT	Diabetes Control and Complication Trial
DEU	Germany
DKA	Diabetic Ketoacidosis
DMF	Drug Master File
DPP-4	Dipeptidyl Peptidase-4
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMPA	Empagliflozin
EOS	End-Of-Study
EOT	End-Of-Treatment
ER	Emergency Room
ESRD	End Stage Renal Disease
ETMF	Electronic Trial Master File
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
FAERS	FDA Adverse Event Reporting System
FAS	Full Analysis Set
FCDP	Fixed Combination Drug Product
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GIP	Glucose-Dependent Insulinotropic Polypeptide

GLP	Good Laboratory Practice
GLP-1	Glucagon-Like Peptide 1
GM	Geometric Mean
GRand	Global Randomization
H	Hour
HAC	Hepatic Adjudication Committee
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HCl	Hydrochloride
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
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
IXRS	Interactive Voice/Web-Based Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LINA	Linagliptin
LLN	Lower Limit of Normal
LOA	Letter of Authorization
LOCF	Last Observation Carried Forward
LT	Long-term
LTSS	Long Term Stability Study
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
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
MI	Multiple Imputation
mITT	Modified Intent-To-Treat
MMRM	Mixed Effects Model with Repeated Measures
MRHD	Maximum Recommended Human Dose
NAI	No Action Indicated
NCF	Non-Completers Failures
NCT	National Clinical Trial Identifier Number

NDA	New Drug Application
NGSP	National Glycohemoglobin Standardization Program
No	Number
NLR	Normal Laboratory Range
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OAI	Official Action Indicated
ObsRO	Observer Reported Outcome
OC	Observed Cases
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PAD	Peripheral Artery Disease
PAS	Periodic Acid Schiff's (staining)
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
PY	Patient-Year
QD	Daily
R	Randomization
RBPM	Regulatory Business Process Manager
REMS	Risk Evaluation and Mitigation Strategy
RH	Relative Humidity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
Scr	Serum Creatinine
SCS	Summary of Clinical Safety
SGLT2	Sodium-Glucose Cotransporter 2
SLC	Safety Labeling Change
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SOP	Standard Operating Procedure
SPOOS	Significant Payments of Other Sorts

ST	Short-term
SUSARS	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	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
UGT	UDP-glucuronosyltransferase
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

TRIJARDY XR (empagliflozin, linagliptin and metformin HCl extended-release) is a new fixed combination drug product (FCDP) submitted for marketing approval by Boehringer Ingelheim (referred to as the Applicant throughout the remainder of this review) as a New Drug Application (NDA 212614) in accordance with Section 505(b)(1) of the Federal Food,[1] Drug and Cosmetic Act and Section 314 of Title 21 CFR 314.50.[2]

The components of TRIJARDY XR are approved antihyperglycemic agents with the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D). Empagliflozin 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] Linagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation.[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.[5-8] The combination of an SGLT2 inhibitor with a DPP-4 inhibitor, added onto background metformin therapy[9-11] and the combination of an SGLT2 inhibitor[5,6,12-14] or a DPP-4 inhibitor[7,8,15-18] with metformin all provide complementary mechanisms of action to improve glycemic control.

The proposed indication for TRIJARDY XR is as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) . TRIJARDY will be available as film-coated tablets for once daily oral administration (with a meal in the morning), and will contain the following empagliflozin/linagliptin/metformin extended-release dosage strengths: 5 mg/2.5 mg/1000 mg; 10 mg/5 mg/1000 mg; 12.5 mg/2.5 mg/1000 mg; 25 mg/5 mg/1000 mg.

In the Applicant's proposed labeling, TRIJARDY XR is contraindicated in patients with moderate to severe renal impairment (estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2). However, the United States Package Inserts (USPIs) for empagliflozin (JARDIANCE)[3] and metformin extended-release (e.g., GLUMETZA) tablets[19] contraindicate the use of these products in patients with an eGFR <30 mL/min/1.73 m^2, and no dosing adjustments based on renal function are recommended in linagliptin (TRADJENTA) product labeling.[4] It is acknowledged that labeling for empagliflozin plus metformin FCDPs (i.e., SYNJARDY[5] and SYNJARDY XR)[6] contraindicate product use

in patients with an eGFR <45 mL/min/1.73 m^2. Both of these products were approved (8/26/2015 and 12/9/2016, respectively) near the time of labeling changes of metformin-containing products (Safety Communication dated April 8, 2016), which expanded the use to patients with moderately reduced kidney function.[20,21] I recommend that the labeled contraindication for renal impairment be revised to an eGFR <30 mL/min/1.73 m^2, consistent with approved empagliflozin and metformin labeling. However, as recommended in JARDIANCE product labeling,[3] Trijardy XR should not be initiated or continued in patients with an eGFR <45 mL/min/1.73 m^2. The Applicant will be requested to make similar revisions to product labeling for SYNJARDY and SYNJARDY XR at the next available opportunity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend an approval action for NDA 212614 (TRIJARDY XR) pending agreement on proposed labeling. In accordance with 21 CFR 314.126(a)(b),[22] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of this Application.

To support the registration of this FCDP for the proposed indication, the Applicant provided clinical data (Studies 1361.3 and 1361.11) to support the bioavailability/bioequivalence of TRIJARDY XR to the single entity components in healthy volunteers. The efficacy and safety data from a single pivotal clinical trial (i.e., 1275.1), previously reviewed to support the approval of their empagliflozin/linagliptin FCDP (i.e., GLYXAMBI, NDA 206073),[23] also was submitted. This 24-week factorial trial (with a 28-week extension phase) compared concomitant administration of empagliflozin (10 mg/day or 25 mg/day) plus linagliptin (5 mg/day) to empagliflozin or linagliptin, all as add-on therapy to metformin (≥1500 mg/day for 12 weeks) in adult T2D patients with inadequate glycemic control (HbA1c ≥7% to ≤10.5%). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in hemoglobin A1c [HbA1c] from baseline to Week 24) for this trial, the triple therapy arms (i.e., empagliflozin 10 mg/linagliptin 5 mg/metformin and empagliflozin 25 mg/linagliptin 5 mg/metformin) resulted in a modest but statistically significant HbA1c reduction compared to the empagliflozin dual therapy arms (i.e., metformin plus empagliflozin 10 or empagliflozin 25 mg): -0.4% (95% confidence interval [CI], -0.6, -0.2) and -0.6% (-0.7, -0.4), respectively; and the linagliptin dual therapy arm: -0.4% [-0.6, -0.2) and -0.5 (-0.7, -0.3), respectively. Statistically significant reductions were also reported for key secondary endpoints (i.e., fasting plasma glucose [FPG] and body weight).

In a Written Response (dated January 25, 2018), the Agency agreed that existing efficacy and safety data from two additional Phase 3 trials (1275.9, and 1275.10) conducted under the empagliflozin/linagliptin FCDP development program (IND 108388) should be submitted as supportive data. Trial 1275.9 was a 24-week, randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial designed to evaluate the efficacy and safety of addition of empagliflozin (10 mg/day and 25 mg/day) to linagliptin 5 mg/day plus metformin compared with the addition of placebo to linagliptin plus metformin in subjects with T2D who had inadequate glycemic control on linagliptin plus maximum tolerated doses of metformin (≥1500 mg/day). Trial

1275.10 was a 24-week, randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial designed to evaluate the efficacy and safety of addition of linagliptin 5 mg/day to empagliflozin (10 mg/day or 25 mg/day) plus metformin compared with the addition of placebo to empagliflozin plus metformin in subjects with T2D who had inadequate glycemic control on empagliflozin plus maximum tolerated doses of metformin (≥1500 mg/day). The results of these two trials were supportive (i.e., the triple therapy arms resulted in statistically significant greater reductions in HbA1c from baseline to Week 24 vs. the dual therapy arms).

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

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Type 2 diabetes 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 glycemic targets. Thus, additional therapeutic options are needed to facilitate individualization of therapy.

TRIJARDY XR is a combination of empagliflozin, a SGLT2 inhibitor, linagliptin, 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 empagliflozin/linagliptin/metformin extended-release tablets (i.e., 5 mg/2.5 mg/1000 mg; 10 mg/5 mg/1000 mg; 12.5 mg/2.5 mg/1000 mg; and 25 mg/5 mg/1000 mg) are intended to support approved doses of empagliflozin (10-25 mg/day),[24] linagliptin (5 mg/day),[25] and metformin (1000-2000 mg/day).[26] 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 empagliflozin and linagliptin, 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 empagliflozin is 10 mg once daily, which is subsequently titrated to 25 mg daily in patients tolerating the 10 mg dose should additional glycemic control be required.

The safety profile of TRIJARDY XR is reflective of individual components of this product. In their 52-week pivotal trial (1275.1), the most common adverse reactions (>5% of subjects) reported in the empagliflozin 10 mg and 25 mg triple therapy arms were upper respiratory tract infections (10.3% and 8%, respectively), urinary tract infections (9.6% and 10.2%), nasopharyngitis (8.1% and 5.8%), diarrhea (6.6% and 2.2%), constipation (5.1% and 5.8%), headache (5.1% in both arms) and gastroenteritis (2.9% and 5.8%), which generally were also common to the linagliptin and/or empagliflozin dual therapy arms. For the 24-week supporting trials, common AEs included urinary tract infections (7.1% and 3.6% of subjects in the empagliflozin 10 mg and 25 mg triple therapy arms, respectively) in Trial 1275.9, and urinary tract infections (9.5% and 13.4%), nasopharyngitis (6.3% and 1.8%) and lipase increased (3.2% and 6.3%) in Trial 1275.10. Although antihyperglycemic FCDPs have a potential for an increased risk of hypoglycemia compared to the individual components, only a single subject in the empagliflozin 25 mg triple therapy arm of Trial 1275.9 experienced hypoglycemia requiring assistance, and there were no reports of symptomatic hypoglycemia (without the need for assistance) with a blood glucose <54 mg/dL across the three trials. Deaths and serious adverse events (SAEs) were limited and not informative.

In summary, the data show that each of the components of the FCDP contribute to improving glycemic control at the doses evaluated in the pivotal and supporting Phase 3 trials. I believe that the overall benefit-risk for patients is favorable and recommend approval of TRIJARDY XR.

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.[27-30] The Center for Disease Control (CDC) estimates that nearly 30 million people in the United States have T2D.[27,31]	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk of morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial (DCCT),[32-38] the United Kingdom Prospective Diabetes (UKPD) study,[30,39-42] and the Kumamoto Study,[43] 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.[44] 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.[44-47] • 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.
Benefit	• The results of the three Phase 3 clinical trials demonstrate that the combination of empagliflozin (10 mg or 25 mg) and linagliptin 5 mg plus maximally tolerated background metformin therapy results in better glycemic control (i.e., greater HbA1c reductions) compared to the individual	The pivotal (1275.1) and two supporting (1275.9 and 1275.10) clinical trials have provided adequate evidence to support efficacy of TRIJARDY XR. Additionally, these trials provide support that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	components (empagliflozin plus metformin or linagliptin plus metformin) at the doses evaluated in the trials.	empagliflozin and linagliptin 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 trial. It also is acknowledged that triple FCDPs may limit flexibility in dose adjustments. However, based on usage data, the proposed dose formulations of TRIJARDY XR should be sufficient for dose adjustments in the majority of the intended patient population.
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 known safety concerns are already included in labeling for GLYXAMBI, and the Applicant proposes to include the same information in Section 6.1 (Clinical Trials Experience) of TRIJARDY XR labeling. • No additional safety signals were identified in Trials 1275.9 and 1275.10. • No risk evaluation and mitigation strategy is recommended for this product.	The clinical risks associated with use of the empagliflozin plus linagliptin plus metformin are what would be expected with the use of these drugs individually. As Trial 1275.1 was the pivotal trial used to support approval of GLYXAMBI (i.e., empagliflozin plus linagliptin FCDP), and only the data from the trial population receiving background metformin therapy will be used to support this NDA, the proposed language for Section 6.1 of labeling for TRIJARDY XR is similar to that from Section 6.1

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		of GLYXAMBI product labeling. No new safety signals were observed with the additional safety data provided from Trials 1275.9 and 1275.10.

1.4. Patient Experience Data

Subject-reported experience data were not submitted or evaluated.

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).[48,49] According to the 2017 National Diabetes Statistics Report, diabetes affects an estimated 30.3 million people within the United States (U.S.),[31] of which T2D accounts for 90-95% of all diagnosed cases.[27,31] 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.[50]

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)[28] and macrovascular (e.g., myocardial infarction, stroke) complications.[29,30] 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.[51] Diabetes remains a leading cause of kidney failure,[52] adult-onset blindness,[53,54] and non-traumatic lower limb amputations.[55,56] 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.[57,58] Several reports suggest that CVD may affect approximately 40% of T1D patients over 65 years of age and 32% of persons with T2D.[59] Diabetes was the seventh leading cause of death in 2015,[31] 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).[60-62] Based on the results of the Diabetes Control and Complication Trial (DCCT),[32-38] the United Kingdom Prospective Diabetes Study (UKPDS),[30,39-42] and the Kumamoto Study,[43] 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 21, Appendix 12.3). The 2015 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement and their 2018[63] and 2019[64] updates advocate the use of a patient-centered approach for the management of T2D, which includes the assessment of glycemic efficacy, hypoglycemia risk, impact on weight, risks for adverse effects, adherence, costs, and patient preference.[46] 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.[65] Age (e.g., individuals over the age of 65 years[66,67]) and comorbidities (e.g., atherosclerotic CVD, heart failure [HF], chronic kidney disease [CKD])[44,64] also should be considered and used to guide selection of an antihyperglycemic regimen. The ADA and EASD recommend the use of an SGLT2 inhibitor or a glucagon-like peptide 1 [GLP-1] receptor agonist with demonstrated CV benefit as part of the antihyperglycemic regimen for T2D patients with established atherosclerotic CVD or indicators of high risk (e.g., age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or left ventricular hypertrophy [LVH]), established kidney disease (e.g., eGFR 30-60 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio [UACR] >30 mg/g), or HF (particularly with a left ventricular ejection fraction [LVEF] <45%), independent of HbA1c and in consideration of the patient-specific factors discussed above.[44,64]

The ADA and EASD recommend initiating antihyperglycemic therapy for the management of T2D with metformin as monotherapy unless it is contraindicated or not tolerated.[44,64] 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.[68] 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 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.[46] Similar recommendations also have been published in the ADA's Standards of Medical Care in Diabetes–2020,[44] and suggested by the American College of Physicians (ACP),[69,70] and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE).[71]

The AACE/ACE also recommends initiating metformin plus a second antihyperglycemic agent for patients presenting with an HbA1c >7.5%.[71] Additionally, when the HbA1c concentration is ≥1.5% above the glycemic target, many patients may require dual combination therapy to achieve their target HbA1c concentration.[72] 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.[73] A meta-analysis of 15 randomized controlled trials reported potential benefit of initial dual combination therapy

with metformin on glycemic outcomes compared to metformin monotherapy across a wide range of baseline HbA1c concentrations in untreated T2D patients.[74] This approach has been reported to be superior to sequential addition of medications for extending primary and secondary failure.[75] Several studies also have reported advantages from adding a third noninsulin agent,[46,76-86] as well as triple therapy with both oral and injectable antihyperglycemic agents.[87-90] 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).[91]

Three FCDPs that contain an SGLT2 inhibitor plus a DPP-4 inhibitor (i.e., empagliflozin/linagliptin,[9,80] dapagliflozin/saxagliptin,[10,92] and ertugliflozin/sitagliptin[11,93]), as well as a triple therapy FCDP containing an SGLT2 inhibitor, DPP-4 inhibitor and biguanide (dapagliflozin/saxagliptin/metformin),[86] were approved primarily based on Phase 3 trials which demonstrated improved glycemic control as add-on combination therapy 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.[44,94] 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).[44] If the basal insulin dose has been titrated to an acceptable FBG concentration or is >0.5 units/kg/day and the HbA1c remains above the desired glycemic target, the ADA suggests that the use of combination therapy with a GLP-1 receptor agonist as add-on to insulin therapy could be considered.[44]

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

Pharmacologic Class	Antihyperglycemic Drug Products*
	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 21, Appendix 12.3.

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.[95-97] Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations (please refer to Table 21).[44,70,98] 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 (CHF), while DPP-4 inhibitors carry a class warning for a risk of HF and severe/disabling arthralgia. Metformin and SGLT2 inhibitors are contraindicated in patients with severe renal dysfunction. Metformin use also may be associated with vitamin B_{12} deficiency and worsening of symptoms of neuropathy.[99] 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, pioglitazone, 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, occurrence of injection site reactions). 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) and is not

recommended for individuals who smoke or recently stopped smoking. More recently, the FDA issued Drug Safety Communications to warn the public of increased risks of lower extremity amputations[100,101] Fournier's gangrene,[102] and a safety labeling change (SLC) informing patients and healthcare providers of the risk of peri-/post-operative diabetic ketoacidosis (DKA) with SGLT2 inhibitors. A SLC also was required for all injectable insulin products to warn prescribers and patients of postmarketing reports of localized cutaneous amyloidosis and associated risks of hyperglycemia with repeated injections into these areas and hypoglycemia with a sudden change to unaffected injection sites.

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.[103] Nonadherence to oral antihyperglycemic agents has been reported in 7%-64% of patients with T2D,[104,105] and has been associated with poor glycemic control,[106,107] diabetes-related hospitalizations[108,109] and increased mortality.[108] For patients requiring combination antihyperglycemic therapy, adherence may improve with a reduction in pill burden through the use of FCDPs.[110-112] 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 12.3, Table 21).

2.3. U.S. Regulatory Actions and Marketing History

EMPAGLIFLOZIN-CONTAINING AND LINAGLIPTIN-CONTAINING PRODUCTS: Empagliflozin (JARDIANCE); Empagliflozin/Linagliptin (GLYXAMBI); Empagliflozin/Metformin (SYNJARDY, SYNJARDY XR); Linagliptin (TRADJENTA); Linagliptin/Metformin (JENTADUETO, JENTADUETO XR)

Empagliflozin (JARDIANCE) 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.[113] JARDIANCE subsequently received approval (December 2, 2016) to reduce the risk of cardiovascular death in adult patients with T2D and established cardiovascular disease following submission of the results from the EMPA-REG cardiovascular outcomes trial (CVOT).[114] Other FDA-approved SGLT2 inhibitors include canagliflozin (approved in 2013),[115] dapagliflozin (approved in 2014),[113] and ertugliflozin (approved in 2017).[116] In 2015, GLYXAMBI, a FCDP containing empagliflozin and linagliptin, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[23] SYNJARDY (empagliflozin plus metformin immediate-release FCDP)[5] and SYNJARDY XR (empagliflozin plus metformin extended-release FCDP)[6] were approved in 2015 and 2016, respectively, with the 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.

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. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE).[117-119] Following administration of 10 mg and 25 mg daily doses of empagliflozin in patients with T2D, these pharmacodynamics changes have been associated with excretion of approximately 64-78 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.[3,120,121] Due to a dependency on glucose filtration at the glomerulus, patients with decreased renal function may have less response to the glycemic lowering effects of empagliflozin.[3,118]

Linagliptin belongs to the class of antihyperglycemic agents known as DPP-4 inhibitors. In patients with T2D, DPP-4 enzyme activity is competitively/selectively/reversibly inhibited for more than 24 hours following oral administration of linagliptin. 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 an 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.[4,122-126] As GLP-1 activity (e.g., insulin secretion) is limited when plasma glucose concentrations fall below approximately 55 mg/dL,[127] DDP-4 inhibitors are associated with a relatively low risk of hypoglycemia.

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.[128] 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.[15] The combination of empagliflozin plus metformin is associated with improved glycemic control.[129-136] As add-on therapy to metformin, the combination of empagliflozin and linagliptin also is associated with improved glycemic control.[9,79-82,137] However, SYNJARDY and SYNJARDY XR product labeling includes a Boxed Warning of postmarketing cases of metformin-associated lactic acidosis resulting in death, hypothermia, hypotension and resistant bradyarrhythmias.[5,6] These cases primarily occurred in patients with significant renal impairment. At the time of the product approval of SYNJARDY (August 26, 2015), 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.[20] 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.[20]

JARDIANCE is formulated as film-coated tablets containing either 10 mg or 25 mg of empagliflozin. The recommended starting dose is 10 mg orally once daily in the morning with or without food and can be increased to 25 mg once daily in patients tolerating this dose who require additional glycemic control. Use of JARDIANCE is not recommended in patients with an eGFR <45 mL/min/1.73 m^2. JARDIANCE is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.[3]

GLYXAMBI is formulated as film-coated tablets containing 10 mg of empagliflozin plus 5 mg of linagliptin and 25 mg of empagliflozin plus 5 mg of linagliptin. The recommended starting dose is 10 mg empagliflozin/5 mg linagliptin orally once daily in the morning with or without food. Initiation or continued use of GLYXAMBI is not recommended with an eGFR <45 mL/min/1.73 m^2, and this product is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease, or patients on dialysis.[9]

SYNJARDY is available as film-coated tablets containing either 5 mg of empagliflozin with 500 mg metformin HCl immediate-release (5 mg/500 mg), 5 mg of empagliflozin with 1000 mg metformin HCl immediate-release (5 mg/1000 mg), 12.5 mg empagliflozin with 500 mg metformin HCl immediate-release (12.5 mg/500 mg), 12.5 mg of empagliflozin with 1000 mg metformin HCl immediate-release (12.5 mg/1000 mg).[5] SYNJARDY is administered orally twice daily with food to reduce gastrointestinal side effects. The starting dose is individualized based on the patient's current treatment regimen. The maximum recommended dose for this product is 12.5 mg empagliflozin/1000 mg metformin HCl immediate-release twice daily. Use of SYNJARDY is contraindicated with an eGFR <45 mL/min/1.73 m^2, ESRD or dialysis.[5] As with TRIJARDY XR labeling, I recommend that labeling be revised (at the next available opportunity) to state that SYNJARDY should not be initiated or continued in patients with an eGFR <45 mL/min/1.73 m^2 and to contraindicate use in individuals with an eGFR <30 mL/min/1.73 m^2.

SYNJARDY XR is available as film-coated tablets containing either 5 mg of empagliflozin with 1000 mg metformin HCl extended-release (5 mg/1000 mg), 10 mg of empagliflozin with 1000 mg metformin HCl extended-release (10 mg/1000 mg), 12.5 mg empagliflozin with 1000 mg metformin HCl extended-release (12.5 mg/1000 mg), or 25 mg of empagliflozin with 1000 mg metformin HCl extended-release (25 mg/1000 mg).[6] SYNJARDY XR is administered orally once daily in the morning with a meal. The starting dose is individualized based on the patient's current treatment regimen. The maximum recommended daily dose for this product is 25 mg

empagliflozin/2000 mg metformin HCl extended-release. Use of SYNJARDY XR is contraindicated with an eGFR <45 mL/min/1.73 m^2, ESRD or dialysis.[6] Similar to the recommendations for SYNJARDY labeling, product labeling should be revised (at the next available opportunity) to state that SYNJARDY XR should not be initiated or continued in patients with an eGFR <45 mL/min/1.73 m^2 and to contraindicate use in individuals with an eGFR <30 mL/min/1.73 m^2.

TRADJENTA is formulated as a film-coated tablet containing 5 mg of linagliptin. The recommended dose is 5 mg orally once daily with or without food. No dose adjustment is recommended for patients with renal impairment.[4]

JENTADUETO is available as film-coated tablets containing either 2.5 mg of linagliptin with 500 mg metformin HCl immediate-release (2.5 mg/500 mg), 2.5 mg of linagliptin with 850 mg metformin immediate-release (2.5 mg/850 mg), or 2.5 mg of linagliptin with 1000 mg metformin immediate-release (2.5 mg/1000 mg).[8] JENTADUETO is administered orally twice daily with meals. The starting dose is individualized based on the patient's current treatment regimen. The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin HCl twice daily. Initiation of JENTADUETO 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.[8]

JENTADUETO XR is available as coated tablets containing either 2.5 mg of linagliptin with 1000 mg metformin HCl extended-release (2.5 mg/1000 mg), or 5 mg of linagliptin with 1000 mg metformin HCl extended-release (5 mg/1000 mg).[7] JENTADUETO XR is administered orally once daily with a meal. The dose is individualized based on both effectiveness and tolerability. Initiation of JENTADUETO 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.[7]

2.4. Summary of Presubmission/Submission Regulatory Activity

The relevant regulatory history for the submitted Applications is summarized in Table 2 below. TRADJENTA (linagliptin), JENTADUETO (linagliptin/metformin immediate-release FCDP), JENTADUETO XR (linagliptin/metformin extended-release FCDP), JARDIANCE (empagliflozin), SYNJARDY (empagliflozin/metformin immediate-release FCDP), SYNJARDY XR (empagliflozin/metformin extended-release FCDP) and GLYXAMBI (empagliflozin/linagliptin FCDP) all previously received marketing approval in the U.S. for the treatment of T2D in adult patients (please see Section 2.3 above). Also of relevance for the current submission is the recent approval (May 2, 2019) of QTERNMET XR, an antihyperglycemic FCDP containing dapagliflozin plus saxagliptin plus metformin XR, for the broad indication 'as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus'.[138] The two clinical trials used to support the efficacy and safety of this FCDP evaluated add-on therapy with dapagliflozin plus saxagliptin in subjects on background metformin therapy, and add-on therapy with saxagliptin in subjects on dapagliflozin plus metformin therapy, respectively. The current Application includes three trials that evaluated

the efficacy and safety of: 1) empagliflozin plus linagliptin as add-on therapy to metformin a (factorial design study); 2) empagliflozin as add-on therapy to linagliptin plus metformin; and 3) linagliptin as add-on therapy to empagliflozin plus metformin.

Table 2: Summary of Presubmission/Submission Regulatory History

Date	Summary of Relevant Agency Interactions
May 2, 2011	NDA 201280 – FDA approves TRADJENTA (linagliptin) once-daily treatment for adults with T2D.[139]
January 30, 2012	NDA 201281 – FDA approves JENTADUETO (linagliptin/metformin immediate-release) twice-daily FCDP for adults with T2D.[140]
August 1, 2014	NDA 204629 – FDA approves JARDIANCE (empagliflozin) once-daily treatment for adults with T2D.[141]
December 12, 2014	Pre-IND 122138 – Submission of a Type C meeting request to discuss the Applicant's clinical development strategy to support registration of their triple FCDP and planned dosage formulations.[142]
January 30, 2015	NDA 206073 – FDA approves GLYXAMBI (empagliflozin/linagliptin) once-daily FCDP for adults with T2D.[23]
February 26, 2015	Pre-IND 122138 – FDA provides written responses to the Applicant's questions submitted in their Type C meeting request (dated December 12, 2014). FDA stated that the Applicant's planned approach to base support for the proposed triple FCDP on a factorial study and sequential add-on studies being performed under the IND for the empagliflozin plus linagliptin FCDP was reasonable assuming that the Phase 3 studies demonstrate a contribution from each component and that an adequate bridge from the Phase 3 studies and the proposed drug product is established. The Applicant also was asked to provide support for the utility and need of this product, as well as justify the selected dosage strengths (empagliflozin/linagliptin/metformin extended-release (5 mg/2.5 mg/1000 mg; 10 mg/5 mg/1000 mg; 12.5 mg/2.5 mg/1000 mg; and 25mg/5 mg/1000 mg).[143]
August 26, 2015	NDA 206111 – FDA approves SYNJARDY (empagliflozin/metformin immediate-release) twice-daily FCDP for adults with T2D.[144]
March 16, 2016	IND 122138 – Submission of Study 1361.1 (a pilot BA study with the Applicant's triple FCDP) to open the IND.
April 18, 2016	IND 122138 – Submission of a Type C Meeting Request to discuss the clinical development strategy for TRIJARDY XR.
May 27, 2016	NDA 208026 – FDA approves JENTADUETO XR (linagliptin/metformin extended-release) once-daily FCDP for adults with T2D.[145]

Date	Summary of Relevant Agency Interactions
June 14, 2016	IND 122138 – FDA provides written responses to the Applicant's questions submitted in their Type C background document (April 18, 2016). The Applicant was asked to clarify how the proposed clinical trials satisfy the requirements under 21 CFR 300.50 and justify the need for a triple antihyperglycemic FCDP. The proposed BA/BE plan, biowaiver requests for the (b) (4) the use of GLUMETZA (metformin extended-release), JARDIANCE (empagliflozin) and TRADJENTA (linagliptin) for reference products in the BA/BE program, a request for a full waiver of pediatric requirements, the proposed rat toxicity study, and stability testing were considered reasonable. An in vitro alcohol-induced dose dumping study and submission of three executed batch records for each dosage strength were recommended.[146]
July 21, 2016	IND 122138 – Submission of a Clinical Information Amendment. The Applicant noted that approximately 48% of patients with T2D do not achieve the ADA recommended HbA1c goal, and that sequential/stepwise approach may lead to prolonged/unacceptable delays in achieving/maintaining glycemic goals. Further, 28% of patients require 2 or more antihyperglycemic medications, with 7-10% requiring three or more medications. TRIJARDY XR would offer patients a once daily triple antihyperglycemic FCDP (with each component providing a complimentary mode of action) and the potential for improved adherence. U.S. IMS data for Glyxambi suggest that (b) (4)% of prescriptions were for patients already on at least one oral antihyperglycemic mediation (the majority being metformin); (b) (4)% for patients prescribed two oral antihyperglycemic medications; (b) (4)% for patients receiving ≥3 antihyperglycemic medications; and (b) (4)% for treatment naïve patients. The Applicant also stated that Trial 1275.1 is an active controlled-factorial design trial which provides evidence of the contribution of empagliflozin when added to linagliptin on background metformin. Trial 1275.9 is an active-controlled filter design trial (i.e., filter out of the study subjects with adequate glycemic control on 16 weeks of linagliptin plus metformin) that provides evidence of the contribution of empagliflozin when added to patients inadequately controlled on linagliptin plus metformin. Trial 1275.10 provides evidence of the contribution of linagliptin when added to patients inadequately controlled on empagliflozin plus metformin. The Applicant also cites regulatory precedence for NDA approval of metformin FCDPs based on results of "add-on" studies (i.e., JANUMET, SYNJARDY) for patients not adequately controlled on metformin alone. Based on the additional information provided the Applicant questioned whether the Agency concurred that the proposed clinical package would be adequate to support an assessment of efficacy and safety for the registration of the Triple FDC and satisfy the requirements defined in 21 CFR 300.50.[147]
November 3, 2016	IND 122138 – FDA provided advice related to the Applicant's Clinical Information Amendment (dated July 21, 2016), stating that the detailed plan for how the proposed studies would support a conclusion that each of the components of TRIJARDY XR would contribute to the claimed effect would be reasonable to initiate a review of the proposed NDA. FDA recommended that the NDA submission should also outline how each submitted trial supports the proposed indication.[148]
December 9, 2016	NDA 208658 – FDA approves SYNJARDY XR (empagliflozin/metformin extended-release) once-daily FCDP for adults with T2D.[149]
December 20, 2017	IND 122138 – Type B (Pre-NDA Meeting) background document submitted.[150]

Date	Summary of Relevant Agency Interactions
January 3, 2018	IND 122138 – Type C background document submitted to discuss dissolution comparability data and their biowaiver application.[151]
January 25, 2018	IND 122138 – FDA provided written responses to the Applicant's questions submitted in their Pre-NDA Meeting background document (December 20, 2017). Generally, the proposed content for the Applicant's NDA would be considered acceptable. ADAM datasets and SAS programs were requested in addition to the SDTM datasets. Additionally, the FDA felt that Trials 1275.9 and 1275.10 provided additional data on concomitant use of the three antihyperglycemic components of the proposed FCDP, and therefore requested that the CSRs be submitted to the NDA. The Applicant was informed that As the study designs are different, it would be reasonable to not pool the three studies (i.e., 1275.1, 1275.9, and 1275.10).[152]
February 13, 2018	IND 122138 – FDA provided written responses to the Applicant's questions submitted in their Type C Meeting background document (dated January 3, 2018). The Applicant was informed that the proposed strengths were (b) (4) the approval (b) (4) would need to be supported based on a dose proportionality study; OR by using a bracketing approach (i.e., demonstration of BE based on the highest and lowest strengths with inclusion of a biowaiver request at the time of NDA submission for the strengths not tested and dissolution profile comparisons with similarity testing between the middle vs. highest and vs. lowest strengths.[153]
April 13, 2018	IND 122138 – Type C background document submitted to discuss the Applicant's proposal for a biowaiver for the (b) (4) tablet strengths.[154]
May 30, 2018	IND 122138 – FDA provided written responses to the Applicant's questions submitted in their Type C Meeting background document (dated April 13, 2018). FDA reiterated their advice/recommendations provided from February 13, 2018.[155]
March 27, 2019	NDA 212614 – The TRIJARDY XR NDA is submitted to the FDA for review.

Source: Adapted from the Applicant's Summary of Relevant FDA Interactions, available at:
Application 212614 - Sequence 0000 - 0000 (1) 03/27/2019 ORIG-1 /Multiple Categories/Subcategories
Abbreviations: ADAM, Analysis Data Model; BA, bioavailability; BE, bioequivalence; CFR, Code of Federal Regulations; CSR, Clinical Study Report; FCDP, fixed combination drug product; FDA, Food and Drug Administration; IMS, Intercontinental Medical Statistics; IND, Investigational New Drug; NDA, New Drug Application; SAS, Statistical Analysis System; SDTM, Study Data Tabulation Model; T2D, type 2 diabetes mellitus; US, United States; and XR, extended-release.

2.5. Foreign Regulatory Actions and Marketing History

TRIJARDY XR is not currently marketed in any country.

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

3.1. Office of Scientific Investigations (OSI)

Dr. Cynthia Kleppinger, from the Office of Scientific Investigations (OSI), was asked to inspect six clinical sites (3 domestic and 3 foreign) for the two supporting Phase 3 clinical trials, accounting

for 51 of 1134 (4.5%) subjects enrolled in Trial 1275.9 and 47 of 1324 (3.5%) subjects enrolled in Trial 1275.10 (Table 3). 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 six selected site 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 those reports, the Agency did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance for five (Drs. Cusco-Prieto, Armas, Terns, Calella, and Castano) of the six study sites (i.e., the data from these sites are considered reliable). A Form FDA-483, Inspectional Observations, was issued to Dr. Binker for not following the protocol: one subject (# (b) (6), from Study 1275.9) was enrolled without meeting inclusion criteria #3 (HbA1c ≥ 8.0% and ≤ 10.5% at Visit 1). The subject's HbA1c value was 7.7% at Visit 1. Following review of the full Establishment Inspection Report and the documents submitted with that report, Dr. Kleppinger concluded that the violations do not 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.

Table 3: Protocol/Site Identification

Investigator Location	Site #	Protocol ID	Subjects Enrolled	Rationale for Site Selection	Classification (Inspection Dates)
Domestic					
Josefa Binker Community Research Foundation, Inc. Miami, FL 33155	1004	1275.9	11	• Ranked #2 for site risk • High site-specific efficacy effect size • Very low numbers of AEs and SAEs reported • Has never been inspected	**VAI** (July 16 – 25, 2019)
Baudilio Cusco-Prieto Clinical Therapeutics Corporation Coral Gables, FL 33134	1010	1275.9	29	• Ranked #5 for site risk • Highest enrolling US site • Higher than average efficacy effect size • Very low numbers of AEs and SAEs reported • Higher than average protocol deviations • Inspected in 2015 (VAI) • Potential double-enrollee (i.e.,	**NAI** (July 9 – 12, 2019)

Investigator Location	Site #	Protocol ID	Subjects Enrolled	Rationale for Site Selection	Classification (Inspection Dates)
				Subjects (b) (6)	
Eddie Armas Well Pharma Medical Research Suite 100 Miami, FL 33143	1011	1275.10 A*	7	• Ranked #1 for site risk • High enrolling US site • Higher than average protocol violations • Low number of AEs reported • Inspected in 2017 (VAI) and 2014 (NAI)	**NAI** (Aug 19–23, 2019)
		1275.10 B*	6		
Foreign					
Manel Terns EAP Vic / Passatge Pla. del Remei Spain	34006	1275.9	11	• Ranked #11 for site risk • High enrolling foreign site • Very high efficacy effect size • Very high number of protocol deviations • Very high number of AEs and SAEs • Has never been inspected	**NAI** (July 8 – 11, 2019)
Pedro Calella Centro Integral de Prevencion y Atencion en Diabetes Argentina	54003	1275.10 A*	10	• Ranked #8 for site risk • High enrolling foreign site • Large amount of study data from Argentina • Has never been inspected	**NAI** (Sept 23 – 26, 2019)
		1275.10 B*	6		
Patricia Castano Instituto Médico Especializado Departamento de Nutrición, Metabolismo y Diabetología Argentina	54013	1275.10 A*	12	• Ranked #3 for site risk • Second highest enroller • Low number of AEs reported • Higher than average protocol violations • Has never been inspected	**NAI** (Oct 21 – 24, 2019)
		1275.10 B*	6		

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

*1275.10 A: linagliptin 5 mg vs. placebo as add-on to empagliflozin 25 mg plus metformin; 1275.10 B: linagliptin 5 mg vs. placebo as add-on to empagliflozin 10 mg plus metformin.

In her review (dated December 4, 2019), Dr. Kleppinger also summarized results of a previous for-cause inspection (November 3-25, 2014) of a domestic site (i.e., Dr. Gilbert J. Martinez, Site 1019) for Trial 1275.9. This site enrolled 18 subjects and randomized 12 subjects, of which none had completed the trial. At the conclusion of the inspection, a Form FDA-483 was issued for failure to conduct the investigation in accordance with the signed statement of the investigator and the investigational plan (i.e., inclusion of Subject (b) (6) who failed to meet blood glucose eligibility criteria). Additionally, Dr. Martinez did not have medical records to support patient eligibility for 16 of 18 subjects enrolled. At the OSI Compliance Enforcement Branch Significant Meeting (February 10, 2015), it was acknowledged that regulatory violations were noted, but the data from this site were considered acceptable. Please refer to Dr. Kleppinger's review for further details.

Based on the above inspections, Dr. Kleppinger felt that the clinical trial data generated are acceptable and can be used to support this NDA. I concur with Dr. Kleppinger's assessment.

In addition to the above FDA inspections, the Office of Study Integrity and Surveillance (OSIS) arranged an inspection (August 12-15, 2019) of Studies 1361-0003 and 1361-0011, conducted at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach An der Riss, Germany. The study records, subject records, informed consent process, protocol compliance, investigational product accountability and storage, randomization, AEs, and Case Report Forms (CRFs) were reviewed. The final inspection classification was NAI. After reviewing the inspectional report, Dr. Xiaohan Cai, from the Division of Generic Drug Study Integrity (DGDSI), OSIS, concluded that the data from these studies were reliable. Please refer to Dr. Cai's review (dated November 15, 2019) for further details.

A surveillance inspection of (b) (4), was conducted by Dr. Kara Schreiber from DGDSI/OSIS on (b) (4), to review the metformin analytical portion of the above two studies. The study records, facilities, laboratory equipment, method validation, and sample analysis were examined, and interviews with the firm's management and staff were conducted. Based on the inspectional findings, Dr. Schreiber concluded that the data from the audited studies were reliable to support a regulatory decision. Please refer to her review (dated December 4, 2019) for additional information.

Additionally, Dr. Yiyue Zhang from DGDSI/OSIS audited (b) (4) from (b) (4). This site was responsible for analysis of empagliflozin plasma concentrations for the above two studies. Based on the review of the inspectional findings (dated (b) (4)), Dr. Zhang concluded that the empagliflozin concentration data from the audited studies were reliable for Agency review.

Dr. Folaremi Adeyemo from DNDBE/OSIS determined that an inspection of the (b) (4) bioanalytic site (i.e., responsible for analysis of linagliptin concentrations in plasma) was not warranted at this time. The rationale for this decision was based on an OSIS inspection of this site in (b) (4), which falls within the surveillance interval. OSIS recommended that all study data from this site be considered acceptable for Agency review at that time. Please refer to Dr. Adeyemo's review (dated (b) (4)) for further details.

I concur with the recommendations of the OSIS scientists.

3.2. Product Quality

The Quality Assessment was performed by the following members of the Quality Review Team: Dr. Muthu Ramaswamy served as the Application Technical Lead (ATL), Dr. Elise Luong was the Drug Product/Environmental Assessment reviewer (drug product composition, excipient compatibility, batch analysis, container closure system, and stability information); Dr. Joseph

Leginus was the Drug Substance reviewer (empagliflozin, linagliptin and metformin drug substance information); Dr. Christina Capacci-Daniel was the Manufacturing Assessment Team reviewer (manufacturing process/control and facility compliance information), Dr. Chen Hansong was the Biopharmaceutics reviewer (dissolution method/data/acceptance criteria, alcohol-induced dumping data, and biowaiver request), and Dr. Leeza Rahimi was the Regulatory Business Process Manager (RBPM). Dr. Ramaswamy also performed a risk assessment for the finished product critical quality attributes (i.e., drug content, drug uniformity, particle size distribution of active pharmaceutical ingredient [API], impurities, appearance, microbial load, and invitro dissolution) and concluded that the final quality risk is low. Based on the respective reviews (dated December 11, 2019), the Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 212614 from a Chemistry and Manufacturing Controls (CMC) perspective, noting that there were no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, environmental analysis, container and carton label. Please refer to the respective reviews for more detailed information.

I concur with the OPQ assessments and recommendations.

Summary of Quality Provided by the Applicant

TRIJARDY XR is a FCDP containing contain the active pharmaceutical ingredients empagliflozin, linagliptin and metformin hydrochloride extended-release as film coated tablets in the following dosage strengths: 5mg/2.5mg/1000mg (2 tablets once daily), 10mg/5mg/1000mg (1 tablet once daily), 12.5mg/2.5mg/1000mg (2 tablets once daily), and 25mg/5mg/1000mg (1 tablet once daily). This FCDP (Figure 1) is a coated tablet comprised of a metformin HCl extended-release core tablet (1000 mg in each tablet strength) (b) (4) . The tablet strengths will be differentiated by the color and imprint on one side of the tablet, and marketed as grey, tan, red and brown oval coated tablets, respectively (Figure 2). In Type C Meeting responses (dated June 14, 2016), the Agency stated that the proposed color differentiation appeared to be appropriate.

Figure 1: Formulation Design of TRIJARDY XR FCDP Tablet

(b) (4)

Source: Adapted from the Applicant's Quality Overall Summary Report, labelled as Figure 1, page 7 of 74, available at: \\cdsesub1\evsprod\nda212614\0000\m2\23-qos\quality-overall-summary.pdf

Figure 2: Photograph of Proposed Tablet Strengths

Source: Adapted from the Applicant's Quality Overall Summary Report, labelled as Figure 2, page 8 of 74, available at: \\cdsesub1\evsprod\nda212614\0000\m2\23-qos\quality-overall-summary.pdf

The Applicant stated that the development approach for TRIJARDY XR used a proven extended-release technology for the metformin component (i.e., (b) (4) , and that the metformin core tablet and empagliflozin and linagliptin (b) (4) (b) (4) (b) (4). They also felt that the film coating and size of TRIJARDY XR tablets support patient compliance.

(b) (4) will be the commercial manufacturing site of drug product. For this Application, they were responsible for manufacturing, analytical (release and

stability) and microbiological testing of drug product and excipients, primary and secondary packaging, and labeling. (b) (4) performed analytical testing of drug product (stability), and (b) (4) performed labeling and secondary packaging. The Applicant requested that the Agency refer to the empagliflozin and linagliptin drug substance details in the JARDIANCE (NDA 204629) and TRADJENTA (NDA 201280) Applications, respectively. Metformin HCl is sourced from (b) (4) (Drug Master File [DMF] # (b) (4)). A Letter of Authorization (LOA) was provided in the submission.[156] The Applicant also requested that the Agency refer to the metformin drug substance section of the JENTADUETO Application. The rate and extent of absorption of empagliflozin, linagliptin and metformin from the FCDP were the same (bioequivalent) as each moiety coadministered as separate products for the high (25 mg/5 mg/1000 mg) and low (5 mg/2.5 mg/1000 mg) tablet strengths (Studies 1361.3[157] and 1361.11[158]) under fed conditions. The Applicant requested a biowaiver for the intermediate strengths (i.e., 10 mg/5 mg/1000 mg and 12.5 mg/2.5 mg/1000 mg tablets; Table 2). In his review, Dr. Chen noted that the dissolution profiles of the intermediate strengths were similar to the dissolution profiles of the highest (25 mg/5 mg/1000 mg) and lowest (5 mg/2.5 mg/1000 mg) strength tablets agreed that the biowaiver could be granted.

The Applicant claims that the excipients of TRIJARDY XR meet regulatory and compendial requirements, are commonly used in similar proportions in approved oral drug products and are compatible with the drug substances. (b) (4) . The Applicant conducted a six-month accelerated (40°C/75% relative humidity [RH]) and 18-month long-term storage (25°C/60% RH) stability studies. Based on these studies, the Applicant felt that all results met the proposed acceptance criteria and proposed a shelf-life of 18 months for this FCDP when stored at 28°C (77°F). The container closure system (i.e., multidose plastic bottle sealed with (b) (4) foil and closed with (b) (4) plastic screw closure; 1-2 desiccant sachets inserted into each strength) provides suitable protection for this product over the proposed shelf-life. Dr. Luong concurred that a shelf-life of 18 months could be granted when stored at 20-25°C (68-77°F; temperature excursions of 15-30°C [59-86°F] permitted) in original packaging (commercial container/closure system). The Applicant also commits to conducting post-approval stability testing of TRIJARDY XR over a 36-month timeframe.

3.3. Clinical Microbiology

Not applicable.

3.4. Nonclinical Pharmacology/Toxicology

The primary objective of the nonclinical development program for this Application was to identify or rule out any unexpected interactions from coadministration of the drug substances in TRIJARDY

XR (empagliflozin, linagliptin, and metformin extended-release). The Applicant stated that the nonclinical characteristics of empagliflozin and linagliptin had been fully evaluated in previous pharmacology, pharmacokinetic and toxicology studies, and metformin had been marketed for many years. On June 14, 2016, the Agency agreed (i.e., as written responses to a Type C meeting) that a 13-week rat toxicity study to bridge the nonclinical data of three individual marketed products (i.e., JARDIANCE [NDA 204629], TRADJENTA [NDA 201280], and GLUMETZA [NDA 021748]) and a cross-reference to other previously submitted nonclinical data (e.g., GLYXAMBI [NDA 206073], SYNJARDY [NDA 206111], SYNJARDY XR [NDA 208658], JENTADUETO [NDA 201281], and JENTADUETO XR [NDA 208026]) should be sufficient to support NDA submission (Table 2).[146]

As recommended, and in accordance with the International Council for Harmonisation (ICH) M3 (R2),[159] a 13-week oral (gavage) rat combination (i.e., empagliflozin/linagliptin/metformin) study (Study 17B039) was conducted in compliance with Good Laboratory Practice (GLP) regulations.[160] This study was intended to bridge previous pharmacology and toxicology assessments of individual and combined drug substances. Drug substance ratios in this study were similar to those in the proposed FCDP tablets, and the doses were chosen to provide approximately 1- to 10-times the clinical exposures at the maximum recommended human doses (MRHDs; empagliflozin 25 mg/day, linagliptin 5 mg/day and metformin 2000 mg/day).

Dr. David Carlson was the Pharmacology/Toxicology reviewer for this NDA. Based on the results of the 13-week rat study, he felt that the observed toxicokinetic drug interactions were modest but not predictive of clinical exposures with coadministration the triple combination compared to the individual drug substances. Further, there was no unexpected/synergistic toxicity. The major target organs were the kidney, heart, liver, and salivary glands. The toxicities that identified the maximum tolerated dose (MTD) and no observable adverse effect levels (NOAEL) were felt to be consistent with the known toxicity of the individual drugs, including empagliflozin effects on the kidney and metformin effects on the heart and liver. Additive toxicity (increased incidence and severity compared to individual drug groups) was observed in the empagliflozin/ linagliptin/metformin mid (30/10/200 mg/kg/day) and high (100/20/500 mg/kg/day) dose groups at approximately 5-times/8-times/6-times and 11-times/14-times/15-times clinical exposures at the MRHD, respectively. The high dose triple combination exceeded the MTD due to mortality/euthanasia in 2/20 females and extensive gross and histopathologic changes seen in target organs of kidney, heart, liver, salivary glands, thymus, and ovaries. Dr. Carlson felt that toxicity with the triple combination was generally driven by the metformin component, possibly exacerbated by additive toxicity or slightly higher metformin exposures due to the limited toxicokinetic interactions. Kidney findings at the mid triple combination dose level identified the lowest observed adverse effect level (LOAEL) dose. The recovery animals showed complete or partial reversibility of all findings after a six-week drug-free period. The NOAEL dose identified with the triple combination was 10/5/90 mg/kg/d empagliflozin/linagliptin/metformin (approximately 1X/3X/3X MRHD).

In accordance with ICH M3,[159] the Applicant did not conduct genotoxicity, carcinogenicity, or reproductive and developmental toxicity studies with the triple combination. Dr. Carlson stated that none of the individual drug substances were found to be genotoxic, and the cross-referenced NDA data did not provide evidence that additional genotoxic, carcinogenicity or reproductive and developmental toxicity assessments were warranted.

Dr. Carlson recommended approval of this Application. In his review (dated December 9, 2019), he acknowledged that the drug substances in TRIJARDY XR have been extensively evaluated in nonclinical studies, and the approved empagliflozin/linagliptin FCDP[9] is used clinically as add-on to background metformin therapy. Dr. Carlson stated that he did not identify any new safety concerns from the individual drug substances or combined treatment in rats. Further, the proposed formulation of Trijardy XR is qualitatively and quantitatively similar to formulations used in the Applicant's approved FCDPs (SYNJARDY XR[149] and JENTADUETO XR[7]). No new or novel excipients were used (all are compendial grade), and no concerns were identified from potential impurities, degradants, or (b) (4).

I concur with Dr. Carlson's assessment.

3.5. Clinical Pharmacology

The Clinical Pharmacology reviewer for this Application, Dr. Sze W. Johnny Lau, evaluated the clinical pharmacology data for this Application, and recommends approval. Please refer to his review (dated December 6, 2019) for a detailed discussion of the Clinical Pharmacology issues relevant to this submission. Below is a brief summary of the Phase 1 studies submitted to this Application.

TRIJARDY XR: To support approval of this triple FCDP, as well as bridge existing safety and efficacy data from clinical trials with empagliflozin, linagliptin and/or metformin HCl extended-release, the Applicant submitted data from a relative bioavailability (BA) study (1361.1)[161] and two pivotal bioequivalence (BE) studies (1361.3[157] and 1361.11[158]). These studies compared TRIJARDY XR to combinations of the individual components of JARDIANCE (empagliflozin), TRADJENTA (linagliptin) and GLUMETZA (metformin HCl extended-release, 500 mg tablets).

Study 1361.1[161] was a single-dose, relative BA study (N=100 healthy volunteers) intended to support the study designs of the Applicant's pivotal BE studies (1361.3 and 1361.11). This randomized, open-label, single-dose, two-sequence crossover (washout ≥35 days) study compared the relative BA of: 1) TRIJARDY XR 25 mg/5 mg/1000 mg tablets to the individual components (empagliflozin 25 mg plus linagliptin 5 mg plus 2x metformin extended-release 500 mg, administered as separate tablets) in a fasted and fed (after a high-fat, high-caloric meal, in accordance with FDA guidance)[162] state, and 2) TRIJARDY XR 10 mg/5 mg/1000 mg tablets to the individual components in a fed state.[162] Although systemic exposures were similar (all 90% CI of

AUC ratios were between 80% to 125%), the linagliptin C_{max} was higher (117.3, 90% CI 103.4-133.1) when administered as a 25 mg/5 mg/1000 mg FCDP in the fasted state than when administered as individual tablets. The Applicant noted that this pilot study was not powered to show BE. There were no deaths or serious adverse events (SAEs) or AEs leading to discontinuation of investigational product (IP) reported in this study.

Studies 1361.3[157] and 1361.11[158] were single-dose, randomized, open-label, two-way crossover (washout ≥35 days) trials (N=30 healthy volunteers each) that evaluated the BE of one TRIJARDY XR 25 mg/5 mg/1000 mg tablet and two TRIJARDY XR 5 mg/2.5 mg/1000 mg tablets to equivalent doses of the combination of empagliflozin plus linagliptin plus metformin extended-release (2 x 500 mg) tablets, respectively, in a fed state.[162] These studies were intended to bracket the proposed highest and lowest strengths of the FCDP. Additionally, in accordance with FDA guidance,[163] biowaivers were requested for the two intermediate TRIJARDY XR dose strengths (i.e., 10 mg/5 mg/1000 mg and 12.5 mg/2.5 mg/1000 mg). Please refer to Dr. Hansong Chen's Biopharmaceutics review for further discussion of biowaiver requests and approval.

In these two studies, all 90% confidence intervals of the geometric mean ratios (AUC_{0-tz}, AUC_{0-72} and C_{max}) were within the 80 to 125 bioequivalence limits. Thus, BE of empagliflozin, linagliptin and metformin were established between TRIJARDY XR (25mg /5 mg/1000 mg and 5 mg/2.5 mg/1000 mg) relative to the corresponding individual reference products when administered in the fed state. The results indicate that switching from the individual components to TRIJARDY XR tablets will produce similar systemic exposures to empagliflozin, linagliptin and metformin extended-release tablets. There were no deaths, SAEs or AEs leading to discontinuation of IP reported in either study.

In his review, Dr. Lau stated that he felt the clinical pharmacology data of this Application were acceptable to support approval. I concur with the recommendations of Dr. Lau.

3.5.1. Mechanism of Action

TRIJARDY XR is a FCDP containing empagliflozin, linagliptin and metformin extended-release. Empagliflozin is an SGLT2 inhibitor which prevents renal glucose reabsorption in the proximal renal tubules, thus increasing renal glucose excretion and improving glycemic control.[3,119,120,164] Linagliptin is a competitive DPP-4 inhibitor that slows inactivation of the incretin hormones (GLP-1 and GIP) which play a role in glucose-dependent insulin secretion and in reducing glucagon secretion from pancreatic alpha cells.[4,122] The net result of the presence of incretin hormones is improved glycemic control.[4,122-125,165] Metformin, a biguanide widely used in the management of T2D since the 1950s, likely improves glycemic control through pleiotropic pharmacologic mechanisms.[128,166]

3.5.2. Pharmacodynamics

Empagliflozin: Increases in the amount of glucose excreted in the urine are observed in both healthy subjects and T2D patients following oral administration of empagliflozin. Empagliflozin doses of 10 and 25 mg per day in patients with T2D results in excretion of approximately 64 and 78 grams/day of glucose in the urine.[3,119] This urinary glucose excretion is associated with increases in urinary volume.[3] The amount of glucose removed may depend on the blood glucose concentration and the glomerular filtration rate.[3,120]

Linagliptin: Oral administration of linagliptin 5 mg in patients with T2D results in >80% inhibition of DPP-4 activity for approximately 24 hours.[126] Following an oral glucose load or meal, there an increase in circulating levels of GLP-1 by several fold.[126] Linagliptin-mediated reductions in degradation of incretin hormones results in increased glucose-dependent insulin secretion, and reductions in glucagon concentrations, hepatic glucose output, fasting plasma glucose (FPG) concentrations, and glucose excursion.[4,126]

Metformin: Oral administration of metformin improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5-8,128,166] 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.[5-8]

3.5.3. Pharmacokinetics

Empagliflozin: Following oral administration of empagliflozin, the C_{max} is typically achieved within 1.5 hours. Both C_{max} and AUC values increase proportionally with an increase in dose within the therapeutic range. Administration of 25 mg empagliflozin following a high-fat and high-calorie meal resulted in slightly lower exposure (AUC decreased by approximately 16% and C_{max} decreased by approximately 37%) compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and therefore empagliflozin may be administered with or without food. Empagliflozin is approximately 86.2% protein bound. No major metabolites of empagliflozin are detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. In vitro studies suggest that metabolism is primarily mediated by uridine 5'-diphospho-glucuronosyltransferase 2B7 (UGT2B7) 1A3 (UGT1A3), 1A8 (UGT1A8), and 1A9 (UGT1A9). Empagliflozin and related metabolites are primarily eliminated in the urine (54.4%) and feces (41.2%). The mean plasma terminal half-life ($t_{1/2}$) for empagliflozin is approximately 12.4 hours.[3] Product labeling of empagliflozin-containing products states that empagliflozin has no clinically relevant effect on the pharmacokinetics of either metformin or linagliptin.[3,5,6,9]

Linagliptin: The PKs of linagliptin are similar in healthy subjects and patients with T2D. Following oral administration of a single 5 mg dose, the C_{max} occurs approximately 1.5 hours post dose (T_{max}). The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced the C_{max} by 15% and increased AUC by 4%. This effect is not considered to be clinically relevant. Linagliptin may be administered with or without food. The AUC values of linagliptin increase in less than a dose proportional manner with doses ranging from 1 to 10 mg. Plasma protein binding is concentration-dependent, with 70-80% of linagliptin bound to plasma proteins at high concentrations. Protein binding is not altered in patients with renal or hepatic impairment. Linagliptin distributes extensively into tissues. The majority of linagliptin is excreted unchanged, with approximately 13% metabolized to a pharmacologically inactive metabolite. Approximately 80% of an oral dose is eliminated enterohepatically and 5% is excreted in the urine. The effective $t_{1/2}$ of linagliptin is 12 hours, while the terminal elimination $t_{1/2}$ is relatively long (>100 hours).[4] Product labeling for linagliptin/metformin FCDPs do not report clinically meaningful changes in systemic exposures of linagliptin and metformin when coadministered.[7,8]

Metformin: Following a single oral dose of metformin extended-release after a meal, the median T_{max} is approximately seven to eight hours. The extent of absorption is increased by approximately 38% and 73% when administered with a low-fat and high-fat meal, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected. 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).[5-8]

3.6. Devices and Companion Diagnostic Issues

Not applicable. This Application does not involve a companion device or diagnostic product.

3.7. Consumer Study Reviews

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

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

To support the efficacy and safety of TRIJARDY XR for the proposed indication, the Applicant has submitted data from three Phase 3 clinical trials (Trials 1275.1, 1275.9, and 1275.10; Table 4).

Trial 1275.1 is the Applicant's pivotal Phase 3 efficacy trial used to support the following proposed indication: as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) . This trial included two independent subpopulations (i.e., drug naïve or metformin-treated), which were analyzed separately. For the intended purpose of this Application (i.e., a FCDP containing metformin) only the cohorts that included metformin treatment arms will be discussed further in this review. This trial, which used a factorial design, was an active-controlled trial that compared dual therapy with empagliflozin plus linagliptin (25 mg/5 mg/day or 10 mg/5 mg/day) to the respective individual monocomponents, each on background metformin therapy (≥1500 mg/day).

Trials 1275.9 and 1275.10 were submitted to provide additional efficacy and safety data to support approval of this Application. Trial 1275.9 compared empagliflozin (10 mg/day or 25 mg/day) to placebo, each as add-on therapy to linagliptin 5 mg/day plus metformin (≥1500 mg/day). Trial 1275.10 compared linagliptin 5 mg/day to placebo as add-on therapy to empagliflozin (25 mg/day [Subpopulation A] or 10 mg/day [Subpopulation B]) plus metformin (≥1500 mg/day). The Applicant intends to include only Trial 1275.1 in Section 14 (Clinical Studies) of labeling.

Table 4: Listing of Clinical Trials Relevant to NDA 212614

Trial Identifier	Trial Design	Regimen/ Schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Biopharmaceutics Studies							
Trial 1361.1[161] (BA Study) NCT02821910 EudraCT2015-005082-23 *Trial Initiation Date: July 25, 2016* *Trial Completion Date:* October 31, 2016	Phase 1, randomized, OL, single-dose, 2-way crossover study with 3 parts, each with 2 treatments (T and R) and 2 treatment sequences (TR or RT)	**Treatment T, Parts 1 (Fed) & 2 (Fasted)*** • TRIJARDY XR: 25 mg/5 mg/ 1000 mg **Treatment R, Parts 1 (Fed) & 2 (Fasted)*** • Individual components: Empa 25 mg + Lina 5 mg + Met XR 1000 mg **Treatment T, Part 3 (Fed)*** • TRIJARDY XR: 10 mg/5 mg/ 1000 mg **Treatment R, Part 3 (Fed)*** • Individual components: Empa 10 mg + Lina 5 mg + Met XR 1000 mg	***Primary*** • Empa C_{max}, AUC_{0-tz} and AUC_{0-72} • Lina C_{max}, AUC_{0-tz} and AUC_{0-72} • Met C_{max}, AUC_{0-tz} and AUC_{0-72}	Each trial part consisted of 2 single oral doses, separated by a washout period (≥35 days)	**Total: 50/50** • Part 1: 15/15 • Part 2: 20/20 • Part 3: 15/15	Healthy subjects	1 Site (BI) 1 Country (DEU)
Trial 1361.3[157] (Pivotal BE Study) NCT03259490 EudraCT2017-000425-12 *Trial Initiation Date: September 4, 2017* *Trial Completion Date:* November 13, 2017	Phase 1, randomized, OL, single-dose, 2-way crossover trial with 2 treatments (T and R) and 2 treatment sequences (TR or RT)	**Treatment T (Fed)*** • TRIJARDY XR: 25 mg/5 mg/ 1000 mg **Treatment R (Fed)*** • Individual components: Empa 25 mg + Lina 5 mg + Met XR 1000 mg	***Primary*** • Empa C_{max}, AUC_{0-tz} and AUC_{0-72} • Lina C_{max}, AUC_{0-tz} and AUC_{0-72} • Met C_{max}, AUC_{0-tz} and AUC_{0-72}	Single oral dose in each treatment period, separated by a washout period (≥35 days)	**30/29**	Healthy subjects	1 Site (BI) 1 Country (DEU)
Trial 1361.11[158] (Pivotal BE Study) NCT03629054 EudraCT2018-001266-42	Phase 1, randomized, OL, single-dose, 2-way crossover trial with 2 treatments (T and R)	**Treatment T (Fed)*** • TRIJARDY XR: 10 mg/5 mg/ 2000 mg **Treatment R (Fed)*** • Individual components:	***Primary*** • Empa C_{max}, AUC_{0-tz} and AUC_{0-72} • Lina C_{max}, AUC_{0-tz} and AUC_{0-72}	Single oral dose in each treatment period, separated by a washout period (≥35 days)	**30/29**	Healthy subjects	1 Site (BI) 1 Country (DEU)

Trial Identifier	Trial Design	Regimen/ Schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Trial Initiation Date: *September 3, 2018* *Trial Completion Date:* November 5, 2018	and 2 treatment sequences (TR or RT)	Empa 10 mg + Lina 5 mg + Met XR 2000 mg	Met C_{max}, AUC_{0-tz} and AUC_{0-72}				
Pivotal Efficacy and Safety Trial							
Trial 1275.1[167] (Pivotal Efficacy/Safety) NCT01422876 EudraCT2011-000383-10 *Trial Initiation Date:* *August 31, 2011* *Trial Completion Date:* September 10, 2013	Phase 3, randomized, double-blind, active-controlled, parallel group, multicenter trial (factorial design) – Add-on to Met (inadequate control Met)	• Empa 25 mg/Lina 5 mg FCDP + OL Met Or Empa 10 mg/Lina 5 mg FCDP + OL Met Vs. • Empa 25 mg + OL Met Or Empa 10 mg + OL Met Vs. • Lina 5 mg + OL Met ≥1500 mg PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary*¶ • FPG • BW • % Subjects HbA1c <7%	24 wks (+ 28-wk DB extension period)	**686/686†** Empa 25 mg + Lina 5 mg + Met 137/137 Empa 10 mg + Lina 5 mg + Met 136/136 Empa 25 mg + Met 141/141 Empa 10 mg + Met 140/140 Lina 5 mg + Met 132/132	• ≥18 years old • T2D • HbA1c ≥7.5 to ≤10.5% • Met (≥1500 mg x ≥12 wks) • BMI ≤45 kg/m²	188 Sites 22 Countries
Supporting Efficacy and Safety Trials							
Trial 1275.9[168] (Efficacy/Safety) NCT01734785 EudraCT2012-002270-31 *Trial Initiation Date:* *March 1, 2013* *Trial Completion Date:* *March 23, 2015*	Phase 3, multicenter, randomized, double-blind, active-controlled, parallel group trial – Add-on to Met + Lina (inadequate control on 16 wks of OL Lina + Met)	• Empa 25 mg/Lina 5 mg FCDP + OL Met Or Empa 10 mg/Lina 5 mg FCDP + OL Met Vs. • Lina 5 mg + OL Met (≥1500 mg) PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary*¶ • FPG • BW	24 wks	**OL Period:** Lina 5 mg + Met 606/606 **DB Period:** Total 333/332 (1:1:1 allocation): Empa 25 mg + Lina 5 mg + Met 111/110 Empa 10 mg + Lina 5 mg + Met 112/112	• ≥18 years old • T2D • HbA1c ≥7 to ≤10.5% on Lina 5 mg + Met (≥1500 mg) x ≥16wks • BMI ≤45 kg/m²	90 Sites 10 Countries

Trial Identifier	Trial Design	Regimen/ Schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
					Placebo + Lina 5 mg + Met 110/110		
Trial 1275.10[169] (Efficacy/Safety) NCT01778049 EudraCT2012-002271-34 *Trial Initiation Date: February 13, 2013* *Trial Completion Date: March 30, 2015*	Phase 3, multicenter, randomized, double-blind, active-controlled, parallel group trial – Add-on to Empa + Met XR (inadequate control on 16 wks of OL Empa + Met XR)	• Empa 25 mg/Lina 5 mg FCDP + OL Met (Subpopulation A) Or Empa 10 mg/Lina 5 mg FCDP + OL Met (Subpopulation B) Vs. • Lina 5 mg + OL Met (≥1500 mg) PO daily	Change from BL to Wk 24: *Primary* • HbA1c *Secondary*¶ • FPG	24 wks	**OL Period:** Empa 25 mg + Met 355/354 Or Empa 10 mg + Met 354/352 **DB Period:** Empa 25 mg/Lina 5 mg FCDP + Met (A) 114/112 Empa 25 mg/Placebo Lina 5 mg + Met (A) 112/112 Empa 10 mg/Lina 5 mg FCDP + Met (B) 126/126 Empa 10 mg/Placebo Lina 5 mg + Met (B) 130/128	• ≥18 years old • T2D • HbA1c ≥7 to ≤10.5% on Empa 25 mg + Met (≥1500 mg) x ≥16wks Or Empa 25 mg + Met (≥1500 mg) x ≥16wks • BMI ≤45 kg/m^2	114 Sites 10 Countries

Source: Adapted from the Applicant's respective Clinical Study Reports[157,158,161,167-169] and Tabular Listing of Clinical Studies, available at: \\cdsesub1\evsprod\nda212614\0000\m5\52-tab-list\us-tabular-listing.pdf

Abbreviations: AUC, area-under-the-curve; BA, bioavailability; BE, bioequivalence; BI, Boehringer Ingelheim Pharma GmbH & Co. KG; BL, baseline; BW, body weight; CGM, continuous glucose monitoring; C_{max}, maximum plasma concentration; DB, double blind; DEU, Germany; Empa, empagliflozin; EuDRACT, European Union Drug Regulating Authorities Clinical Trials number; FCDP, fixed combination drug product; FCDP 25 mg/5 mg/1000 mg, Trijardy 25 mg/5 mg/1000 mg; FPG, fasting plasma glucose; H, hour; HbA1c, hemoglobin A1c (glycosylated hemoglobin); INF, infinity; Lina, linagliptin; LT, long-term treatment period; Met, metformin; NCT, National Clinical Trial identifier; OL, open-label; PK, pharmacokinetic; PO, oral; PPG, postprandial glucose; SBP, systolic blood pressure; T2D, type 2 diabetes; wks, weeks; and XR, extended-release.

* Fed: administered with a high-fat/high-caloric meal; and Fasted: ≥10 hours overnight.

¶ Secondary endpoints presented according to sequential testing procedure for the trials used to support efficacy (i.e., 1275.1, 1275.9, 1275.10).[167-169]

† Sample size does not reflect treatment naïve cohorts (i.e., not on background metformin therapy), which were not relevant for this Application.

4.2. Review Strategy

The Applicant intends to include the efficacy and safety findings from their pivotal Phase 3 trial (1275.1; Table 4) in proposed product labeling. This trial was previously submitted to the Agency to support the approval of GLYXAMBI (NDA 206073) on January 30, 2015. For clarity, the relevant efficacy and safety data from this trial (1275.1) will be summarized throughout the review (typically as side-by-side comparisons). Please refer to the Clinical Review by Dr. William Chong (dated January 30, 2015) for a more detailed information of this trial.

This review will focus primarily on the additional efficacy and safety findings (i.e., the prespecified primary and secondary endpoints) from the two supporting Phase 3 clinical trials (i.e., Trials 1275.9 and 1275.10). For a detailed discussion of the statistical analyses of these trials, please refer to the Statistical Review of Dr. Yi Ren (pending at the time of this review), the primary statistical reviewer for this Application. The review strategy for the safety findings is presented in Section 7.1 (Safety Review Approach).

5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. Phase 3 Trials

5.1.1. Overview and Objectives

The following three Phase 3 clinical trials were used to support the efficacy of TRIJARDY XR for the proposed indication:

1. **Trial 1275.1:** *A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control*

   Primary Objective: To evaluate the efficacy, safety, and tolerability of the FCDPs empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg compared with the individual components (empagliflozin 25 mg or 10 mg, and linagliptin 5 mg) given once daily for 52 weeks in treatment naïve and metformin-treated (≥1500 mg/day or highest tolerated/local-approved dose for ≥12 weeks) subjects with T2D and insufficient glycemic control (HbA1c ≥7% to ≤10.5%).

   Since only the clinical data from the metformin-treated population is relevant for the proposed FCDP, the results for the treatment naïve population will not be discussed further.

The Applicant intends to use this factorial design study as their pivotal study to show that the combined therapy of empagliflozin (10 mg or 25 mg daily) and linagliptin 5 mg daily, administered as add-on therapy to metformin background therapy, provides improved glycemic control compared to the individual components alone (i.e., empagliflozin or linagliptin) as add-on therapy to metformin.

2. **Trial 1275.9:** *A phase III, randomized, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy*

   Primary Objective: To compare the efficacy, safety, and tolerability of empagliflozin (25 mg or 10 mg daily) to placebo, each administered as add-on therapy to linagliptin 5 mg and metformin, over 24 weeks in patients with T2D, who have inadequate glycemic control (HbA1c ≥7% to ≤10.5%) after 16 weeks of open-label treatment with linagliptin 5 mg and metformin (≥1500 mg/day or highest tolerated/local-approved dose for ≥12 weeks) background therapy.

   This Phase 3 trial is intended provide supporting efficacy data that show improved glycemic control with add-on empagliflozin therapy compared to placebo in subjects with inadequate glycemic control on linagliptin plus metformin background therapy.

3. **Trial 1275.10:** *A phase III, randomized, double-blind, parallel group study to evaluate efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combinations with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with empagliflozin 10 mg or 25 mg once daily on metformin background therapy*

   Primary Objective: To compare the efficacy, safety, and tolerability of linagliptin 5 mg to placebo, each administered as add-on therapy to empagliflozin (25 mg or 10 mg) and metformin, over 24 weeks in patients with T2D, who had inadequate glycemic control (HbA1c ≥7% to ≤10.5%) after 16 weeks of open-label treatment with empagliflozin (25 mg or 10 mg daily) and metformin background treatment (≥1500 mg/day or highest tolerated/local-approved dose for ≥12 weeks).

   This supporting Phase 3 trial is intended to show that add-on therapy with linagliptin compared to placebo provides improved glycemic control in subjects with inadequate glycemic control on empagliflozin plus metformin background therapy.

5.1.2. Study Designs

The study designs for the three efficacy trials are presented in Appendix 12.4. These trials were all multicenter, randomized, double-blinded, controlled trials, and met regulatory standards for adequate and well-controlled studies (21 CFR 314.126).[22] The Applicant intends to use these trials to demonstrate superiority of the empagliflozin plus linagliptin plus metformin combination treatment arms to dual therapy with metformin plus the individual components (i.e., empagliflozin or linagliptin). This triple therapy combination arm was compared to the individual components (i.e., empagliflozin or linagliptin as add-on to metformin background therapy) using a factorial design in Trial 1275.1). A sequential add-on treatment approach was used for Trials 1275.9 and 1275.10. For Trial 1275.9, open-label linagliptin 5 mg/day was initially added to metformin for a 16-week treatment period, and subjects were then randomized to empagliflozin (10 mg/day or 25 mg/day) or placebo. For Trial 1275.10, open-label empagliflozin (10 mg/day or 25 mg/day) was initially added to metformin for a 16-week treatment period, and subjects were then randomized to linagliptin 5 mg/day or placebo. Trials 1275.9 and 1275.10 were 24 weeks in duration, while Trial 1275.1 included a 24-week double-blind treatment phase with a 28-week double-blind long term (LT) extension period. The design of Trial 1275.1 consisted of a screening visit, 2-week single-blind placebo run-in period, a 52-week double-blind treatment period, and a 4-week follow-up period. Trials 1275.9 and 1275.10 included a screening visit, 16-week open-label, add-on to metformin period (empagliflozin 10 mg or 25 mg and linagliptin 5 mg, respectively), 1-week open-label placebo add-on period, 24-week double-blind double-dummy treatment period, and a 1-week follow-up period.

5.1.3. Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria for the three 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	1275.1	1275.9	1275.10
INCLUSION CRITERIA			
Age ≥18 years	X	X	X
T2D men/women	X	X	X
HbA1c ≥7 to ≤10.5% (for randomization)	X	X	X
HbA1c ≥8 to ≤10.5% (for entering 16 wks OL period)		X	X
Background metformin ≥1500 mg/d or maximum tolerated/local approved dose (for ≥12 wks)	X	X	X
BMI ≤45 kg/m^2	X	X	X
EXCLUSION CRITERIA			
FPG >240 mg/dL	X		
FPG >270 mg/dL		X	X
Treatment with prohibited antihyperglycemics except metformin (within 12 wks prior randomization)	X	X	X

Trials	1275.1	1275.9	1275.10
Prespecified CV/vascular disease (within 3 mos)*	X	X	X
Hematological/oncological disease¶	X	X	X
Hypersensitivity/intolerance/contraindication to IPs	X	X	X
Bariatric or GI surgeries causing malabsorption, weight loss program, or use of weight loss meds (within 3 mos) or herbal nutritional supplements affecting IP or BG	X	X	X
Hereditary galactose intolerance		X	X
Systemic corticosteroid therapy	X	X	X
Pregnant/breastfeeding/not using acceptable BC	X	X	X
Alcohol or drug abuse within 3 months	X	X	X
Change in dosage of thyroid meds (within 6 wks) or other uncontrolled endocrine disorders besides T2D	X	X	X
Abnormal clinical labs			
eGFR <60 mL/min/1.73 m^2	X	X	X
ALT or AST >3x ULN	X	X	X
Alkaline phosphatase >3x ULN	X	X	X
Any other condition that may jeopardize subject safety	X	X	X

Source: Adapted from the Applicants' CSRs for Trials 1275.1 (pages 74-76 of 1879),[167] 1275.9 (pages 45-47 of 2552),[168] 1275.10 (pages 57-59 of 3544),[169] available at:
\\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf
\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0009\1275-0009--1-15--study-report-body.pdf
\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0010\1275-0010--1-15--study-report-body.pdf

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BC, birth control; BG, blood glucose; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA1c, hemoglobin A1c; meds, medications; mos, months; T2D, type 2 diabetes mellitus; ULN, upper limit of normal; and wks, weeks.

* Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or transient ischemic attack (TIA).

¶ Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell (e.g., malaria, babesiosis, hemolytic anemia) which may affect HbA1c, malignancy within 5 years (except basal cell carcinoma).

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).

5.1.4. Study Treatments

The IP for the respective trials was administered orally once daily and provided by the Applicant as follows:

- **1275.1:** Empagliflozin 25 mg/linagliptin 5 mg tablets; empagliflozin 10 mg/linagliptin 5 mg tablets; empagliflozin 25 mg tablets; empagliflozin 10 mg tablets; linagliptin 5 mg tablets; and matching placebo tablets (empagliflozin/linagliptin, empagliflozin, and linagliptin).

- **1275.9:** Empagliflozin 25 mg/linagliptin 5 mg tablets; empagliflozin 10 mg/linagliptin 5 mg tablets; linagliptin 5 mg tablets; and matching placebo tablets (empagliflozin/linagliptin and linagliptin).

- **1275.10:** Empagliflozin 25 mg/linagliptin 5 mg tablets; empagliflozin 10 mg/linagliptin 5 mg tablets; empagliflozin 25 mg tablets; empagliflozin 10 mg tablets; and matching placebo tablets (empagliflozin/linagliptin, or empagliflozin).

The Applicant used the empagliflozin/linagliptin FCDP for all Phase 3 trials. It also is noted that all subjects were required to receive open-label background therapy of metformin (≥1500 mg or maximum tolerated dose or maximum dose as per local labeling for ≥12 weeks), which was not always provided by the Applicant. Additionally, subjects were not required to take extended-release metformin formulations. However, investigators were asked to continue subjects on stable doses of this medication (i.e., doses were to have remained unchanged if possible). Although it would have been better if the Applicant provided these products as study medications and used only metformin extended-release formulations for all trials, I think that this is acceptable and consistent with the use of background metformin therapy in other antihyperglycemic FCDP clinical development programs.

Rationale for Dose Selection:

The proposed doses of IP (i.e., empagliflozin 10 mg or 25 mg doses;[3] empagliflozin 25 mg/linagliptin 5 mg or empagliflozin 10 mg/linagliptin 5 mg;[9] and linagliptin 5 mg) have been widely studied in clinical development and are labeled doses for which efficacy and safety have been established (i.e., have favorable benefit/risk profiles). The Applicant also notes that metformin has been commercially available for more than 50 years and doses of 1000 mg and 2000 mg are the most commonly used doses in clinical practice. Further, the pivotal Phase 3 trial (1275.1) used to support approval of GLYXAMBI (empagliflozin/linagliptin FCDP) was based on the efficacy and safety of this combination on a background of metformin.

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 (i.e., Clinical Trial Support), and the Applicant's drug safety representatives (e.g., to unblind certain data for reporting Serious Unexpected Suspected Adverse Reactions [SUSARs]). Subjects and trial site staff also remained blinded until completion of the 28-week long-term extension period for Trial 1275.1.

Subjects were randomized into each study arm using a 1:1:1:1:1 (Trial 1275.1) or 1:1:1 (Trial 1275.9) and 1:1 (Trial 1275.10 for subpopulations A and B) treatment allocation (i.e., for five,

three and two arm comparisons, respectively), and typically stratified by baseline HbA1c (<8.5%; ≥8.5%), renal function (60 <eGFR <90 mL/min/1.73 m^2; ≥90 mL/min/1.73 m^2) and region (Europe; North America; Latin America; and/or Asia). Randomization was performed centrally using a phone/web based IXRS (Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS]), with subjects being assigned randomly using a computer-generated randomization (verified/validated by a trial-independent statistician).

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

Dose Modifications of Study Medications:

Dose titration of blinded study medication in all three trials was not permitted at any time during the trials. Additionally, open-label metformin doses were to remain unchanged during the double-blind treatment periods if possible (e.g., modifications could be made at the discretion of the investigator for repeated symptomatic hypoglycemia or severe hypoglycemia).

5.1.5. Administrative Structure of the TRIJARDY XR Development Program

The responsible parties for the administrative structure of the three Phase 3 trials are presented in Table 6.

Table 6: Administrative Structure of the Phase 3 Efficacy Trials

Trials	1275.1	1275.9	1275.10
ACTIVITY			
Trial sponsor	BI	BI	BI
Monitoring/management	BI	BI	BI
Manufacturing of IP	BI	BI	BI
IP labeling/management	(b) (4)		
Randomization of IP	BI	BI	BI
CEC, CECP, and/or HAC	Yes	Yes	Yes
CRO	(b) (4)		
Emergency unblinding			
IXRS service			
Central laboratory			
Pharmacogenomics	BI	BI	BI
Central ECG assessment	(b) (4)	—	—
Data management/analysis	BI	BI	BI
Medical Writing	BI	BI	BI

Source: Adapted from the Applicants' CSRs for Trials 1275.1,[167] 1275.9 (pages 30-33 of 2552),[168] and 1275.10,[169] available at: \\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf

\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0009\1275-0009--1-15--study-report-body.pdf
\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0010\1275-0010--1-15--study-report-body.pdf

Abbreviations: —, not reported; BI, Boehringer Ingelheim; CEC, Clinical Events Committee; CECP, Clinical Events Committee for adjudication of pancreatic events; CRO, Clinical Research Organization; ECG, electrocardiogram; ePRO, electronic patient reported outcomes; HAC, Hepatic Adjudication Committee; IP, investigational product; and IXRS, Interactive Voice/Web-Based Response System.

Suspected serious CV, pancreatic (Trial 1275.9) and hepatic adverse events were adjudicated by a blinded, independent Clinical Event Committee (CEC), Clinical Event Committee for adjudication of pancreatic events (CECP), and/or a Hepatic Adjudication Committee (HAC), respectively. These committees conducted all their operations in accordance with International Conference on Harmonization (ICH) GCP guidelines. Adjudication was performed in a blinded fashion. All trials also included a Central Laboratory for efficacy and safety laboratory assessments. The Applicant was responsible for data management, statistical analyses of research data and medical writing.

5.1.6. Protocol Procedures and Schedule

All three trials included a screening/enrollment period, 1- to 2-week placebo add-on/run-in period, and a 24-week primary efficacy assessment (see Appendix 12.4). Trials 1275.9 and 1275.10 also included a 16-week open-label period (linagliptin and empagliflozin, respectively), while Trial 1275.1 included a 28-week double-blind long-term extension phase. The study visits for the 24-week double-blind treatment phases for all trials were scheduled at baseline and Weeks 6, 12, 18 and 24. For the extension phase of Trial 1275.1, visits were scheduled at Weeks 32, 40, 52 and 56. Adverse event monitoring and assessments of vital signs, clinical laboratory parameters and adherence to IP were usually performed at most study visits. A 12-lead-ECG was performed at baseline and end-of-treatment (EOT).

Dietary Restrictions/Instructions:

Subjects received counseling on dietary and life-style modifications by a dietician or qualified healthcare professional (based on local standards and included a food log) at the open-label treatment period and at the start or throughout the treatment period. Investigational sites also reinforced diet and exercise counseling during the randomized treatment period.

Concurrent Medications:

All three trials required the use of open-label background metformin therapy (≥1500 mg; Section 5.1.4). 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 allowed. Use of medications that could affect body weight or herbal/nutritional supplements that could affect IP or blood glucose (BG) concentrations was prohibited (Table 5).

Adherence to Study Treatment:

Investigators were required to assess subject compliance with IP, and subjects were asked to bring in any used or unused bottles at each visit. Adherence to IP (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% or >120% compliant.

Rescue Medication:

For the three trials, subjects with inadequate glycemic control during the double-blind treatment period were eligible to receive open-label rescue medication based on the criteria presented in Table 7. These criteria were based on two measurements, with at least one measurement performed at the investigational site after an overnight fast (central or local laboratory testing allowed), and are consistent with the 2008 Diabetes Guidance.[170] The choice and dose of rescue medication was at the discretion of the investigator in accordance with the local prescribing information. However, DPP-4 inhibitors, GLP-1 RAs and SGLT2 inhibitors were not allowed as rescue therapy. Rescue medication could be used until the end of the trial, and subjects were asked to continue taking blinded IP and keep their planned study visits. Prior to initiating rescue therapy, a blood sample was taken to measure HbA1c (unless measured within 4 weeks) and FPG at the central laboratory. Adjustments (dose reduction/discontinuation) in glycemic rescue or background metformin therapy could be made with severe or recurrent symptomatic episodes of hypoglycemia, with adjustments to ongoing rescue medication first before adjusting metformin dosing. Subjects with inadequate glycemic control despite rescue medication were discontinued from the trial. Overall, I felt that the glycemic rescue criteria for all trials were adequate.

Table 7: Criteria for Initiation of Antihyperglycemic Rescue Therapy (Double -Blind Period)

Study Visits	Rescue Laboratory Criteria*	Trial 1275.1	Trial 1275.9	Trial 1275.10
Weeks 1-6	FPG >270 mg/dL	—	X	X
Weeks 1-12	FPG >240 mg/dL	X	—	—
Weeks 6-12	FPG >240 mg/dL	—	X	X
Weeks 12-24	FPG >200 mg/dL	X	X	X
After Week 24	FPG >180 mg/dL and/or HbA1c >8%	X	—	—

Source: Adapted from the Applicants' Clinical Protocols or CSRs for Trials 1275.1 (page 82 of 7879),[167] 1275.9 (page 55 of 2552),[168] and 1275.10 (page 68 of 3544),[169] available at:
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Abbreviations: —, not applicable; FPG, fasting plasma glucose, and HbA1c, hemoglobin A1c.

* Note: To meet the FPG criteria, a repeat/confirmatory measurement was performed on a separate day, with at least one measurement performed at the investigational site after an overnight fast.

Subject Withdrawal/Discontinuation:

Subjects were usually discontinued from IP or assessments during the double-blind phase for the following reasons:

- Withdrawal of informed consent
- Subject is no longer able to participate for other medical reasons (e.g. surgery, AEs, or other diseases)
- Pregnancy (subjects to be followed until birth/termination)
- Need/use of concomitant medications (including herbal/nutritional supplements) that interfere with IP
- Rescue therapy due to hyperglycaemia or high HbA1c does not lead to sufficient treatment efficacy (rescue criteria still met)
- Hypoglycemia that may put the patient at risk with continued participation (e.g. repeated hypoglycaemic episodes)
- Pancreatitis is suspected
- Eligibility criteria are violated, or subject fails to comply with the protocol

In cases where a decision was made to discontinue IP, subjects were asked to have an EOT visit (within 7 days after the last dose of IP) and follow-up visit (preferably within 7 days of the EOT visit) performed onsite. For Trials 1275.1 and 1275.9, subjects also were asked to continue with their remaining visits as scheduled. Subjects who discontinued IP or withdrew from the study were not replaced.

5.1.7. Study Endpoints

Primary Efficacy Endpoint:

- Mean change from baseline in HbA1c (%) at Week 24

The primary efficacy endpoint for all three 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.[171]
- 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%.[172,173]

- HbA1c has excellent reliability, predicts some of the diabetes-specific complications, and provides a basis for treatment decisions in patients with T2D.[174,175]
- Lowering HbA1c reduces microvascular complications[38,39,174,176] and may lower the risk of macrovascular complications[30,34] 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."[170] Scheduled measurements of HbA1c used for eligibility criteria, efficacy analyses, and need for glycemic rescue, were performed at a Central Laboratory. To test the primary efficacy endpoint, Trial 1275.10 was powered separately for each subpopulation (i.e., A: linagliptin 5 mg vs. placebo, as add-on to empagliflozin 25 mg plus metformin); and B: linagliptin 5 mg vs. placebo, as add-on to empagliflozin 10 mg plus metformin), with analyses conducted separately for each subgroup.

Key Secondary Endpoints:

In addition to the primary efficacy endpoint, the Applicant also evaluated other glycemic endpoints (FPG in all three trials and the proportion of subjects with an HbA1c <7% (Trial 1275.1), and changes in BW (Trials 1275.1 and 1275.9). The key secondary endpoints were assessed at Week 24 for all three trials. The following secondary endpoints were included in the Applicant's hierarchical testing procedure:

- Mean change from baseline at Week 24 in:
  - FPG (mg/dL)
  - BW (kg)
- Proportion of subjects at Week 24 with an:
  - HbA1c <7%

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 8.

Table 8: Sequential Testing Order for Key Secondary Endpoints by Trial

Trials	1275.1	1275.9	1275.10
SECONDARY ENDPOINTS	• FPG • BW • HbA1c <7%	• FPG • BW	• FPG

Source: Adapted from the Applicants' Clinical Protocols or CSRs for Trials 1275.1,[167] 1275.9,[168] and 1275.10,[169] available at: \\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf

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Abbreviations: BW, body weight; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c.

The glycemic endpoints, FPG and proportion of subjects achieving an HbA1c <7%, are considered a supportive measures of efficacy in Phase 3 trials,[170] and has been included in product labeling for other approved antihyperglycemic products. The analyses of these endpoints were based on measurements performed by a Central Laboratory. To control for Type I error due to multiple testing, the above secondary efficacy endpoints were included in the Applicant's prespecified testing sequence.

Other Relevant Endpoints:

- Exploratory glycemic efficacy endpoints: Proportions of subjects at Week 24 with an HbA1c <6.5%, reductions in HbA1c ≥0.5%, systolic blood pressure (SBP) ≥3 mmHg and body weight >2%; changes from baseline in waist circumference, SBP and diastolic blood pressure (DBP); and use of glycemic rescue therapy
- Safety: Adverse events (AEs), and clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings

5.1.8. Statistical Analysis Plan

Dr. Yi Ren was the Statistical Reviewer for this Application. Since Trial 1275.1 was previously reviewed by Dr. Jennifer Clark for the original GLYXAMBI Application (NDA 206073), Dr. Ren did not reanalyze these data. This section will include a brief discussion of the statistical analysis plan (SAP) for the analyses included in GLYXAMBI product labeling,[9] which the Applicant also intends to include in TRIJARDY XR labeling. For a detailed discussion of the statistical issues of this trial, please refer to Dr. Clark's review, dated October 15, 2014.

For the analysis of changes from baseline in HbA1c and FPG in Trial 1275.1, a mixed model repeated measures (MMRM) analytical approach was used. The MMRM model included terms for treatment group, renal function (eGFR), geographical region, visit, visit-by-treatment interaction, and baseline HbA1c value. The change from baseline in BW was analyzed using an analysis of covariance (ANCOVA) model. The secondary endpoint (proportion of subjects with an EOT HbA1c <7%) was evaluated using logistic regression, imputing missing data as failures. The model included factors for treatment, baseline renal function, geographical region and baseline HbA1c value. Although odds ratios (ORs), 95% CIs and p-values were calculated, only numbers (%) of subjects achieving an HbA1c <7% were included in proposed product labeling (as reported in Glyxambi product labeling).[9] The analysis population for all analyses was the Full Analysis Set (FAS, i.e., observed cases [OC]). However, the analysis that compared the proportion of subjects achieving an HbA1c <7% only included subjects with an HbA1c >7% at baseline.

For Trials 1275.9 and 1275.10, the Applicant's prespecified approach for analyzing primary and key secondary endpoints used an ANCOVA model with a last observation carried forward (LOCF) approach for handling missing data. However, the SAP was amended (Global Amendment #2, dated December 17, 2013 and November 27, 2013, respectively) to use a MMRM (OC) model that included treatment, region, baseline renal function, visit, and visit-by-treatment interaction as the main effects and baseline HbA1c (or FPG or BW, depending on the respective key secondary endpoints) as a covariate, based on advice provided by a health authority (dated April 24, 2013). The Applicant stated that according to published literature,[177] the MMRM analytical approach appears to be a superior for controlling Type I error rates and minimizing bias as compared to single imputation approaches (e.g. LOCF ANCOVA), particularly in the presence of missing at random (MAR) data. However, due to the MAR assumption (i.e., missing data for those off-treatment are considered to be the same as that of observed data for those subjects who remained on treatment in the same arm), the MMRM approach is not consistent with current Agency recommendations. In response to an advice letter (dated May 6, 2019), the Applicant was asked to reanalyze the primary and key secondary efficacy endpoints using analytical approaches that handle missing data based on data from retrieved dropouts (to include post dropout and post glycemic rescue data) or consistent with the intent-to-treat estimand (e.g., estimating the treatment effect in a manner consistent with what the measurement would have been if it had been measured). The Applicant performed the requested analyses and submitted these data on June 12, 2019.[178] Based on the revised analyses, the Agency felt that the an ANCOVA approach using a multiple imputation washout method was acceptable (i.e., missing data from both treatment arms were imputed using observed data from the placebo arms).

5.1.9. 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 NDA. However, as noted above, the primary analysis methodology for Trials 1275.9 and 1275.10 was changed from ANCOVA (LOCF) to MMRM (OC). The Agency no longer recommends the use of a MMRM approach due to the MAR assumption. Since the Applicant also reanalyzed the primary and key secondary endpoints of these trials using the Agency's preferred analytical approach (i.e., ANCOVA with multiple imputation washout method), and results were similar between both methodologies, I do not feel that this global amendment across these trials alters the respective efficacy findings.

5.1.10. Study Results

Compliance with Good Clinical Practice:

The Applicant states that all three trials in their Phase 3 clinical development program were conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant Standard Operating Procedures (SOPs) of the Applicant.

Financial Disclosure:

In Dr. Chong's clinical review (NDA 206073; GLYXAMBI), he stated that the Applicant certified that they had not entered into a financial arrangement with any of the clinical investigators (n=940) participating in Trial 1275.1. For their current submission, the Applicant also has submitted a Form FDA 3454 for each of the covered trials (i.e., Trials 1275.9, 1275.10, 1361.1, 1361.3, and 1361.11; 894 investigator/subinvestigators). They again certified that no principal investigators or subinvestigators held financial interests requiring disclosure for these trials. There were 28 investigators for whom the Applicant was unable to provide certification of an absence of financial arrangements (i.e., investigator did not participate in trial, the trial was not initiated at the study site, or the site was no longer a study site).

Based on review of these data, I do not feel that there was any undue bias that would affect the efficacy findings of these trials. Please see Section 12.2 below for additional information.

Patient Disposition:

The disposition of subjects across the three clinical trials relevant to the evaluation of efficacy is presented in Table 9. Approximately 89% to 96% of subjects completed the 24-week treatment phase. The most common reasons for not completing the 24-week treatment period included adverse events (1.4-3.9% of subjects across all arms) and lost to follow-up (0.7-4.5% of subjects). Differences in the limited numbers of disposition events between triple and dual therapy arms were not clinically meaningful, and no obvious trends were observed. Additionally, for Trials 1275.9 and 1275.10, SAEs were not reported for the subjects with disposition events of 'Lost to follow-up', 'Subject refused to continue IP', and 'Other'.

Table 9: Subject Disposition for Phase 3 Efficacy Trials (Treated Population) – Week 24

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met	Empa 10mg + Met	Empa 25mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met	Lina 5mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met	Empa 10mg + Met	Empa 25mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized	132	140	141	136	137	110	112	110	128	112	126	112
Complete 24-week phase	118 (89.4)	124 (88.6)	131 (92.9)	129 (94.9)	126 (92.0)	105 (95.5)	103 (92.0)	106 (96.4)	118 (92.2)	105 (93.8)	111 (88.1)	102 (91.1)
Prematurely discontinue IP	14 (10.6)	16 (11.4)	10 (7.1)	7 (5.1)	11 (8.0)	5 (4.5)	9 (8.0)	4 (3.6)	10 (7.8)	7 (6.3)	15 (11.9)	10 (8.9)
Adverse events	4 (3.0)	5 (3.6)	2 (1.4)	3 (2.2)	3 (2.2)	2 (1.8)	3 (2.7)	0	5 (3.9)	2 (1.8)	4 (3.2)	3 (2.7)
Worsening of study Dx	1 (0.8)	0	0	0	0	0	0	0	1 (0.8)	0	1 (0.8)	0
Worsening of other Dx	0	1 (0.7)	0	0	1 (0.7)	0	0	0	0	0	0	0
Other adverse events	3 (2.3)	4 (2.9)	2 (1.4)	3 (2.2)	2 (1.5)	2 (1.8)	3 (2.7)	0	4 (3.1)	2 (1.8)	3 (2.4)	3 (2.7)
Lack of efficacy	0	0	0	0	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Noncompliance	0	2 (1.4)	0	0	1 (0.7)	1 (0.9)	1 (0.9)	0	0	0	2 (1.6)	0
Lost to follow-up	4 (3.0)	4 (2.9))	4 (2.8)	2 (1.5)	1 (0.7)	2 (1.8)	4 (3.6)	2 (1.8)	1 (0.8)	2 (1.8)	4 (3.2)	5 (4.5)
Subject refuse to continue IP	2 (1.5)	3 (2.1)	1 (0.7)	1 (0.7)	3 (2.2)	0	0	2 (1.8)	2 (1.6)	1 (0.9)	1 (0.8)	0
Other	4 (3.0)	2 (1.4)	3 (2.1)	1 (0.7)	3 (2.2)	0	0	0	2 (1.6)	1 (0.9)	4 (3.2)	2 (1.8)

Source: Adapted from the Applicant's Summary of Clinical Efficacy,[179] labeled as Tables 3.1.1.3:1, 3.1.1.1:1, 3.1.1.3:1, pages 23-25 of 82, respectively, and the CSRs for Trials 1275.1,[167] 1275.9,[168] and 1275.10,[169] available at:
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Abbreviations: CSRs, Clinical Study Reports; Dx, disease; Empa, empagliflozin; FAS, full analysis set; IP, investigational product; Lina, linagliptin; Met, metformin; N, sample size.

Protocol Violations/Deviations:

Important protocol violations were defined as violations that lead to exclusion from analysis populations. These violations could potentially impact the primary efficacy analysis of trial results or subject safety. Across the Phase 3 clinical program, important protocol violations were reported in approximately 9.5% of subjects (65 subjects) in Trial 1275.1; 21.4% (70 subjects) in Trial 1275.9; 8.6% (40 subjects) in Trial 1275.10. The most common violations for these trials in the triple therapy arms included noncompliance with IP (overall study treatment compliance outside 80% and 120% or treatment compliance <80% in the last visit interval before primary endpoint assessment), renal insufficiency/impairment (exclusion criterion checked or eGFR <60 mL/min/1.73 m^2), restricted medication used within seven days after treatment discontinuation, additional background therapy, and missing on-treatment HbA1c measurement(s). A review of these violations within each trial did not reveal any obvious/important trends or treatment differences across trial arms.

Table of Demographic Characteristics:

The baseline demographics and clinical characteristics (Table 10) of randomized subjects are summarized below. Within and across trials, treatment groups were reasonably balanced for demographics and clinical characteristics at baseline. Overall, the trial populations were predominantly White, and relatively young (mean age approximately 56 years). A limited number of subjects (<3%) were over 75 years of age. The trials were conducted worldwide; with the approximately 34% of randomized subjects residing in the North American region. The mean body mass index (BMI) was approximately 31 kg/m^2 across all trials. The mean baseline HbA1c concentrations ranged from 7.8% to 8.0%, and the average duration of diabetes was greater than five years. Since subjects with an eGFR <60 mL/min/1.73m^2 were to be excluded from study participation, the mean eGFR was approximately 90 mL/min/1.72 m^2 in all trials.

Table 10: Baseline Demographics and Clinical Characteristics for Phase 3 Efficacy Trials (FAS Population)*

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met	Empa 10mg + Met	Empa 25mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met	Lina 5mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met	Empa 10mg + Met	Empa 25mg + Met	Empa 10mg + Lina 5mg + Met	Empa 25mg + Lina 5mg + Met
Randomized	N=128	N=137	N=140	N=135	N=134	N=108	N=109	N=110	N=125	N=110	N=122	N=110
Demographics												
Age, mean ± SD — yr	56.18 [10.00]	56.13 [10.47]	55.51 [10.01]	56.24 [10.31]	57.12 [10.19]	55.93 [9.70]	54.31 [9.57]	55.39 [9.95]	56.83 [9.40]	56.06 [10.58]	56.64 [9.55]	56.62 [9.82]
<65 yr — no. (%)	101 (78.9)	111 (81.0)	115 (82.1)	110 (81.5)	102 (76.1)	89 (82.4)	93 (85.3)	95 (86.4)	100 (80.0)	92 (83.6)	98 (80.3)	87 (79.1)
≥65 yr to <75 yr — no. (%)	24 (18.8)	19 (13.9)	21 (15.0)	21 (15.6)	28 (20.9)	17 (15.7)	15 (13.8)	13 (11.8)	21 (16.8)	15 (13.6)	20 (16.4)	22 (20.0)
≥75 yr — no. (%)	3 (2.3)	7 (5.1)	4 (2.9)	4 (3.0)	4 (3.0)	2 (1.9)	1 (0.9)	2 (1.8)	4 (3.2)	3 (2.7)	4 (3.3)	1 (0.9)
Sex — no. (%)												
Male	64 (50.0)	78 (56.9)	65 (46.4)	83 (61.5)	72 (53.7)	60 (55.6)	66 (60.6)	71 (64.5)	70 (56.0)	63 (57.3)	69 (56.6)	52 (47.3)
Female	64 (50.0)	59 (43.1)	75 (53.6)	52 (38.5)	62 (46.3)	48 (44.4)	43 (39.4)	39 (35.5)	55 (44.0)	47 (42.7)	53 (43.4)	58 (52.7)
Race - no. (%)												
White	96 (75.0)	103 (75.2)	100 (71.4)	102 (75.6)	97 (72.4)	59 (54.6)	67 (61.5)	65 (59.1)	119 (95.2)	106 (96.4)	120 (98.4)	107 (97.3)
Asian	14 (10.9)	20 (14.6)	20 (14.3)	18 (13.3)	22 (16.4)	32 (29.6)	26 (23.9)	30 (27.3)	1 (0.8)	0	0	0
Black/African American	9 (7.0)	8 (5.8)	13 (9.3)	12 (8.9)	7 (5.2)	9 (8.3)	9 (8.3)	11 (10.0)	3 (2.4)	4 (3.6)	2 (1.6)	3 (2.7)
American Indian/Alaska Native	9 (7.0)	6 (4.4)	7 (5.0)	3 (2.2)	8 (6.0)	4 (3.7)	5 (4.6)	4 (3.6)	2 (1.6)	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0	0	0	4 (3.7)	2 (1.8)	0	0	0	0	0
Region — no. (%)												
Europe	39 (30.5)	39 (28.5)	37 (26.4)	37 (27.4)	39 (29.1)	33 (30.6)	35 (32.1)	34 (30.9)	62 (49.6)	52 (47.3)	62 (50.8)	50 (45.5)
North America	54 (42.2)	62 (45.3)	65 (46.4)	63 (46.7)	59 (44.0)	36 (33.3)	37 (33.9)	38 (34.5)	26 (20.8)	25 (22.7)	22 (18.0)	26 (23.6)
Latin America	18 (14.1)	19 (13.9)	20 (14.3)	18 (13.3)	18 (13.4)	15 (13.9)	14 (12.8)	14 (12.7)	37 (29.6)	33 (30.0)	38 (31.1)	34 (30.9)
Asia	17 (13.3)	17 (12.4)	18 (12.9)	17 (12.6)	18 (13.4)	24 (22.2)	23 (21.1)	24 (21.8)	0	0	0	0
Clinical Characteristics												
Weight, kg — mean ± SD	85.01 (18.34)	86.14 (18.19)	87.68 (17.61)	86.57 (19.01)	85.47 (20.36)	82.34 (19.77)	88.41 (20.76)	84.38 (19.23)	85.59 (18.02)	89.91 (16.12)]	88.43 (16.84)	85.66 (16.73)
BMI, mg/m2 — mean ± SD	30.59 (5.41)	31.02 (5.27)	31.80 [5.28]	30.79 [5.60]	30.61 [5.69]	29.64 (5.73)	31.17 (5.92)	29.90 (5.27)	30.76 (4.75)	32.01 (5.25)	31.26 (5.39)	30.79 (4.63)
T2D Duration — no. (%)												
<=1 yr	10 (7.8)	13 (9.5)	10 (7.1)	19 (14.1)	10 (7.5)	9 (8.3)	6 (5.5)	7 (6.4)	16 (12.8)	9 (8.2)	7 (5.7)	8 (7.3)
>1 to 5 yr	44 (34.4)	51 (37.2)	50 (35.7)	49 (36.3)	46 (34.3)	31 (28.7)	30 (27.5)	41 (37.3)	40 (32.0)	33 (30.0)	42 (34.4)	31 (28.2)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	**Lina 5mg + Met**	**Empa 10mg + Met**	**Empa 25mg + Met**	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Lina 5mg + Met**	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10mg + Met**	**Empa 25mg + Met**	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**
Randomized	**N=128**	**N=137**	**N=140**	**N=135**	**N=134**	**N=108**	**N=109**	**N=110**	**N=125**	**N=110**	**N=122**	**N=110**
>5 to 10 yr	43 (33.6)	39 (28.5)	50 (35.7)	41 (30.4)	46 (34.3)	38 (35.2)	42 (38.5)	35 (31.8)	37 (29.6)	39 (35.5)	40 (32.8)	40 (36.4)
>10 yr	31 (24.2)	34 (24.8)	30 (21.4)	26 (19.3)	32 (23.9)	30 (27.8)	31 (28.4)	27 (24.5)	32 (25.6)	29 (26.4)	33 (27.0)	31 (28.2)
HbA1c, % — mean ± SD	8.02 (0.90)	8.00 (0.93)	8.02 (0.83)	7.95 [0.80]	7.90 (0.79)	7.97 (0.85)	7.97 (0.84)	7.97 (0.82)	8.03 (0.85)	7.88 (0.90)	8.04 (0.96)	7.81 (0.71)
eGFR, mL/min/1.73 m^2 — mean ± SD	90.03 (20.14)	91.12 (19.52)	90.23 (18.31)	89.10 (18.38)	87.28 (17.15)	92.71 (16.20)	90.83 (19.10)	93.42 (18.65)	89.80 (19.60)	91.06 (19.68)	91.95 (19.47)	88.97 (18.48)
60 TO <90	65 (50.8)	68 (49.6)	78 (55.7)	77 (57.0)	72 (53.7)	49 (45.4)	60 (55.0)	52 (47.3)	69 (55.2)	53 (48.2)	51 (41.8)	59 (53.6)
>=90	57 (44.5)	64 (46.7)	60 (42.9)	57 (42.2)	58 (43.3)	57 (52.8)	47 (43.1)	57 (51.8)	54 (43.2)	54 (49.1)	66 (54.1)	47 (42.7)
45 TO <60	0	0	0	0	0	2 (1.9)	2 (1.8)	1 (0.9)	2 (1.6)	2 (1.8)	4 (3.3)	4 (3.6)
30 TO <60	6 (4.7)	5 (3.6)	2 (1.4)	1 (0.7)	3 (2.2)	0	0	0	0	0	0	0
<45	0	0	0	0	0	0	0	0	0	1 (0.9)	1 (0.8)	0
<30	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0

Source: Derived from the adsl.xpt dataset and adapted from the Applicant's Summary of Clinical Efficacy,[179] labeled as Tables 3.1.3.1.1:1, 3.1.3.1.2:1, 3.1.3.1.3:1, 3.1.3.2.1:1, 3.1.3.2.2:1, 3.1.3.2.3:1, pages 26-32of 82, available at:
\\cdsesub1\evsprod\nda212614\0000\m2\27-clin-sum\2-7-3-summary-clin-efficacy-empa-lina-met-fdc.pdf
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; FAS, full analysis set population; HbA1c, hemoglobin A1c; Lina, linagliptin; Met, metformin (≥1500 mg/day); no., number; SD, standard deviation; T2D, type 2 diabetes; and yr, years.
*Full Analysis Set (FAS), all subjects randomized who received ≥1 dose of investigational product.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use:

In the three 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.[104] Additionally, prospective electronic monitoring studies have documented that patients took 67-85% of their oral antihyperglycemic doses as prescribed.[104] Although there is no universally accepted definition for what constitutes adequate adherence, a compliance rate of >80% is reasonable.[108,109,180] During the 24-week double-blind treatment period compliance rates with administration of IP were reported to be 97.3% in Trial 1275.1, >95.7% in Trial 1275.9, and 97% (Subpopulation A: 98.2%; Subpopulation B: 96%) in Trial 1275.10. 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 5.1.6). Use of glycemic rescue was a secondary or exploratory endpoint in all trials. However, 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 24-week 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 Ren noted that data for the primary efficacy analysis (i.e., HbA1c at Weeks 24) were missing for 5.4% to 8.8% of subjects across the three trials. To account for missing data for Trials 1275.9 and 1275.10, Dr. Ren reanalyzed the efficacy data using an ANCOVA with multiple imputation washout method (i.e., missing data in an endpoint from both arms were imputed using observed data from the placebo arm). Please refer to her review for further discussion.

Efficacy Results – Primary Endpoint:

The results of the primary efficacy analyses (i.e., control-subtracted change in HbA1c from baseline to Week 24) performed by the Applicant, and the Agency's reanalysis of these data, are presented in Table 11 below. Compared to use of the individual components of the FCDP (i.e., empagliflozin 10 mg or 25 mg plus metformin or linagliptin 5 mg plus metformin), triple combination therapy with empagliflozin (10 mg or 25 mg) plus linagliptin (5 mg) plus metformin resulted in modest but statistically significant reductions in HbA1c.

Table 11: Adjusted HbA1c Change from Baseline at Week 24 Analyses (Phase 3 Trials)

Analysis	Triple Therapy Arm	Triple Therapy Arm	Comparator	Comparator	Comparator
Trial 1275.1 *(Add-on Therapy with Empa 10 mg or 25 mg + Lina 5 mg vs. Individual Components in Subjects Inadequately Controlled on Met)*					
HbA1c (%)					
Labeled Analysis (MMRM, OC)[a]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10 mg + Met**	**Empa 25 mg + Met**	**Lina 5 mg + Met**
Sample size, N[b]	135	133	137	139	128
Mean baseline	8.0	7.9	8.0	8.0	8.0
Mean change from baseline	-1.1	-1.2	-0.7	-0.6	-0.7
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-0.4 (-0.6, -0.2)	-0.6 (-0.7, -0.4)			
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-0.4 (-0.6, -0.2)	-0.5 (-0.7, -0.3)			
Trial 1275.9 *(Add-on Therapy with Empa 10 mg or 25 mg vs. Placebo in Subjects Inadequately Controlled on Lina 5 mg + Met)*					
HbA1c (%)					
Applicant's Analysis (MMRM, OC)[a]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**			**Lina 5 mg + Met**
Sample Size, N[b]	109	110			108
Mean baseline (SE)	8.00 (0.08)	7.97 (0.08)			7.96 (0.08)
Patients analyzed at Wk 24, N	100	100			88
Adjusted mean change from baseline (SE)	-0.65 (0.08)	-0.56 (0.08)			0.14 (0.09)
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-0.79 (-1.02, -0.55)	-0.70 (-0.93, -0.46)			
p-value	<0.0001	<0.0001			
FDA's Analysis (ANCOVA, MI)[c]					
Sample Size, N[d]	112	110			110
Mean baseline (SE)	8.00 (0.08)	7.97 (0.08)			7.99 (0.08)
Patients analyzed, N	112	110			110
Adjusted mean change from baseline (SE)	-0.61 (0.08)	-0.56 (0.08)			0.07 (0.08)
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-0.69 (-0.91, -0.46)	-0.63 (-0.86, -0.41)			
p-value	<0.0001	<0.0001			

Analysis	Triple Therapy Arm	Triple Therapy Arm	Comparator	Comparator	Comparator
Trial 1275.10 *(Add-on Therapy with Lina 5 mg vs. Placebo in Subjects Inadequately Controlled on Empagliflozin 10 mg or 25 mg + Met)*					
HbA1c (%)					
Applicant's Analysis (MMRM, OC)[a]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10 mg + Met**	**Empa 25 mg + Met**	
Sample Size, N[b]	122	110	122	110	
Mean baseline (SE)	8.04 (0.09)	7.82 (0.07)	8.03 (0.08)	7.88 (0.09)	
Patients analyzed at Wk 24, N	111	98	110	98	
Adjusted mean change from baseline (SE)	-0.53 (0.07)	-0.58 (0.07)	-0.21 (0.07)	-0.10 (0.07)	
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-0.32 (-0.52, -0.13)	-0.47 (-0.66, -0.28)			
p-value	0.0013	<0.0001			
FDA's Analysis (ANCOVA, MI)[c]					
Sample Size, N[d]	126	112	128	112	
Mean baseline (SE)	8.03 (0.08)	7.83 (0.07)	8.01 (0.08)	7.89 (0.08)	
Patients analyzed at Wk 24, N	126	112	128	112	
Adjusted mean change from baseline (SE)	-0.56 (0.07)	-0.56 (0.07)	-0.23 (0.07)	-0.15 (0.07)	
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-0.34 (-0.53, -0.15)	-0.40 (-0.59, -0.22)			
p-value	0.0006	<0.0001			

Source: Adapted from GLYXAMBI product labeling[9] (b) (4), Dr. Ren's statistical review (dated December 19, 2019), and the Applicant's response to the agency's information request (dated June 12, 2019), available at:
\\cdsesub1\evsprod\nda210874\0001\m1\ (b) (4) .pdf

Abbreviations: +, plus; ANCOVA, analysis of covariance; CI, confidence interval; Empa, empagliflozin; HbA1c, hemoglobin A1c; Lina, linagliptin; Met, metformin (≥1500 mg/day); MI, multiple imputation washout method; mITT, modified intent to treat; MMRM, mixed model repeated measures; OC, observed cases; SE, standard error; Wk, week.

[a] MMRM model included treatment, baseline eGFR, geographical region, visit, visit by treatment interaction as fixed effects, and baseline HbA1c as a covariate.

[b] N included the FAS (OC).

[c] Analysis of covariance model included baseline HbA1c as a covariate and baseline eGFR, geographical region, and treatment as fixed effects.

[d] N included the mITT (MI), defined as a patient set including all randomized patients who were treated with at least one dose of study drug during the double-blind (DB) part of the trial and had a baseline measurement.

Data Quality and Integrity:

As noted in Section 3.1 above, OSI was consulted to conduct additional audits/site inspections for this Application, primarily for Trials 1275.9 and 1275.10. Based on these inspections, the data were considered acceptable. Additionally, the submission was in the electronic common technical document (eCTD) form with an xml backbone. Study datasets were provided as SAS XPORT transport files for all three trials. In her review, Dr. Ren noted that the quality of the submitted datasets was acceptable. She also confirmed and reanalyzed the analyses (primary and sensitivity) performed by the Applicant. Based on the above findings, I feel that the data quality for this submission was acceptable.

Efficacy Results – Secondary and Other Relevant Endpoints:

Key secondary analyses performed by the Applicant are presented in Table 12. For this portion of the review, only the key secondary endpoints will be discussed. For more detailed information on the evaluation of secondary endpoints, please refer to Dr. Clark's and Ren's respective reviews. The empagliflozin + linagliptin + metformin triple therapy arms generally resulted in higher proportions of subjects achieving an HbA1c of <7%, and modest reductions in FPG and body weight. Although these results are supportive, the long-term clinical relevance of the observed differences between arms is uncertain. Additionally, although some weight loss was consistent across Trials 1275.1 and 1275.9, the magnitude of these reductions (↓2-3 kg; ↓3-4% in total body weight) would not be sufficient to pursue a weight loss claim (i.e., would not meet the FDA guidance criteria for weight management).[181] In overweight individuals, especially those with comorbidities such as T2D, weight >5% may be associated with improvement in various metabolic and cardiovascular risk factors.[182,183]

Table 12: Secondary Endpoint Analyses (Phase 3 Trials)

Analysis	Triple Therapy Arm	Triple Therapy Arm	Comparator	Comparator	Comparator
Trial 1275.1 *(Add-on Therapy with Empa 10 mg or 25 mg + Lina 5 mg vs. Individual Components in Subjects Inadequately Controlled on Met)*					
HbA1c <7%, N (%)[a]	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
Labeled Analysis (MMRM, OC)[b]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10 mg + Met**	**Empa 25 mg + Met**	**Lina 5 mg + Met**
Sample size, N[c]	133	131	136	137	125
Mean baseline	157	155	162	160	156
Mean change from baseline	-33	-36	-21	-21	-13
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-12 (-18, -5)	-15 (-22, -9)			
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-20 (-27, -13)	-23 (-29, -16)			
Body Weight (kg)					
Labeled Analysis (MMRM, OC)[b]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10 mg + Met**	**Empa 25 mg + Met**	**Lina 5 mg + Met**
Sample size, N[c]	135	134	137	140	128
Mean baseline	87	85	86	88	85
Mean change from baseline	-3.1	-3.4	-3.0	-3.5	-0.7
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	0.0 (-0.9, 0.8)	0.1 (-0.8, 0.9)			
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-2.4 (-3.3, -1.5)	-2.7 (-3.6, -1.8)			
Trial 1275.9 *(Add-on Therapy with Empa 10 mg or 25 mg vs. Placebo in Subjects Inadequately Controlled on Lina 5 mg + Met)*					
FPG (mg/dL)					
Applicant's Analysis (MMRM, OC)[b]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**			**Lina 5 mg + Met**
Sample Size, N[c]	109	110			108
Mean baseline (SE)	167.9 (3.8)	170.1 (4.1)			162.9 (3.1)
Patients analyzed at Wk 24, N	97	96			84
Adjusted mean change from baseline (SE)	-26.3 (3.3)	-31.6 (3.3)			6.1 (3.4)

Analysis	Triple Therapy Arm	Triple Therapy Arm	Comparator	Comparator	Comparator
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-32.4 (-41.7, -23.0)	-37.7 (-47.0, -28.3)			
p-value	<0.0001	<0.0001			
FDA's Analysis (ANCOVA, MI)[d]					
Sample Size, N[e]	112	110			110
Mean baseline (SE)	168.0 (3.7)	169.9 (4.0)			163.2 (3.1)
Patients analyzed, N	112	110			110
Adjusted mean change from baseline (SE)	-23.4 (3.6)	-29.9 (3.7)			4.0 (3.6)
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-27.3 (-37.4, -17.3)	-33.9 (-44.0, -23.7)			
p-value	<0.0001	<0.0001			
Body Weight (kg)					
Applicant's Analysis (MMRM, OC)[b]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**			**Lina 5 mg + Met**
Sample Size, N[c]	109	110			108
Mean baseline (SE)	88.41 (1.99)	84.38 (1.83)			82.26 (1.94)
Patients analyzed at Wk 24, N	98	97			88
Adjusted mean change from baseline (SE)	-3.06 (0.25)	-2.52 (0.25)			-0.30 (0.26)
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-2.77 (-3.47, -2.07)	-2.22 (-2.92, -1.52)			
p-value	<0.0001	<0.0001			
FDA's Analysis (ANCOVA, MI)[d]					
Sample Size, N[e]	112	110			110
Mean baseline (SE)	88.33 (1.95)	84.38 (1.83)			82.26 (1.87)
Patients analyzed, N	112	110			110
Adjusted mean change from baseline (SE)	-2.71 (0.25)	-2.40 (0.25)			-0.21 (0.25)
Difference vs. Lina 5 mg + Met adjusted mean (95% CI)	-2.50 (-3.20, -1.81)	-2.19 (-2.87, -1.51)			
p-value	<0.0001	<0.0001			

Analysis	Triple Therapy Arm	Triple Therapy Arm	Comparator	Comparator	Comparator
Trial 1275.10 *(Add-on Therapy with Lina 5 mg vs. Placebo in Subjects Inadequately Controlled on Empagliflozin 10 mg or 25 mg + Met)*					
FPG (mg/dL)					
Applicant's Analysis (MMRM, OC)[b]	**Empa 10mg + Lina 5mg + Met**	**Empa 25mg + Lina 5mg + Met**	**Empa 10 mg + Met**	**Empa 25 mg + Met**	
Sample Size, N[c]	122	110	125	110	
Mean baseline (SE)	157.9 (3.1)	152.3 (2.8)	155.6 (2.8)	155.0 (3.6)	
Patients analyzed at Wk 24, N	108	93	107	94	
Adjusted mean change from baseline (SE)	-8.0 (3.2)	-12.3 (2.8)	3.7 (3.2)	-4.4 (2.8)	
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-11.7 (-20.6, -2.8)	-7.9 (-15.6, -0.2)			
p-value	0.0103	0.0452			
FDA's Analysis (ANCOVA, MI)[d]					
Sample Size, N[e]	126	112	128	112	
Mean baseline (SE)	160.6 (3.6)	152.9 (2.8)	156.6 (3.1)	156.1 (3.5)	
Patients analyzed at Wk 24, N	126	112	128	112	
Adjusted mean change from baseline (SE)	-8.3 (3.2)	-11.0 (2.8)	1.7 (3.1)	-5.2 (2.7)	
Difference vs. Empa 10 mg or 25 mg + Met adjusted mean (95% CI)	-10.0 (-18.7, -1.2)	-5.8 (-13.4, 1.9)			
p-value	0.0254	0.1391			

Source: Adapted from GLYXAMBI product labeling[9] (b) (4), Dr. Ren's statistical review (dated December 19, 2019), and the Applicant's response to the agency's information request (dated June 12, 2019), available at:
\\cdsesub1\evsprod\nda210874\0001\m1\us (b) (4) .pdf

Abbreviations: +, plus; ANCOVA, analysis of covariance; CI, confidence interval; Empa, empagliflozin; HbA1c, hemoglobin A1c; Lina, linagliptin; Met, metformin (≥1500 mg/day); MI, multiple imputation washout method; mITT, modified intent to treat; MMRM, mixed model repeated measures; OC, observed cases; SE, standard error; Wk, week.

[a] Patients with HbA1c >7% at baseline: Empa 25 mg + Lina 5 mg + Met, n=123; Empa 10 mg + Lina 5 mg + Met, n=128; empagliflozin 25 mg, n=132; empagliflozin 10 mg, n=125; linagliptin 5 mg, n=119. Non-completers were considered failures (NCF).

[b] MMRM model included treatment, baseline eGFR, geographical region, visit, visit by treatment interaction as fixed effects, and baseline HbA1c as a covariate.

[c] N included the FAS (OC).

[d] Analysis of covariance model included baseline HbA1c as a covariate and baseline eGFR, geographical region, and treatment as fixed effects.

[e] N included the mITT (MI), defined as a patient set including all randomized patients who were treated with at least one dose of study drug during the double-blind (DB) part of the trial and had a baseline measurement.

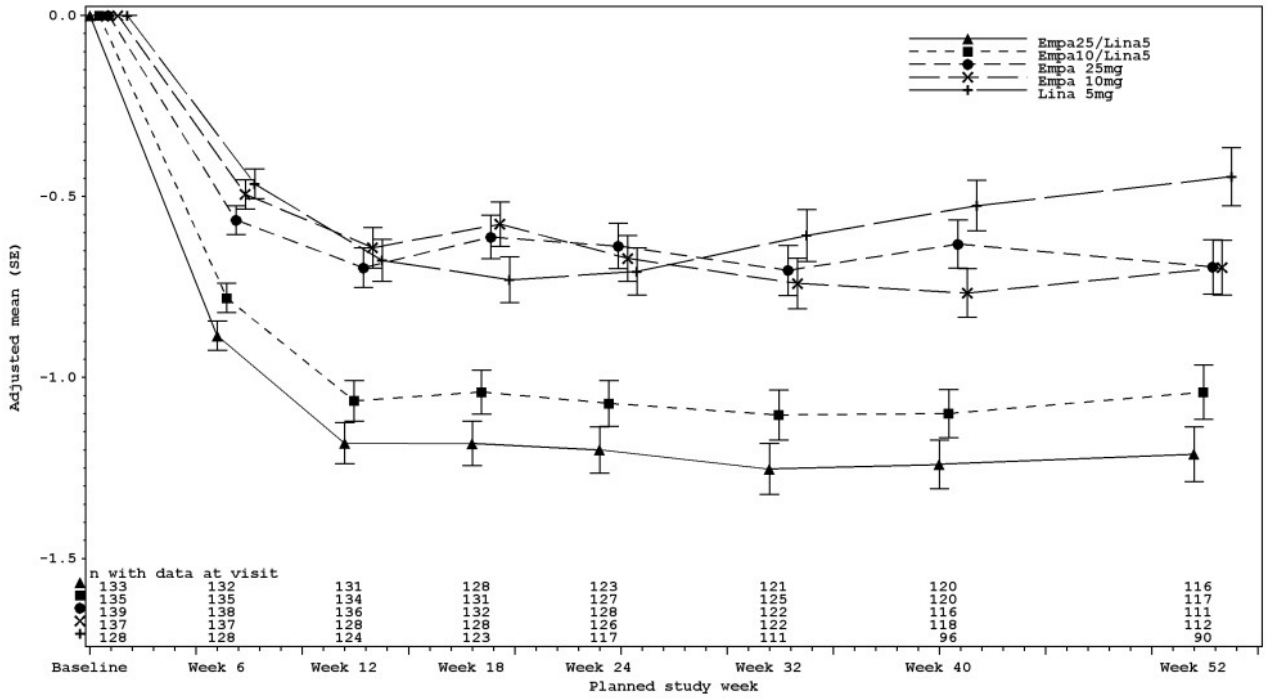
Dose/Dose Response:

These trials were not intended to evaluate a dose response for the proposed TRIJARDY XR dose formulations. Additionally, the linagliptin dose was fixed at 5 mg/day, and metformin was administered as background therapy at doses of ≥1500 mg daily for all three trials. Although empagliflozin 10 mg and 25 mg triple therapy arms were included in each trial, these trials were not designed for formal comparisons between these arms (e.g., not prespecified in the respective SAPs). Based on informal review of the data, an obvious benefit from the higher empagliflozin dose over lower dose triple combinations was not apparent across these trials. For Trials 1275.1 and 1275.10 (Table 11 and Figure 3), the higher empagliflozin triple therapy arms appeared to be associated with numerically higher reductions in HbA1c, while the lower dose triple therapy arm was associated with a greater reduction in Trial 1275.9.

Durability of Response:

The primary efficacy finding of change from baseline in HbA1c of Trial 1275.1 (Figure 3), provides some support for the use of combination therapy with empagliflozin, linagliptin and metformin for 52 weeks (i.e., 24-week ST plus 28-week LT double-blind treatment periods). I feel that these data are supportive for showing a durability of glycemic response.

Figure 3: Change from Baseline to Week 52 in HbA1c for Trial 1275.1



Source: Reproduced from the Applicant's CSR for Trial 1275.1,[167] labeled as Figure 11.A.4.1.1.2: 1, page 162 of 7879, available at: \\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf
Abbreviations: Empa, empagliflozin; Lina, linagliptin; n, sample size; and SE, standard error.

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 empagliflozin, linagliptin and metformin following treatment discontinuation.

Additional Analyses Conducted on the Individual Trial:

The Applicant performed other secondary (exploratory) efficacy analyses (e.g., proportions of subjects with an HbA1c <6.5%; reductions in HbA1c ≥0.5%, systolic blood pressure (SBP) ≥3 mmHg and body weight >2%; changes in waist circumference, blood pressure; and use of glycemic rescue therapy). These endpoints were not included in the Applicant's hierarchical testing strategy for any of the trials, the clinical relevance of the findings is uncertain, and most of these endpoints (with the exception of reductions in SBP) are not included in product labeling for approved antihyperglycemic products. Therefore, I feel that these endpoints should not be included in labeling.

6. Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

6.1.1. Primary Endpoints

The Applicant intends to include only the efficacy findings from Trial 1275.1 in product labeling for TRIJARDY XR. These data are already reported in Section 14 of GLYXAMBI labeling.[9] It is noted that the study designs for the three Phase 3 trials were diverse (please refer to Appendix 12.4). Thus, an integrated analysis of the primary efficacy endpoint across these trials was not performed. Nevertheless, to better understand the contribution of each of the individual components to the FCDP, it is helpful to show 24-week HbA1c changes from baseline in each trial. Dr. Ren reanalyzed the data from the two supporting trials (1275.9 and 1275.10) using the Agency's preferred analyses (Table 13). Based on her results, these trials achieved modest, but statistically significant, HbA1c reductions. I consider these differences to be clinically relevant. For completeness, the data from Dr. Clark's analysis of the primary efficacy data for Trial 1275.1 also are shown (as presented in GLYXAMBI labeling).

Table 13: Mean Change in HbA1c from Baseline to Week 24 for Phase 3 Trials

Trial	Empa 10 mg + Lina 5 mg + Met vs.	HbA1c Difference (95% CI)	Empa 25 mg + Lina 5 mg + Met vs.	HbA1c Difference (95% CI)
1275.1	Empa 10 mg + Met	–0.4 (–0.6, –0.2)	Empa 25 mg + Met	–0.6 (–0.7, –0.4)
	Lina 5 mg + Met	–0.4 (–0.6, –0.2)	Lina 5 mg + Met	–0.5 (–0.7, –0.3)
1275.9	Lina 5 mg + Met	–0.7 (–0.9, –0.5)	Lina 5 mg + Met	–0.6 (–0.9, –0.4)

Trial	Empa 10 mg + Lina 5 mg + Met vs.	HbA1c Difference (95% CI)	Empa 25 mg + Lina 5 mg + Met vs.	HbA1c Difference (95% CI)
1275.10	Empa 10 mg + Met	–0.3 (–0.5, –0.2)	Empa 25 mg + Met	–0.4 (–0.6, –0.2)

Source: Adapted from Drs. Clark's (dated October 15, 2014) and Ren's Statistical Reviews.
Abbreviations: CI, confidence interval; Empa, empagliflozin; HbA1c, hemoglobin A1c; Lina, linagliptin; and Met, metformin.

6.1.2. Secondary and Other Endpoints

The key secondary endpoints intended to be included in product labeling are presented above in Section 5.1.10. Also, please refer to Drs. Clark's and Ren's respective review for additional information on the evaluation of secondary endpoints for each of the Phase 3 trials.

6.1.3. Subpopulations

Dr. Clark performed subgroup analyses of Trial 1275.1. Please refer to her review (dated October 15, 2014) for detailed information. For Trials 1275.9 and 1275.10, Dr. Ren conducted subgroup analyses by gender, race (Caucasian, Black, Asian and Other), age (<65, 65 to <75 and 75 to <85 years), region (North America, Europe, Asia, and Latin America), ethnicity (Hispanic/Latino and not Hispanic/Latino), baseline HbA1c (<8.5 and ≥8.5%), baseline renal function (eGFR ≥90 and 60 to <90 mL/min/1.73 m^2) metformin posology (850 mg bid, 1000 mg bid and other), baseline BMI (<25, 25 to <30, 30 to <35 and ≥35 kg/m^2), baseline BW (≤25, 25 to <30, 30 to <35 and ≥35 kg), and time since diagnosis of T2D (≤1, >1 to 5, >5 to 10 and >10 years). Dr. Ren felt that the results of these analyses were generally consistent across subgroups and that there was no indication of differential treatment effects among subgroups (all p-values ≥0.1). However, for Trial 1275.9, she noted that the reductions in HbA1c for the triple therapy arms were greater in subjects with a higher baseline HbA1c concentrations or shorter times since T2D diagnosis. Greater reductions in HbA1c in subjects with higher baseline values,[184-187] and improved glycemic response in subjects with a shorter duration of time since the diagnosis of T2D[188,189] are patient disease characteristics known to potentially impact the efficacy of antihyperglycemic medications and are not necessarily unanticipated findings.

6.1.4. Dose and Dose-Response

Please refer to Sections 5.1.4 and 5.1.10 for discussion of dose and dose-response, respectively.

6.1.5. 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 three Phase 3 clinical trials included a 24- or 52-week double-blind treatment period. Please refer to Section 5.1.10 above for discussion related to the duration and durability of glycemic efficacy related to Trial 1275.1.

6.2. Additional Efficacy Considerations

6.2.1. 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 empagliflozin and linagliptin 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, making interpretation and generalizability of efficacy findings in these patient populations difficult.

6.2.2. 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 21), 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., SGLT2 inhibitor plus DDP-4 inhibitor plus biguanide) could be of benefit to patients and may improve adherence to prescribed therapy.

6.3. Integrated Assessment of Effectiveness

To demonstrate the efficacy of TRIJARDY XR, the Applicant provided clinical data from three previously conducted trials; a pivotal Phase 3 trial (1275.1) and two supportive clinical trials (1275.9 and 1275.10). Trial 1275.1 was a 24-week randomized, double-blind, parallel-group comparison factorial study (with a 28-week extension phase) that compared concomitant administration of empagliflozin (10 mg/day or 25 mg/day) plus linagliptin (5 mg/day) to empagliflozin or linagliptin, all as add-on therapy to metformin (≥1500 mg/day) in adult T2D patients with inadequate glycemic control (HbA1c ≥7% to ≤10.5%). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in hemoglobin A1c [HbA1c] from baseline to Week 24) for this trial, the triple therapy arms (i.e., empagliflozin 10 mg/linagliptin 5 mg/metformin and empagliflozin 25 mg/linagliptin 5 mg/metformin) resulted in a modest but statistically significant HbA1c reduction compared to the empagliflozin dual therapy arms (i.e., metformin plus empagliflozin 10 or empagliflozin 25 mg): -0.4% (95% confidence interval [CI], -0.6, -0.2) and -0.6% (-0.7, -0.4), respectively; and the linagliptin dual therapy arm: -0.4% [-0.6, -0.2) and -0.5 (-0.7, 0.3), respectively. Statistically significant reductions were also reported for key secondary endpoints (i.e., fasting plasma glucose [FPG], body weight and proportion of subjects achieving an HbA1c <7%).

Trial 1275.9 was a 24-week randomized, double-blind, parallel group study that compared the

efficacy and safety of empagliflozin (10 mg/day or 25 mg/day) as add-on therapy to linagliptin 5 mg/day plus metformin (≥1500 mg/day) compared to dual therapy with linagliptin plus metformin. Using the Agency's preferred analysis, the triple therapy empagliflozin 10 mg (-0.69% [95% CI -0.91%, -0.46%]) and 25 mg (-0.63% [95% CI -0.86%, -0.41%]) arms resulted in a statistically significant HbA1c reduction compared to the linagliptin dual therapy arm. Although the reductions in HbA1c for the triple therapy arms are considered clinically meaningful, there did not appear to be added benefit (HbA1c reduction) with the higher dose for this trial. Compared to the linagliptin dual therapy arm, statistically significant reductions in FPG and BW also were reported.

Trial 1275.10 was a 24-week randomized, double-blind, parallel group study that compared the efficacy and safety of linagliptin 5 mg/day as add-on therapy to empagliflozin (10 mg/day or 25 mg/day) plus metformin (≥1500 mg/day) to dual therapy with empagliflozin plus metformin. Using the Agency's preferred analysis, the triple therapy empagliflozin 10 mg (-0.34% [95% CI -0.53%, -0.15%]) and 25 mg (-0.40% [95% CI -0.59%, -0.22%]) arms resulted in a statistically significant HbA1c reduction compared to the respective empagliflozin dual therapy arm. A statistically significant reduction in FPG also was reported.

Dr. Ren, the statistical reviewer for this Application, felt that Trials 1275.9 and 1275.10 provided supportive data to show that TRIJARDY XR is superior in reducing HbA1c, FPG, and body weight (Study 1275.9) at 24 weeks compared to the respective monotherapies (linagliptin 5 mg for Trial 1275.9 and empagliflozin 25 mg or 10 mg for Trial 1275.10) as add-on to metformin background therapy.

I concur with Dr. Ren's assessment. Based on the totality of the data from Trials 1275.1, 1275.9, and 1275.10, and in accordance with 21 CFR 314.126(a)(b),[22] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of TRIJARDY XR.

7. Review of Safety

7.1. Safety Review Approach

The safety assessment of Trijardy XR was based on the clinical data and information from the Applicant's three Phase 3 clinical trials (i.e., Trials 1275.1, 1275.9, and 1275.10). In the Meeting Request-Written Responses (dated January 25, 2018), the Agency acknowledged the differences in study designs, and agreed that it would be reasonable not to pool the data from these trials.[152] I concur that pooling of safety data from these diverse trials (e.g., varied designs, comparators, and treatment exposures) would not be meaningful. However, for completeness and to provide supportive evidence, the Applicant provided pooled safety data for the Phase 3 trials as an Appendix to their Summary of Clinical Safety (SCS).[190] Additionally, the Applicant intends to only include the safety data from Trial 1275.1 (their 52-week factorial trial) in proposed product labeling. As the safety assessment of this trial was previously performed by Dr. William Chong for NDA 206073 (GLYXAMBI), the safety evaluation for the current Application will focus primarily on the additional safety data from Trials 1275.9 and 1275.10. However, to better inform safety for regulatory decision-making, relevant clinical data from Trial 1275.1 will be presented in tables that display side-by-side comparisons of the three trials. Please refer to Dr. Chong's review (dated January 29, 2015) for detailed information on the safety findings of Trial 1275.1.

As stated previously, Trial 1275.1 was used for the approval of GLYXAMBI (January 30, 1015).[23] The AEs for this trial were originally coded from the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 (the version current at the time of submission). Trials 1275.9 and 1275.10 used MedDRA coding dictionary version 17.1. For pooling, the Applicant recoded the AEs for Trial 1275.1 to MedDRA version 17.1 and provided updated datasets. The Applicant primarily reported AEs per subject (not by number of events) and, for select AEs, performed analyses adjusted by exposure (i.e., incidence rates by 100 patient years [PYs]) or time-to-event (i.e., Kaplan-Meier method).

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]). The Applicant analyzed all AEs, AEs leading to discontinuation of IP (including non-serious and serious events), AEs by intensity, AEs by outcome, investigator-defined drug-related AEs, SAEs (with non-fatal and fatal outcome, both together and separately), other significant AEs (based on the ICH E3 definition[191]), and AESIs. To identify AESI, the Applicant searched the AE databases using standardized MedDRA queries (SMQs) or predefined lists of MedDRA preferred terms (PTs) when an SMQ was not available (i.e., Boehringer Ingelheim-customized MedDRA queries [BIcMQ]. They also established independent adjudication committees to evaluate hepatic events, pancreatitis, and CV events (including deaths). Additionally, clinical study reports and analysis and tabulation datasets were reviewed for safety.

Selected AEs and laboratory abnormalities were crosschecked with those provided with the NDA documents.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The safety database was comprised of all subjects randomized and treated (i.e., took at least one dose of double-blind IP). A summary of the size of the safety population and duration of exposure to IPs in the three Phase 3 trials is presented in Table 14. Overall, 1496 subjects were randomized and treated, of which 733 received the triple combination (464.5 total PYs of exposure). By design, Trial 1275.1 had the longest treatment exposure (364 day median exposure in the triple therapy arms) compared to Trials 1275.9 (169 days) and 1275.10 (170 days). On average, 30.7% (225/733) of subjects in the triple therapy arms across all trials were exposed for ≥52 weeks.

Table 14: Safety Population, Size and Duration of Exposure (Phase 3 Trials)

Phase 3 Trials	Lina 5 mg + Met	Empa 10 mg + Met	Empa 25 mg + Met	Empa 10 mg + Lina 5 mg + Met	Empa 25 mg + Lina 5 mg + Met
Total Number of Subjects — N	**242**	**268**	**253**	**372**	**361**
1275.1— N	132	140	141	136	137
Exposure — days					
Mean (SD)	333.0 (90.5)	329.6 (94.2)	343.5 (72.3)	349.7 (60.5)	338.3 (83.5)
Median	364.5	364.0	364.0	365.0	364.0
Range	(1, 378)	(1, 377)	(1, 378)	(7, 375)	(1, 379)
Total exposure — PY	120.3	126.3	132.6	130.2	126.9
1275.9	110			110	112
Exposure — days					
Mean (SD)	165.9 (22.8)			163.1 (30.3)	166.3 (22.1)
Median	169.0			168.0	169.0
Range	(1, 188)			(1, 183)	(24, 190)
Total exposure — PY	50.0			50.0	50.1
1275.10 — N		128	112	126	112
Exposure — days					
Mean (SD)		162.2 (33.2)	165.9 (25.5)	163.8 (28.1)	165.6 (26.6)
Median		170.0	170.0	170.0	171.0
Range		(6, 193)	(28, 190)	(21, 184)	(43, 198)
Total exposure — PY		56.8	50.9	56.5	50.8

Source: Adapted from the Applicant's Summary of Clinical Safety (Appendix, labeled as Tables 4.3.3.7, 4.3.1.1, and 4.3.2.1, pages 1176, 1104, and 1122 of 8155),[190] available at: \\cdsesub1\evsprod\nda212614\0000\m2\27-clin-sum\2-7-4-summary-clin-safety-empa-lina-met-fdc.pdf
Abbreviations: Empa, empagliflozin; Lina, linagliptin; Met, metformin; N, sample size; and PY, patient-years.

7.2.2. Relevant Characteristics of the Safety Population

The demographics and clinical characteristics for the three Phase 3 trials are presented in Table 10. Overall, the baseline demographic and clinical characteristics appeared to be reasonably similar across the treatment arms. Please refer to Section 5.1.10 for additional information.

7.2.3. Adequacy of the safety database:

At the time of approval for GLYXAMBI (JANUARY 30, 2015),[23] the Applicant provided a safety database that included 257.1 PY of exposure to empagliflozin + linagliptin 5 mg as add-on to background metformin therapy from Trial 1275.1. The safety database for the current Application included data from two additional trials (i.e., 1275.9 and 1275.10), and now provides 464.5 PY of exposure to triple therapy. These trials allow for comparisons of the empagliflozin + linagliptin + metformin triple therapy arms with dual therapy (i.e., individual components added to metformin). Based on the additional clinical data, I feel that the exposure and safety data provided are adequate.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. 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 this Application. 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. Please refer to Section 3.1 (Office of Scientific Investigations) for additional information on data integrity/quality.

7.3.2. Categorization of Adverse Events

The safety 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 16.0 (Trial 1275.1; subsequently recoded to version 17.1) and 17.1 (Trials 1275.9 and 1275.10).

An AE was defined as any new untoward medical occurrence, including worsening of a pre-existing medical condition in a subject administered IP, 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 double-blind treatment period up to 7 days after the last dose of

IP (considered the residual effect period for on-treatment AEs). A 30-day washout period was used for AEs associated with hepatic injury or transaminase elevations and the last day of contact was used for malignancies or deaths. 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), seriousness, action taken with IP, 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:** Awareness of event but easily tolerated
- **Moderate:** Discomfort enough to cause some interference with usual activity
- **Severe:** Incapacitating or causing inability to work or carry out usual activity

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

- Resulted in death
- Was immediately life-threatening
- Required or prolongs hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions

All nonserious and serious AEs were to be followed until resolution or until the study site determined that no further information can be obtained.

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 (BIcMQ) for identifying AESI from lists of prespecified PTs or SMQs. These AESI were primarily related to safety findings in the empagliflozin, linagliptin and metformin 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: decreased renal function, hepatic injury, pancreatitis, urinary tract infections (UTIs), genital infections, hypoglycemia, bone fracture, volume depletion, malignancies, hypersensitivity reactions, venous embolic and thrombotic events, cardiac failure, increased urination, skin reactions, ketoacidosis, Fournier's gangrene, 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 12.5. Assessments for AESIs will be described in more detail in the relevant sections.

7.3.3. Routine Clinical Tests

The frequency of clinical laboratory safety assessments for each of the three 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 double-blind periods, every 8-12 weeks during double-blind LT extension period (Trial 1275.1), and at the follow-up (Week 25 for Trials 1275.9 and 1275.10 or Week 56 for Trial 1275.1) or early termination visits. 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 abnormal/marked abnormalities (MAs). The safety laboratory panels and the frequency of assessments were adequate, based on the known toxicity profiles of empagliflozin, linagliptin and metformin, the patient population studied, and the proposed indication. 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.

7.4. Safety Results

A summary of the AEs reported in the three Phase 3 trials is presented in Table 15. Overall, 62% of subjects across all treatment arms and trials experienced at least one AE (i.e., 70% of subjects in Trial 1275.1, 58% in Trial 1275.9, and 54% in Trial 1275.10). Categories of events between the individual trials were similar. As anticipated, based on the pharmacologic mechanisms of action, events of hypoglycemia were limited, and no subjects in any treatment arm discontinued IP due to hypoglycemia. The numbers of deaths also were limited and are discussed further below (Section 7.4.1). As noted in Section 7.2.1, the safety data for Trial 1275.1 included longer treatment exposures (52 weeks) than Trials 1275.9 and 1275.10 (24 weeks), which should be considered when reviewing event counts for the respective studies.

Table 15: Summary of Adverse Events (Phase 3 Trials)

Trial / Treatment Arm	1275.1					1275.9			1275.10			
	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects with Events – no. (%)												
At least 1 AE	91 (68.9)	96 (68.6)	103 (73.0)	94 (69.1)	98 (71.5)	75 (68.2)	62 (55.4)	57 (51.8)	71 (55.5)	66 (58.9)	61 (48.4)	59 (52.7)
≥1 Hypoglycemic event*	3 (2.3)	2 (1.4)	5 (3.5)	3 (2.2)	5 (3.6)	1 (0.9)	0	3 (2.7)	0	3 (2.7)	0	0
Symptomatic/BG <54 mg/dL¶	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Major event†	0	0	0	0	0	0	0	1 (0.9)	0	1 (0.9)	0	0
AE leading to D/C of IP	4 (3.0)	9 (6.4)	4 (2.8)	2 (1.5)	3 (2.2)	2 (1.8)	2 (1.8)	0	3 (2.3)	3 (2.7)	4 (3.2)	3 (2.7)
At least one SAE	8 (6.1)	6 (4.3)	10 (7.1)	9 (6.6)	6 (4.4)	10 (9.1)	5 (4.5)	4 (3.6)	5 (3.9)	4 (3.6)	4 (3.2)	3 (2.7)
SAE leading to D/C of IP	1 (0.8)	2 (1.4)	1 (0.7)	0	1 (0.7)	1 (0.9)	0	0	0	1 (0.9)	2 (1.6)	2 (1.8)
Deaths	0	1 (0.7)	0	1 (0.7)	0	0	0	0	0	0	0	0

Source: Derived from the adsl.xpt and adae.xpt datasets and adapted from the Applicant's Summary of Clinical Safety, pages 35-37 of 107,[190] and Summary of Clinical Safety Supplement, pages 4198, 4233 and 4350 of 8155,[192] available at: \\cdsesub1\evsprod\nda212614\0000\m2\27-clin-sum\2-7-4-summary-clin-safety-empa-lina-met-fdc.pdf and \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\scs-supplement\scs-supplement-published-output.pdf

Abbreviations: ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; D/C, discontinuation; Empa, empagliflozin; IP, investigational product; Lina, linagliptin; Met, metformin; no., number; and SAE, serious adverse event.

***Confirmed hypoglycemia:** Included all investigator-reported symptomatic and asymptomatic AEs with plasma glucose concentrations ≤70 mL/dL, or where the assistance of another person was required.

¶**Clinically significant hypoglycemia:** Symptomatic with a BG <54 mg/dL and not requiring assistance (ADA Level 2).[174]

†**Major hypoglycemia:** The hypoglycemic AE required assistance of another person.[174]

7.4.1. Deaths

In Trial 1275.1, there were only two deaths, one subject randomized to the empagliflozin 10 mg + linagliptin 5 mg + metformin (Hypertensive heart disease; Subject (b) (6), a 53-year-old White male on day 172), and one subject randomized to the empagliflozin 10 mg + metformin arm (Metastatic lung cancer; Subject (b) (6), a 61-year-old White male on Day 375). In his review, Dr. Chong noted that there was minimal information regarding Subject (b) (6), but he felt that this death may have been associated with a stroke or myocardial infarction. In addition to T2D, this subject was obese, had a smoking history, and a past medical history hypertension and hyperlipidemia. I concur with Dr. Chong's assessment that a causal association of death was possibly related to preexisting comorbidities in this at-risk subject. For additional information, please refer to Dr. Chong's Clinical Review (dated January 29, 2015).

In Trials 1275.9 and 1275.10, there were no additional deaths in any treatment arm. The overall incidence of death across the three trials was low (0.13%; 2/1496 subjects). No deaths also were reported in the Phase 1 studies (13612.1, 1361.3, 1361.11).

7.4.2. Serious Adverse Events

In the Phase 3 trials, the occurrences of SAEs were relatively limited (i.e., approximately 4.9%; 74/1496 subjects), with similar proportions of subjects experiencing these events across treatment arms within the individual trials (Table 16). Except for 'Osteomyelitis' reported in two subjects in the empagliflozin + metformin arm of Trial 1275.10, there were no MedDRA PTs occurring in more than one subject within any treatment arm of the individual trials. Review of events by MedDRA High Level Term (HLT), High Level Group Term (HLGT), System Organ Class (SOC), or exposure-adjusted analyses also was not informative. The SOC with the highest number of subjects in any empagliflozin triple therapy arm was 'Neoplasms benign, malignant and unspecified', which included three subjects ('Breast cancer', 'Basal cell carcinoma', and 'Renal cancer') in the empagliflozin 25 mg + linagliptin 5 mg + metformin arm of Trial 1275.1. The onset latencies of events were between 58-337 days. These events were all previously reported during the original NDA review of NDA 206073 (GLYXAMBI) and will not be discussed further in this review. No malignancies were reported in Trial 1275.10, and one additional case (Subject 27501; a 57-year-old White female with 'Breast cancer' on Day 19) in Trial 1275.9 had an SAE coded to this SOC. An onset of 19 days makes it unlikely that this event was related to IP.

There were no SAEs reported for the Phase 1 Trials (13612.1, 1361.3, 1361.11).

In general, there were no apparent trends to suggest that the empagliflozin + linagliptin + metformin arms were associated an increased risk of specific SAEs over the individual components (i.e., empagliflozin or linagliptin added to background metformin therapy.

Table 16: Summary of Serious Adverse Events (Phase 3 Trial)*

Trial	1275.1					1275.9			1275.10			
Treatment Arm Serious Adverse Events	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met* (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects with SAEs – no. (%)	**8 (6.1)**	**6 (4.3)**	**10 (7.1)**	**9 (6.6)**	**6 (4.4)**	**10 (9.1)**	**5 (4.5)**	**4 (3.6)**	**5 (3.9)**	**4 (3.6)**	**4 (3.2)**	**3 (2.7)**
Angina pectoris	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Basal cell carcinoma	0	0	1 (0.7)	0	1 (0.7)	0	0	0	0	0	0	0
Breast cancer	0	0	0	0	1 (0.7)	0	1 (0.9)	0	0	0	0	0
Confusional state	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Encephalitis viral	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Encephalopathy	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Lethargy	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Mental status changes	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Renal cancer	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Transient ischaemic attack	0	1 (0.7)	0	0	1 (0.7)	0	0	0	0	0	0	0
Cerebrovascular accident	1 (0.8)	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Cholecystitis acute	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Coronary artery disease	1 (0.8)	0	0	0	0	1 (0.9)	0	0	1 (0.8)	0	0	0
Dehydration	1 (0.8)	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Hypotension	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Pancreatitis chronic	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Parathyroid tumour benign	1 (0.8)	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Pyelonephritis acute	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Renal failure acute	1 (0.8)	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Squamous cell carcinoma	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain	0	1 (0.7)	0	0	0	0	0	1 (0.9)	0	0	0	0
Adenoid cystic carcinoma	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Chest pain	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0
Coronary artery occlusion	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Lung neoplasm	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	1 (0.7)	0	0	0	0	0	0	1 (0.8)	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm Serious Adverse Events	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met* (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Non-small cell lung cancer metastatic	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Pulmonary embolism	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Urosepsis	0	1 (0.7)	0	0	0	1 (0.9)	0	0	0	0	0	0
Acute coronary syndrome	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Fibula fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Metastases to peritoneum	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Osteoarthritis	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0
Ovarian cancer	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Ovarian cyst	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Postmenopausal haemorrhage	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Pyelonephritis chronic	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Syncope	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Tendon rupture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Urinary tract infection	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.8)	0
Uterine leiomyoma	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Cerebral infarction	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Colitis ischaemic	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Gastrointestinal carcinoma	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Hypertensive heart disease	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Joint dislocation	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Lower limb fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Myofascial pain syndrome	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Non-cardiac chest pain	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Palpitations	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Rotator cuff syndrome	0	0	0	1 (0.7)	0	0	0	0	1 (0.8)	0	0	0
Accidental overdose	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Benign prostatic hyperplasia	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Bladder neoplasm	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm Serious Adverse Events	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met* (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Calculus ureteric	0	0	0	0	0	1 (0.9)	0	1 (0.9)	0	0	0	0
Cervical radiculopathy	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Erysipelas	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Hydrocephalus	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Hypertransaminasaemia	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Intervertebral disc disorder	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Mania	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Metabolic acidosis	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Oedema	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Umbilical hernia	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Arthralgia	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Colitis	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Pneumothorax	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Abortion induced	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Hydronephrosis	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Intervertebral disc protrusion	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Nephrolithiasis	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Wound infection	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Balanoposthitis	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Neck pain	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Osteomyelitis	0	0	0	0	0	0	0	0	0	2 (1.8)	0	0
Haemarthrosis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Intestinal polyp	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Fall	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Extremity necrosis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Back pain	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
General physical health deterioration	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm Serious Adverse Events	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met* (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Pancreatitis acute	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Pneumonia	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Rhabdomyolysis	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Dermatitis bullous	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Dyshidrotic eczema	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Pharyngeal lesion	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Tachycardia	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Atrial flutter	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)

Source: Derived from the adsl.xpt and adae.xpt datasets and adapted from the Applicant's Summary of Clinical Safety Supplement, pages 3058-3279 of 8155,[192] available at: \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\scs-supplement\scs-supplement-published-output.pdf
Abbreviations: Empa, empagliflozin; Lina, linagliptin; Met, metformin; no., number; N, sample size; and SAE, serious adverse event.
*Sorted by the high-dose (empagliflozin 25 mg plus linagliptin 5 mg plus metformin) triple therapy arm for Trial 1275.1.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs in the Phase 3 trials were few (<3%, 43/1496 subjects). The only MedDRA PT reported in more than one subject across all three trials was 'Blood creatinine increased' (two subjects in the empagliflozin 25 mg + linagliptin 5 mg + metformin treatment arm of Trial 1275.1). Review of events by MedDRA HLT, HLGT, and SOC did not reveal any obvious imbalances of this disposition term between triple therapy and dual therapy treatment arms.

For the Phase 1 trials, no subjects discontinued IP due to AEs.

Table 17: Summary of Discontinuations Due to Adverse Events (Phase 3 Trials)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects Discontinuing IP due to AEs – no. (%)	**4 (3.0)**	**9 (6.4)**	**4 (2.8)**	**2 (1.5)**	**3 (2.2)**	**2 (1.8)**	**2 (1.8)**	**0**	**3 (2.3)**	**3 (2.7)**	**4 (3.2)**	**3 (2.7)**
Blood creatinine increased	0	0	0	0	2 (1.5)	0	0	0	0	0	0	0
Cough	0	0	0	0	1 (0.7)	0	0	0	1 (0.8)	0	0	0
Fatigue	0	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0
Renal cancer	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Weight decreased	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Dehydration	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Dizziness	1 (0.8)	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Hypotension	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Renal failure acute	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Angioedema	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Adenoid cystic carcinoma	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Cystitis	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Hepatitis toxic	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Lipase increased	0	1 (0.7)	0	0	0	0	1 (0.9)	0	0	0	1 (0.8)	0
Migraine	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Polyuria	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Urge incontinence	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Urinary tract infection	0	1 (0.7)	0	0	0	0	0	0	1 (0.8)	0	1 (0.8)	1 (0.9)
Vaginal haemorrhage	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Hyperglycaemia	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.9)	0	0
Ovarian cancer	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Vulvovaginal mycotic infection	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Genital infection fungal	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Headache	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Hypertransaminasaemia	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Hepatitis E	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Abdominal pain upper	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Amylase increased	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Bronchitis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Osteomyelitis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Vulvovaginal pruritus	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Back pain	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Pancreatitis acute	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Dyshidrotic eczema	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Dysphagia	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Pharyngeal lesion	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Dermatitis bullous	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)

Source: Derived from the adsl.xpt and adae.xpt datasets and adapted from the Applicant's Summary of Clinical Safety Supplement, pages 2952, 2970, and 3022-3023 of 8155,[192] available at: \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\scs-supplement\scs-supplement-published-output.pdf
Abbreviations: AE, adverse event; D/C, discontinuation; Empa, empagliflozin; IP, investigational product; Lina, linagliptin; Met, metformin; no., number; and N, sample size.
Note: Subjects with more than one disposition event were counted only once in column totals.

7.4.4. Significant Adverse Events

Adverse events meeting the International Council for Harmonization (ICH) E3 definition of other significant adverse events[191] are primarily discussed in Section 7.5 (Analysis of Submission-Specific Safety Issues). Categorization of AEs, definitions, and search strategies used by the Applicant were described previously in Section 7.3.2.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The common TEAEs (≥5% of subjects in Trial 1275.1) included in GLYXAMBI labeling and the proposed labeling for TRIJARDY XR are 'Upper respiratory tract infection', 'Urinary tract infection', 'Nasopharyngitis', 'Diarrhea', and 'Headache' (Table 18). However, 'Gastroenteritis' and 'Constipation' also were reported in more than 5% of subjects in one or both empagliflozin triple therapy arms for this trial. During labeling negotiations, the Applicant was asked to clarify why these events were excluded from proposed TRIJARDY XR and approved GLYXAMBI labeling (i.e., the common adverse reactions table in Section 6.1). In their response (dated December 20, 2019), the Applicant stated that they did not propose to include these events based on the following: in the Clinical Overview the Applicant concluded that no new or additional safety concerns were identified for the triple FCDP compared to the individual monocomponents; the medical assessment of the reported frequencies for these two AEs concluded that there is no reasonable association with TRIJARDY XR; and the respective USPIs (SYNJARDY, GLYXAMBI) do not list these events. Although constipation[193-196] is a common gastrointestinal AE in diabetic populations and the investigators did not code any of the 'Gastroenteritis' AEs as being related to IP, the proportions of subjects experiencing constipation or gastroenteritis AEs in one or both triple therapy arms were higher than the respective dual therapy arms, and these events were identified by the Applicant in their Summary of Clinical Safety Supplement as events occurring in >5% of subjects (Table 5.2.3.3.14, page 2394).[192] Further, inclusion of additional MedDRA PTs (e.g., 'Gastroenteritis viral' and 'Gastroenteritis norovirus') resulted in an even higher number of subjects with gastroenteritis events in the empagliflozin 25 mg + linagliptin 5 mg + metformin arm (i.e., 7.3%, 10/137 subjects). Labeling negotiations are ongoing, and a final decision on proposed labeling is pending.

In addition, with the inclusion of the two supporting clinical trials, 'Lipase increased' was reported in 6.3% of subjects in both the empagliflozin 25 mg triple and dual therapy arms for Trial 1275.10. As the incidence was similar in groups with and without linagliptin, and an increase in lipase and acute pancreatitis are already included in proposed product labeling, I do not feel that these data need to be added to the common TEAEs table in proposed labeling, which reflects the safety findings of Trial 1275.1.

Table 18: Summary of Common Treatment Emergent Adverse Events (Safety Population)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
SUBJECTS WITH TEAEs — no. (%)	**91 (68.9)**	**96 (68.6)**	**103 (73.0)**	**94 (69.1)**	**98 (71.5)**	**75 (68.2)**	**62 (55.4)**	**57 (51.8)**	**71 (55.5)**	**66 (58.9)**	**61 (48.4)**	**59 (52.7)**
MedDRA Preferred Term	118 (89.4)	124 (88.6)	131 (92.9)	129 (94.9)	126 (92.0)	105 (95.5)	103 (92.0)	106 (96.4)	118 (92.2)	105 (93.8)	111 (88.1)	102 (91.1)
Urinary tract infection	15 (11.4)	13 (9.3)	17 (12.1)	12 (8.8)	12 (8.8)	7 (6.4)	8 (7.1)	3 (2.7)	6 (4.7)	7 (6.3)	10 (7.9)	11 (9.8)
Upper respiratory tract infection	4 (3.0)	11 (7.9)	9 (6.4)	14 (10.3)	11 (8.0)	1 (0.9)	1 (0.9)	3 (2.7)	2 (1.6)	2 (1.8)	0	2 (1.8)
Constipation*	3 (2.3)	3 (2.1)	4 (2.8)	7 (5.1)	8 (5.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	0
Rate per 100 PY	2.47	2.36	3.01	5.46	6.44	1.94	1.92	1.92	1.69	1.90	1.70	0
Gastroenteritis*	4 (3.0)	2 (1.4)	2 (1.4)	4 (2.9)	8 (5.8)	0	2 (1.8)	3 (2.7)	0	2 (1.8)	2 (1.6)	1 (0.9)
Rate per 100 PY	3.31	1.56	1.50	3.05	6.42	0	3.90	5.82	0	3.82	3.44	1.90
Nasopharyngitis	12 (9.1)	7 (5.0)	5 (3.5)	11 (8.1)	8 (5.8)	8 (7.3)	5 (4.5)	4 (3.6)	3 (2.3)	8 (7.1)	8 (6.3)	2 (1.8)
Headache	8 (6.1)	10 (7.1)	6 (4.3)	7 (5.1)	7 (5.1)	8 (7.3)	3 (2.7)	2 (1.8)	2 (1.6)	2 (1.8)	4 (3.2)	1 (0.9)
Lipase increased*	2 (1.5)	2 (1.4)	1 (0.7)	0	5 (3.6)	6 (5.5)	4 (3.6)	3 (2.7)	1 (0.8)	7 (6.3)	4 (3.2)	7 (6.3)
Rate per 100 PY	1.63	1.56	0.74	0	3.94	11.95	7.87	5.84	1.69	13.51	6.93	13.68
Diarrhoea	0	6 (4.3)	4 (2.8)	9 (6.6)	3 (2.2)	4 (3.6)	4 (3.6)	3 (2.7)	2 (1.6)	1 (0.9)	0	0

Source: Derived from the adsl.xpt and adae.xpt datasets and adapted from the Applicant's Summary of Clinical Safety Supplement, pages 1326-1343, 1473-1488, and 2072-2109 of 8155,[192] available at: \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\scs-supplement\scs-supplement-published-output.pdf
Abbreviations: Empa, empagliflozin; Lina, linagliptin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; N, sample size; no., number; and TEAEs, treatment emergent adverse events.
*MedDRA PTs not included in Applicant's proposed product labeling.

7.4.6. Laboratory Findings

This section will primarily focus on laboratory abnormalities and observed changes from baseline in relevant laboratory tests (i.e., common to SGLT2 inhibitors, DPP-4 inhibitors, and biguanides).

Laboratory Abnormalities

A summary table of select clinical laboratory changes reported for the three Phase 3 trials is presented in Table 19. Generally, the numbers of subjects with laboratory abnormalities were limited. Across all trials, increases in hematocrit (normal laboratory range [NLR] to >upper laboratory limit of normal [ULN]) and decreases in bicarbonate (NLR to <lower limit of normal [LLN]) were reported in higher proportions of subjects in at least one of the triple therapy arms. It is noted that there were no cases of venous embolic or thrombotic events, ketoacidosis or lactic acidosis reported in the triple therapy arms. Arms that included empagliflozin were typically associated with increases in hemoglobin, hematocrit, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) concentrations, while groups that included linagliptin were more often associated with increases in creatine kinase and lipase concentrations. Although a relatively high proportion of subjects (18.6%) in the empagliflozin 25 mg triple therapy arm of Trial 1275.10 experienced lipase elevation >ULN, none of these subjects had an adjudicated event of pancreatitis. Overall, review of the laboratory data did not identify any new safety signals or clinically meaningful laboratory changes beyond those known and labeled for approved empagliflozin, linagliptin and metformin products.

Mean Changes from Baseline in Select Clinical Laboratory Parameters

Across the three trials, small, but not clinically relevant, changes in hematology parameters from baseline to EOT were observed in mean hemoglobin (increases up to 0.9 g/dL) and hematocrit (increases up to 5%) concentrations for the empagliflozin + linagliptin + metformin arms, which were consistent with the observed changes in the empagliflozin + metformin arms. Changes in serum chemistries for subjects in the triple therapy treatment arms also were typical of those observed for the individual products.

Table 19: Summary of Select Clinical Laboratory Changes from Baseline to Last On-Treatment Value (Phase 3 Trials)

Trial	1275.1 (Week 52)					1275.9 (Week 24)			1275.10 (Week 24)			
Treatment Arm Laboratory Parameters	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
HEMATOLOGY												
Hemoglobin, g/dL — no. (%)	124	131	137	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	13.7 (1.5)	13.8 (1.2)	13.9 (1.3)	13.7 (1.3)	13.8 (1.2)	13.7 (1.4)	13.6 (1.5)	13.6 (1.2)	14.7 (1.3)	14.7 (1.4)	14.6 (1.4)	14.7 (1.4)
EOT* — mean (SD)	13.7 (1.4)	14.5 (1.4)	14.6 (1.4)	14.5 (1.4)	14.8 (1.4)	13.7 (1.5)	14.3 (1.5)	14.6 (1.2)	14.8 (1.1	14.8 (1.6)	14.8 (1.4)	14.7 (1.3)
Difference — mean (SD)¶	0 (1.0)	0.7 (0.9)	0.8 (1.1)	0.9 (1.0)	0.9 (0.8)	0 (1.0)	0.7 (0.9)	0.9 (0.8)	0 (0.9)	0.1 (0.7)	0.2 (0.9)	0 (0.9)
Subject <LLN — no. (%)†	**6/116 (5.2)**	**4/123 (3.3)**	**4/128 (3.1)**	**2/120 (1.7)**	**0/124**	**7/96 (7.3)**	**3/101 (3.0)**	**0/103**	**1/120 (0.8)**	**3/104 (2.9)**	**1/112 (0.9)**	**3/106 (2.8)**
Subjects >ULN — no. (%)†	**1/116 (0.9)**	**0**	**3/128 (2.3)**	**1/120 (0.8)**	**3/124 (2.4)**	**0/96**	**2/101 (2.0)**	**2/103 (1.9)**	**1/120 (0.8)**	**4/104 (3.8)**	**3/112 (2.7)**	**1/106 (0.9)**
Hematocrit, % — no. (%)	124	131	137	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	41.3 (5.5)	41.6 (4.3)	41.9 (5.0)	40.9 (4.8)	41.7 (4.7)	42.7 (5.1)	42.3 (5.4)	42.1 (4.4)	47.2 (4.7)	46.9 (5.1)	47.1 (5.4)	47.2 (4.9)
EOT* — mean (SD)	42.7 (5.2)	45.9 (4.8)	46.5 (5.0)	45.9 (5.2)	46.7 (5.2)	42.9 (5.6)	45.6 (5.5)	46.3 (4.7)	47.4 (4.2)	47.4 (5.8)	47.4 (5.3)	47.0 (5.0)
Difference — mean (SD)¶	1.3 (3.8)	4.2 (3.6)	4.6 (4.0)	5.0 (4.1)	5.0 (3.3)	0.2 (3.9)	3.3 (3.6)	4.2 (3.6)	0.2 (3.9)	0.5 (3.3)	0.4 (4.1)	-0.1 (3.7)
Subject <LLN — no. (%)†	**1/115 (0.9)**	**1/120 (0.8)**	**3/128 (2.3)**	**2/117 (1.7)**	**0/123**	**7/99 (7.1)**	**1/99 (1.0)**	**0/102**	**0/115**	**0/100**	**3/109 (2.8)**	**2/100 (2.0)**
Subjects >ULN — no. (%)†	**2/115 (1.7)**	**7/120 (5.8)**	**6/128 (4.7)**	**5/117 (4.3)**	**11/123 (8.9)**	**1/99 (1.0)**	**5/99 (5.1)**	**8/102 (7.8)**	**4/115 (3.5)**	**6/100 (6.0)**	**8/109 (7.3)**	**2/100 (2.0)**
Lymphocyte, x $10^3/\mu L$ — no. (%)	124	131	137	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	2.3 (0.9)	2.3 (0.9)	2.4 (1.0)	2.3 (0.9)	2.3 (0.9)	2.4 (0.7)	2.4 (0.8)	2.4 (0.6)	2.5 (0.8)	2.7 (1.7)	2.5 (0.7)	2.4 (0.7)
EOT* — mean (SD)	2.2 (0.9)	2.3 (0.9)	2.4 (0.9)	2.2 (0.9)	2.1 (0.8)	2.5 (0.7)	2.4 (0.8)	2.4 (0.7)	2.4 (0.7)	2.7 (1.8)	2.5 (0.7)	2.3 (0.7)
Difference — mean (SD)¶	-0.1 (0.6)	-0.1 (0.7)	0 (0.5)	-0.1 (0.6)	-0.1 (0.6)	0 (0.5)	0 (0.6)	0 (0.4)	-0.1 (0.5)	0 (0.5)	-0.1 (0.5)	-0.1 (0.5)
Subject <LLN — no. (%)†	**3/117 (2.6)**	**2/124 (1.6)**	**3/130 (2.3)**	**1/128 (0.8)**	**3/127 (2.4)**	**0/100**	**0/101**	**1/102 (1.0)**	**3/113 (2.7)**	**0/97**	**1/111 (0.9**	**0/103**
Subjects >ULN — no. (%)†	**3/117 (2.6)**	**1/124 (0.8)**	**4/130 (3.1)**	**0/128**	**0/127**	**4/100 (4.0)**	**6/101 (5.9)**	**2/102 (2.0)**	**4/113 (3.5)**	**3/97 (3.1)**	**4/111 (3.6)**	**1/103 (1.0)**
CHEMISTRY												
Creatinine, mg/dL — no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	0.88 (0.14)	0.88 (0.13)	0.88 (0.12)	0.89 (0.12)	0.88 (012)	0.86 (0.12)	0.88 (0.12)	0.87 (0.12)	0.88 (0.13)	0.87 (0.15)	0.86 (0.14)	0.87 (0.13)
EOT* — mean (SD)	0.88 (0.15)	0.88 (0.14)	0.88 (0.13)	0.89 (0.14)	0.90 (0.14)	0.88 (0.14)	0.89 (0.13)	0.88 (0.13)	0.88 (0.14)	0.88 (0.14)	0.87 (0.12)	0.88 (0.15)
Difference — mean (SD)¶	0.01 (0.09)	0 (0.08)	0 (0.09)	0 (0.09)	0.01 (0.09)	0.02 (0.09)	0.01 (0.07)	0.02 (0.08)	0 (0.07)	0 (0.12)	0.01 (0.08)	0.01 (0.08)
Subject <LLN — no. (%)†	**0/125**	**0/130**	**0/136**	**0/132**	**0/132**	**0/107**	**0/109**	**0/110**	**0/125**	**0/109**	**0/120**	**0/109**
Subjects >ULN — no. (%)†	**5/125 (4.0)**	**2/130 (1.5)**	**1/136 (0.7)**	**1/132 (0.8)**	**3/132 (2.3)**	**2/107 (1.9)**	**0/109**	**1/110 (0.9)**	**1/125 (0.8)**	**1/109 (0.9)**	**0/120**	**2/109 (1.8)**

Trial	1275.1 (Week 52)					1275.9 (Week 24)			1275.10 (Week 24)			
Treatment Arm Laboratory Parameters	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
eGFR, mL/min/1.73 m^2 — no.(%)‡	132	140	141	136	137	110	112	110	128	112	126	112
Baseline — mean (SD)	89.63 (20.17)	91.06 (19.61)	90.15 (18.27)	89.13 (18.31)	87.46 (17.98)	92.61 (15.84)	92.12 (18.92)	93.77 (16.76)	89.38 (19.57)	91.10 (19.66)	91.53 (19.51)	88.93 (18.71)
EOT* — mean (SD)	88.52 (19.17)	92.05 (20.14)	90.80 (20.33)	89.08 (20.97)	86.08 (17.50)	90.12 (15.94)	88.66 (19.02)	90.39 (18.84)	89.81 (20.19)	91.28 (20.70)	90.04 (18.36)	87.42 (21.08)
Difference — mean (SD)¶	-1.70 (12.39)	-0.13 (11.87)	1.10 (12.65)	0.19 (11.95)	-1.72 (10.60)	-1.84 (10.54)	-2.67 (10.60)	-2.83 (11.13)	0.33 (10.69)	-0.56 (13.59)	-1.29 (12.04)	-0.94 (10.47)
Sodium, mEq/L— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	141 (2)	141 (2)	140 (2)	141 (2)	140 (2)	141 (2)	141 (1)	141 (2)	141 (2)	141 (2)	141 (2)	141 (1)
EOT* — mean (SD)	141 (2)	141 (2)	141 (2)	142 (2)	142 (2)	141 (2)	141 (2)	141 (2)	141 (2)	141 (2)	141 (2)	141 (2)
Difference — mean (SD)¶	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)
Subject <LLN — no. (%)†	**0/123**	**0.139**	**1/136 (0.7)**	**0/131**	**0/133**	**1/108 (0.9)**	**0/109**	**0/109**	**0/123**	**0/109**	**1/122 (0.8)**	**0/106**
Subjects >ULN — no. (%)†	**2/123 (1.6)**	**2/130 (1.5)**	**2/136 (1.5)**	**3/131 (2.3)**	**3/133 (2.3)**	**1/108 (0.9)**	**1/109 (0.9)**	**2/109 (1.8)**	**2/123 (1.6)**	**1/109 (0.9)**	**2/122 (1.6)**	**0/106**
Potassium, mEq/L— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	4.1 (0.3)	4.2 (0.3)	4.2 (0.3)	4.1 (0.3)	4.1 (0.3)	4.2 (0.3)	4.2 (0.3)	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)
EOT* — mean (SD)	4.2 (0.3)	4.2 (0.4)	4.2 (0.3)	4.2 (0.3)	4.2 (0.3)	4.3 (0.3)	4.2 (0.3)	4.3 (0.3)	4.4 (0.4)	4.2 (0.3)	4.3 (0.3)	4.2 (0.3)
Difference — mean (SD)¶	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0 (0.3)	0 (0.3)	0 (0.3)	0 (0.3)	0 (0.4)	0 (0.3)	0 (0.3)	0 (0.3)
Subject <LLN — no. (%)†	**0/125**	**0/129**	**0/136**	**1/133 (0.8)**	**0/133**	**1/106 (0.9)**	**1/109 (0.9)**	**0/109**	**1/120 (0.8)**	**0/110**	**1/119 (0.8)**	**0/108**
Subjects >ULN — no. (%)†	**1/125 (0.8)**	**2/129 (1.6)**	**1/136 (0.7)**	**1/133 (0.8)**	**1/133 (0.8)**	**0/106**	**2/109 (1.8)**	**3/109 (2.8)**	**4/120 (3.3)**	**2/110 (1.8)**	**4/119 (3.4)**	**0/108**
Calcium, mg/dL— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	9.8 (0.4)	9.8 (0.3)	9.8 (0.4)	9.8 (0.4)	9.8 (0.4)	9.7 (0.4)	9.8 (0.4)	9.7 (0.4)	9.8 (0.4)	9.9 (0.4)	9.8 (0.4)	9.8 (0.3)
EOT* — mean (SD)	9.7 (0.5)	9.7 (0.5)	9.7 (0.4)	9.7 (0.4)	9.8 (0.4)	9.8 (0.4)	9.8 (0.4)	9.9 (0.4)	9.9 (0.7)	9.8 (0.4)	9.8 (0.4)	9.8 (0.4)
Difference — mean (SD)¶	-0.1 (0.5)	-0.1 (0.5)	0 (0.6)	0 (0.4)	0 (0.4)	0.1 (0.4)	0 (0.4)	0.1 (0.4)	0 (0.7)	0 (0.3)	0.1 (0.4)	0 (0.4)
Subject <LLN — no. (%)†	**0/127**	**1/126 (0.8)**	**1/135 (0.7)**	**1/126 (0.8)**	**0/127**	**1/105 (1.0)**	**3/103 (2.9)**	**1/106 (0.9)**	**3/118 (2.5)**	**1/104 (1.0)**	**0/117**	**1/106 (0.9)**
Subjects >ULN — no. (%)†	**3/127 (2.4)**	**5/126 (4.0)**	**3/135 (2.2)**	**5/126 (4.0)**	**3/127 (2.4)**	**8/105 (7.6)**	**5/103 (4.9)**	**6/106 (5.7)**	**7/118 (5.9)**	**1/104 (1.0)**	**6/117 (5.1)**	**2/106 (1.9)**
Magnesium, mEg/dL— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	1.9 (0.2)	1.9 (0.2)	1.8 (0.2)	1.9 (0.2)
EOT* — mean (SD)	1.8 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.7 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Difference — mean (SD)¶	0 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0 (0.1)	0.1 (0.2)	0.2 (0.1)	0 (0.2)	0 (0.1)	0 (0.1)	0 (0.1)
Subject <LLN — no. (%)†	**6/105 (5.7)**	**0/114**	**0/123**	**1/118 (0.8)**	**1/117 (0.9)**	**7/91 (7.7)**	**1/90 (1.1)**	**2/99 (2.0)**	**4/116 (3.4)**	**0/99**	**1/112 (0.9)**	**3/107 (2.8)**
Subjects >ULN — no. (%)†	**1/105 (1.0)**	**3/114 (2.6)**	**0/123**	**0/118**	**0/117**	**0/91**	**1/90 (1.1)**	**0/99**	**0/116**	**0/99**	**0/112**	**0/107**

Trial	1275.1 (Week 52)					1275.9 (Week 24)			1275.10 (Week 24)			
Treatment Arm Laboratory Parameters	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Phosphate, mg/dL— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	3.7 (0.3)	3.7 (0.2)	3.7 (0.2)	3.7 (0.2)	3.7 (0.2)	3.7 (0.2)	3.7 (0.2)	3.7 (0.3)	3.7 (0.2)	3.8 (0.3)	3.7 (0.3)	3.8 (0.3)
EOT* — mean (SD)	3.7 (0.3)	3.8 (0.2)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)	3.7 (0.3)	3.8 (0.2)	3.8 (0.2)	3.7 (0.2)	3.7 (0.3)	3.7 (0.3)	3.8 (0.3)
Difference — mean (SD)¶	0 (0.2)	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)	0 (0.3)	0.1 (0.2)	0.1 (0.2)	0 (0.2)	-0.1 (0.3)	0 (0.3)	0 (0.3)
Subject <LLN — no. (%)†	**1/124 (0.8)**	**0/131**	**1/138 (0.7)**	**1/134 (0.7)**	**0/133**	**1/107 (0.9)**	**0/108**	**0/108**	**0/125**	**1/109 (0.9)**	**0/119**	**0/108**
Subjects >ULN — no. (%)†	**2/124 (1.6)**	**2/131 (1.5)**	**2/138 (1.4)**	**1/134 (0.7)**	**2/133 (1.5)**	**2/107 (1.9)**	**2/108 (1.9)**	**0/108**	**0/125**	**1/109 (0.9)**	**0/119**	**4/108 (3.7)**
Bicarbonate, mEg/dL— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	22.1 (2.6)	21.9 (2.7)	22.0 (2.7)	22.2 (2.7)	21.9 (2.5)	23.9 (1.8)	23.6 (1.8)	23.4 (1.5)	23.0 (1.8)	22.9 (2.0)	23.3 (1.8)	23.5 (1.7)
EOT* — mean (SD)	21.4 (2.4)	21.3 (2.2)	21.2 (2.5)	21.6 (2.4)	20.6 (2.5	23.5 (1.9)	23.2 (1.7)	22.9 (1.6)	23.3 (1.9)	23.3 (1.8)	23.4 (1.6)	23.5 (2.0)
Difference — mean (SD)¶	-0.6 (2.5)	-0.6 (2.8)	-0.8 (2.9)	-0.7 (3.1)	-1.3 (2.9)	-0.4 (2.2)	-0.4 (1.9)	-0.5 (1.9)	0.3 (1.9)	0.4 (2.0)	0.1 (2.1)	0 (2.2)
Subject <LLN — no. (%)†	**19/90 (21.1)**	**19/88 (21.6)**	**25/97 (25.8)**	**23/95 (24.2)**	**39/98 (39.8)**	**7/104 (6.7)**	**11/104 (10.6)**	**7/106 (6.6)**	**6/113 (5.3)**	**5/97 (5.2)**	**5/117 (4.3)**	**10/106 ((9.4)**
Subjects >ULN — no. (%)†	**0/90**	**0/88**	**0/97**	**0/95**	**0/98**	**2/104 (1.9)**	**0/104**	**1/106 (0.9)**	**0/113**	**0/97**	**0/117**	**1/106 (0.9)**
Creatine kinase, U/L— no. (%)	125	131	138	134	133	108	109	110	125	110	123	110
Baseline — mean (SD)	227 (201)	230 (200)	249 (277)	255 (207)	241 (162)	214 (166)	234 (231)	245 (195)	221 (233)	202 (131)	193 (118)	223 (185)
EOT* — mean (SD)	292 (611)	202 (136)	210 (135)	257 (256)	231 (160)	237 (209)	237 (319)	213 (117)	201 (169)	203 (183)	209 (137)	231 (175)
Difference — mean (SD)¶	65 (519)	-28 (186)	-39 (236)	2 (165)	-10 (138)	23 (181)	3 (284)	-32 (176)	-20 (246)	0 (171)	16 (90)	7 (133)
Subject <LLN — no. (%)†	**0/112**	**0/118**	**0/120**	**0/113**	**0/115**	**0/100**	**0/96**	**0/97**	**0/114**	**0/103**	**0/113**	**0/99**
Subjects >ULN — no. (%)†	**9/112 (8.0)**	**5/118 (4.2)**	**4/120 (3.3)**	**8/113 (7.1)**	**6/115 (5.2)**	**5/100 (5.0)**	**1/96 (1.0)**	**4/97 (4.1)**	**6/114 (5.3)**	**6/103 (5.8)**	**8/113 (7.1)**	**8/99 (8.1)**
Lipase, U/L— no. (%)	125	131	138	134	133	108	109	110	125	110	123	110
Baseline — mean (SD)	111 (53)	117 (3)	114 (76)	120 (88)	120 (135)	159 (117)	187 (205)	167 (180)	128 (108)	123 (75)	120 (82)	115 (70)
EOT* — mean (SD)	127 (77)	121 (3)	111 (58)	131 (70)	140 (97)	160 (143)	175 (209)	132 (79)	141 (151)	139 (150)	138 (116)	148 (133)
Difference — mean (SD)¶	17 (63)	4 (2)	-4 (70)	11 (72)	19 (134)	1 (154)	-12 (169)	-35 (172)	13 (107)	16 (137)	1 (103)	32 (137)
Subject <LLN — no. (%)†	**0/107**	**0/113**	**0/117**	**0/113**	**0/121**	**0/74**	**0/71**	**0/79**	**0/102**	**0/85**	**0/106**	**0/102**
Subjects >ULN — no. (%)†	**16/107 (15.0)**	**8/113 (7.1)**	**5/117 (4.3)**	**14/113 (12.4)**	**19/121 (15.7)**	**10/74 (13.5)**	**6/71 (8.5)**	**7/79 (8.9)**	**9/102 (8.8)**	**10/85 (11.8)**	**11/106 (10.4)**	**19/102 (18.6)**
Uric acid, mg/dL— no. (%)	125	131	138	134	133	108	109	110	125	110	122	110
Baseline — mean (SD)	5.03 (1.94)	5.04 (1.95)	5.20 (1.99)	5.13 (1.91)	4.92 (1.93)	5.21 (1.99)	5.06 (2.09)	5.00 (1.95)	4.37 (1.67)	4.39 (1.59)	3.92 (2.02)	4.09 (1.59)
EOT* — mean (SD)	5.19 (1.80)	4.28 (1.78)	4.13 (1.69)	4.11 (1.67)	3.98 (1.70)	5.34 (2.12)	4.27 (1.88)	4.31 (1.52)	4.37 (1.61)	4.22 (1.67)	3.99 (1.78)	4.17 (1.72)
Difference — mean (SD)¶	0.16 (1.24)	-0.75 (1 33)	-1.07 (1.59)	-1.02 (1.29)	-0.94 (1 38)	0.13 (1.48)	-0.79 (1.48)	-0.69 (1.36)	0 (1.21)	-0.17 (1.11)	0.07 (1.26)	0.08 (1.24)

Trial	1275.1 (Week 52)					1275.9 (Week 24)			1275.10 (Week 24)			
Treatment Arm Laboratory Parameters	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subject <LLN — no. (%)†	1/115 (0.9)	2/123 (1.6)	2/123 (1.6)	5/124 (4.0)	3/123 (2.4)	0/96	4/97 (4.1)	1/104 (1.0)	0/116	3/106 (2.8)	4/114 (3.5)	4/104 (3.8)
Subjects >ULN — no. (%)†	2/115 (1.7)	2/123 (1.6)	1/123 (0.8)	1/124 (0.8)	1/123 (0.8)	5/96 (5.2)	1/97 (1.0)	0/104	1/116 (0.9)	1/106 (0.9)	2/114 (1.8)	2/104 (1.9)
LIPIDS												
Cholesterol, mg/dL — no. (%)	124	131	138	130	128	108	108	107	116	104	113	99
Baseline — mean (SD)	178.5 (65.3)	179.2 (59.9)	178.6 (64.8)	164.6 (56.4)	168.2 (55.7)	174.2 (57.8)	178.5 (54.1)	171.9 (54.1)	202.4 (72.7)	190.4 (58.9)	195.5 (60.6)	198.8 (70.0)
EOT* — mean (SD)	179.5 (61.9)	184.6 (69.8)	184.4 (62.2)	172.8 (60.1)	179.0 (58.8)	170.6 (55.3)	185.3 (69.4)	181.1 (59.3)	200.2 (67.4)	199.9 (75.2)	198.2 (80.1)	198.4 (73.0)
Difference — mean (SD)¶	1.0 (50.1)	5.4 (48.4)	5.8 (61.0)	8.2 (48.4)	10.7 (51.8)	-3.6 (46.1)	6.9 (47.8)	9.2 (44.0)	-2.3 (54.7)	9.5 (58.8)	2.8 (58.0)	-0.4 (54.2)
Subject <LLN — no. (%)†	6/69 (8.7)	6/84 (7.1)	6/86 (7.0)	8/89 (9.0)	3/83 (3.6)	6/65 (9.2)	6/71 (8.5)	1/74 (1.4)	2/53 (3.8)	2/59 (3.4)	3/55 (5.5)	2/45 (4.4)
Subjects >ULN — no. (%)†	12/69 (17.4)	20/84 (23.8)	20/86 (23.3)	19/89 (21.3)	21/83 (25.3)	11/65 (16.9)	15/71 (21.1)	15/74 (20.3)	12/53 (22.6)	12/59 (20.3)	12/55 (21.8)	9/45 (20.0)
HDL-C, mg/dL — no. (%)	124	131	138	130	128	108	108	107	116	104	112	99
Baseline — mean (SD)	43.01 (5.61)	42.88 (6.49)	43.56 (6.61)	42.71 (5.39)	43.69 (6.29)	43.20 (5.29)	43.52 (6.40)	43.63 (6.18)	44.44 (5.51)	44.88 (6.49)	44.15 (7.15)	44.6 (5.99)
EOT* — mean (SD)	43.72 (5.98)	44.64 (7.14)	45.69 (7.03)	44.29 (6.39)	45.67 (6.40)	43.06 (5.76)	45.30 (7.12)	44.91 (6.54)	44.79 (5.77)	45.06 (6.48)	43.96 (6.74)	44.6 (5.72)
Difference — mean (SD)¶	0.71 (2.97)	1.76 (3.65)	2.13 (4.23)	1.58 (3.77)	1.97 (3.19)	-0.14 (3.82)	1.78 (4.27)	1.28 (3.80)	0.34 (2.98)	0.19 (3.04)	-0.18 (4 61)	0 (3.88)
Subject <LLN — no. (%)†	7/83 (8.4)	5/87 (5.7)	3/95 (3.2)	6/95 (6.3)	5/92 (5.4)	8/79 (10.1)	6/75 (8.0)	1/83 (1.2)	7/97 (7.2)	7/82 (8.5)	6/76 (7.9)	6/81 (7.4)
Subjects >ULN — no. (%)†	1/83 (1.2)	3/87 (3.4)	2/95 (2.1)	3/95 (3.2)	1/92 (1.1)	0/79	1/75 (1.3)	2/83 (2.4)	0/97	1/82 (1.2)	0/76	1/81 (1.2)
LDL-C, mg/dL — no. (%)	124	131	138	130	128	108	108	107	116	104	112	99
Baseline — mean (SD)	80.72 (31.73)	80.60 (28.71)	77.54 (26.17)	74.83 (27.62)	76.76 (25.69)	75.74 (24.83)	78.64 (24.32)	75.63 (27.81)	88.07 (30.63)	81.56 (27.78)	83.39 (26.27)	87.18 (32.20)
EOT* — mean (SD)	80.09 (29.41)	81.72 (31.52)	80.28 (27.65)	77.12 (27.93)	79.58 (27.06)	75.06 (25.81)	80.17 (28.35)	79.43 (27.75)	87.97 (31.58)	83.76 (29.65)	84.30 (27.03)	86.32 (33.0)
Difference — mean (SD)¶	-0.63 (24.18)	1.12 (23.76)	2.75 (24.12)	2.28 (23.56)	2.82 (24.76)	-0.69 (20.83)	1.53 (25.43)	3.80 (20.25)	-0.09 (21.74)	2.19 (24.19)	0.91 (22.83)	-0.86 (22.76)
Subject <LLN — no. (%)†	0/93	0/108	0/115	0/109	0/104	0/89	0/88	0/90	0/78	0/80	0/80	0/63
Subjects >ULN — no. (%)†	6/93 (6.5)	15/108 (13.9)	21/115 (18.3)	12/109 (11.0)	15/104 (14.4)	7/89 (7.9)	15/88 (17.0)	10/90 (11.1)	12/78 (15.4)	13/80 (16.3)	11/80 (13.8)	9/63 (14.3)
Triglycerides, mg/dL — no. (%)	124	131	138	130	128	108	108	107	116	104	113	99
Baseline — mean (SD)	108.9 (57.3)	112.7 (62.3)	120.1 (111.9)	102.6 (51.5)	97.4 (49.8)	121.8 (77.5)	118.9 (75.1)	113.7 (81.5)	127.3 (102.1)	123.7 (88.4)	135.7 (119.6)	117.6 (69.2)
EOT* — mean (SD)	109.6 (65.6)	109.4 (69.9)	107.5 (61.8)	104.3 (58.1)	96.2 (52.4)	119.6 (79.7)	113.3 (128.5)	109.5 (90.5)	119.2 (78.8)	137.0 (190.6)	138.5 (214.2)	123.9 (122.7)
Difference — mean (SD)¶	0.7 (49.9)	-3.3 (44.5)	-12.6 (97.0)	1.7 (49.4)	-1.2 (48.8)	-2.3 (53.5)	-5.5 (109.7)	-4.2 (67.8)	-8.1 (77.6)	13.3 (128.3)	2.8 (134.0)	6.3 (78.0)
Subject <LLN — no. (%)†	0/105	0/106	0/107	0/114	1/114 (0.9)	0/84	0/85	0/96	0/94	0/80	0/88	3/78 (3.8)
Subjects >ULN — no. (%)†	7/105 (6.7)	3/106 (2.8)	12/107 (11.2)	9/114 (7.9)	11/114 (9.6)	4/84 (4.8)	9/85 (10.6)	6/96 (6.3)	5/94 (5.3)	4/80 (5.0)	6/88 (6.8)	9/78 (11.5)

Source: Adapted from the Applicant's CSRs for Trials 1275.1,[167] 1275.9,[168] and 1275.10,[169] available at:

\\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf
\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0009\1275-0009--1-15--study-report-body.pdf
\\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0010\1275-0010--1-15--study-report-body.pdf

Abbreviations: eGFR, estimated glomerular filtration rate; Empa, empagliflozin; EOT, end-of-treatment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lina, linagliptin; LLN, lower laboratory limit of normal; MDRD, Modification in Diet and Renal Disease; Met, metformin; N, sample size; NLR, normal laboratory range; no., number; SD, standard deviation; and ULN, upper laboratory limit of normal.

* Last on-treatment measurement.

¶ Normalized.

† Shift for subjects with baseline measurement within the NLR.

‡ Estimated eGFR by MDRD formula.

7.4.7. Vital Signs

The SGLT2 pharmacologic class, including empagliflozin, has been associated with diuresis and volume depletion.[3,197,198] Therefore, assessments of vital signs were performed throughout the treatment periods of the respective trials. The reported mean changes from baseline to EOT in vital signs of subjects in the empagliflozin 10 mg and 25 mg triple therapy arms across all three trials included heart rate changes of -0.73 to 0.70 and -0.8 to 0.8 beats per minute, SBP changes of -4.1 to 0 and -5.6 to -0.2 mmHg, and DBP changes of -2.6 to 0.4 and -3.6 to 0 mmHg, respectively. Generally, baseline vital signs were similar across treatment arms in the respective trials, and changes were modest and consistent with those associated with SGLT2 inhibitors.

Additionally, change from baseline in body weight was considered a key secondary endpoint for Trials 1275.1 and 1275.9 (please refer to Table 12).

7.4.8. Electrocardiograms (ECGs)

Clinically significant findings in electrocardiograms (ECGs) at screening were regarded by the Applicant as baseline conditions. New findings thereafter were recorded as AEs and are reported elsewhere in the review when appropriate. Review of datasets for possible ECG-related AEs (e.g., conduction/rhythm changes) reported in the Phase 3 trials did not show any obvious imbalances between triple and dual therapy treatment arms (Table 23). However, it is acknowledged that the number of events was limited. Review of these data for clinically relevant AEs (i.e., deaths, SAEs, or discontinuations due to AEs) identified two subjects in the triple therapy arms who experienced SAEs (Subjects (b) (6), and (b) (6) discussed below).

- **Subject (b) (6):** a 51-year-old White male with T2D randomized to the empagliflozin 25 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.10, experienced SAEs of tachycardia and atrial flutter on Days 109 and 110, respectively. Besides T2D and obesity, he had no other known medical conditions, and did not receive any concomitant medications. He presented to the emergency room (ER) with tachycardia on Day 109. Clinical laboratory findings were not informative. He recovered from the episode of tachycardia and was discharged on aspirin that same day. The following day, an ECG showed atrial flutter with a rapid ventricular response for which he was hospitalized. He underwent a transesophageal echocardiography guided ablation and was ablated back to sinus rhythm. He was treated with aspirin and apixaban for the event. He was subsequently discharged on Day 111. No action was taken by the investigator and the subject remained on IP until Day 181. The investigator judged the events of tachycardia and atrial to be unrelated to IP.

- **Subject** (b) (6) a 32-year-old White male with T2D randomized to the empagliflozin 25 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.9, experienced an SAE of

atrial fibrillation on Day 28 requiring hospitalization. Besides T2D and obesity, his past medial history included atrial fibrillation, hypertriglyceridemia, anxiety, gastro-esophageal reflux disease, allergic rhinitis, back pain, and headache. Concomitant medications included aspirin, alprazolam, omega 3 fish oil, gemfibrozil, ranitidine, and verapamil. On Day 28, he presented to the ER complaining of heart palpitation. An ECG showed atrial fibrillation with a ventricular response of 138 beats per minute (bpm). The subject apparently consumed excess alcohol the previous night and had previously experienced two episodes of atrial fibrillation associated binge drinking. A repeat ECG that day showed normal sinus rhythm. The subject was treated with diltiazem. The subject remained on IP until Day 177 (completion of the double-blind treatment period). The investigator considered this event to be unrelated to IP.

Based on the limited available information for Subject (b) (6) it is not possible to determine a causal association with IP. For Subject (b) (6) I concur that preexisting medical conditions and excessive alcohol intake[199] make it unlikely that IP was causally associated with this event. It also should be acknowledged that diabetes is an independent risk factor for development of atrial fibrillation and flutter,[200-203] and that tachycardia and atrial arrhythmias are not typically associated with SGLT2 inhibitors, DPP-4 inhibitors or metformin. However, in a published case report, recurrent atrial fibrillation occurred following repeated administration of metformin, felt to be associated with increased lactate and reduced bicarbonate serum concentrations.[204] No relevant changes in bicarbonate serum concentrations were observed in either Subject (b) (6) or (b) (6) Conversely, metformin[205] and metformin plus a DPP-4 inhibitor were associated with a decreased risk of atrial fibrillation[206] in population-based cohort studies. The literature also suggests use of empagliflozin in T2D patients with established CVD and atrial fibrillation may not be harmful.[207] Currently, information is lacking to show that SGLT2 inhibitors and DPP-4 inhibitors accelerate or decelerate the development of new onset atrial fibrillation.[200]

For additional information, please refer to the previously completed reviews of the individual components for discussion of electrocardiographic changes.

7.4.9. QT

A Thorough QT (TQT) study was not conducted for this Application. However, according to JARDIANCE product labeling, empagliflozin was not associated with clinically meaningful prolongation of QTc interval at doses up to 200 mg (8 times the MRHD) in a study of healthy subjects.[3] Similarly, TRADJENTA product labeling states that no increase in QTc was observed in healthy subjects following a single oral dose of either the recommended linagliptin dose of 5 mg or a 100 mg dose (20 times the MRHD).[4] Published literature also suggests that metformin is not associated with prolongation of the QTc interval in T2D patients.[208] Additionally, no AEs associated with QT prolongation (e.g., 'Electrocardiogram QT interval abnormal'; Electrocardiogram QT prolonged'; 'Long QT syndrome'; 'Sudden cardiac death'; 'Sudden death'; and 'Torsade de pointes') were identified through a search of the adae.xpt datasets for the

respective Phase 3 trials.

7.4.10. Immunogenicity

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

7.5. Analysis of Submission-Specific Safety Issues

The Applicant searched for AESI related to safety findings in the empagliflozin, linagliptin 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: decreased renal function; hepatic injury; pancreatitis; urinary tract infection; genital infection; confirmed hypoglycemia; bone fracture; volume depletion; malignancy; hypersensitivity reactions. A summary of AESI is presented in Table 20. In general, meaningful trends or imbalances in the numbers/proportions of AESIs between triple and dual therapy arms were not observed. Additionally, the Applicant also considered the following events as other AEs of interest: venous embolic and thrombotic events; cardiac failure; increased urination; skin reactions; metabolic acidosis (ketoacidosis and lactic acidosis; and necrotising fasciitis (Fournier's gangrene). These events are discussed further in the respective sections below.

Table 20: Summary of Adverse Events of Special Interest (Phase 3 Trials)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects with Events – no. (%)												
Decreased renal function	1 (0.8)	0	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Hepatic injury	0	4 (2.9)	1 (0.7)	0	2 (1.5)	2 (1.8)	0	0	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Pancreatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Urinary tract infection	20 (15.2)	16 (11.4)	19 (13.5)	13 (9.6)	14 (10.2)	8 (7.3)	8 (7.1)	4 (3.6)	10 (7.8)	9 (8.0)	12 (9.5)	15 (13.4)
Genital infection	3 (2.3)	11 (7.9)	12 (8.5)	8 (5.9)	3 (2.2)	2 (1.8)	2 (1.8)	5 (4.5)	4 (3.1)	9 (8.0)	3 (2.4)	3 (2.7)
Confirmed hypoglycemia*	3 (2.3)	2 (1.4)	5 (3.5)	3 (2.2)	5 (3.6)	1 (0.9)	0	3 (2.7)	0	3 (2.7)	0	0
Bone fracture	0	0	4 (2.8)	4 (2.9)	1 (0.7)	1 (0.9)	0	0	1 (0.8)	0	0	1 (0.9)
Volume depletion	4 (3.0)	1 (0.7)	2 (1.4)	2 (1.5)	1 (0.7)	0	0	1 (0.9)	1 (0.8)	1 (0.9)	0	0
Malignancy	1 (0.8)	2 (1.4)	2 (1.4)	1 (0.7)	3 (2.2)	1 (0.9)	1 (0.9)	0	0	0	0	0
Hypersensitivity	5 (3.8)	5 (3.6)	4 (2.8)	4 (2.9)	7 (5.1)	2 (1.8)	3 (2.7)	5 (4.5)	1 (0.8)	2 (1.8)	2 (1.6)	1 (0.9)

Source: Adapted from the Applicant's Summary of Clinical Safety, labeled as Tables 2.1.1:1-3 , pages 35-37 of 107,[190] available at: \\cdsesub1\evsprod\nda212614\0000\m2\27-clin-sum\2-7-4-summary-clin-safety-empa-lina-met-fdc.pdf
Abbreviations: AESI, adverse event of special interest; Empa, empagliflozin; Lina, linagliptin; Met, metformin; and no., number.

7.5.1. Decreased Renal Function

The SGLT2 inhibitor pharmacologic class has been associated with postmarketing reports of acute kidney injury (AKI).[209] On June 14, 2016, the FDA strengthened the existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin.[210] 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.[211,212] A recent meta-analysis of 30 SGLT2 inhibitor clinical trials did not report an increased risk of acute kidney injury-related AEs with these products.[213] Proposed TRIJARDY XR labeling includes acute kidney injury and impairment of renal function in Section 5 (Warnings and Precautions).

In the Phase 3 trials, the AESI events of decreased renal function were limited (0.5%; 7/1496 subjects, with only three subjects in the empagliflozin triple therapy arms experiencing these events (Table 20). In Trial 1275.1, an 81-year-old white male (Subject (b) (6)) with a diagnosis of T2D for more than 10 years, and numerous comorbidities developed a nonserious AE of renal impairment (eGFR decreased from approximately 66 to 45 mL/min/1.73 m^2 and serum creatinine increased from 1.1 to 1.5 mg/dL from screening to the day of randomization), and the investigator did not consider the event to be related to IP. In his review, Dr. Chong also noted that this case was confounded by concurrent use of trimethoprim/sulfamethoxazole. Based on the subject's age, limited exposure to IP, preexisting comorbidities and concomitant medication,[214-216] I concur with this assessment.

In Trials 1275.9 and 1275.10, the following two additional subjects had AESI events of decreased renal function:

- **Subject (b) (6):** a 76-year-old White female with T2D randomized to the empagliflozin 10 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.10, experienced an AESI of renal impairment on Day 46. Her medical history included obesity, hypertension, hypothyroidism, back pain, osteoarthritis, cystitis and chronic/recurrent genital infections. Concomitant medications included levothyroxine, metoprolol, enalapril/hydrochlorothiazide and diclofenac. At screening her eGFR was 83 mL/min/1.73 m^2, which decreased to 68 mL/min/1.73 m^2 at the end of the open-label treatment period (baseline) with empagliflozin 10 mg + metformin. On Day 46, she experienced an AE of 'Renal impairment', which was associated with a doubling of her serum creatinine (0.7 mg/dL to 1.4 mg/dL from screening to Day 43, and a reduction in eGFR from 83 to 36 mL/min/1.73 m^2). Diclofenac was discontinued and she was started on ibuprofen. Her serum creatinine (0.9 mg/dL) and eGFR (60 mL/min/1.73 m^2) returned towards baseline values on Day 86. The subject remained on IP until Day 168 (study completion). The investigator judged the AE of 'Renal impairment' to be unrelated to IP.

Although I feel that this event was confounded by concomitant use of nonsteroidal anti-

inflammatory drugs (NSAIDs), it appears that empagliflozin use contributed to the reduction in eGFR in this subject, as evidenced by approximately an 18% reduction from screening to baseline measurements. Proposed TRIJARDY XR labeling includes a precaution of acute kidney injury with concomitant NSAID use.

- **Subject** (b) (6)**:** a 62-year-old White male with T2D randomized to the empagliflozin 25 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.10, experienced an AESI of renal impairment on Day 141. Besides T2D, his other medical conditions included dyslipidemia, hypertension, benign prostatic hypertrophy, and lower extremity dermatitis. Concomitant medications included aspirin and enalapril. The AE was associated with an increase in serum creatinine from 1.1 mg/dL (NLR 0.5-1.3 mg/dL) at baseline to 1.4 mg/dL. Other laboratory parameters, including the estimated creatinine clearance were reported as normal, and no other AEs were reported at that time. No action was taken by the investigator and the subject remained on IP until Day 181. The investigator judged the event to be unrelated to IP.

Although the serum creatinine in this subject increased above the ULN and remained slightly elevated during treatment with IP, this change is consistent with anticipated changes observed with SGLT2 inhibitors. Additionally, proposed labeling includes a precaution of acute kidney injury with concomitant angiotensin converting enzyme inhibitor (ACEi) use.

In his review of Trial 1275.1 for NDA 206073 (GLYXAMBI), Dr. Chong stated that it appears that compared with the individual components that make up the FCDP (i.e., empagliflozin + linagliptin), the FCDP product does not result in an increase in renal events (either reported as an AE or by changes in laboratory tests). Based on the additional data from Trials 1275.9 and 1275.10, which only included subjects with normal or mild renal impairment, the empagliflozin triple therapy arms across all three trials were not associated with an increased risk of acute kidney injury and renal impairment.

7.5.2. Confirmed Adjudicated Hepatic Events

Across all three Phase 3 trials, adjudicated hepatic events were low (0.9%; 13/1496 subjects), without any trends or imbalances noted between arms (Table 20). Additionally, in the triple therapy arms, no subjects had an ALT or AST >3x ULN with total bilirubin >2x ULN within 30 days (i.e., biochemical Hy's law constellation). However, one subject ((b) (6); a 62-year-old White male) randomized to the empagliflozin 10 mg triple therapy arm of Trial 1275.10 had laboratory values consistent with biochemical Hy's law constellation (~Day 12) based on results from a local laboratory. The laboratory findings were not confirmed by the central laboratory. The event was associated with an SAE of 'Diabetic hepatopathy' and elevated transaminase concentrations during the placebo run-in period (following the 16-week treatment period with open-label empagliflozin + metformin). This event was subsequently adjudicated as a mild to moderate hepatic injury with a possible causal relationship with the study medication, but not as a Hy's law case.

Based on the additional data from Trials 1275.9 and 1275.10, no additional hepatic safety concerns were identified with this Application.

7.5.3. 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.[217] , Additionally, a higher proportion of subjects experienced acute pancreatitis in the linagliptin arm (0.3%; 9/3492 subjects) vs. placebo arm (5/3485 subjects) of the Applicant's linagliptin CVOT (i.e., CARMELINA).[4,218]

In the Phase 3 trials, only two AESI events of pancreatitis were reported; one subject ((b) (6); 'Pancreatitis chronic') in the linagliptin + metformin arm of Trial 1275.1, and one subject ((b) (6); 'Pancreatitis acute') in the empagliflozin 10 mg triple therapy arm of Trial 1295.10 (discussed below).

- **Subject** (b) (6)**:** a 52-year-old White female with T2D randomized to the empagliflozin 10 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.10, experienced an AE of 'Pancreatitis acute' on Day 79. Her medical history included dyslipidemia, pancreatic steatosis, hepatic steatosis, and hypertension. Concomitant medications included bisoprolol, candesartan, hydrochlorothiazide, simvastatin, pantoprazole, and clotrimazole. On Day 79, the subject was diagnosed with an AE of 'Lipase increased' and received hymecromone and metoclopramide. Ongoing AEs included gastritis and vulvovaginitis. Relevant laboratory parameters included a lipase of 1881 U/L (NLR 0-60 U/L) and an amylase of 445 U/L (NLR 20-112 U/L), which were improved by Day 112 (lipase 227 U/L and amylase 148 U/L). No action was taken by the investigator and the subject remained on IP until Day 176. The investigator considered the event to be unrelated to IP. This AESI was adjudicated as an acute pancreatitis without organ failure.

I do not feel that this isolated event in the triple therapy arm alters the pancreatic safety profile of TRIJARDY XR. Additionally, proposed labeling includes a warning of pancreatitis in Section 5 (Warnings and Precautions).

7.5.4. Urinary Tract Infections

Type 2 diabetic patients receiving SGLT2 inhibitors may be at increased risk for urinary tract infections (UTIs),[219-221] and warnings related to this risk are included in proposed TRIJARDY XR labeling.

In the Phase 3 trials, UTIs were reported in: 9.9% (148/1496) of subjects across all treatment arms, with events reported in 3.6-13.4% of subjects randomized to the empagliflozin triple therapy arms (Table 20). No obvious trends were noted across trials. Events of UTI were more

common in females compared to male participants in all trials. In Trials 1275.9, no subjects had UTIs classified as SAEs, discontinued IP or had recurrent events in the triple therapy arms, while one subject in Trial 1275.10 had an SAE, two subjects discontinued IP due to UTIs and seven subjects had recurrent events. No events of urosepsis or pyelonephritis were reported in the triple therapy arms for both trials. No additional safety concerns associated with the risk of UTIs were identified based on submission of the additional clinical trial data from these studies.

7.5.5. Genital Infections

Diabetic patients, especially those with poor glycemic control, are at risk for developing genital mycotic infections, such as vulvovaginal candidiasis in women and candida balanitis in men.[222] Further, SGLT2 inhibitors appear to increase this risk,[219,220,223-225] possibly mediated through glucosuria. The risk of genital infections is included in Section 5 (Warnings and Precautions) of proposed TRIJARDY XR labeling.

In the Phase 3 trials, AEs of genital infection were reported in: 5.7% (86/1496) of subjects across all treatment arms, with 1.8-5.9% of subjects in the triple therapy arms having these events (Table 20). As anticipated, genital infections were typically more common in female subjects receiving empagliflozin, with most subjects experiencing a single event. In the triple therapy arms for Trials 1275.9 and 1275.10, none of the events were coded as an SAE and no subjects discontinued IP. The results from all three trials are consistent with the known risks for genital infections associated with SGLT2 inhibitors.

7.5.6. Hypoglycemia

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

- *Confirmed Hypoglycemia (ADA Levels 1-3):* Included all investigator-reported symptomatic and asymptomatic AEs with plasma glucose concentrations ≤70 mL/dL, or where the assistance of another person was required.
- *Major Hypoglycemia (ADA Level 3):* The hypoglycemic AE required assistance of another person.

As anticipated based on the pharmacodynamics of the study medications and the patient population studied, the number of subjects experiencing at least one confirmed hypoglycemic event across all treatment arms in the three Phase 3 trials was relatively low (1.7%; 25/1496 subjects; Table 20). No subjects in any treatment arm discontinued therapy due to hypoglycemia or experienced ADA Level 2 hypoglycemia (BG <54 mg/dL; please refer to Table 15). Two subjects required assistance from another person, one subject ((b) (6)) randomized to the empagliflozin 25 mg + metformin dual therapy arm of Trial 1275.10, and one subject ((b) (6)) in the empagliflozin 25 mg triple therapy arm of Trial 1275.9 (limited information on this event was provided).

7.5.7. 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.[226] 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.[227]

In the Phase 3 trials, AEs of fracture were limited (0.8%; 12/1496 subjects), of which six subjects were randomized to the triple therapy arms (five from Trial 1275.1 and one [wrist fracture] from Trial 1275.10). The fracture sites for these six subjects included the wrist (2 subjects), clavicle, lower limb, and foot (two subjects), and an event reported as a traumatic fracture. There were no AEs reported of falls or hypoglycemia for these subjects. Based on the proportions of subjects with fractures and varied anatomic sites (acknowledging the limited number of events), I don't feel there is an increased risk of fracture with the empagliflozin triple therapy combination over the individual components.

7.5.8. Volume Depletion

The SGLT2 inhibitors, including empagliflozin, 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).[3,24,210,228,229] A recent meta-analysis of 92 SGLT2 inhibitor clinical trials also reported an increased risk of volume depletion-related AEs (OR 1.20; 95% CI 1.10-1.31).[213]

There were limited events of volume depletion reported in the Phase 3 trials, with only four subjects in the triple therapy arms having an event across trials (hypotension for 3 subjects and syncope for one subject). Proposed labeling adequately addresses the risk of volume depletion-related AEs associated with TRIJARDY XR.

7.5.9. Malignancies

Malignancies were reported in only 11 of 1496 subjects (0.7%) across the Phase 3 trials, which included three subjects randomized to the triple therapy arms. Due to the relatively short treatment durations of Trials 1275.9 and 1275.10, a limited number of events was anticipated. Additionally, please refer to Section 7.4.2 above for additional discussion of this AESI.

7.5.10. Severe Hypersensitivity Reactions

In the Phase 3 trials, no obvious imbalances in hypersensitivity reactions between treatment arms were apparent, with 0.9% to 5.1% of subjects in the triple therapy arms experiencing an event. Only a single subject ((b) (6)) had an AE ('Dermatitis bullous') coded as serious (discussed below).

- **Subject (b) (6) :** a 59-year-old White female with T2D randomized to the empagliflozin 25 mg + linagliptin 5 mg + metformin treatment arm in Trial 1275.10, experienced an AE of 'Dermatitis bullous' on Day 93. Her medical history included hypercholesterolemia and hypertension. Concomitant medication included rosuvastatin. On Day 93, the subject developed SAEs of 'Dermatitis bullous' and 'Dyshidrotic eczema' on her hands and feet, treated with zinc oxide. These events were recurrent, and the subject had not experienced these events prior to initiating IP. On Day 123, the IP was discontinued permanently, and the subject recovered by Day 148. The investigator considered the events of bullous dermatitis and dyshidrosis to be related to IP.

Based on the positive challenge and dechallenge, I concur that these events were likely related to IP. Hypersensitivity reactions, including skin reactions, are included in proposed TRIJARDY XR labeling.

7.5.11. Venous Embolic and Thrombotic Events

No venous embolic or thrombotic AEs were reported for the triple therapy arms across all three Phase 3 trials.

7.5.12. Cardiac Failure

No subjects had AEs of heart failure across the Phase 3 trials.

7.5.13. Increased Urination

Polyuria AEs were limited (1.3%; 19/1496 subjects), with no apparent differences between arms. There were no events coded as SAEs.

7.5.14. Severe Cutaneous Adverse Reactions

Linagliptin products include warnings of bullous pemphigoid and exfoliative skin conditions,[4,7-9] and are included in proposed TRIJARDY XR labeling. In the Phase 3 trials, the Applicant did not report any events of severe cutaneous adverse reactions in addition to the serious cutaneous hypersensitivity reaction (bullous dermatitis) discussed above.

7.5.15. Metabolic Acidosis (Ketoacidosis and Lactic Acidosis)

Lactic acidosis is a boxed warning for metformin-containing products (e.g., JENTADUETO, JENTADUETO XR, SYNJARDY and SYNJARDY XR),[5-8] and diabetic ketoacidosis is a labeled warning for SGLT2 inhibitors, including empagliflozin-containing products.[3,5,6,9] There were no events of lactic acidosis or diabetic ketoacidosis (DKA) reported in the Phase 3 trials.

7.5.16. Necrotising Fasciitis (Fournier's Gangrene)

No AEs of Fournier's gangrene were reported across the Phase 3 trials.

7.5.17. 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; and 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 22).

It also is noted that lower limb amputations were not recorded as AESI for this Application. According to the Centers for Disease Control and Prevention (CDC), diabetes remains the leading cause of lower limb amputations,[230] resulting in approximately 108,000 hospitalizations for a lower-extremity amputation each year (i.e., 5 per 1000 persons with diabetes).[31] 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.[231]

The potential risk of lower limb amputation with the use of SGLT2 inhibitors has emerged as a potential safety concern.[100,101,232-238] 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).[101] 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.[100] 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.[239,240] 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.[11,14,229]

For the current Application, the datasets, CSRs, and 4MSU were searched for the occurrence of amputations. Based on this review, no events were identified in the triple therapy arms. During the clinical development programs for most SGLT2 inhibitors, including empagliflozin, 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 three clinical trials submitted to the current Application included relatively young, healthy T2D patient populations and limited treatment exposures, amputation events would not be anticipated.

7.6. Safety Analyses by Demographic Subgroups

In general, there were no obvious imbalances in AEs between the empagliflozin triple therapy arms and comparators across age, gender or racial subgroups. However, it is acknowledged that the TRIJARDY XR Phase 3 program only enrolled adult subjects, 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 pediatric patients and 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 empagliflozin,

linagliptin, or metformin development programs, and proposed TRIJARDY XR labeling caution prescribers on use in elderly patients and individuals with renal impairment.

7.7. Specific Safety Studies/Clinical Trials

Not applicable.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

No carcinogenicity or genotoxicity studies were performed for this Application. Studies of the individual drugs were deemed to be adequate for assessment of the carcinogenicity and genotoxicity of the combination.

7.8.2. Human Reproduction and Pregnancy

Women who were pregnant or breastfeeding were excluded from study participation in all trials, as there is limited experience in pregnant or lactating females with empagliflozin- and linagliptin-containing products (i.e., insufficient data to determine possible drug-associated risks). In nonclinical studies, empagliflozin (at 13x MRHD) resulted in adverse renal changes (i.e., increased kidney weights and renal tubular and pelvic dilatation) in rats during a period of renal development corresponding to the late second and third trimesters of human pregnancy.[3] No adverse effects were observed when linagliptin or metformin were administered to pregnant rats or rabbits. Published data in humans from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy.

There is limited information regarding the presence of empagliflozin, linagliptin or metformin in human milk. Metformin is present in human milk (infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1), while nonclinical studies report that both empagliflozin and linagliptin are present in rat milk. Because of the potential for serious adverse reactions in breastfed infants, including the potential for empagliflozin to affect postnatal renal development, use of TRIJARDY XR is not recommend while breastfeeding in proposed product labeling.

In the TRIJARDY XR development program, three subjects in Trial 1275.9 became pregnant while receiving IP; two in the comparator arms (IP for both subjects was stopped and pregnancy outcomes included a healthy baby and a miscarriage). The third (Subject (b) (6)) was a 37-year-old Asian female randomized to the empagliflozin 10 mg + linagliptin 5 mg + metformin arm. She was found to have a positive pregnancy test on Day 85 during a scheduled study visit. She was informed to stop the study mediations immediately, and IP was temporarily interrupted. She underwent an elective abortion on Day 87 of the double-blind treatment period. On Day 99, IP

was restarted. She completed the treatment period on Day 175. Although this subject may not have received IP for up to two weeks, potential effects on efficacy would have favored the control arm.

7.8.3. Pediatrics and Assessment of Effects on Growth

With their NDA, the Applicant requested that the Agency waive the pediatric assessment requirements (21 CFR 314.55)[241] for the proposed product. In their Initial Pediatric Study Plan (iPSP), dated December 14, 2017), they stated that it would not be feasible to conduct pediatric assessments in children <10 years of age due to the low incidence rate of T2D in this pediatric subset (approximately 0.8/100,000 PY), and that their FCDP would not represent a significant therapeutic benefit over existing treatments. In addition, they felt that the use of an empagliflozin/linagliptin/metformin FCDP is unlikely in pediatric patients ages 10 to 17 years, as it would be considered third-line therapy (e.g., when metformin plus one of the two class agents under consideration is not adequate to maintain glycemic control). The need for third-line antihyperglycemic therapy usually occurs later in the course of T2D, limiting the number of pediatric patients eligible to participate in an appropriate study. Therefore, they felt that clinical studies conducted with their FCDP in children and adolescents below 18 years of age with T2D would be highly impractical and not reasonably feasible (21 CFR 314.55(c)(2)(ii)). On January 8, 2018, the Agency agreed to the Applicant's iPSP, and on October 29, 2019, the Pediatric Review Committee (PeRC) agreed with granting the Applicant's request for a full wavier of all pediatric age groups.

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

The Applicant searched the Phase 3 clinical trial datasets for any MedDRA PTs that contained the word overdose and identified only a single subject randomized to the placebo + linagliptin + metformin arm of Trial 1275.9 (Subject (b) (6), a 50-year-old White male with an AE coded as 'Accidental overdose' on Day 144). I also searched the Applicant's datasets using the following MedDRA PTs: 'Accidental overdose'; 'Completed suicide'; 'Drug abuse'; 'Drug withdrawal syndrome'; 'Intentional overdose'; 'Intentional product misuse'; 'Overdose'; 'Prescribed overdose'; 'Rebound effect'; 'Suicide attempt'; 'Suspected suicide'; 'Suspected suicide attempt' and "Withdrawal syndrome'. No additional cases were identified. Additionally, the FDA Adverse Event Reporting System (FAERS) database was searched using Empirical Signal™ and the same MedDRA PTs. No postmarketing case reports (Form FDA 3500) associated with SAEs of overdose, abuse or withdrawal were identified that included the combination of empagliflozin, linagliptin and metformin.

According to the most recent Periodic Benefit-Risk Evaluation Report (PBRER, dated January 10, 2019) for NDA 206073 (GLYXAMBI; empagliflozin/linagliptin FCDP),[242] there were no new cases of overdose reported in clinical trials during the reporting period (i.e., May 11, 2018, to November 10, 2019). Cumulatively there have been two case reports of accidental overdose for this product, both reported as nonserious. Similarly, the Applicant's PBRERs for other relevant FCDPs,

included, one nonserious case of accidental overdose and one nonserious case of overdose for NDAs 201281 (SYNJARDY; empagliflozin/metformin immediate-release FCDP) and 208658 (SYNJARDY XR; empagliflozin/metformin extended-release FCDP),[243] and two nonserious cases of accidental overdose, two cases of intentional overdose (one serious), 16 nonserious cases of overdose, and six reports of nonserious prescribed overdose for NDAs 206111 (JENTADUETO; linagliptin/metformin immediate-release FCDP) and 208026 (JENTADUETO XR; linagliptin/metformin extended-release FCDP).[244]

Based on the known pharmacological properties of empagliflozin, linagliptin, and 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).[245,246] 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,[247] as well as reports of unintentional and intentional exposures to DPP-4 inhibitors.[248-250] In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. No published reports associated with empagliflozin overdose, abuse or misuse were readily identified, and removal of empagliflozin by hemodialysis has not been studied. However, in the empagliflozin clinical development program, single doses up to 800 mg (32x MRHD) were tolerated (NCT02172170). Product labeling states that removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.[4] Cases of overdose, abuse or misuse of linagliptin were not identified in the published literature. The Applicant states that during a controlled clinical trial (NCT02173665) in healthy subjects, single doses of linagliptin up to 600 mg (120x MRHD) have been tolerated. With extensive, worldwide use of metformin since the 1950s, cases of metformin overdose have been published in the medical literature,[251-285] including in combination with a DPP-4 inhibitor.[256] Hypoglycemia has not been seen with metformin hydrochloride doses of up to 85 grams, although lactic acidosis has occurred in such circumstances. High overdoses of metformin or concomitant risks may lead to lactic acidosis.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

The TRIJARDY XR FCDP is not approved in any country, and there is no postmarketing experience with this product. While empagliflozin, linagliptin and metformin are each approved as individual products or FCDPs, clinical experience with the use of the combination of the three components outside of the clinical trial setting is limited. GLYXAMBI, the Applicant's empagliflozin/linagliptin FCDP, has marketing approval in 27 countries worldwide. In the most recent PBRER (dated January 10, 2019) for this FCDP, the following actions for safety reasons were taken during the reporting period (May 11, 2018, to November 10, 2019):

- *Fournier's gangrene:* A labelling supplement pertaining to the risk of necrotizing fasciitis of the perineum (Fournier's gangrene) was submitted in the USA. The Ministry of Health

in Israel distributed a Direct Health Care Professional Communication among health care professionals with respect to Fournier´s gangrene.

- *Diabetic ketoacidosis:* The Australian Health Authority requested the addition of a new surgery precaution and update of the diabetic ketoacidosis to the product information of empagliflozin-containing products.

During the reporting period, approximately 3015 subjects received empagliflozin plus linagliptin in the GLYXAMBI development program, and post-approval exposure worldwide was estimated to be approximately 158,491 p-y (43,370 p-y during the reporting period). The CCDS for this product was updated to include Fournier's gangrene as a warning and adverse reaction. The most recent PBRER reports that SYNJARDY has marketing authorization in more than 80 countries, and the development program includes 739,415 PY of cumulative post-authorization exposure. During the reporting interval (April 18, 2018, to April 17, 2019), the Company Core Data Sheet (CCDS) was revised to include Fournier's gangrene as a special warning and precaution and adverse reaction.[243] JENTADUETO is authorized in 85 countries (cumulative post-authorization exposure of 3,007,529 PY).[244] The CCDS was revised to add 'Amylase increased' (observed in CAROLINA, the Applicant's CVOT) to the tabulated summary of adverse drug reactions.

Based on my review of the above information reported in the respective PBRERs, I do not feel that the cumulative efficacy and safety information (e.g., nonclinical data, clinical trial and postmarketing experience, and literature) alter the known benefit-risk profiles of TRIJARDY XR or warrant significant changes to proposed labeling. However, on October 21, 2019, the Applicant was informed of postmarketing reports of peri-/post-operative diabetic ketoacidosis occurred in patients using SGLT2 inhibitors. Similar to the Australian Health Authority, the Agency determined that these events represented a class safety concern, as well as "new safety information" as defined in Section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA). In accordance with Section 505(o)(4) of the FDCA, holders of approved SGLT2 inhibitor applications, including empagliflozin applications (i.e., NDAs 204629, 206073, 208658, and 206111), are required to make safety labeling changes based upon this new safety information.[286] Although labeling negotiations are ongoing at this time, TRIJARDY XR labeling also will include this same information.

7.9.2. Expectations on Safety in the Postmarket Setting

TRIJARDY XR is intended for patients with T2D who have not met their glycemic treatment goals with metformin. The recommended starting dose of empagliflozin is 10 mg once daily, with up-titration to the 25mg dose in patients who are tolerating therapy but require additional glycemic control.[3] With approval of TRIJARDY XR, there is the potential that this FCDP could be prescribed for patients who are metformin-naïve or 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 dosage formulations for this product allow for initiating therapy with the lower empagliflozin 10 mg and metformin extended-release 1000 mg doses.

Additionally, older patients with T2D who require additional glycemic control may be placed on TRIJARDY XR. As discussed above, there is scant clinical data and experience with empagliflozin + linagliptin + metformin combination therapy in this population. However, there is some data from the individual components to suggest what might be expected in terms of safety. TRADJENTA (linagliptin) product labeling[4] notes that no overall difference in safety or effectiveness was observed between subjects ≥65 years old (which included 1085 linagliptin-treated subjects ≥65 years old and 82 subjects ≥75 years old) and younger subjects. JARDIANCE labeling[3] also states that no dosage change is recommended based on age. In the clinical development program, 2721 empagliflozin-treated subjects were 65 years of age and older, of which 491 were ≥75. The risk of volume depletion-related AEs and UTIs was higher in the 75 year old cohort. The Applicant's labeling for their metformin-containing FCDPs[5-8] acknowledges that the clinical studies conducted for approval of metformin-containing products did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. The risk of metformin-associated lactic acidosis also may increase with the patient's age, as elderly patients may have a greater likelihood of having hepatic, renal or cardiac impairment. However, metformin has been widely used worldwide in the management of T2D since the 1950s. Additionally, the patient population prescribed TRIJARDY XR will likely include patients already treated with (and presumably tolerating) metformin as mono- or combination therapy.

I believe that the above safety concerns can be adequately addressed with proposed labeling and routine pharmacovigilance. In conclusion, no risk evaluation and mitigation strategy is recommended for this product.

7.9.3. 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.

7.10. Integrated Assessment of Safety

The safety profile of TRIJARDY XR reflects the safety profile of its individual components, i.e., empagliflozin, linagliptin and metformin. The most common adverse reactions (reported in >5% of subjects) in the Applicant's 52-week pivotal Phase 3 trial (1275.1) in the empagliflozin 10 mg and 25 mg triple therapy arms were upper respiratory tract infections (10.3% and 8%, respectively), urinary tract infections (9.6% and 10.2%), nasopharyngitis (8.1% and 5.8%), diarrhea (6.6% and 2.2%), constipation (5.1% and 5.8%), headache (5.1% in both arms) and gastroenteritis (2.9% and 5.8%), which generally also were common to the linagliptin and/or empagliflozin dual therapy arms. For the 24-week supporting trials, common AEs included urinary tract infections (7.1% and 3.6% of subjects in the empagliflozin 10 mg and 25 mg triple therapy

arms, respectively) in Trial 1275.9, and urinary tract infections (9.5% and 13.4%), nasopharyngitis (6.3% and 1.8%) and lipase increased (3.2% and 6.3%) in Trial 1275.10. Review of the safety data from these two trials did not identify any new safety concerns other than those already included or proposed in product labeling.

Antihyperglycemic FCDPs have the potential for an increased risk of hypoglycemia compared to the individual components. However, only a single subject in the empagliflozin 25 mg triple therapy arm of Trial 1275.9 experienced hypoglycemia requiring assistance, and there were no reports of symptomatic hypoglycemia (without the need for assistance) with a blood glucose <54 mg/dL across the three trials.

Deaths and serious adverse events (SAEs) were limited and not informative.

8. Advisory Committee Meeting and Other External Consultations

No Advisory Committee (AC) was held to discuss this Application which is the subject of this review.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The proposed labeling for TRIJARDY XR conforms 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,[287] available at: https://www.govinfo.gov/content/pkg/FR-2006-01-24/pdf/06-545.pdf.

Labeling was reviewed for consistency with approved labeling for JARDIANCE (NDA 204629),[3] GLYXAMBI (NDA 206073),[9] TRADJENTA,[4] SYNJARDY (NDA 206111),[5] SYNJARDY XR (NDA 208658),[6] and GLUMETZA (NDA 021748)[19] and to remove any reassuring language that might imply safety and efficacy 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." The Division has recently made the decision to simplify labeling of antihyperglycemic FCDPs with this indication,[10,86,288,289] including the recent approval of another SGLT2 inhibitor/DPP-4 inhibitor/metformin extended-release FCDP (QTERNMET XR [NDA 210874]).[86,138]

- The following statement be removed: "the effectiveness of TRIJARDY XR on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established." Approximately 74% of subjects in the Applicant's empagliflozin CVOT (i.e., EMPA-REG) and approximately 54% of subjects in their linagliptin CVOT (i.e., CARMELINA) were receiving background metformin therapy, and the MACE results from CARMELINA were neutral (i.e., the estimated hazard ratio of time to first occurrence of MACE was 1.02, with an upper bound of the 95% CI excluding the 1.3 risk margin). Based on these data, the Division felt that the statement was not informative for prescribers or patients and therefore did not need to remain in labeling.

Section 2.2. PATIENTS WITH RENAL IMPAIRMENT:

- State that no dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73 m2.
- Do not initiate or continue Trijardy XR if eGFR is below 45 mL/min/1.73 m2.
- Contraindicate use if the eGFR is <30 mL/min/1.73 m2.

Similar information is included in JARDIANCE labeling.[3]

Section 4. CONTRAINDICATIONS:

- Revise this section to state that TRIJARDY XR is contraindicated if the eGFR is <30 mL/min/1.73 m^2. It is noted that empagliflozin (JARDIANCE)[3], empagliflozin/linagliptin (GLYXAMBI)[9] and metformin extended-release (e.g. GLUMETZA[19]) product labeling all include a contraindication for use in patients with an eGFR <30 mL/min/1.73 m^2. Additionally, no dosage adjustments are necessary for renal function with linagliptin (TRADJENTA).[4]

Section 5. WARNINGS AND PRECAUTIONS:

- Section 5.5 (Ketoacidosis) should include safety information from the recent Section 901 Safety Labeling Change (SLC) notification (issued October 21, 2019) informing healthcare professionals and patients of the risk of ketoacidosis following surgical procedures. The final agreed-upon language for labeling of the Applicant's other empagliflozin-containing products (JARDIANCE, GLYXAMBI, SYNJARDY, and SYNJARDY XR) is pending.

Section 6. ADVERSE REACTIONS:

- The information on hypoglycemia in Section 6.1 (Clinical Trials Experience) should be simplified to include only clinically meaningful hypoglycemia (e.g., Level 2 and Level 3).[174]

Section 8. USE IN SPECIFIC POPULATION:

- Revise Section 8.6 (Renal Impairment) to include the following statement: "TRIJARDY XR is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease or dialysis."

Section 12. CLINICAL PHARMACOLOGY:

- Remove the information on [redacted] from Section 12.3 (Pharmacokinetics) in accordance with FDA guidance (i.e., the term "[redacted]" or the [redacted] should not be included in labeling).[290]

Section 14. CLINICAL STUDIES:

- Abbreviate the description of CARMELINA in Section 14.3 (Linagliptin Cardiovascular Safety Trial), as this trial was neutral (i.e., did not show either an increased CV risk or benefit).

Additionally, Dr. Ariane Conrad from the Division of Medication Error Prevention and Analysis (DMEPA) performed a risk assessment of the proposed prescribing information (PI), medication guide, container labels, and professional sample labels and labeling to identify areas of vulnerability that could lead to medication errors. Based on the findings from her preliminary review, the Applicant submitted revised container labels and carton labeling for TRIJARDY XR on November 22, 2019. Dr. Conrad determined that the revised carton and container labels were acceptable from a medication error perspective. Please refer to her reviews (dated November 6, 2019, and November 26, 2019) for additional information.

Labeling negotiations are ongoing at the time of this review.

9.2. Nonprescription Drug Labeling

Not applicable for these submissions.

10. Risk Evaluation and Mitigation Strategies (REMS)

Given the known safety profiles of empagliflozin, linagliptin 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.

11. Postmarketing Requirements and Commitments

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

12.Appendices

12.1. References

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12.2. Financial Disclosure

The Applicant submitted a Form FDA 3454 for 5 covered trials. They report no investigators with positive financial disclosures, and 28 investigators for which a signed Investigator Financial Interests and Disclosure Statement Form was never received (i.e., investigator did not participate in trial, the trial was not initiated at the study site, or the site was no longer a study site).

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

- Not applicable.

Significant payments of other sorts:

- Not applicable.

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

- Not applicable.

There was no undue bias/influence that could affect the outcome of these trials.

Covered Clinical Study (Name and/or Number): 1275.9, 1275.10, 1361.1, 1361.3, and 1361.11

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 894		
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): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ 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: _____		

Sponsor of covered study: 275.9, 1275.10, 1361.1, 1361.3, and 1361.11		
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)

The Applicant has submitted a list of 894 investigators that participated in Trials 275.9, 1275.10, 1361.1, 1361.3, and 1361.11. There were 28 investigators for whom the Applicant was unable to provide certification of an absence of financial arrangements. None of these investigators enrolled any patients, and none were in contact with any patients. This information is not likely to influence the outcome of the study or affect the review of the NDA. There has been adequate disclosure of financial arrangements and interests for the investigators that participated in the covered trials.

12.3. Antihyperglycemic Products Approved in the United States

Table 21: Summary Table of Approved Antihyperglycemic Products

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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			of miglitol in patients with creatinine clearance <25 mL/min. Therefore, treatment of these patients with miglitol is not recommended.	flatulence, diarrhea); and frequent dosing schedule.[44,46]
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. • When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[44,46]
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. • Do not mix pramlintide and insulin: Mixing can alter the pharmaco-kinetics of both products. Administer as separate injections.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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.[44,46]
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. • 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	• Metformin use is contraindicated in patients with an eGFR <30 mL/minute/1.73 m^2. • Obtain an eGFR prior to initiating metformin therapy. • Initiating metformin in patients with an eGFR between 30 to 45 mL/min/1.73 m^2 is not recommended. • Obtain an eGFR at least annually in all patients taking metformin; assess renal function more frequently in patients at increased risk for renal impairment (e.g., elderly patients). • Assess the benefits of continuing metformin treatment in patients whose eGFR falls below 45 mL/min/1.73 m^2; discontinue metformin if the eGFR falls below 30 mL/min/1.73 m^2. • Discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR between 30 to 60 mL/min/1.73 m^2, in patients with a history of hepatic disease, alcoholism, or heart failure, and/or in patients who will receive intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours	**BOXED WARNING:** • Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		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).	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.	**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}
Combination Products **GLUCOVANCE** (glyburide + metformin)	021178 (July 31, 2000)	**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.		

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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.		deficiency; multiple contraindications.[44,46] *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,

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			(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.[46]
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 there are postmarketing reports of stroke in this patient population).

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				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.[46]
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 receive an initial dose of sitagliptin 50 mg and metformin 1000 mg twice daily.	**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 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.	**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. • Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks

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JANUMET XR (sitagliptin + metformin extended-release)	202270 (February 2, 2012)	**JANUMET XR:** • Sitagliptin 100 mg daily plus current daily dose of metformin given once daily; maximum: sitagliptin 100 mg/metformin 2000 mg daily. Patients currently receiving immediate release metformin 850 to 1000 mg twice daily should receive sitagliptin/metformin extended release at an initial dose of sitagliptin 100 mg and metformin 2000 mg once daily.	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.*	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 effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class.[44,46]

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				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. 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	**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 treatment in patients at risk for heart failure. • There have been postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema and severe cutaneous

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			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.	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. **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.[44,46]

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Combination Products				
KAZANO (alogliptin + metformin)	203414 (January 25, 2013)	KAZANO: • Individualize the starting dose based on the patient's current regimen. • Should be taken twice daily with food. May adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.	FOR KAZANO: **Prior to initiation, assess renal function with eGFR.** **Do not use in patients with eGFR below 60 mL/min/1.73 m^2.** CONTRAINDICATION: **Severe renal impairment eGFR below 30/mL/min/1.73 m^2.**	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: 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.	FOR SAXAGLIPTIN MONOTHERAPY: **CrCl >50 mL/min: No dosage adjustment is recommended.** **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	CONTRAINDICATIONS: • eGFR <30 mL/min/1.73 m^2 (for KOMBIGLYZE XR). • 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).

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			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 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	**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. • 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

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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.	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*	pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class (statistically significant increase incidence observed in the CVOT, SAVOR).[44,46] *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, angioedema, and exfoliative skin conditions.
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.** **Assess risk/benefit of continuing if eGFR falls below 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.	**Discontinue if eGFR falls below 30 mL/min/173 m².** *Also, refer to Biguanides for metformin-containing FCDPs and SGLT2 inhibitors for empagliflozin-containing FCDRs.*	• 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.[44,46] *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 m^2: No dosage adjustment necessary; monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function.** **eGFR 15 to 29 mL/min/1.73 m^2: There are no dosage adjustments provided in product labeling (limited data); exposure is increased in these patients. Monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function.** **eGFR <15 mL/min/1.73 m^2: Use is not recommended (has not been studied).** • Lixisenatide is presumed to be eliminated through glomerular filtration, and proteolytic degradation. After multiple dose administration in patients with T2D, the mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h. • Compared to healthy subjects [CrCl using Cockcroft-Gault ≥90 mL/min (N=4)], plasma Cmax of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild [CrCl 60–89 mL/min (N=9)], moderate [CrCl 30–59 mL/min (N=11)], and severe [CrCl 15–29 mL/min (N=8)] renal impairment. Plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively. • In patients with mild renal impairment (eGFR: 60–89 mL/min/1.73 m^2) no dose adjustment is required, but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because a higher incidence of	**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); increase in heart rate; uncertain risk
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 lixisenatide) given subcutaneously once daily.		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• 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.	for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[44,46]
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 subsequent proteolytic degradation. The mean	**BOXED WARNING:** • Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including MTC in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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.	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.	• 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 severe gastrointestinal disease (e.g., gastroparesis).

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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.[44,46]
OZEMPIC (semaglutide)	209637 (December 5, 2017)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly. • Administer once weekly at any time of day, with or without meals. • If a dose is missed administer within 5 days of missed dose	**No dose adjustment of OZEMPIC is recommended for patients with renal impairment. In subjects with renal impairment including ESRD, no clinically relevant change in semaglutide PK was observed.** • The apparent clearance of semaglutide in patients with T2D is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose. • Renal impairment does not impact the PK of semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg semaglutide in patients with different degrees of renal	**BOXED WARNING:** • In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. • Semaglutide is contraindicated in patients with a personal or family

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.	impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for subjects with both T2D and renal impairment based on data from clinical studies. • The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The primary excretion routes of semaglutide-related material is via the urine and feces. • Approximately 3% of the dose is excreted in the urine as intact semaglutide.	history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. **ADDITIONAL CONTRAINDICATIONS:** • Known hypersensitivity to semaglutide or to any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors. • Pancreatitis. • Diabetic retinopathy complications. • Never share a semaglutide pen between patients. • Hypoglycemia: Can occur when used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin. • Acute kidney injury. • Hypersensitivity reactions. **DISADVANTAGES:** Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/ medullary thyroid tumors in animals;

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				injectable; and training requirements.[44]
RYBELSUS (semaglutide)	209637 (September 20, 2019)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Start at 3 mg once daily at least 30 minutes before the first food, beverage, or other oral medications with no more than 4 ounces of water only. • Do not cut, crush, or chew tablets. • After 30 days, the dose may be increased to 7 mg once daily, and further increased after another 30 days to 14 mg once daily if additional glycemic control is needed.	**No dose adjustment of RYBELSUS is recommended for patients with renal impairment. In patients with renal impairment including ESRD, no clinically relevant change in semaglutide PK was observed.** • The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the absorbed dose is excreted in the urine as intact semaglutide. • In patients with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. This was shown in a study with 10 consecutive days of once daily oral doses of semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for subjects with both T2D and renal impairment based on data from clinical studies. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.	**BOXED WARNING:** • In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. • Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. **ADDITIONAL CONTRAINDICATIONS:** • Known hypersensitivity to semaglutide or to any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors. • Pancreatitis. • Diabetic retinopathy complications.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• Hypoglycemia: Can occur when used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin. • Acute kidney injury. • Hypersensitivity reactions. **DISADVANTAGES OF GLP-1 RAS:** 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.[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. • Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control. • If a dose is missed, administer within 3 days of missed dose.	**No dosage adjustment necessary. Use caution when initiating or escalating doses.** • Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed. Because albiglutide is an albumin fusion protein, it likely follows a metabolic pathway similar to native human serum albumin which is catabolized primarily in the vascular endothelium. The mean apparent clearance of albiglutide is 67 mL/h with an elimination half-life of approximately 5 days, making albiglutide suitable for once-weekly administration. • In a population pharmacokinetic analysis including a Phase 3 trial in patients with mild, moderate, and severe renal impairment, exposures were increased by approximately 30% to 40% in severe renal impairment compared with those observed in T2D patients with normal renal function.	**BOXED WARNING:** • Carcinogenicity of albiglutide could not be assessed in rodents, but other GLP-1 receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether albiglutide causes thyroid C-cell tumors, including MTC, in humans. • Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to albiglutide or any of the product components.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[44,46]
TRULICITY (dulaglutide)	(BLA) 125469 (September 18, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Administer once weekly at any time of day. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 0.75 mg subcutaneously once weekly. • Dose can be increased to 1.5 mg once weekly for additional glycemic control. If a dose is missed, administer within three days of missed dose.	**No dosage adjustments necessary; use caution when initiating or escalating doses.** • Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways. The mean apparent clearance at steady state of dulaglutide is approximately 0.111 L/h for the 0.75 mg dose, and 0.107 L/h for the 1.5 mg dose. The elimination half-life of dulaglutide for both doses is approximately 5 days. • Dulaglutide systemic exposure was increased by 20, 28, 14 and 12% for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in Cmax were 13, 23, 20 and 11%, respectively.	**BOXED WARNING:** • Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether dulaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance could not be determined from clinical or nonclinical studies. • Dulaglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to dulaglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors in animals.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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.[44,46]
VICTOZA (liraglutide)	022341 (January 25, 2010)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with T2D. To reduce the risk of major adverse CV events in adults with T2D and established CV disease. • Inject subcutaneously in the abdomen, thigh or upper arm. • Administer once daily at any time of day, independently of meals. • Initiate at 0.6 mg per day for one week then increase to 1.2 mg. • Dose can be increased to 1.8 mg for additional glycemic control	**No dosage adjustments are provided in product labeling; however, use with caution, due to reports of acute renal failure and exacerbation of chronic renal failure and limited experience in patients with severe renal impairment.** • During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • During episodes of hypoglycemia (for XULTOPHY).

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 **XULTOPHY** (insulin degludec/liraglutide)	208583 (November 21, 2016)	**XULTOPHY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • 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. • 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.	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.	• 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. • 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,

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		• Do not dilute or mix with any other insulin products or solutions.		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.[44,46]
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)	209196 (December 11, 2017) 022472 (June 27, 2014) 021629 (April 16, 2004) 208751 (September 29, 2017) 020563 (June 14, 1996) 020986 (June 7, 2000)	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.[44]	**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:[291,292] — 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	**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. • Repeated injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia.

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Short-Acting **HUMULIN R** (insulin human) **NOVOLIN R** (insulin human) *Intermediate-Acting* **HUMULIN N** (insulin isophane) **NOVOLIN N** (insulin isophane) *Basal Analogs* **BASAGLAR** (insulin glargine) **LANTUS** (insulin glargine) **LEVEMIR** (insulin detemir) **LUSDUNA** (insulin glargine) **TOUJEO** (insulin glargine) **TRESIBA** (insulin degludec)	018780 (October 28, 1982) 019938 (June 25, 1991) 018781 (October 28, 1982) 19959 (July 1, 1991) 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)	***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 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.	by either peritoneal or hemodialysis; supplemental dose is not necessary. — CRRT: Administer at 75% of recommended dose. • Polypeptides and low-molecular proteins, such as insulin, can be actively reabsorbed by the proximal tubules through luminal endocytosis, followed by hydrolysis by the digestive enzymes in the lysosomes to peptide fragments and amino acids. The amino acids are then reabsorbed by a carrier-mediated, energy-dependent transport mechanism. Approximately one-third of the insulin dose may undergo degradation in the kidneys. Azotemia may be associated with a prolonged half-life of insulin, and an increased risk of hypoglycemia. Patients with CKD treated with insulin should closely monitor their blood glucose to minimize this risk, and dose adjustments made as necessary. Initiation of peritoneal dialysis may require an increase in the insulin dosage due to the absorption of glucose from the dialysate through the peritoneal cavity.[293,294]	• 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, pulmonary toxicity (inhaled insulin).[44,46] 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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Combination Products **HUMALOG MIX** (insulin lispro protamine + insulin lispro) **NOVOLOG MIX** (insulin aspart protamine + insulin aspart) **RYZODEC** (insulin degludec + insulin aspart)	021017 (December 22, 1999) 021018 December 22, 1999 021172 (November 1, 2001) 203313 (September 25, 2015)			
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	**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.

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			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.	• 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.[44,46] *Also, refer to Biguanides for metformin-containing FCDPs.*
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.*	

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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 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.	**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.[44,46]
SGLT2 Inhibitors				
FARXIGA (dapagliflozin)	202293 (January 8, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. To reduce the risk of hospitalization for heart failure in adults with type 2	**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.**	**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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors • 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. • To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg once daily.	• 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. • 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.	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). • 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.[295,296] • 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).

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				• 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 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).[44,46] *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:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D.	**FOR QTERN:** **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‡
		• 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. • 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	**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‡
		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. • 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 (May 2, 2019)	**INDICATION:** 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.	**FOR QTERNMET XR:** **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‡
		• Swallow whole. Do not cut, crush or chew. • 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

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.	low systolic blood pressure, and in patients on diuretics. • Ketoacidosis.[295,296] • 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).[44,46] *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 canagliflozin and metformin is appropriate.		**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 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. • Gradually escalate metformin dose to reduce the gastrointestinal side effects		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		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 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	**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.[295,296] • 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 hypoglycemia when initiating JARDIANCE. • Necrotizing fasciitis of the perineum (Fournier's gangrene).

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			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.	• 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).[44,46]
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 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.	**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‡
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. 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.	**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 be discontinued at time of, or prior to, iodinated contrast imaging procedures.** *Also, refer to Biguanides for metformin-containing FCDPs.*	**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‡
		• 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.		
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. *Also, refer to Biguanides for metformin-containing FCDPs and to DPP-4 inhibitors for linagliptin-containing FCDPs.*	**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.[295,296] • 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).

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• 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. • 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.		

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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. • After 5-7 days of initiation, subsequent daily dosages may be increased or decreased by 50-125 mg at 3- to 5-day intervals. • The maintenance dose is 100-250 mg daily (500 mg/day may be required; avoid doses >750 mg/day).	**No specific dosage adjustment provided in product labeling. In patients with impaired renal function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.** **Alternate recommendations:** **eGFR >50 mL/min: Administer 50% of the recommended dose.[291]** **eGFR ≤50 mL/min, hemodialysis, peritoneal dialysis, or CRRT: Avoid use.[291]** • Chorpropamide undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as hydroxylated or hydrolyzed metabolites. The biological half-life of chlorpropamide averages about 36 hours. Within 96 hours, 80% to 90% of a single oral dose is excreted in the urine. However, long-term administration of therapeutic doses does not result in undue accumulation in the blood, since absorption and excretion rates become stabilized in about 5 to 7 days after the initiation of therapy.	**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. • 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.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			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.	• 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.[297] 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 prospective trial (UKPDS, 1998)[40] have not supported an association. **DISADVANTAGES:** Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[46]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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.[298]** • 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 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	**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 prospective trial (UKPDS, 1998)[40] have not supported an association. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[44,46]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			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.*	
GLUCOTROL (glipizide)	017783 (May 8, 1984)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 5 mg, given orally before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. • Dosage adjustments should ordinarily be in increments of 2.5–5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. • If response to a single dose is not satisfactory, dividing that dose may prove effective. • The maximum recommended once daily dose is 15 mg. Doses above 15	**FOR GLIPIZIDE MONOTHERAPY:** **There are no specific dosage adjustments provided in product labeling.** **Glipizide is primarily converted to inactive metabolites and may be less likely to cause hypoglycemia in patients with renal impairment compared to other sulfonylureas.** **A reduced dose may be necessary,[298] and a 50% reduction in dose has been suggested with an eGFR ≤50 mL/min.[291]** **Avoidance of the sustained-release formulation has also been suggested.[299]** • 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	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • T1D. • DKA, with or without coma. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[40] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce severe hypoglycemia. Proper patient

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		mg should ordinarily be divided and given before meals of adequate caloric content. • The maximum recommended total daily dose is 40 mg.	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.*	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, 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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 the lowest recommended dose, and observe patients for hypoglycemia.		more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[46] **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. • 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)[40] have not supported an association.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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.**[298] • 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)[40] 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 glyburide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, quinolones and beta-adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[46]
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		**DIABETA CONTRAINDICATIONS:** • Known hypersensitivity to the drug or any of its excipients. • T1D. • DKA, with or without coma. • Treated with bosentan.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily.		**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)[40] 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 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-

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				inflammatory agents, 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. • 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.	**There are no specific dosage adjustments provided in product labeling for patients with renal impairment; however, conservative initial and maintenance doses are recommended because tolazamide is metabolized to active metabolites, which are eliminated in the urine.** • 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.	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • DKA, with or without coma • T1D. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[40] have not supported an association. • Hypoglycemia: All sulfonylurea drugs can produce severe hypoglycemia. Proper patient

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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, 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[46]
(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 tolbutamide tablets should be done conservatively.	**There is no dosage adjustment provided in product labeling for patients with renal impairment; however, conservative initial and maintenance doses are recommended.** **Hemodialysis: Tolbutamide is not dialyzable (0% to 5%).** • Tolbutamide undergoes hepatic via CYP2C9 to hydroxymethyltolbutamide (mildly active) and carboxytolbutamide (inactive) and has an elimination half-life of 4.5-6.5 hours. Approximately 75-85% is eliminated in the urine, primarily as metabolites.	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug. • DKA, with or without coma • T1D. **WARNINGS AND PRECAUTIONS:** • Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased CV mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS, 1998)[40] 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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, 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.[46]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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 ause, treat (if possible) and follow appropriately.	**FOR PIOGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/h. • The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance [CrCl] 30 to 50 mL/min) and severe (CrCl <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required with pioglitazone monotherapy. • In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related. In postmarketing experience, reports of new onset or 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.	**BOXED WARNING:** • Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients. After initiation of Actos, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of ACTOS must be considered. ACTOS is not recommended in patients with symptomatic heart failure. **CONTRAINDICATIONS:** • Initiation in patients with established NYHA Class III or IV heart failure. • Known hypersensitivity to pioglitazone or any other component of ACTOS. **WARNINGS AND PRECAUTIONS:** • Congestive heart failure: Fluid retention may occur and can 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

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, DPP-4 inhibitors for alogliptin-containing FCDPs, and Sulfonylureas for glimepiride-containing FCDPs.	lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia. • Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt Actos and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ACTOS if liver injury is confirmed and no alternate etiology can be found. • Bladder cancer: May increase the risk of bladder cancer. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. • Edema: Dose-related edema may occur. • Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. • Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes 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

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				macrovascular risk reduction with ACTOS or any other antidiabetic drug. **DISADVANTAGES:** Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[44,46]

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
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. • Do not initiate Avandia if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels.	**FOR ROSIGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral or intravenous administration of [^{14}C] rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C] related material ranged from 103 to 158 hours. • There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving rosiglitazone monotherapy. • Rosiglitazone should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone should be used with caution in patients at risk for heart failure. 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.	**BOXED WARNING:** • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of AVANDIA, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If these signs or symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered. AVANDIA is not recommended in patients with symptomatic heart failure. **CONTRAINDICATIONS:** • Initiation in patients with established NYHA Class III or IV heart failure. • Hypersensitivity to rosiglitazone or any of the product's ingredients. **WARNINGS AND PRECAUTIONS:** • 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

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 Sulfonylureas for glimepiride-containing FCDPs.	confirmed in a long-term CV outcome trial versus metformin or sulfonylurea. • Dose-related edema and weight gain may occur. • Measure liver enzymes prior to initiation and periodically thereafter. Do not initiate therapy in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Discontinue therapy if ALT levels remain >3X the upper limit of normal or if jaundice is observed. • Macular edema has been reported. • Increased incidence of bone fracture was observed in long-term trials. • Dose-related decreases in hemoglobin and hematocrit have occurred. • When used in combination with other hypoglycemic agents, a dose reduction of the concomitant agent may be necessary to reduce the risk of hypoglycemia. **DISADVANTAGES:** • Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[46]

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.

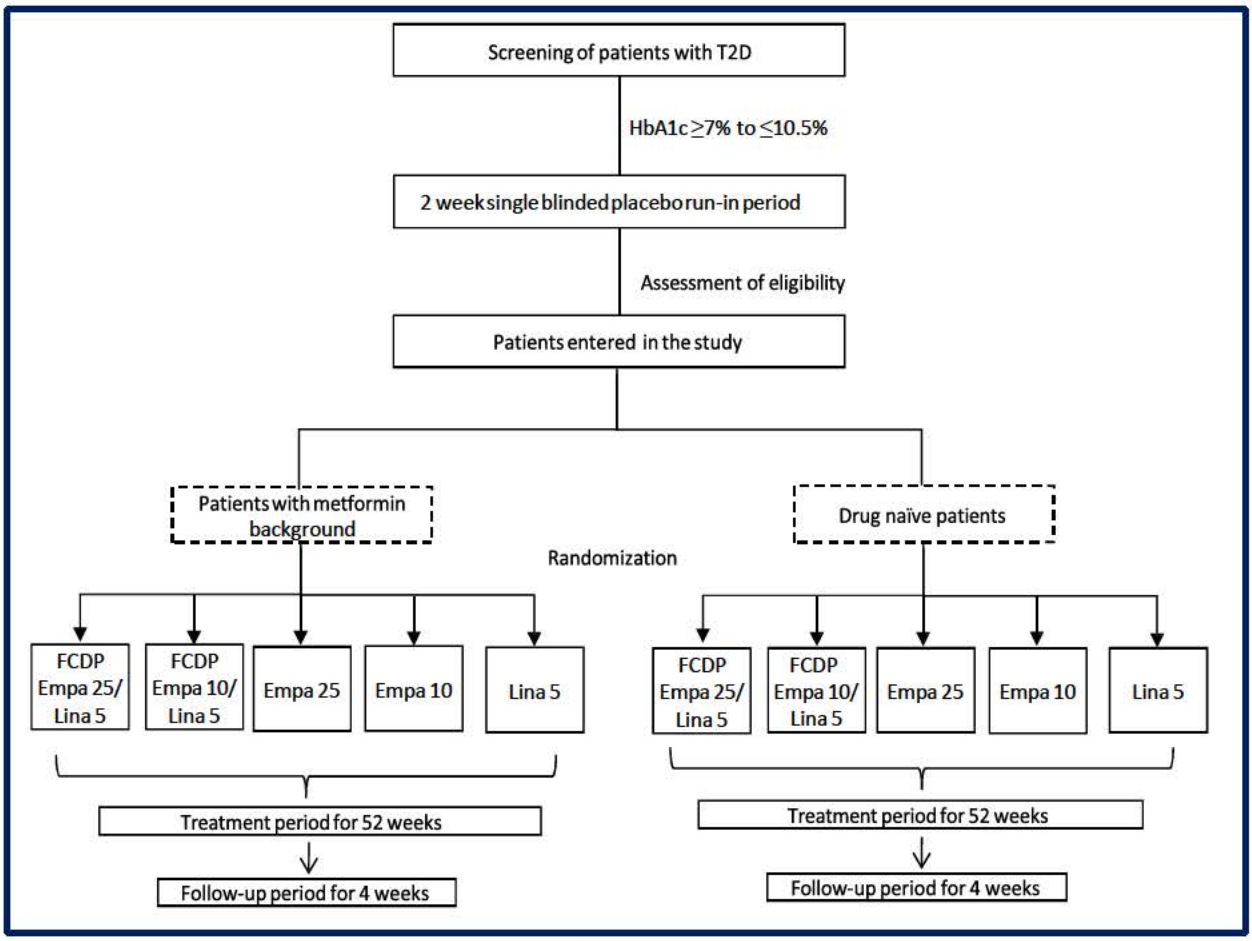
†Dosing guidelines for the mono-component of the FCDP, except in the case of JUVISYNC (sitagliptin + simvastatin).
¶Reference Listed Drug (RLD); approved under an Abbreviated New Drug Application (ANDA).
‡Contraindications and Warnings and Precautions relate to the mono-component of the FCDP unless specified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

12.4. Study Designs for the Relevant Phase 3 Trials

The study designs of the three Phase 3 clinical trials relevant to NDA 212614 are presented below.

Trial 1275.1 was a randomized, double-blind, parallel-group comparison study. Subjects were randomized in a 1:1:1:1:1 allocation ratio to: FCDP empagliflozin 25 mg/linagliptin 5 mg; FCDP empagliflozin 10 mg/linagliptin 5 mg; empagliflozin 25 mg; empagliflozin 10 mg; or linagliptin 5 mg. A 2-week single-blind placebo run-in period preceded randomization. The total randomized treatment period was 52 weeks (primary efficacy endpoint evaluated at Week 24). Randomization was stratified by screening HbA1c, renal function at screening (assessed based on eGFR values according to MDRD staging criteria), and geographical region. Patients were to be followed-up for 4 weeks after end-of-treatment or until the end of study after prematurely discontinuing trial medication.

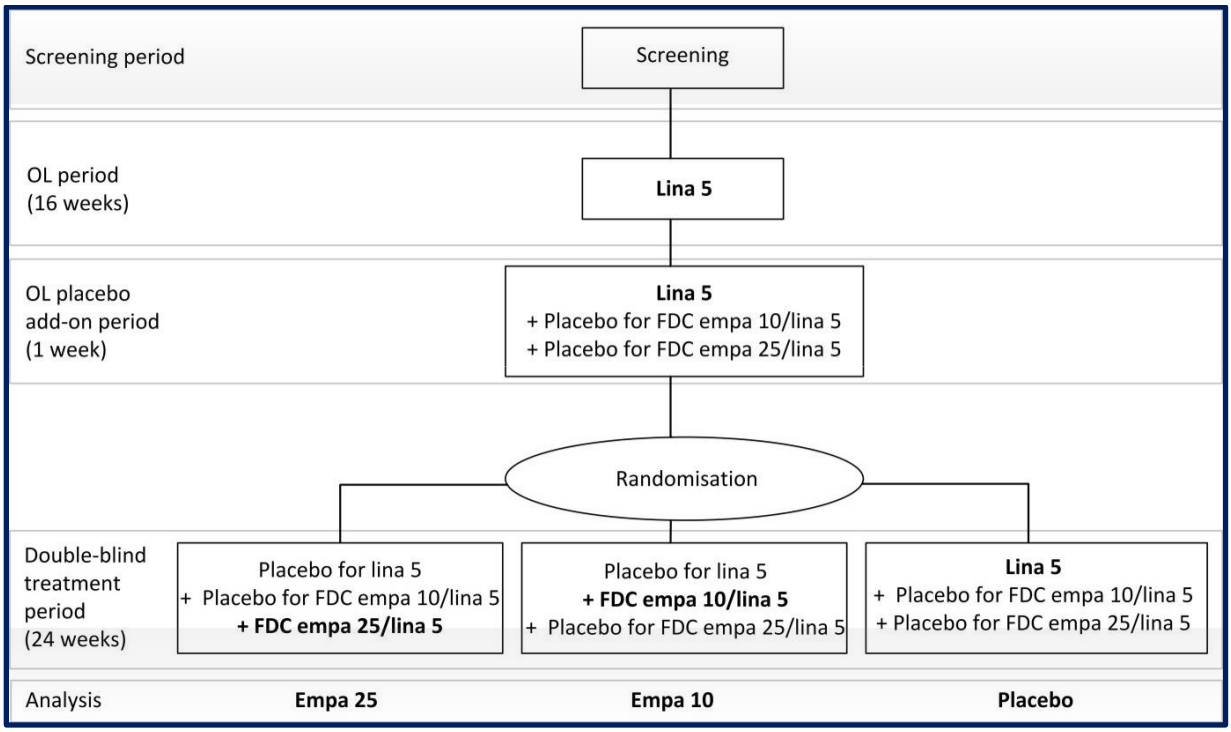
Figure 4: Study Design of Trial 1275.1



Source: Adapted from the Applicant's CSR for Trial 1275.1,[167] labeled as Figure 9.1:1, page73 of 7879, available at: \\cdsesub1\evsprod\nda206073\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-type-2\5351-stud-rep-contr\1275-0001\1275-0001--01-15--study-report-body.pdf
Abbreviations: Empa, empagliflozin; FCDP, fixed combination drug product; HbA1c, hemoglobin A1c; and Lina, linagliptin.

Trial 1275.9 was a randomized, double-blind, parallel group comparison study. Patients were recruited and randomized at a 1:1:1 ratio to empagliflozin 25 mg, empagliflozin 10 mg, or placebo, each as add-on to linagliptin 5 mg and metformin. The double-blind treatment period with empagliflozin and placebo as add-on to linagliptin 5 mg and metformin was preceded by a 16-week open-label treatment period with linagliptin 5 mg and metformin. The double-blind randomized treatment period was 24 weeks. Randomization was stratified by baseline HbA1c, renal function (assessed based on eGFR values according to MDRD staging criteria), and geographical region. Patients were to be followed-up for 7 days after end-of-treatment or prematurely discontinuing trial medication.

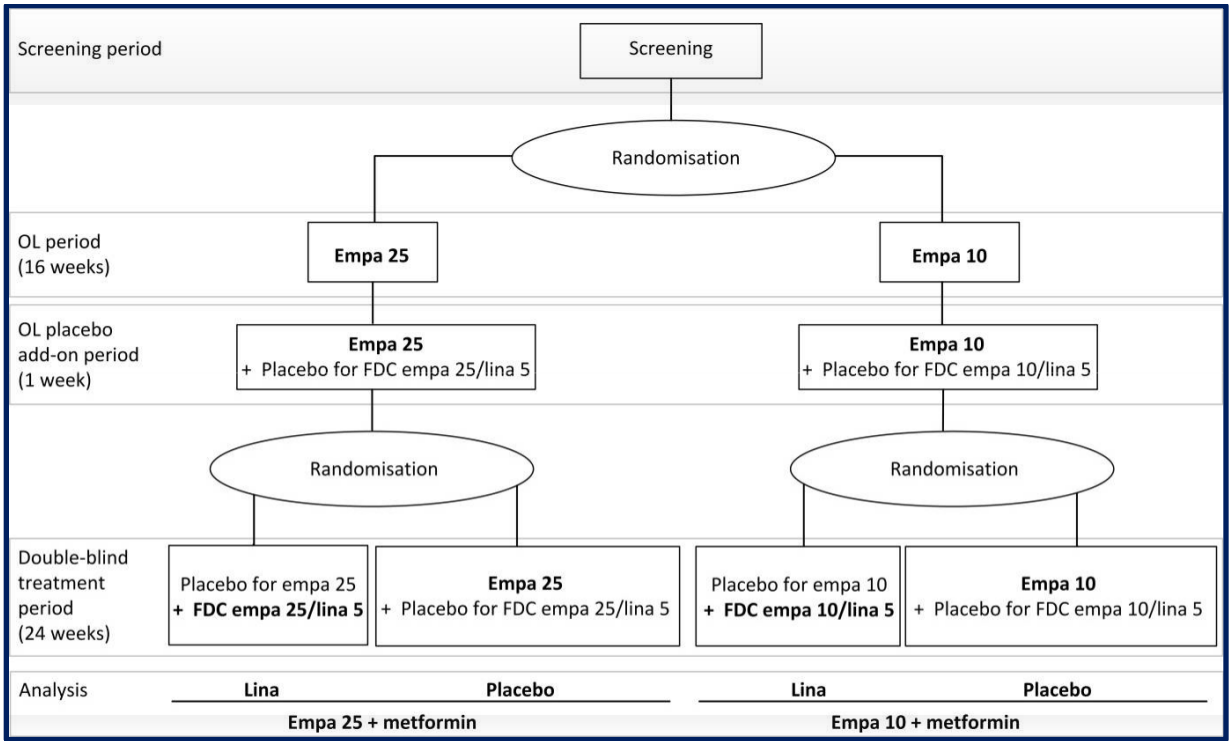
Figure 5: Study Design of Trial 1275.9



Source: Reproduced from the Applicant's CSR for Trial 1275.9,[168] labeled as Figure 9.1:1, page 42 of 2552, available at: \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0009\1275-0009--1-15--study-report-body.pdf
Abbreviations: Empa, empagliflozin; FDC, fixed drug combination; Lina, linagliptin; and OL, open-label.

Trial 1275.10 was a randomized, double-blind, parallel-group comparison study. For the double-blind treatment, patients were randomized in a 1:1 ratio to linagliptin 5 mg or placebo, each as add-on to empagliflozin (10 mg or 25 mg) and metformin. The double-blind treatment period was preceded by a 16-week open-label treatment period with empagliflozin (10 mg or 25 mg) and metformin. The double-blind treatment period was 24 weeks. Randomization was stratified by baseline HbA1c, renal function (assessed based on eGFR values according to MDRD staging criteria), and geographical region. Patients were to be followed-up for 7 days after end-of-treatment or prematurely discontinuing trial medication.

Figure 6: Study Design of Trial 1275.10



Source: Adapted from the Applicant's CSR for Trial 1275.10,[169] labeled as Figure 9.1:1, page 53 of 3544, available at: \\cdsesub1\evsprod\nda212614\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\1275-0010\1275-0010--1-15--study-report-body.pdf
Abbreviations: Empa, empagliflozin; FDC, fixed drug combination; Lina, linagliptin; and OL, open-label.

12.5. 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

* PREFERRED TERMS (PTS) USED IN THE APPLICANT'S SYSTEM MEDDRA QUERIES (BICMQS)

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 acute*; 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

12.6. Adverse Events of Special Interest (Broad CMQs)

Table 22: Summary of AESI by Custom MedDRA Query (Phase 3 Trials)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
HYPERSENSITIVITY	**18 (13.6)**	**18 (12.9)**	**16 (11.3)**	**18 (13.2)**	**20 (14.6)**	**16 (14.5)**	**13 (11.6)**	**15 (13.6)**	**9 (7.0)**	**11 (9.8)**	**5 (4.0)**	**8 (7.1)**
Cough	2 (1.5)	2 (1.4)	2 (1.4)	6 (4.4)	5 (3.6)	2 (1.8)	1 (0.9)	3 (2.7)	2 (1.6)	0	0	1 (0.9)
Pruritus	2 (1.5)	1 (0.7)	0	2 (1.5)	2 (1.5)	3 (2.7)	3 (2.7)	4 (3.6)	1 (0.8)	1 (0.9)	0	2 (1.8)
Oedema peripheral	2 (1.5)	2 (1.4)	4 (2.8)	0	2 (1.5)	1 (0.9)	1 (0.9)	0	0	0	0	0
Rhinitis allergic	0	0	1 (0.7)	1 (0.7)	2 (1.5)	1 (0.9)	0	2 (1.8)	1 (0.8)	0	0	1 (0.9)
Conjunctivitis	2 (1.5)	3 (2.1)	3 (2.1)	2 (1.5)	2 (1.5)	1 (0.9)	0	0	2 (1.6)	1 (0.9)	0	1 (0.9)
Dermatitis contact	1 (0.8)	2 (1.4)	1 (0.7)	0	1 (0.7)	1 (0.9)	0	1 (0.9)	0	0	0	0
Erythema	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.9)	0	0	0	1 (0.8)	0
Genital rash	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Hypotension	2 (1.5)	1 (0.7)	0	1 (0.7)	1 (0.7)	0	0	1 (0.9)	0	2 (1.8)	0	0
Drug hypersensitivity	0	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.9)
Angioedema	1 (0.8)	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Chest discomfort	0	1 (0.7)	0	1 (0.7)	1 (0.7)	0	1 (0.9)	1 (0.9)	0	0	0	0
Rash	0	0	1 (0.7)	2 (1.5)	1 (0.7)	2 (1.8)	0	0	0	0	1 (0.8)	0
Eczema	2 (1.5)	1 (0.7)	2 (1.4)	0	1 (0.7)	2 (1.8)	0	1 (0.9)	0	1 (0.9)	0	0
Eosinophil count increased	1 (0.8)	1 (0.7)	0	0	0	1 (0.9)	2 (1.8)	0	0	0	0	0
Stomatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Dyspnoea	1 (0.8)	2 (1.4)	0	0	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Dermatitis infected	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Eosinophilia	1 (0.8)	1 (0.7)	0	0	0	0	0	0	0	1 (0.9)	0	0
Neurodermatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Pneumonitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Seasonal allergy	1 (0.8)	1 (0.7)	0	1 (0.7)	0	0	0	0	0	0	0	0
Vulval ulceration	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Hypersensitivity	0	1 (0.7)	0	0	0	0	1 (0.9)	0	1 (0.8)	0	0	0
Oedema	0	0	2 (1.4)	0	0	1 (0.9)	0	0	0	0	0	0
Urticaria	0	0	0	1 (0.7)	0	2 (1.8)	0	1 (0.9)	0	0	1 (0.8)	0
Sneezing	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Blister	0	0	0	1 (0.7)	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Dermatitis allergic	0	0	0	0	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Respiratory failure	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Dermatitis	0	0	0	0	0	0	2 (1.8)	1 (0.9)	2 (1.6)	0	0	0
Eye pruritus	0	0	0	0	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Dermatitis acneiform	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Conjunctivitis allergic	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Asthma	0	0	0	0	0	0	0	1 (0.9)	0	0	0	1 (0.9)
Bronchial hyperreactivity	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Sensation of foreign body	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Immune thrombocytopenic purpura	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Peripheral swelling	0	0	0	0	0	0	0	0	0	0	2 (1.6)	1 (0.9)
Ocular hyperaemia	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Dermatitis bullous	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Skin exfoliation	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
URINARY TRACT INFECTIONS	**22 (16.7)**	**17 (12.1)**	**21 (14.9)**	**14 (10.3)**	**15 (10.9)**	**14 (12.7)**	**12 (10.7)**	**9 (8.2)**	**19 (14.8)**	**15 (13.4)**	**17 (13.5)**	**26 (23.2)**
Urinary tract infection	15 (11.4)	13 (9.3)	17 (12.1)	12 (8.8)	12 (8.8)	11 (10.0)	10 (8.9)	8 (7.3)	11 (8.6)	10 (8.9)	12 (9.5)	16 (14.3)
Cystitis	4 (3.0)	2 (1.4)	1 (0.7)	0	2 (1.5)	0	0	0	4 (3.1)	4 (3.6)	2 (1.6)	1 (0.9)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Dysuria	1 (0.8)	0	4 (2.8)	1 (0.7)	1 (0.7)	3 (2.7)	0	2 (1.8)	0	1 (0.9)	0	1 (0.9)
Pyelonephritis acute	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Prostatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Asymptomatic bacteriuria	1 (0.8)	0	1 (0.7)	0	0	0	0	2 (1.8)	4 (3.1)	1 (0.9)	2 (1.6)	6 (5.4)
Pyelonephritis	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Leukocyturia	0	1 (0.7)	0	0	0	0	1 (0.9)	0	0	0	0	0
Urosepsis	0	1 (0.7)	0	0	0	1 (0.9)	0	0	0	0	0	0
Genitourinary tract infection	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Pyelonephritis chronic	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Escherichia urinary tract infection	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Pyuria	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Bacteriuria	0	0	0	0	0	0	0	0	1 (0.8)	0	0	2 (1.8)
Urethritis	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
White blood cells urine positive	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Urine leukocyte esterase positive	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Urinary tract infection bacterial	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
MYOPATHY/RHABDOMYOLYSIS	**19 (14.4)**	**18 (12.9)**	**16 (11.3)**	**18 (13.2)**	**15 (10.9)**	**13 (11.8)**	**10 (8.9)**	**10 (9.1)**	**14 (10.9)**	**7 (6.3)**	**11 (8.7)**	**11 (9.8)**
Back pain	7 (5.3)	9 (6.4)	2 (1.4)	5 (3.7)	6 (4.4)	5 (4.5)	7 (6.3)	7 (6.4)	5 (3.9)	6 (5.4)	5 (4.0)	2 (1.8)
Myalgia	0	4 (2.9)	1 (0.7)	5 (3.7)	3 (2.2)	2 (1.8)	0	0	2 (1.6)	0	1 (0.8)	1 (0.9)
Blood creatine phosphokinase increased	1 (0.8)	0	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.9)	0	1 (0.9)	2 (1.6)	0	1 (0.8)	1 (0.9)
Blood creatinine increased	1 (0.8)	0	0	0	2 (1.5)	0	0	0	0	0	0	0
Pain in extremity	2 (1.5)	2 (1.4)	5 (3.5)	3 (2.2)	1 (0.7)	3 (2.7)	0	3 (2.7)	1 (0.8)	0	1 (0.8)	4 (3.6)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Muscle spasms	1 (0.8)	2 (1.4)	5 (3.5)	0	1 (0.7)	0	0	0	1 (0.8)	0	1 (0.8)	1 (0.9)
Musculoskeletal discomfort	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Renal impairment	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.9)
Glomerular filtration rate decreased	2 (1.5)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.9)	1 (0.9)	0	2 (1.6)	0	1 (0.8)	1 (0.9)
Flank pain	3 (2.3)	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Musculoskeletal pain	3 (2.3)	2 (1.4)	1 (0.7)	4 (2.9)	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.8)	0	1 (0.8)	0
Non-cardiac chest pain	1 (0.8)	0	0	1 (0.7)	0	0	1 (0.9)	0	1 (0.8)	0	0	1 (0.9)
Muscle rupture	1 (0.8)	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Myositis	0	1 (0.7)	0	0	0	1 (0.9)	0	0	0	0	0	0
Muscle spasticity	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Musculoskeletal chest pain	0	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	1 (0.9)
Blood calcium decreased	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Rhabdomyolysis	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
PANCREATITIS	**12 (9.1)**	**5 (3.6)**	**9 (6.4)**	**9 (6.6)**	**12 (8.8)**	**16 (14.5)**	**13 (11.6)**	**9 (8.2)**	**11 (8.6)**	**14 (12.5)**	**15 (11.9)**	**8 (7.1)**
Lipase increased	2 (1.5)	2 (1.4)	1 (0.7)	0	5 (3.6)	7 (6.4)	6 (5.4)	5 (4.5)	6 (4.7)	8 (7.1)	7 (5.6)	7 (6.3)
Nausea	4 (3.0)	1 (0.7)	4 (2.8)	4 (2.9)	4 (2.9)	5 (4.5)	3 (2.7)	2 (1.8)	2 (1.6)	2 (1.8)	4 (3.2)	0
Abdominal pain	2 (1.5)	1 (0.7)	1 (0.7)	2 (1.5)	3 (2.2)	0	0	2 (1.8)	0	0	1 (0.8)	1 (0.9)
Abdominal pain upper	3 (2.3)	0	2 (1.4)	2 (1.5)	2 (1.5)	3 (2.7)	2 (1.8)	0	2 (1.6)	1 (0.9)	2 (1.6)	0
Hyperlipasaemia	0	0	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Vomiting	1 (0.8)	1 (0.7)	1 (0.7)	2 (1.5)	1 (0.7)	3 (2.7)	2 (1.8)	1 (0.9)	0	3 (2.7)	2 (1.6)	0
Abdominal distension	1 (0.8)	0	0	1 (0.7)	1 (0.7)	0	0	1 (0.9)	0	0	1 (0.8)	0
Pancreatitis chronic	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal sounds abnormal	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Amylase increased	0	0	0	0	0	3 (2.7)	4 (3.6)	3 (2.7)	4 (3.1)	3 (2.7)	3 (2.4)	1 (0.9)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Hyperamylasaemia	0	0	0	0	0	0	1 (0.9)	0	1 (0.8)	0	1 (0.8)	0
Pancreatitis acute	0	0	0	0	0	0	0	0	0	0	2 (1.6)	0
ACCIDENTS AND INJURIES	**7 (5.3)**	**8 (5.7)**	**13 (9.2)**	**13 (9.6)**	**11 (8.0)**	**8 (7.3)**	**11 (9.8)**	**6 (5.5)**	**5 (3.9)**	**4 (3.6)**	**6 (4.8)**	**10 (8.9)**
Ligament sprain	1 (0.8)	0	1 (0.7)	1 (0.7)	2 (1.5)	2 (1.8)	1 (0.9)	1 (0.9)	0	0	1 (0.8)	3 (2.7)
Post-traumatic pain	0	0	0	0	1 (0.7)	0	0	1 (0.9)	0	0	0	0
Muscle strain	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.9)	0	1 (0.8)	0	0	0
Limb injury	0	0	0	1 (0.7)	1 (0.7)	0	0	1 (0.9)	0	0	0	0
Traumatic haematoma	0	0	0	0	1 (0.7)	0	0	1 (0.9)	1 (0.8)	0	0	0
Wound	1 (0.8)	1 (0.7)	1 (0.7)	0	1 (0.7)	1 (0.9)	2 (1.8)	0	0	0	0	0
Laceration	1 (0.8)	1 (0.7)	0	0	1 (0.7)	0	2 (1.8)	0	0	0	1 (0.8)	1 (0.9)
Foot fracture	0	0	0	1 (0.7)	1 (0.7)	1 (0.9)	0	0	0	0	0	0
Eye injury	0	0	0	0	1 (0.7)	0	1 (0.9)	0	0	0	0	0
Excoriation	1 (0.8)	1 (0.7)	1 (0.7)	0	1 (0.7)	0	0	0	0	0	0	0
Contusion	2 (1.5)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.9)	2 (1.8)	2 (1.8)	1 (0.8)	0	0	2 (1.8)
Meniscus injury	1 (0.8)	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Muscle rupture	1 (0.8)	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Road traffic accident	0	2 (1.4)	1 (0.7)	2 (1.5)	0	1 (0.9)	0	0	0	0	0	1 (0.9)
Fall	0	2 (1.4)	2 (1.4)	1 (0.7)	0	0	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	0
Soft tissue injury	0	1 (0.7)	0	0	0	1 (0.9)	0	0	0	0	0	0
Sunburn	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Joint injury	0	1 (0.7)	2 (1.4)	0	0	0	2 (1.8)	0	0	1 (0.9)	0	0
Traumatic ulcer	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Thermal burn	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Tibia fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Upper limb fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Femur fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Tendon rupture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Fibula fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Head injury	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Neck injury	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Humerus fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Post-traumatic neck syndrome	0	0	0	1 (0.7)	0	0	0	0	1 (0.8)	0	0	0
Joint dislocation	0	0	0	1 (0.7)	0	0	0	1 (0.9)	0	0	0	0
Clavicle fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Animal bite	0	0	0	1 (0.7)	0	0	1 (0.9)	0	0	0	1 (0.8)	0
Wrist fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.8)	0
Lower limb fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Traumatic fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Rib fracture	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Laryngeal injury	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Scratch	0	0	0	0	0	0	0	0	1 (0.8)	0	0	1 (0.9)
Ankle fracture	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Ligament injury	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Ligament rupture	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Skin abrasion	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Foreign body in eye	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Tooth fracture	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
ACUTE KIDNEY INJURY/ CHRONIC KIDNEY DISEASE	**8 (6.1)**	**5 (3.6)**	**7 (5.0)**	**4 (2.9)**	**7 (5.1)**	**6 (5.5)**	**7 (6.3)**	**2 (1.8)**	**5 (3.9)**	**5 (4.5)**	**4 (3.2)**	**6 (5.4)**
Microalbuminuria	1 (0.8)	0	2 (1.4)	0	3 (2.2)	2 (1.8)	2 (1.8)	0	1 (0.8)	1 (0.9)	0	1 (0.9)
Blood creatinine increased	1 (0.8)	0	0	0	2 (1.5)	0	0	0	0	0	0	0
Glomerular filtration rate decreased	2 (1.5)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.9)	1 (0.9)	0	2 (1.6)	0	1 (0.8)	1 (0.9)
Encephalopathy	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Nephropathy	0	1 (0.7)	0	0	1 (0.7)	1 (0.9)	0	0	0	0	1 (0.8)	0
Renal impairment	0	0	0	0	1 (0.7)	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.9)
Blood sodium decreased	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Renal failure acute	1 (0.8)	0	0	0	0	2 (1.8)	0	0	0	0	0	0
Bone cyst	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Renal failure chronic	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Leukocyturia	0	1 (0.7)	0	0	0	0	1 (0.9)	0	0	0	0	0
Urine albumin/ creatinine ratio increased	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (0.9)	0	0
Diabetic nephropathy	0	1 (0.7)	2 (1.4)	1 (0.7)	0	0	0	0	0	0	0	1 (0.9)
Blood potassium increased	0	0	1 (0.7)	0	0	0	2 (1.8)	0	0	0	0	0
Hyperkalaemia	0	0	0	1 (0.7)	0	0	0	1 (0.9)	1 (0.8)	0	0	0
Blood parathyroid hormone increased	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Blood bicarbonate decreased	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Metabolic acidosis	0	0	0	0	0	2 (1.8)	0	0	0	0	0	0
Blood calcium decreased	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Proteinuria	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	1 (0.9)	1 (0.8)	2 (1.8)
Renal failure	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.9)	0	0
Albuminuria	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
White blood cells urine positive	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Blood urea increased	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Protein urine present	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
HYPOGLYCEMIA	**3 (2.3)**	**4 (2.9)**	**6 (4.3)**	**4 (2.9)**	**5 (3.6)**	**3 (2.7)**	**5 (4.5)**	**3 (2.7)**	**1 (0.8)**	**5 (4.5)**	**1 (0.8)**	**0**

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Hypoglycaemia	3 (2.3)	4 (2.9)	6 (4.3)	4 (2.9)	5 (3.6)	2 (1.8)	3 (2.7)	3 (2.7)	1 (0.8)	5 (4.5)	1 (0.8)	0
Neuroglycopenia	0	0	0	0	0	1 (0.9)	2 (1.8)	0	0	0	0	0
DIABETIC MICROVASCULAR COMPLICATIONS	**2 (1.5)**	**1 (0.7)**	**4 (2.8)**	**2 (1.5)**	**5 (3.6)**	**4 (3.6)**	**3 (2.7)**	**2 (1.8)**	**1 (0.8)**	**3 (2.7)**	**2 (1.6)**	**4 (3.6)**
Microalbuminuria	1 (0.8)	0	2 (1.4)	0	3 (2.2)	2 (1.8)	2 (1.8)	0	1 (0.8)	1 (0.9)	0	1 (0.9)
Diabetic neuropathy	0	0	0	1 (0.7)	1 (0.7)	2 (1.8)	0	1 (0.9)	0	0	0	0
Diabetic foot infection	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Diabetic retinopathy	1 (0.8)	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Diabetic nephropathy	0	1 (0.7)	2 (1.4)	1 (0.7)	0	0	0	0	0	0	0	1 (0.9)
Proteinuria	0	0	0	0	0	0	1 (0.9)	1 (0.9)	0	1 (0.9)	1 (0.8)	2 (1.8)
Retinopathy	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Protein urine present	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
HEART FAILURE/ CARDIOMYOPATHY	**5 (3.8)**	**4 (2.9)**	**10 (7.1)**	**4 (2.9)**	**5 (3.6)**	**3 (2.7)**	**5 (4.5)**	**2 (1.8)**	**1 (0.8)**	**6 (5.4)**	**3 (2.4)**	**3 (2.7)**
Oedema peripheral	2 (1.5)	2 (1.4)	4 (2.8)	0	2 (1.5)	1 (0.9)	1 (0.9)	0	0	0	0	0
Chest pain	2 (1.5)	1 (0.7)	3 (2.1)	0	1 (0.7)	0	0	0	1 (0.8)	4 (3.6)	0	1 (0.9)
Cardiomegaly	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Cardiac aneurysm	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Mental status changes	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Dyspnoea	1 (0.8)	2 (1.4)	0	0	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Palpitations	1 (0.8)	0	0	2 (1.5)	0	0	1 (0.9)	2 (1.8)	0	0	1 (0.8)	0
Orthostatic hypotension	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Cardiomyopathy	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Syncope	0	0	2 (1.4)	1 (0.7)	0	0	0	0	0	0	0	0
Oedema	0	0	2 (1.4)	0	0	1 (0.9)	0	0	0	0	0	0
Electrocardiogram abnormal	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.9)	0	0
Blood pressure inadequately controlled	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Nocturia	0	0	0	0	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Electrocardiogram change	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Cardiac failure congestive	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Peripheral swelling	0	0	0	0	0	0	0	0	0	0	2 (1.6)	1 (0.9)
Arrhythmia	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
CORONARY ARTERY DISEASE	**3 (2.3)**	**2 (1.4)**	**3 (2.1)**	**2 (1.5)**	**4 (2.9)**	**4 (3.6)**	**0**	**2 (1.8)**	**5 (3.9)**	**0**	**1 (0.8)**	**1 (0.9)**
Blood creatine phosphokinase increased	1 (0.8)	0	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.9)	0	1 (0.9)	2 (1.6)	0	1 (0.8)	1 (0.9)
Angina pectoris	0	1 (0.7)	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0
Myocardial infarction	0	1 (0.7)	0	0	1 (0.7)	0	0	0	1 (0.8)	0	0	0
Myocardial ischaemia	1 (0.8)	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Coronary artery disease	1 (0.8)	0	0	0	0	1 (0.9)	0	0	2 (1.6)	0	0	0
Coronary artery occlusion	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Acute coronary syndrome	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Electrocardiogram T wave inversion	0	0	0	0	0	1 (0.9)	0	1 (0.9)	0	0	0	0
Blood creatine phosphokinase MB increased	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Angina unstable	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
ARTHROPATHIES	**10 (7.6)**	**7 (5.0)**	**12 (8.5)**	**10 (7.4)**	**4 (2.9)**	**5 (4.5)**	**10 (8.9)**	**4 (3.6)**	**8 (6.3)**	**5 (4.5)**	**3 (2.4)**	**4 (3.6)**
Neck pain	2 (1.5)	1 (0.7)	1 (0.7)	0	1 (0.7)	2 (1.8)	2 (1.8)	1 (0.9)	1 (0.8)	0	0	2 (1.8)
Arthralgia	6 (4.5)	3 (2.1)	7 (5.0)	6 (4.4)	1 (0.7)	2 (1.8)	4 (3.6)	3 (2.7)	2 (1.6)	2 (1.8)	3 (2.4)	2 (1.8)
Osteoarthritis	2 (1.5)	1 (0.7)	1 (0.7)	2 (1.5)	1 (0.7)	1 (0.9)	3 (2.7)	0	3 (2.3)	0	0	0
Gouty arthritis	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Arthritis reactive	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Spinal osteoarthritis	1 (0.8)	0	0	1 (0.7)	0	1 (0.9)	0	0	0	0	0	0
Joint swelling	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Spondylitis	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Joint range of motion decreased	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Synovitis	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Gout	0	0	1 (0.7)	2 (1.5)	0	0	0	0	0	1 (0.9)	0	0
Chondromalacia	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Arthritis	0	0	1 (0.7)	1 (0.7)	0	0	0	0	2 (1.6)	0	0	0
Patellofemoral pain syndrome	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Periarthritis	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Spinal pain	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.9)	0	0
Chondrocalcinosis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
GENITAL INFECTIONS	**3 (2.3)**	**13 (9.3)**	**12 (8.5)**	**10 (7.4)**	**4 (2.9)**	**4 (3.6)**	**2 (1.8)**	**6 (5.5)**	**14 (10.9)**	**13 (11.6)**	**12 (9.5)**	**7 (6.3)**
Vaginal infection	0	1 (0.7)	2 (1.4)	4 (2.9)	1 (0.7)	0	0	0	0	1 (0.9)	1 (0.8)	3 (2.7)
Genital rash	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Genital infection fungal	0	2 (1.4)	2 (1.4)	0	1 (0.7)	0	0	2 (1.8)	0	1 (0.9)	0	1 (0.9)
Endometriosis	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Vulvovaginitis	1 (0.8)	0	0	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.9)	3 (2.4)	1 (0.9)
Prostatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Orchitis	1 (0.8)	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Balanitis candida	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Balanoposthitis	0	1 (0.7)	0	0	0	0	0	1 (0.9)	5 (3.9)	6 (5.4)	2 (1.6)	1 (0.9)
Genital infection	0	1 (0.7)	0	0	0	0	0	0	2 (1.6)	1 (0.9)	0	0
Vulvovaginal candidiasis	0	1 (0.7)	2 (1.4)	1 (0.7)	0	1 (0.9)	2 (1.8)	1 (0.9)	0	1 (0.9)	0	0
Vulvovaginal mycotic infection	0	1 (0.7)	3 (2.1)	0	0	1 (0.9)	0	0	4 (3.1)	2 (1.8)	1 (0.8)	1 (0.9)

Trial	1275.1					1275.9			1275.10			
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Genitourinary tract infection	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Penile infection	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Pruritus genital	0	1 (0.7)	0	2 (1.5)	0	0	0	0	0	0	1 (0.8)	1 (0.9)
Vaginal discharge	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Vaginal haemorrhage	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Vulvovaginal burning sensation	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Vulvovaginal pruritus	0	0	2 (1.4)	2 (1.5)	0	1 (0.9)	0	1 (0.9)	1 (0.8)	1 (0.9)	2 (1.6)	0
Genital candidiasis	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.8)	0
Vulvovaginal discomfort	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Phimosis	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Vulvovaginal dryness	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.8)	0
Epididymitis	0	0	0	0	0	1 (0.9)	0	0	1 (0.8)	0	0	0
HEPATOTOXICITY	**0**	**4 (2.9)**	**1 (0.7)**	**0**	**3 (2.2)**	**2 (1.8)**	**0**	**1 (0.9)**	**2 (1.6)**	**3 (2.7)**	**3 (2.4)**	**2 (1.8)**
Hepatic steatosis	0	2 (1.4)	0	0	2 (1.5)	0	0	0	1 (0.8)	1 (0.9)	2 (1.6)	1 (0.9)
Blood alkaline phosphatase increased	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Hepatitis toxic	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Liver function test abnormal	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Aspartate aminotransferase increased	0	0	1 (0.7)	0	0	0	0	1 (0.9)	0	1 (0.9)	0	0
Hypertransaminasaemia	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Ocular icterus	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
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Gamma-glutamyltransferase increased	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.9)	0	0
Hepatic neoplasm	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Diabetic hepatopathy	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Hepatic enzyme increased	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
MALIGNANCY/ PREMALIGNANCY	**3 (2.3)**	**2 (1.4)**	**2 (1.4)**	**2 (1.5)**	**3 (2.2)**	**1 (0.9)**	**2 (1.8)**	**0**	**0**	**2 (1.8)**	**0**	**1 (0.9)**
Basal cell carcinoma	0	0	1 (0.7)	0	1 (0.7)	0	0	0	0	0	0	0
Renal cancer	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Breast cancer	0	0	0	0	1 (0.7)	0	1 (0.9)	0	0	0	0	0
Prostatic specific antigen increased	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Large intestine polyp	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Squamous cell carcinoma	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Colon adenoma	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Non-small cell lung cancer metastatic	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Lung neoplasm	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Adenoid cystic carcinoma	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Ovarian cancer	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Metastases to peritoneum	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Gastrointestinal carcinoma	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Actinic keratosis	0	0	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.9)
Bladder neoplasm	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
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Adenocarcinoma of colon	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Intestinal polyp	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Hepatic neoplasm	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
SKIN REACTIONS	**4 (3.0)**	**5 (3.6)**	**3 (2.1)**	**3 (2.2)**	**2 (1.5)**	**1 (0.9)**	**1 (0.9)**	**0**	**2 (1.6)**	**2 (1.8)**	**0**	**3 (2.7)**
Conjunctivitis	2 (1.5)	3 (2.1)	3 (2.1)	2 (1.5)	2 (1.5)	1 (0.9)	0	0	2 (1.6)	1 (0.9)	0	1 (0.9)
Stomatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Skin ulcer	1 (0.8)	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Vulval ulceration	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Blister	0	0	0	1 (0.7)	0	0	1 (0.9)	0	0	1 (0.9)	0	0
Dermatitis bullous	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Skin exfoliation	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
FOURNIER'S GANGRENE	**1 (0.8)**	**2 (1.4)**	**2 (1.4)**	**4 (2.9)**	**2 (1.5)**	**0**	**0**	**2 (1.8)**	**1 (0.8)**	**2 (1.8)**	**4 (3.2)**	**3 (2.7)**
Penis disorder	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Vaginal infection	0	1 (0.7)	2 (1.4)	4 (2.9)	1 (0.7)	0	0	0	0	1 (0.9)	1 (0.8)	3 (2.7)
Vulvovaginitis	1 (0.8)	0	0	0	0	0	0	1 (0.9)	1 (0.8)	1 (0.9)	3 (2.4)	1 (0.9)
Penile infection	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Penile pain	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
VASCULAR INSUFFICIENCY	**2 (1.5)**	**1 (0.7)**	**0**	**0**	**2 (1.5)**	**0**	**0**	**0**	**0**	**3 (2.7)**	**1 (0.8)**	**0**
Diabetic foot infection	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Peripheral vascular disorder	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Skin ulcer	1 (0.8)	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Peripheral arterial occlusive disease	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Arteriosclerosis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Peripheral coldness	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Extremity necrosis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0

Trial	1275.1					1275.9			1275.10			
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Peripheral venous disease	0	0	0	0	0	0	0	0	0	0	1 (0.8)	0
OSMOTIC DIURESIS	**2 (1.5)**	**5 (3.6)**	**5 (3.5)**	**1 (0.7)**	**2 (1.5)**	**5 (4.5)**	**1 (0.9)**	**3 (2.7)**	**5 (3.9)**	**7 (6.3)**	**6 (4.8)**	**4 (3.6)**
Polyuria	0	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.9)	0	2 (1.8)	2 (1.6)	4 (3.6)	1 (0.8)	1 (0.9)
Pollakiuria	1 (0.8)	2 (1.4)	2 (1.4)	0	1 (0.7)	1 (0.9)	0	1 (0.9)	0	1 (0.9)	0	1 (0.9)
Micturition urgency	1 (0.8)	0	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.9)
Dry mouth	0	1 (0.7)	0	0	0	1 (0.9)	0	0	2 (1.6)	0	3 (2.4)	1 (0.9)
Dry throat	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
Polydipsia	0	0	2 (1.4)	0	0	1 (0.9)	0	0	0	3 (2.7)	1 (0.8)	0
Thirst	0	0	0	0	0	1 (0.9)	0	0	0	0	1 (0.8)	1 (0.9)
Nocturia	0	0	0	0	0	1 (0.9)	0	0	0	1 (0.9)	0	0
Micturition disorder	0	0	0	0	0	0	1 (0.9)	0	1 (0.8)	0	0	0
LACTIC ACIDOSIS	**0**	**0**	**0**	**1 (0.7)**	**1 (0.7)**	**2 (1.8)**	**0**	**0**	**0**	**0**	**0**	**0**
Acidosis	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Blood bicarbonate decreased	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Metabolic acidosis	0	0	0	0	0	2 (1.8)	0	0	0	0	0	0
KETOACIDOSIS	**0**	**0**	**0**	**1 (0.7)**	**1 (0.7)**	**2 (1.8)**	**0**	**0**	**0**	**0**	**0**	**1 (0.9)**
Acidosis	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Blood bicarbonate decreased	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Metabolic acidosis	0	0	0	0	0	2 (1.8)	0	0	0	0	0	0
Ketonuria	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
CEREBROVASCULAR DISEASE	**1 (0.8)**	**1 (0.7)**	**1 (0.7)**	**1 (0.7)**	**1 (0.7)**	**0**	**0**	**0**	**1 (0.8)**	**0**	**0**	**0**
Transient ischaemic attack	0	1 (0.7)	0	0	1 (0.7)	0	0	0	0	0	0	0
Cerebrovascular accident	1 (0.8)	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Acute coronary syndrome	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Cerebral infarction	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
BONE FRACTURES	**0**	**0**	**4 (2.8)**	**4 (2.9)**	**1 (0.7)**	**2 (1.8)**	**0**	**0**	**1 (0.8)**	**0**	**1 (0.8)**	**0**
Foot fracture	0	0	0	1 (0.7)	1 (0.7)	1 (0.9)	0	0	0	0	0	0
Humerus fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Fibula fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Femur fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Tibia fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Upper limb fracture	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Traumatic fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Lower limb fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Clavicle fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Wrist fracture	0	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.8)	0
Rib fracture	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Ankle fracture	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
VOLUME DEPLETION	**4 (3.0)**	**1 (0.7)**	**2 (1.4)**	**3 (2.2)**	**1 (0.7)**	**1 (0.9)**	**0**	**1 (0.9)**	**1 (0.8)**	**2 (1.8)**	**1 (0.8)**	**0**
Hypotension	2 (1.5)	1 (0.7)	0	1 (0.7)	1 (0.7)	0	0	1 (0.9)	0	2 (1.8)	0	0
Dehydration	2 (1.5)	0	1 (0.7)	0	0	1 (0.9)	0	0	1 (0.8)	0	1 (0.8)	0
Orthostatic hypotension	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Syncope	0	0	2 (1.4)	1 (0.7)	0	0	0	0	0	0	0	0
Urine flow decreased	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
STOMATITIS/MOUTH ULCER	**3 (2.3)**	**2 (1.4)**	**4 (2.8)**	**3 (2.2)**	**0**	**2 (1.8)**	**3 (2.7)**	**0**	**2 (1.6)**	**0**	**1 (0.8)**	**1 (0.9)**
Oesophageal ulcer	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Oropharyngeal pain	1 (0.8)	2 (1.4)	3 (2.1)	3 (2.2)	0	2 (1.8)	3 (2.7)	0	1 (0.8)	0	1 (0.8)	1 (0.9)
Stomatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Odynophagia	0	0	1 (0.7)	0	0	0	0	0	1 (0.8)	0	0	0
NEPHROLITHIASIS	**2 (1.5)**	**1 (0.7)**	**2 (1.4)**	**1 (0.7)**	**0**	**1 (0.9)**	**0**	**2 (1.8)**	**0**	**0**	**0**	**1 (0.9)**
Renal colic	1 (0.8)	0	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Calculus urinary	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Nephrolithiasis	0	1 (0.7)	2 (1.4)	0	0	1 (0.9)	0	2 (1.8)	0	0	0	0
Hydronephrosis	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Urinary sediment present	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
VENOUS THROMBOEMBOLIC EVENT	**0**	**1 (0.7)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Pulmonary embolism	0	1 (0.7)	0	0	0	0	0	0	0	0	0	0
THROMBOCYTOPENIA	**0**	**0**	**0**	**1 (0.7)**	**0**	**0**	**0**	**0**	**0**	**1 (0.9)**	**0**	**0**
Thrombocytopenia	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Immune thrombocytopenic purpura	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
BONE AND JOINT INFECTIONS	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.9)**	**0**	**0**
Osteomyelitis	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0

Source: Derived from the adsl.xpt and adae.xpt datasets, available at:
Application 206073 - Data Analysis Data –
Application 212614 - Sequence 0000 - Data Analysis Data -
Application 212614 - Sequence 0000 - Data Analysis Data -
Abbreviations: Empa, empagliflozin, Lina, linagliptin; Met, metformin; N, sample size.

12.7. Electrocardiogram-Related Adverse Events

Table 23: Summary of ECG-Related Adverse Events (Phase 3 Trials)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
ECG-RELATED AEs	**3 (2.3)**	**0**	**4 (2.8)**	**1 (0.7)**	**3 (2.2)**	**1 (0.9)**	**1 (0.9)**	**1 (0.9)**	**3 (2.3)**	**3 (2.7)**	**3 (2.4)**	**2 (1.8)**
Left ventricular hypertrophy	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Sinus bradycardia	1 (0.8)	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Atrial tachycardia	0	0	0	0	1 (0.7)	0	0	0	0	0	0	0
Sinus tachycardia	1 (0.8)	0	0	0	0	0	0	0	0	0	0	0
Tachycardia	1 (0.8)	0	0	0	0	0	0	0	0	0	1 (0.8)	1 (0.9)
Acute coronary syndrome	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Electrocardiogram QRS complex abnormal	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Electrocardiogram abnormal	0	0	1 (0.7)	0	0	0	0	0	0	1 (0.9)	0	0
Supraventricular extrasystoles	0	0	1 (0.7)	0	0	0	0	0	0	0	0	0
Supraventricular tachycardia	0	0	0	1 (0.7)	0	0	0	0	0	0	0	0
Electrocardiogram T wave inversion	0	0	0	0	0	1 (0.9)	0	0	0	0	0	0
Electrocardiogram change	0	0	0	0	0	0	1 (0.9)	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	1 (0.9)	0	0	0	0
Bundle branch block left	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Bundle branch block right	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Atrioventricular block	0	0	0	0	0	0	0	0	1 (0.8)	0	0	0
Extrasystoles	0	0	0	0	0	0	0	0	0	1 (0.9)	1 (0.8)	0

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Bradycardia	0	0	0	0	0	0	0	0	0	1 (0.9)	0	0
Atrioventricular block first degree	0	0	0	0	0	0	0	0	0	0	2 (1.6)	0
Atrial flutter	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
Arrhythmia	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at:
Application 206073 - Data Analysis Data –
Application 212614 - Sequence 0000 - Data Analysis Data -
Application 212614 - Sequence 0000 - Data Analysis Data -
Abbreviations: Empa, empagliflozin, Lina, linagliptin; Met, metformin; N, sample size.

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/s/

FRANK PUCINO
01/18/2020 09:48:25 PM

PATRICK ARCHDEACON
01/21/2020 08:58:49 AM