CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA) and Efficacy Supplements (sNDAs)
Application Number(s)	NDA 209091, sNDAs 22350/S-018, and sNDA 200678/S-018
Priority or Standard	Standard
Submit Date(s)	April 27, 2016
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Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	February 21, 2017
Established Name	Saxagliptin and Dapagliflozin Fixed Combination Drug Product (FCDP)
(Proposed) Trade Name	QTERN
Applicant	AstraZeneca
Formulation(s)	Saxagliptin 5 mg/dapagliflozin 10 mg FCDP tablet
Dosing Regimen	Saxagliptin 5 mg /dapagliflozin 10 mg tablet taken once daily in the morning
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) (b) (4) [redacted] *Limitations of Use:* Should only be used in patients who tolerate 10 mg dapagliflozin
Intended Population(s)	Patients with T2D
Recommendation on Regulatory Action	Approval (pending labeling negotiations)
Recommended Indication(s) (if applicable)	**NDA 209091:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on dapagliflozin or who are already treated with dapagliflozin and saxagliptin **NDA 022350:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus **NDA 200678:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate

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Glossary

AC	Advisory Committee
ACEI	Angiotensin Converting Enzyme Inhibitor
ADA	American Diabetes Association
AE	Adverse Event
AEOSI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area-Under-the-Curve
B-cell	Beta-Cell
BE	Bioequivalence
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CABG	Coronary Artery Bypass Grafting
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CK	Creatine Kinase
C_{max}	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Controls
CMQ	Custom MedDRA Query
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRL	Complete Response Letter
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
CT	Computerized Tomography
CV	Cardiovascular
CVOT	Cardiovascular Outcomes Trial
CYP3A4/5	Cytochrome P450 3A4/5
DBP	Diastolic Blood Pressure

DCCT	Diabetes Control and Complication Trial
DMC	Data Monitoring Committee
DMF	Drug Master File
DPP-4	Dipeptidyl Peptidase-4
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
eGFR	Estimated Glomerular Filtration Rate
EOS	End-of-Study
ETD	Early Treatment Discontinuation
FCDP	Fixed Combination Drug Product
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	Fasting Plasma Glucose
FT4	Free Thyroxine
GCP	Good Clinical Practice
GM	Geometric Mean
GRMP	Good Review Management Practice
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HDL-C	High-Density Lipoprotein Cholesterol
HLGT	High Level Group Term
HLT	High Level Term
HPF	High-Power Field
ICH	International Conference on Harmonization
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IVR	Interactive Voice Response
LDL-C	Low-Density Lipoprotein Cholesterol
LTSS	Long-term Stability Study
MDRD	Modification in Diet and Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MTT	Meal Tolerance Test
MRHD	Maximum Recommended Human Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NGSP	National Glycohemoglobin Standardization Program

NME	New Molecular entity
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCTA	Percutaneous Transluminal Coronary Angioplasty
PD	Pharmacodynamics
PI	Prescribing Information
PIND	Pre-Investigational New Drug
PK	Pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PPG	Postprandial Glucose
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
PT	Preferred Term
P-Y	Patient-Year
REMS	Risk Evaluation and Mitigation Strategy
SA	Sickle Cell Trait
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVOR	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SBP	Systolic Blood Pressure
Scr	Serum Creatinine
SEALD	Study Endpoints and Labeling Development
SGE	Special Government Employee
SGLT-2	Sodium-Glucose Cotransporter 2
SMQ	System MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System Organ Class
$T_{1/2}$	Elimination Half-Life
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TG	Triglycerides
TEAE	Treatment-Emergent Adverse Event

TIA	Transient Ischemic Attack
T_{max}	Time to Maximum Concentration
Total-C	Total Cholesterol
TSH	Thyroid-Stimulating Hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
XR	Extended-release

1 Executive Summary

1.1. Product Introduction

QTERN (saxagliptin and dapagliflozin) is a new fixed combination drug product (FCDP) submitted for marketing approval by the AstraZeneca Pharmaceuticals LP (referred to as the Applicant throughout the remainder of this review) as a New Drug Application (NDA 209091) in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act[1] and Section 314 of Title 21 CFR 314.50.[2]

The components of QTERN (i.e., saxagliptin and dapagliflozin) are approved antihyperglycemic agents with an indication as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Saxagliptin is a competitive dipeptidyl peptidase-4 (DPP-4) inhibitor that slows the inactivation of the incretin hormones, thereby increasing their concentrations in the blood and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus (T2D).[3] Dapagliflozin is a sodium glucose cotransporter 2 (SGLT-2) inhibitor that reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.[4]

Both saxagliptin and dapagliflozin are approved antihyperglycemic agents with an indication as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The proposed indication for QTERN is as an adjunct to diet and exercise to improve glycemic control in adults with T2D [redacted](b) (4) QTERN is not indicated for the treatment of type 1 diabetes mellitus (T1D) or diabetic ketoacidosis (DKA), and should only be used in patients who tolerate 10 mg dapagliflozin.

QTERN will be available as a film-coated tablet for once daily oral administration, and will contain 5 mg of saxagliptin and 10 mg of dapagliflozin.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend an approval action for this NDA, pending agreement on proposed labeling. In accordance with 21 CFR 314.126(a)(b),[5] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of this FCDP with an amended indication (i.e., T2D patients who tolerate, but have inadequate glycemic control, with dapagliflozin 10 mg/day or who are already on both therapies).

To support the proposed indication, the Applicant has provided clinical data from Trial CV181168, a 24-week (with a 28-week long-term [LT] extension), randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial designed to evaluate the efficacy and safety of stepwise (sequential) addition of saxagliptin to dapagliflozin and metformin compared with the addition of placebo to dapagliflozin and metformin in subjects with T2D who had inadequate glycemic control on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to week 24), the saxagliptin triple therapy arm resulted in a modest but statistically significant HbA1c reduction compared to the placebo dual therapy arm (-0.3%; 95% confidence interval [CI], -0.2% to -0.5%). The Applicant intends to include only this trial in Section 14 of product labeling.

Efficacy and safety data from two additional Phase 3 trials (i.e., CV181169 and MB102129) were also submitted to support the pivotal efficacy trial. Trial CV181169 was a 24-week randomized, double-blind, active-controlled, parallel-group trial that compared the addition of saxagliptin 5 mg/day plus dapagliflozin 10 mg/day (dual therapy) versus placebo plus saxagliptin 5 mg/day and versus placebo plus dapagliflozin 10 mg/day, when administered concomitantly to metformin in adults with T2D who had inadequate glycemic control on a stable dose of metformin monotherapy. The Applicant asserts that this supportive trial fulfils the requirements of 21 CFR 300.50.[6] However, only the highest dose (i.e., 10 mg) of the two approved dapagliflozin doses (i.e., 5 and 10 mg) was studied. Trial MB102129 was a 24-week (with a 28-week LT extension) that evaluated the efficacy and safety of the sequential addition of dapagliflozin 10 mg/day in T2D patients who had inadequate glycemic control on the maximum tolerated dose of saxagliptin (5 mg/day) and metformin (≥1500 mg/day).

In summary, the chemical and pharmacologic characteristics of saxagliptin and dapagliflozin are well-known, and there is extensive clinical experience with their use worldwide. Further, the established efficacy and safety profiles of these products, and the overall risk/benefit assessment of saxagliptin in combination with dapagliflozin in patients with T2D who have inadequate glycemic control with maximum doses of metformin and dapagliflozin supports approval of this Application with an amended indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2D) is a condition of chronic impaired glucose homeostasis that leads to chronic hyperglycemia and increases the risk for vascular complications (both microvascular and macrovascular). Therapies for T2D have focused on improving glycemic control as assessed by change in hemoglobin A1c (HbA1c). While there are multiple drug products approved both as individual drugs and as FCDPs, many patients are unable to achieve glucose targets. Thus, additional therapeutic options are needed to facilitate individualization of therapy.

This FCDP is a combination of saxagliptin 5 mg, a DPP-4 inhibitor, and dapagliflozin 10 mg, a SGLT-2 inhibitor. The two active pharmaceutical ingredients are combined at a fixed dosage which allows for dosing of both via a single tablet formulation. Only a single dosage strength which combines the maximum approved dose of both saxagliptin and dapagliflozin has been submitted for approval. Adjustment of the dosage of the individual components is not possible.

The contribution of both components to the claimed effect has been demonstrated at the dose studied in the pivotal and supporting Phase 3 clinical trials. The results of these trials provide evidence that the combination of maximum recommended doses of saxagliptin and dapagliflozin, added to maximum tolerated background metformin (≥1500 mg/day), is statistically superior to either of the individual components in reducing HbA1c at 24 weeks. It is notable that the labeled recommended starting dose of dapagliflozin is 5 mg once daily, which is subsequently titrated to 10 mg daily in patients tolerating the 5 mg dose should additional glycemic control be required. Whether other combinations using approved doses of saxagliptin (i.e., 2.5 mg) and dapagliflozin (i.e., 5 mg) would enhance the safety profile of the FCDP, while maintaining an added glycemic benefit over either product alone, is not known.

The safety profile of the FCDP is reflective of saxagliptin and dapagliflozin. The most common adverse reactions (reported in >5% of subjects) were respiratory tract infections (13.6%), urinary tract infections (5.7%), and dyslipidemia (5.1%), which are also common to either saxagliptin and/or dapagliflozin separately. Although antihyperglycemic FCDPs have a potential for an increased risk of hypoglycemia compared to the individual components, the incidence of hypoglycemia in the pooled safety population was relatively low (1.4%), and no subjects discontinued study medication due to hypoglycemia or experienced major hypoglycemia (defined as a symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration).

One unique finding has to do with elevations in serum creatine kinase (CK). In the pooled safety analysis, an imbalance in the number of subjects who experienced marked serum CK elevations >10x the upper limit of normal (a marker of muscle injury/necrosis) was observed in the saxagliptin plus dapagliflozin treatment arms. These marked laboratory changes were reported in five (1%) saxagliptin plus dapagliflozin plus metformin treated subjects compared to one subject (0.3%) randomized to dapagliflozin plus metformin, and no subjects randomized to saxagliptin plus metformin. Although these laboratory abnormalities were typically asymptomatic, transient (approximately two weeks in duration), and did not require discontinuation of therapy, rhabdomyolysis was reported for one of the five subjects with CK elevations with no other obvious cause identified. Pre-existing comorbidities in this subject make the assessment of causality challenging.

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

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. The Center for Disease Control (CDC) estimates that there are over 29 million patients with T2D in the United States.	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads an increased risk for morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes (UKPD) study, improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., reduced	Despite the many available treatment options, many patients continue to have difficulty with achieving the desired degree of glycemic control. Further, T2D is a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	microvascular complications). • There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class), approved to improve glycemic control in patients with T2D. Many of these medications are also approved as fixed combination drug products (FCDPs). • There are different safety concerns for each class. Metformin is often considered first-line therapy with the choice of subsequent therapies individualized by prescribers based on the patient. • While all of the approved antihyperglycemic medications have been shown to improve glycemic control, data on the ability of individual agents to improve clinical outcomes is generally limited or not available.	progressive disorder and patients typically need additional agents added as the course of the disease progresses.
Benefit	• The results from Trial CV181168 demonstrate that the addition of saxagliptin 5 mg added to dapagliflozin plus metformin results in greater HbA1c reductions compared to adding placebo to dapagliflozin plus metformin. Additionally, the totality of the data from the Phase 3 clinical program provides support that the combination of saxagliptin plus dapagliflozin results in better glycemic control than the use of the individual components at the doses evaluated in the trials. However, clinical experience with this FCDP has been limited to the 5 mg saxagliptin and 10 mg dapagliflozin dose. Whether combining the 5 mg dapagliflozin dose with the 5 mg saxagliptin dose results in better glycemic control than using the individual components is not known.	The pivotal clinical trial (i.e., CV181168) has provided sufficient evidence to support efficacy. Additionally, this trial and the supporting Phase 3 clinical trials (i.e., CV181169 and MB102129) provide support that the saxagliptin and dapagliflozin FCDP added to metformin background antihyperglycemic therapy has added benefit on glycemic control over each of the individual components at the doses used in these studies. The benefit of this product would be most relevant to the population of T2D patients with inadequate glycemic control despite maximum tolerated

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		treatment with metformin (≥1500 mg/day) and dapagliflozin (10 mg/day), as this population was evaluated in the pivotal Phase 3 clinical trial. Study of a combination containing dapagliflozin 5 mg has not yet been submitted for regulatory approval.
Risk	• The risk associated with the FCDP are consistent with would be expected by combining the safety profile of the two individual products. • The main new safety issue identified in this Application was a numeric imbalance of marked laboratory elevations of creatinine kinase (i.e., >10 times the upper laboratory limits) occurring in the saxagliptin plus dapagliflozin plus metformin treatment arms, with one case of rhabdomyolysis reported.	The clinical risks associated with use of the saxagliptin plus dapagliflozin are what would be expected with the use of the two drugs. However, a numeric imbalance in the number of cases of marked elevations in serum CK concentrations (i.e., >10x the upper laboratory reference limit) was observed in subjects randomized to the saxagliptin plus dapagliflozin treatment arms. Although these marked laboratory changes were typically asymptomatic, transient in nature, and did not require discontinuation of investigational product, a case of rhabdomyolysis was reported in a patient with other comorbidities for which other obvious causes were not identified. This potential safety signal can be addressed with appropriate labeling and continued pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No risk evaluation and mitigation strategy is recommended for this product.	The adverse reactions and safety profile of the FCDP can be adequately labeled to communicate the above safety concerns.

2 Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1D; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2D; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia).[7] According to 2016 statistics from the Center for Disease Control and Prevention (CDC), diabetes affects more than 29 million people within the United States, of which T2D accounts for 90-95% of all diagnosed cases.[8] 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.[9]

Patients with T1D may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2D can be asymptomatic. As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT),[10-16] the United Kingdom Prospective Diabetes Study (UKPDS),[17-21] and the Kumamoto Study,[22] 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 and associated safety concerns is presented in Table 34, Appendix 9.4). The 2015 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement advocates the use a patient-centered approach for the management of T2D, which includes the assessment of glycemic efficacy, hypoglycemia risk, impact on weight, adverse effects, costs, and patient preference.[23] In this report, they recommend initiating antihyperglycemic therapy for the management of T2D with metformin as monotherapy. Should a single agent alone fail to achieve/maintain the HbA1c target over three months, the next step would be to add a second agent (e.g., sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, basal insulin), with addition of a third agent should dual antihyperglycemic therapy fail to achieve the desired HbA1c target over the subsequent three-month period.[23] Similar recommendations also have been published in the *Standards of*

Medical Care in Diabetes–2017,[24] and suggested by the American College of Physicians.[25] Several studies have also reported advantages from adding a third noninsulin agent to a two-drug combination that is not yet or no longer achieving the glycemic target,[23,26,27] as well as triple therapy with both oral and injectable antihyperglycemic agents.[28-30] 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).[31] Additionally, another FCDP (i.e., GLYXAMBI),[32] containing the DPP-4 inhibitor linagliptin and the SGLT-2 inhibitor empagliflozin, was approved on January 30, 2015, primarily based on a Phase 3 trial which demonstrated improved glycemic control as second-line therapy in subjects with T2D inadequately controlled on metformin.[33,34]

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.[35-37] Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations (please refer to Table 34). For example, thiazolidinediones may be associated with edema and weight gain and are not recommended for use in many patients with congestive heart failure, while metformin and SGLT-2 inhibitors are contraindicated in patients with severe renal dysfunction. Additionally, SGLT-2 inhibitors are associated with genital mycotic infections and urinary tract infections (especially in females), as well as volume depletion/orthostatic hypotension. 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 be associated with intolerable gastrointestinal side effects, while pancreatitis and allergic reactions have been reported with DPP-4 inhibitors and GLP-1 receptor agonists. Additionally, metabolic acidosis (e.g., lactic acidosis, ketoacidosis) has occurred with the use of metformin and SGLT-2 inhibitors. Antihyperglycemic products administered by inhalation or injection require training, and patients may be reluctant to self-inject (e.g., aversion to needles).

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.[38] Nonadherence to oral antihyperglycemic agents has been reported in 7%-64% of patients with T2D,[39,40] and has been associated with poor glycemic control,[41,42] diabetes-related hospitalizations[43,44] and increased mortality.[43] For patients requiring combination antihyperglycemic therapy, adherence may improve with a reduction in pill burden through the use of FCDPs.[45-47]

For these reasons, and because T2D is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there remains a need for new antihyperglycemic treatment options and the use of combination therapy. In this NDA, the Applicant has provided results from Study CV181168, a Phase 3 clinical trial intended to determine whether the addition of saxagliptin 5 mg to dapagliflozin 10 mg plus metformin therapy would improve glycemic response compared to continuing dapagliflozin plus metformin. Additional supportive safety and efficacy data are also included.

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

Pharmacologic Class	Antihyperglycemic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Alogliptin plus metformin; Alogliptin plus pioglitazone; Linagliptin; Linagliptin plus empagliflozin; Linagliptin plus metformin; Linagliptin plus metformin extended-release; Saxagliptin; Saxagliptin plus metformin extended-release; Sitagliptin plus metformin; Sitagliptin plus metformin extended-release
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Liraglutide plus insulin degludec; Lixisenatide; Lixisenatide plus insulin glargine
INSULINS AND INSULIN ANALOGUES	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin degludec plus liraglutide; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin aspart; Insulin regular (human); Pre-mixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide; Repaglinide plus metformin
SGLT-2 INHIBITORS	Canagliflozin; Canagliflozin plus metformin; Dapafliflozin; Dapagliflozin plus metformin; Empagliflozin; Empagliflozin plus linagliptin; Empagliflozin plus metformin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizided extended-release; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Pioglitazone plus alogliptin; pioglitazone plus glimepiride; Pioglitazone plus Metformin; Pioglitazone plus metformin extended-release; Rosiglitazone; Rosiglitazone plus glimepiride; Rosiglitazone plus metformin

Source: Drugs@FDA: FDA Approved Drug Products, available at: http://www.accessdata.fda.gov/scripts/cder/daf/.[48]
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter 2.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

QTERN is a fixed combination drug product (FCDP) containing saxagliptin 5 mg and dapagliflozin 10 mg as a film-coated tablet. Although this product is not marketed within or outside of the United States (U.S.), the individual active moieties at the proposed doses are approved as individual drug products and in combination with metformin.

Saxagliptin (ONGLYZA) / Saxagliptin/Metformin Extended-Release (KOMBIGLYZE XR)

Saxagliptin (ONGLYZA) belongs to the class of antihyperglycemic agents known as dipeptidyl peptidase-4 (DPP-4) inhibitors, and is administered orally once daily. This product was approved by the Food and Drug Administration (FDA) in 2009 as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[3] Other approved DPP-4 inhibitors include alogliptin (approved in 2013), linagliptin (approved in 2011) and sitagliptin (approved in 2006).[48] In 2010, KOMBIGLYZE XR, a FCDP containing saxagliptin and extended-release metformin, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both saxagliptin and metformin is appropriate.[49]

In patients with T2D, DPP-4 enzyme activity is inhibited for a 24-hour period following oral administration of saxagliptin. Inhibition of DPP-4 slows inactivation of incretin hormones (e.g., glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]), resulting in a two- to three-fold increase in incretin blood concentrations. Subsequently, glucagon concentrations decrease and glucose-dependent insulin secretion from pancreatic beta cells increases. These pharmacodynamics changes are associated with lower HbA1c and fasting glucose concentrations, and reduced glucose excursion following an oral glucose load or a meal.[3,50]

Metformin improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 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.[49] The combination of saxagliptin[51-58] with metformin is associated with improved glycemic control.

ONGLYZA is formulated as film-coated tablets containing either 2.5 mg or 5 mg of saxagliptin.[3] KOMBIGLYZE XR is available as film-coated tablets containing either 5 mg of saxagliptin with 500 mg metformin hydrochloride (HCl) extended-release (5 mg/500 mg), 5 mg saxagliptin with 1000 mg metformin HCl extended-release (5 mg/1000 mg), or 2.5 mg of saxagliptin with 1000 mg metformin HCl extended release (2.5 mg/1000 mg).[49]

Dapagliflozin (FARXIGA) / Dapagliflozin/Metformin Extended-Release (XIGDUO XR)

Dapagliflozin (FARXIGA) belongs to the class of antihyperglycemic agents known as SGLT-2 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.[4] Other approved DPP-4 inhibitors include canagliflozin (approved in 2013), and empagliflozin (approved in 2014).[48] In 2014, XIGDUO XR, a FCDP containing dapagliflozin and extended-release metformin, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both dapagliflozin and metformin is appropriate.[59]

Sodium-glucose cotransporter 2 (SGLT-2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT-2. By inhibiting SGLT-2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. In patients with T2D, these pharmacodynamics changes are associated with excretion of approximately 70 grams of glucose in the urine per day, increases in urinary volume, lower HbA1c and fasting glucose concentrations, and reductions in body weight and systolic blood pressure (SBP).[4,60]

As discussed above, the use of metformin in patients with T2D improves glucose tolerance, typically without worsening hyperinsulinemia[49] or the risk of hypoglycemia. Similarly, the combination of dapagliflozin[61-70] and metformin is associated with improved glycemic control.

FARXIGA is formulated as film-coated tablets containing either 5 mg or 10 mg of dapagliflozin.[4] XIGDUO XR is available as film-coated tablets containing either 5 mg of dapagliflozin with 500 mg metformin hydrochloride (HCl) extended-release (5 mg/500 mg), 5 mg dapagliflozin with 1000 mg metformin HCl extended-release (5 mg/1000 mg), 10 mg of dapagliflozin with 500 mg metformin hydrochloride (HCl) extended-release (10 mg/500 mg), or 10 mg of dapagliflozin with 1000 mg metformin HCl extended release (10 mg/1000 mg).[59]

3.2. Summary of Presubmission/Submission Regulatory Activity

The relevant regulatory history for the proposed FCDP is presented in Table 2 below. Both of the active components of the proposed FCDP, saxagliptin (ONGLYZA; approved on July 31, 2009)

and dapagliflozin (FARXIGA; approved January 8, 2014), received previous marketing approval in the U.S. for the treatment of T2D in adult patients. Additionally, portions of this NDA had been submitted to NDA (b) (4) A complete response letter (CRL) was issued on October 15, 2015 for NDA (b) (4) for the following reasons: (b) (4) On December 17, 2015, a Type A meeting was held between the Agency and AstraZeneca to discuss possible paths forward for marketing approval of this FCDP. In the meeting responses, the Agency stated the following:

> *"Use of the combination may be useful in patients failing to achieve adequate control on a maximally effective dose of dapagliflozin* (b) (4) *If you believe study CV181168 provides sufficient efficacy data to inform labeling for this intended use (i.e., patients inadequately controlled on 10 mg of dapagliflozin) then you could submit these data* (b) (4) *"*

> *"The submission* (b) (4) *would not address the deficiencies outlined in the CR letter, therefore it should be submitted as a new NDA.* (b) (4) *In the same NDA, the applicant may incorporate clinical data by reference from NDA* (b) (4) *"*

In response to this meeting, the Applicant has subsequently submitted NDA 209091 for a saxagliptin 5 mg/dapagliflozin 10 mg FCDP. To support efficacy and safety, a new pivotal trial (i.e., CV181168) was submitted to the NDA, as well as updated safety data from the completed Phase 3 clinical trials (i.e., CV181169, and MB102129), including analyses of specific safety concerns (i.e., CK, musculoskeletal, and renal).

Table 2: Summary of Presubmission/Submission Regulatory History for NDA 209091

Date	Summary of Relevant Agency Interactions
July 31, 2009	NDA 22350 – FDA approves ONGLYZA (saxagliptin) once-daily treatment for adults with T2D.
November 5, 2010	NDA 200678 – FDA approves KOMBIGLYZE XR (saxagliptin/metformin extended-release) once-daily treatment for adults with T2D.
November 28, 2011	IND 63634 (saxagliptin) – The Sponsor submitted a request for FDA review and comment on the protocol synopsis/proposed study design for Study CV181169.
April 10, 2012	IND 63634 – Advice/Information Request Letter provided by FDA in response to the Sponsor's request for protocol review of Study CV181169. In the written responses, it was stated that "approvability of your proposed (b) (4) NDA for the saxagliptin/dapagliflozin fixed-dose combination tablet will be contingent upon the FDA's approval of dapagliflozin."
July 3, 2012	IND 63634 – The Sponsor submitted a response to the FDA's letter of April 4, 2012, along with the final protocol for Study CV181169.
June 17, 2013	PIND 118840 – Pre-IND meeting request was received and FDA agreed to provide written responses to the Sponsor's questions.
June 25, 2013	PIND 118840 – Submission of Change in Sponsor Contact.
July 8, 2013	PIND 118840 – Submission of Pre-IND Briefing Document Question 1 – Design of long-term stability study (LTSS) Question 2 – proposal for tests included and excluded in the LTSS study Question 3 – proposed dissolution test method for use in the LTSS study Question 4 – biowaiver proposal for BE studies.
July 18, 2013	PIND 118840 – Submission of Amendment to the PIND Briefing Document – Dissolution Test Method and Sponsor questions.
August 5, 2013	PIND 118840 FDA's written response to Questions #1, #2, and #4 in the July 8, 2013 Briefing Document and additional FDA comments.
August 19, 2013	PIND 118840 – Submission of Sponsor's clarification of FDA August 5, 2013 response on long-term stability testing + dissolution testing response (justification of dissolution method for saxagliptin/dapagliflozin film coated combination tablets, (b) (4) 5/10mg).
September 16, 2013	PIND 118,840 – FDA's Response to Sponsor's clarifying follow up questions submitted August 19, 2013 Question 1 (stability requirements) and Question 3 (dissolution testing).
November 22, 2013	PIND 118840 – FDA Advice/Information Request Letter - indicated which stability data should be included in the initial NDA submission.
January 8, 2014	NDA 202293 – FDA approves FARXIGA (dapagliflozin) tablets for the treatment of adult patients with T2D.

Date	Summary of Relevant Agency Interactions
January 22, 2014	IND 118840 – Submission of initial IND application for the saxagliptin/dapagliflozin FCDP (including submission of protocol for BE Study CV181341).
March 6, 2014	IND 118840 – FDA Non-hold comments on initial IND 118840 application of January 22, 2014.
March 7, 2014	IND 118840 – Submission of transfer of ownership and regulatory responsibility for IND 118840 from BMS to AstraZeneca.
March 18, 2014	IND 118840 – Submission of AstraZeneca response to March 6, 2014 FDA non-hold comments on IND 118840 application.
April 16, 2014	IND 118840 – Saxagliptin/Dapagliflozin FCDP Tablet; submission of iPSP.
April 25, 2014	IND 118840 – Submission of Saxagliptin/Dapagliflozin FCDP Tablet: Request for Type B Pre-NDA meeting.
April 30, 2014	IND 118840 – FDA letter granting the Pre-NDA meeting on June 23, 2014.
May 9, 2014	IND 118840 – Submission of Request for separate CMC-focused Type B Pre-NDA meeting to discuss format and content of the CMC sections of the saxagliptin/dapagliflozin FCDP NDA.
May 23, 2014	IND 118840 – Submission of pre-NDA briefing document (dated May 19, 2014 – BMS) for the June 23, 2014 pre-NDA meeting.
May 28, 2014	IND 118840 – FDA letter granting a separate CMC-focused Pre-NDA meeting on July 2, 2014
June 6, 2014	IND 118840 – Submission of CMC Pre-NDA meeting background document for the July 2, 2014 meeting.
June 16, 2014	IND 118840 – FDA issuance of pre-NDA Meeting Preliminary Comments.
June 24, 2014	IND 118840 – FDA's Preliminary Meeting Comments for CMC pre-NDA meeting between FDA and AstraZeneca. AstraZeneca determined that the FDA's letter sufficiently addressed the Sponsor questions, and the meeting scheduled for July 2, 2014 was cancelled.
June 27, 2014	IND 118840 – AstraZeneca provided information on Study D1690C00010 to address the FDA's issue regarding duration of exposure for the safety review of the FCDP.
June 30, 2014	IND 118840 – Submission of Regulatory contact change from BMS to AstraZeneca.
July 14, 2014	IND 118,840 FDA Correspondence recommending AstraZeneca submit a revised iPSP requesting a waiver of pediatric studies.

Date	Summary of Relevant Agency Interactions
July 23, 2014	IND 118840 – FDA official minutes of the June 23, 2014 Saxagliptin/Dapagliflozin pre-NDA meeting between FDA and AstraZeneca. The FDA determined that clinical studies were required (b) (4)
July 30, 2014	IND 118840 – Submission of Request for Proprietary Name Review.
August 5, 2014	IND 118840 – Sponsor submission in follow up to Pre-NDA meeting on June 23, 2014, addressing one of the issues requiring further discussion; support for the efficacy of all possible dose combinations.
August 14, 2014	IND 118840 – Sponsor submission in follow-up to FDA Pre-NDA meeting on July 23, 2014, addressing one of the Issues Requiring Further Discussion; the duration of exposure for the safety review.
August 19, 2014	IND 118840 – FDA granting of written response to an AstraZeneca meeting request to discuss safety and efficacy issues relating to the IND.
September 12, 2014	IND 118840 – Submission of response to FDA request for information; consolidated List of Sponsor Questions for Request for FDA Feedback
October 7, 2014	IND 118840 – Submission of revised initial Pediatric Study Plan following FDA advice (July 14, 2014) recommending AstraZeneca request a waiver of pediatric studies for all ages.
October 16, 2014	IND 118840 – FDA response to AstraZeneca's correspondence, dated July 30, 2014, requesting review of the proposed proprietary name QTERN for saxagliptin/dapagliflozin FCDP; FDA completed its review and proprietary name is conditionally acceptable.
October 23, 2014	IND 118840 – FDA Meeting Request –Written Responses. FDA response to Sponsor's questions in August 14, 2014, and September 12, 2014, background package. The Sponsor made the decision of submitting the NDA for only the saxagliptin 5mg/dapagliflozin 10mg dosage strength of the FCDP, and this was determined to be acceptable by FDA.
October 29, 2014	NDA 205649 – FDA approves XIGDUO XR (dapagliflozin/metformin HCl extended-release) once-daily treatment for adults with T2D.
November 14, 2014	IND 118840 – FDA Pediatric Review Committee confirms agreement to AstraZeneca's revised iPSP, including the waiver requested, with request for revisions to the final iPSP.
(b) (4)	

Date	Summary of Relevant Agency Interactions
[redacted] (b) (4)	
December 19, 2015	NDA (b) (4) – Request to review the tradename QTERN.
April 15, 2015	NDA (b) (4) – Submission of 4-Month Safety Update.
October 15, 2015	NDA (b) (4) – FDA issues Complete Response Letter (CRL), (b) (4) To address these deficiencies, the Applicant would need to submit additional (b) (4) clinical trial data.
November 17, 2015	NDA (b) (4) – Type A meeting request and briefing package to discuss Complete Response (CR).
January 14, 2016	NDA (b) (4) – FDA official minutes from Type A meeting held on December 17, 2015. AstraZeneca asked whether a 5 mg saxagliptin/10 mg dapagliflozin FCDP can be approved (b) (4) In the written responses, the FDA stated that if the Applicant believes Trial CV181168 provides sufficient efficacy data to inform labeling for the intended use (i.e., patients inadequately controlled on 10 mg of dapagliflozin), then they could submit these data (b) (4)
April 27, 2016	Submission of NDA 209091, which includes the completed Trials CV181168 (pivotal), CV11869 (supportive) and MB102129 (supportive) to support efficacy and safety of the FCDP.

Source: Adapted from the Applicant's Summary of Relevant FDA Interactions, labelled as Table 1, pages 3-8 of 8, available at: \\cdsesub1\evsprod\nda209091\0000\m1\us\summary-of-fda-interactions.pdf.
Abbreviations: BE, bioequivalence; BMS, Bristol-Myers Squibb; CMC, Chemistry, Manufacturing, and Controls; CR, Complete Response; CRL, Complete Response Letter; FCDP, fixed combination drug product; FDA, Food and Drug Administration; IND, Investigational New Drug; iPSP, initial pediatric study plan; LTSS, long-term stability study; NDA, New Drug Application; PIND, pre-Investigational New Drug; T2D, type 2 diabetes mellitus; and XR, extended-release.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable – QTERN is currently not marketed in any country.

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

4.1. Office of Scientific Investigations (OSI)

In the original NDA application for QTERN (i.e., N (b) (4)), Dr. Cynthia Kleppinger, from the Office of Scientific Investigations (OSI), was asked to inspect five domestic clinical sites and the contract research organization (i.e., (b) (4)) for the supporting Phase 3 clinical trial, CV181169. Regulatory violations were noted for four sites inspected, and a Form FDA-483 was issued for each of the four respective clinical investigators. Dr. Kleppinger felt that the violations would not significantly impact primary safety and efficacy analyses, and that the "reliability of data from these sites was acceptable for use in support of the indication." For more detailed information, please refer to Dr. Kleppinger's review (dated August 19, 2015, filed under NDA (b) (4)).

For the current NDA submission (NDA 209091), OSI was not re-consulted with a request to conduct additional audits/site inspections.

4.2. Product Quality

Dr. Suong Tran is the Product Quality Application Technical Lead for this Application, and the drug product review was completed by John Amartey, the manufacturing process and microbiology review by Daniel Peng, the manufacturing facilities review by Vipul Dholakia, and the biopharmaceutics review by Peng Duan.

For the original NDA submission (i.e., NDA (b) (4)), the same saxagliptin/dapagliflozin FCDP was evaluated. This product consists of a film-coated tablet (b) (4) The reviewers from the Office of Product Quality (OPQ) recommended Approval for this Application, and there were no quality issues pending at that time.

Much of the CMC information from NDA (b) (4) is now cross-referenced to NDA 209091. On May 24, 2016, the Applicant submitted a Quality Information Amendment summarizing the differences between the CMC information (including facilities) previously submitted to NDA (b) (4) and the new/updated CMC information submitted to NDA 209091 (Please refer to: \\cdsesub1\evsprod\nda209091\0002\m1\us\qtern-nda-comparison-209-091-vs-207-982.pdf). The OPQ review consists of the drug product review of this new and updated information, with

a cross-reference to the OPQ review of NDA (b) (4). The Drug Master Files (DMFs) for this NDA are considered adequate by OPQ, and there are no novel excipients. Additionally, stability data supports a (b) (4)-month shelf-life for this FCDP, and the Applicant commits to conducting long-term stability studies post-approval.

The Office of Pharmaceutical Quality recommends approval of the Application. Please refer to the respective reviews for more detailed information.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There have been no additional nonclinical studies conducted in the Qtern development program since the original NDA submission (NDA (b) (4)). In this Application, safety findings to support the combination of saxagliptin plus dapagliflozin came from a three-month rat toxicology study and an in vitro human liver microsomal metabolism study. In these studies, co-administration of the two drugs was evaluated. Dr. Fred Alavi was the primary Pharmacology/Toxicology reviewer for the original NDA submission and these nonclinical studies. In his review, he noted that the combination of saxagliptin + dapagliflozin was consistent with the known toxicology profile of each component (i.e., a synergistic effect on the individual toxicity profile of each component was not observed). With the exception of increased proteinuria in male rats at doses 6x the maximum recommended human dose (MRHD) of the FCDP, no new/clinically relevant toxicity findings were observed in rats. Additionally, neither saxagliptin nor dapagliflozin are inhibitors or inducers of CYP enzymes or substrates to cellular uptake transporters, and no PK interactions between dapagliflozin and saxagliptin in rats were noted. Based on these data, Dr. Alavi concluded that the nonclinical data submitted to NDA (b) (4) support approval of the Application.

Carcinogenesis, mutagenesis, and reproductive development/fertility were not assessed for the current NDA submission, nor was any information provided related to lactation (e.g., presence in human milk, changes in milk production, and/or effects in breastfed infants) for this combination. The Applicant relies on the previous findings from the individual saxagliptin and dapagliflozin development programs.

The Pharmacology/Toxicology reviewer for this Application, Dr. Jeffrey Quinn, felt that the existing nonclinical data support approval of the current submission (i.e., NDA 209091), and that no additional nonclinical studies would be recommended. He noted that the pregnancy section of proposed product labeling would need to be updated in accordance with the

Pregnancy and Lactation Labeling Rule (PLLR). Please refer to his completed review (dated January 18, 2017) for detailed discussion of the nonclinical findings.

4.5. Clinical Pharmacology/Biopharmaceutics

Two pharmacokinetic/biopharmaceutics studies were submitted to support the NDA. The first was a PK study (CV181191) intended to evaluate a potential drug-drug interaction between saxagliptin and dapagliflozin. This Phase 1 study was a randomized, open-label, single-dose, 3-treatment, 3-period crossover study to determine the PKs of saxagliptin 5 mg and dapagliflozin 10 mg individually and when coadministered to fasted healthy subjects. Saxagliptin had no effect on the PKs of dapagliflozin. The geometric mean (GM) ratios (90% confidence intervals [CIs]) for dapagliflozin Cmax (ng/mL), AUC_{0-T} (ng•h/mL), and AUC_{INF} (ng•h/mL) were 0.943 (0.867, 1.026), 0.990 (0.966, 1.014), and 0.984 (0.961, 1.008), respectively. Similarly, dapagliflozin did not affect these same PK parameters for saxagliptin (i.e., 0.927 [0.883, 0.972]; 0.991 [0.960, 1.022]; and 0.991 [0.961, 1.022], respectively), 5-hydroxy saxagliptin (i.e., 1.055 [1.004, 1.109]; 1.085 [1.058, 1.1113]; and 1.085 [1.058, 1.113], respectively), or saxagliptin total activity moiety (i.e., 0.994 [0.960, 1.030]; 1.046 [1.029, 1.064]; and 1.046 [1.029, 1.064], respectively). All GM ratios were close to 1, with 90% CIs contained within the required 0.80 and 1.25 range. These results provide support that there isn't a drug-drug interaction between saxagliptin 5 mg and dapagliflozin 10 mg.

The second study (i.e., CV181341) was designed to demonstrate the bioequivalence of the FCDP (i.e., saxagliptin 5 mg/dapagliflozin 10 mg) with the co-administration of the individual components, and also included an assessment of food effect. Under fasted conditions, the FCDP vs. individual components resulted in GM ratios (90% CIs) for dapagliflozin Cmax (ng/mL), AUC_{0-T} (ng•h/mL), and AUC_{INF} (ng•h/mL) of 0.946 (0.878, 1.019), 1.036 (1.010, 1.062), and 1.035 (1.008, 1.063), respectively. These results support bioequivalence. When comparing the PKs of the FCDP under fed vs. fasted condition, these same PK parameters were 0.648 (0.565, 0.743), 0.931 (0.908, 0.955), and 0.943 (0.919, 0.968), respectively. While the total exposure measures, reflected by AUC, supported bioequivalence, the plasma dapagliflozin GM ratios of Cmax <1.00, suggests a reduction in the peak systemic exposure due to a possible food effect. Under fasted conditions, the FCDP vs. individual components resulted in GM ratios (90% CIs) for saxagliptin Cmax (ng/mL), AUC_{0-T} (ng•h/mL), and AUC_{INF} (ng•h/mL) of 1.059 (0.993, 1.129), 1.007 (0.973, 1.042), and 1.003 (0.969, 1.038), respectively. When comparing the PKs of the FCDP under fed vs. fasted condition, these same saxagliptin PK parameters were 0.925 (0.837, 1.022), 1.155 (1.117, 1.194), and 1.155 (1.118, 1.194), respectively. These PK analyses support bioequivalence of saxagliptin, without an obvious food effect.

The Clinical Pharmacology reviewer for this Application was Dr. S.W. Johnny Lau. Since this Application contains the same clinical pharmacology information previously reviewed for NDA [redacted], he has submitted memorandum (dated January 30, 2017) as a cross-reference to his Clinical Pharmacology review of NDA 209091 (August 24, 2015). Additionally, he is also recommending that labeling for the current Application be revised to recommend that QTERN be discontinued in patients with eGFR values persistently between 45-60 mL/min/1.73 m^2 (i.e., in lieu of the Applicant's proposed language that specifies this range as between [redacted] mL/min/1.73 m^2). The recommended dose of saxagliptin for patients with an eGFR <45 mL/min/ 1.73 m^2 is 2.5 mg. [redacted] It will be recommended that QTERN be contraindicated in patients with an eGFR <45 mL/min/1.73 m^2 for this same reason. Please refer to Dr. Lau's original review and memorandum for detailed discussion of the clinical pharmacology findings.

4.5.1. **Mechanism of Action**

QTERN is a FCDP composed of saxagliptin and dapagliflozin. Saxagliptin is a competitive DPP-4 inhibitor that slows inactivation of the incretin hormones which play a role in glucose-dependent insulin secretion and in reducing glucagon secretion. The net result of the presence of incretin hormones is improved glycemic control.[3] Dapagliflozin is an SGLT-2 inhibitor which prevents renal glucose reabsorption in the proximal renal tubules, thus increasing renal glucose excretion and improving glycemic control. The amount of glucose removed is dependent on the blood glucose concentration and the glomerular filtration rate.[4]

4.5.2. **Pharmacodynamics**

Saxagliptin: Oral administration of saxagliptin in patients with T2D results in inhibition of DPP-4 activity for approximately 24 hours. Following an oral glucose load or meal, there is a two- to three-fold increase in circulating levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations, and increased glucose-dependent insulin secretion, which are associated with a rise in insulin concentrations, a decrease in glucagon concentrations, lower fasting glucose concentrations, and reduced glucose excursion.[3]

Dapagliflozin: Increases in the amount of glucose excreted in the urine are observed in both healthy subjects and T2D patients following oral administration of dapagliflozin. Dapagliflozin doses of 5 and 10 mg per day in patients with T2D results in excretion of approximately 70 grams/day of glucose in the urine. This urinary glucose excretion is associated with increases in urinary volume.[4]

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

4.5.3. **Pharmacokinetics**

QTERN: Bioequivalence (BE) between QTERN (saxagliptin 5 mg/dapagliflozin 10 mg tablet) and the individual saxagliptin 5 mg and dapagliflozin 10 mg tablets was observed following single dose administration in a fasted state in healthy volunteers (please refer to Study CV181341 above). Compared with the PKs of QTERN administered in a fasted state, administration with a high-fat meal resulted in a decrease in the dapagliflozin C_{max} by >40%, and prolonged the time to maximum concentration (T_{max}) by approximately two hours. However, the AUC was not altered as compared with the fasted state. Similar food effects were observed with dapagliflozin, which were not considered to be clinically meaningful.[4] No food effect was observed for saxagliptin.

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

Dapagliflozin: Following oral administration of dapagliflozin in a fasted state, the C_{max} is typically achieved within two hours. Both C_{max} and AUC values increase proportionally with an increase in dose within the therapeutic range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is approximately 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs the T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food. Dapagliflozin is approximately 91% protein bound, and protein binding is not altered with renal or hepatic impairment. The metabolism of dapagliflozin is primarily mediated

by uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9), with minor metabolic clearance through CYP-mediated metabolism. Dapagliflozin is extensively metabolized, primarily to dapagliflozin 3-O-glucuronide, an inactive metabolite, accounting for approximately 61% of an administered dose. Dapagliflozin and related metabolites are primarily eliminated in the urine (75%, with 2% as parent drug) and feces (21%, with 15% as parent drug). The mean plasma terminal $t_{1/2}$ for dapagliflozin is approximately 12.9 hours.[4]

4.6. Devices and Companion Diagnostic Issues

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

4.7. Consumer Study Reviews

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

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

To support the NDA, the Applicant has submitted data from six clinical trials (Table 3). Trial CV181168 is the pivotal Phase 3 efficacy trial intended to support the proposed indication for this FCDP (saxagliptin 5 mg/dapagliflozin 10 mg) as an adjunct to diet and exercise to improve glycemic control in adults with T2D (b) (4) Because one of the proposed limitations of use is that QTERN should only be used in patients who tolerate dapagliflozin 10 mg/day, the Applicant intends to only include this trial in labeling. However, two other Phase 3 trials (i.e., CV181169 and MB102129) were submitted to provide supporting efficacy and safety data, and three Phase 1 trials (i.e., CV181191, CV181341 (b) (4)) were submitted to demonstrate bioequivalence of the FCDP. Study CV181191 was conducted to demonstrate a lack of drug-drug interactions between saxagliptin and dapagliflozin. Study CV181341 was the pivotal BE study. Study (b) (4) was a BE study (b) (4) and was included in this NDA to provide data to complement the pivotal BE trial (i.e., CV181341).

Table 3: Listing of Clinical Trials Relevant to this NDA

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Randomized/ Completed	Study Population	No. of Centers and Countries
Pivotal Efficacy and Safety Trial							
CV181168	Phase 3, randomized, double-blind, placebo-controlled, parallel group efficacy and safety trial – Sequential add-on to Met (inadequate control on Dapa+Met)	• Saxa 5 mg • OL Dapa 10 mg • Placebo • OL Met IR (≥1500 mg) • PO QD	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • 2-h PPG • FPG • % Subjects HbA1c <7%	ST: 24 wks ST+LT: 52 wks	ST: 315/298 ST+LT: 297/280	• ≥18 years old • T2D • HbA1c ≥8 to ≤11.5% • Met (≥1500 mg x ≥8wks)	79 Sites 9 Countries
Supporting Efficacy and Safety Trials							
CV181169	Phase 3, randomized, double-blind, active-controlled, parallel group efficacy and safety trial – Add-on to Met (inadequate control on Met)	• Saxa 5 mg • Dapa 10 mg • Placebo • OL Met XR (1500-2000 mg) • PO QD	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • 2-h PPG • FPG • % Subjects HbA1c <7% • BW	24 wks	534/490	• ≥18 years old • T2D • HbA1c ≥8 to ≤11.5% • Met • (≥1500 mg x ≥8 wks)	145 Sites 8 Countries
MB102129	Phase 3, randomized, double-blind, placebo-controlled, parallel group efficacy and safety trial – Sequential add-on to Met (inadequate control on Saxa+Met)	• Dapa 10 mg • OL Saxa 5 mg • Placebo • OL Met IR (≥1500 mg) • PO QD	Change from BL to Wk 24: *Primary* • HbA1c *Secondary* • 2-h PPG • FPG • % Subjects HbA1c <7% • BW	ST: 24 wks ST+LT: 52 wks	ST: 320/298 ST+LT: 294/281	• ≥18 years old • T2D ***Stratum A:*** • HbA1c ≥8 to ≤11.5% at screening ***Stratum B*** • HbA1c ≥7.5 to ≤10.5% at screening	64 Sites 8 Countries

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Randomized/ Completed	Study Population	No. of Centers and Countries
						Stratum C • HbA1c ≥7 to ≤10.5% prior randomization; Met (≥1500 mg x ≥8 wks	
Pharmacokinetic Study							
CV181191	Phase 1, OL, randomized, 3-treatment, 3-period, crossover DDI study	• Saxa 5 mg • Dapa 10 mg • Saxa 5 mg + Dapa 10 mg • PO	***Primary*** • Saxa C_{max} and AUC_{INF} • Dapa C_{max} and AUC_{INF} ***Secondary*** • PK parameters for dapagliflozin, saxagliptin, 5-OH saxagliptin, total active saxagliptin moiety	Single dose	42/41	Healthy subjects	1 Site 1 Country
Biopharmaceutics Studies							
CV181341	Phase 1, OL, randomized, 3-treatment, 3-period crossover BE study	• Saxa 2.5 mg + Dapa 5 mg • Saxa 5 mg + Dapa 10 mg • PO	***Primary*** • Saxa C_{max}, AUC_{0-T} and AUC_{INF} • Dapa C_{max}, AUC_{0-T} and AUC_{INF} ***Secondary*** • PK parameters for dapagliflozin, saxagliptin, 5-OH saxagliptin	Single dose	72/72	Fed and fasted healthy subjects	1 Site 1 Country

Trial Identifier	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Randomized/ Completed	Study Population	No. of Centers and Countries
(b) (4)							

Source: Adapted from the Applicants Tabular Listing of All Clinical Studies, available at: \\cdsesub1\evsprod\nda209091\0000\m5\52-tab-list\tabular-listing.pdf.
Abbreviations: 5-OH, 5-hydroxy; AUC, area-under-the-curve; BE, bioequivalence; BW, body weight; C_{max}, maximum plasma concentration; Dapa, dapagliflozin; DDI, drug-drug interaction; FCDP, fixed combination drug product; FPG, fasting plasma glucose; H, hour; HbA1c, hemoglobin A1c (glycosylated hemoglobin); IR, immediate-release; LT, long-term treatment period; Met, metformin; OL, open-label; PK, pharmacokinetic; PPG, postprandial glucose; Saxa, saxagliptin; ST, short-term treatment period; T2D, type 2 diabetes mellitus; wks, weeks; and XR, extended-release.

5.2. **Review Strategy**

This review will focus primarily on the efficacy findings from Trial CV181168 and the integrated safety findings from Trials CV181168, CV181169, and MB102129. For discussion of the CMC information, nonclinical findings, and clinical pharmacology information please refer to the brief discussion above, and the respective primary reviews.

Trial CV181168 is the Applicant's pivotal Phase 3 trial, and it is the only efficacy trial to be included in Section 14 (CLINICAL STUDIES) of product labeling. In this trial, efficacy and safety was evaluated based on the sequential (stepwise) addition of saxagliptin 5 mg/day or placebo in adult patients with T2D who have inadequate glycemic control (i.e., HbA1c ≥7.0% to ≤10.5%) on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). The trial consisted of a 24-week, randomized, double-blind, placebo-controlled, short-term (ST) treatment period, followed by a 28-week long-term (LT) site- and subject-blind treatment period (i.e., 52-week total treatment duration).

Trial CV181169 is intended to provide additional efficacy and safety data which the Applicant claims will provide support that co-administration of saxagliptin and dapagliflozin fulfils the combination rule for an FCDP product (21 CFR300.50).[2] This 24-week, randomized, double-blind, active-controlled, parallel-group trial compared the efficacy and safety of concomitant (dual) addition of saxagliptin 5 mg and dapagliflozin 10 mg daily to the individual components (i.e., vs. saxagliptin 5 mg/day and vs. dapagliflozin 10 mg/day) in patients with T2D who had inadequate glycemic control (i.e., HbA1c ≥8.0% to ≤12.0%) on metformin therapy (≥1500 mg/day).

Trial MB102129 provides additional supporting safety data for this NDA. This 24-week, randomized, double-blind, placebo-controlled, parallel-group trial that included a 28-week LT site- and subject-blind treatment phase (52-week total duration) evaluated the efficacy and safety of the sequential (stepwise) addition of dapagliflozin 10 mg/day in patients with T2D who had inadequate glycemic control (i.e., HbA1c ≥7.0% to ≤10.5%) on maximum tolerated doses of saxagliptin (i.e., 5 mg/day) and metformin (≥1500 mg/day).

For more detailed discussion of efficacy findings from the two supporting Phase 3 trials (i.e., CV181169 and MB102129), please refer to the Statistical Review for the current submission (i.e., NDA 209091) by Dr. Anna Kettermann (dated January 5, 2017).

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial CV181168

6.1.1. Study Design

Overview and Objective

Title of Trial:

CV181168 – A Multicenter, Randomized, Double-Blind Placebo- Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin Added to Dapagliflozin in Combination with Metformin Compared to Therapy with Placebo Added to Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who have Inadequate Glycemic Control on Metformin and Dapagliflozin Trial Design.

Dates of Trial Conduct:

- **Trial Initiation Date:** June 29, 2012
- **Trial Completion Dates:** August 27, 2014 (database lock) for ST; January 12, 2015 for ST+LT
- **Report Dates:** November 25, 2014 (ST); May 18, 2015 (ST+LT)

Primary Objective:

To compare the mean HbA1c change from baseline to Week 24 with saxagliptin added to dapagliflozin+metformin vs. placebo added to dapagliflozin+metformin.

Secondary Objectives:

To compare between treatment arms the changes from baseline to Week 24 for the following:

- 2-hour postprandial glucose (PPG) following a liquid meal tolerance test (MTT)
- Fasting plasma glucose (FPG)
- Proportion of subjects with an HbA1c <7%

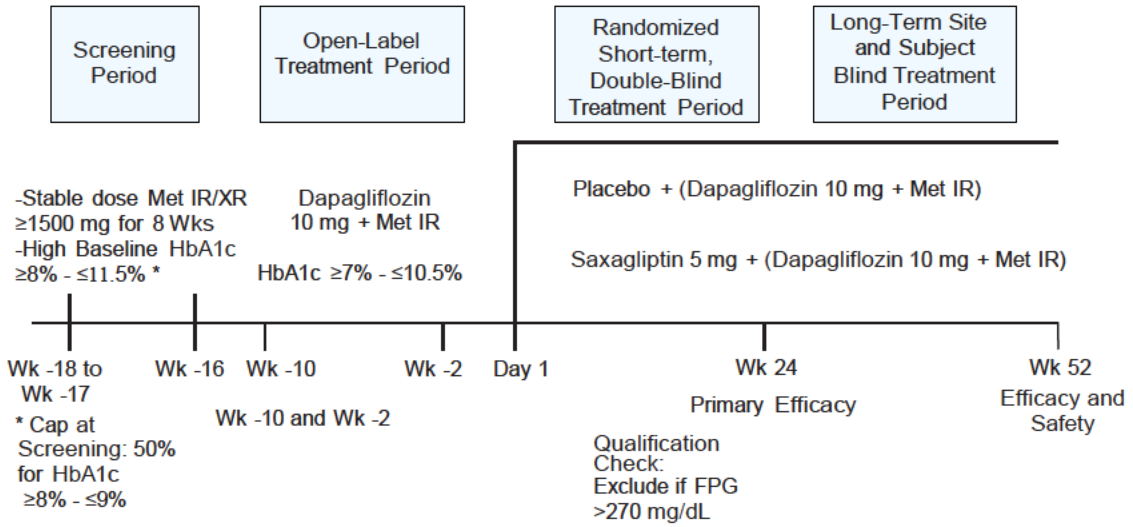
Methods:

CV181168 was a Phase 3, randomized, double-blind, placebo-controlled, trial that enrolled 857 adult subjects with T2D who had inadequate glycemic control (HbA1c ≥8 to <11.5%; with no more than 50% of subjects having HbA1c ≥8% to <9%) while receiving stable doses (≥1500 mg/day for ≥8

weeks) of metformin IR or XR tablets. Eligible subjects entered an open-label treatment period, which included maximum tolerated doses of open-label metformin IR 500 mg tablets and dapagliflozin 10 mg tablets. Subjects receiving metformin IR or XR tablets during the screening period were switched to the nearest multiple of open-label metformin IR 500 mg tablets, with the total daily dose administered as a twice daily dose with food. If the Week -2 HbA1c was between ≥7% to ≤10.5%, subjects were eligible for randomization to saxagliptin 5 mg/day or placebo, as add-on therapy to metformin + dapagliflozin, for a 24-week, ST, double-blind treatment period. Following completion of the ST treatment period, subjects were eligible to enter a 28-week site- and subject- blind LT treatment period. The trial design for this study is presented in Figure 1 below.

Overall, the trial design, patient population, and treatment duration were adequate and consistent with antihyperglycemic Phase 3 trials submitted to the Division. Although the combination of saxagliptin + dapagliflozin was only evaluated as add-on to background metformin therapy, this would likely be a population for whom antihyperglycemic FCDPs would be used (i.e., patients sequentially failing monotherapy and then dual therapy).

Figure 1: Study Design of Trial CV181168



Source: Adapted from the Applicants CV181168 ST Clinical Study Report (labeled as Figure 3.1-1, page 51 of 3639) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168\cv181168-clinical-study-report.pdf.
Abbreviations: FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IR, immediate-release; Met, metformin; and WK, week.

Subjects with lack of glycemic control were eligible to receive open-label rescue medication, in addition to their current double-blind treatment. All rescue decisions were based on central laboratory FPG and repeat, confirmatory FPG. It was mandatory for subjects who met rescue

criteria in the double-blind treatment period to first complete the rescue visit procedures before receiving open-label rescue medication in order to ensure important trial endpoint measurements were collected. Following completion of the rescue visit, subjects were given open-label antidiabetic rescue medication (insulin or other antidiabetic agents except glucagon-like peptide-1 (GLP-1) analogs, other dipeptidyl peptidase-4 (DPP4)/sodium-glucose transporter-2 (SGLT2) inhibitors or metformin) to be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their double-blinded study medication. Rescued subjects then continued in the double-blind treatment period according to their original visit schedule.

Key Inclusion Criteria:

- Men and women, age ≥18 years old
- T2D with HbA1c ≥8.0% and ≤11.5% (measured at a central laboratory) at screening
  - HbA1c ≥7% and ≤10.5% for randomization into the ST, double-blind treatment period
- Stable metformin therapy (≥1500 mg/day for ≥8 weeks)
- C-peptide ≥1.0 ng/mL
- BMI ≤45.0 kg/m^2
- Use of an acceptable method of contraception throughout the trial by women of childbearing potential (WOCBP) and by sexually active fertile men if their partners are WOCBP
- Negative serum or urine pregnancy test for WOCBP
- Women could not be breastfeeding

Key Exclusion Criteria:

- Estimated glomerular filtration rate (eGFR) <60 $mL/min/1.73m^2$ (Modification in Diet and Renal Disease [MDRD]) or serum creatinine (Scr) ≥1.5 mg/dL in males or ≥1.4 mg/dL in females
- Systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg
- Cardiovascular diseases within 3 months of screening (i.e., myocardial infarction [MI], cardiac surgery or revascularization [CABG/PTCA], unstable angina, stroke or transient ischemic attack [TIA])
- Congestive heart failure as New York Heart Association (NYHA) class IV, unstable or acute congestive heart failure (CHF)
- Conditions of congenital renal glucosuria

- Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency, including subjects with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and or total bilirubin >2.5x ULN
- History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis
- Male subjects with microscopic hematuria present at Week -18 or Week -16 and no common cause that could be confirmed (male subjects with a confirmed common cause could enter into the open-label treatment period with a documented negative result for hematuria microscopic urinalysis performed by the central laboratory; females subjects with hematuria had to be investigated according to local standards and best clinical practices)
- Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma)
- Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus
- Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of >400 mL of blood during the 6 months prior to the screening visit
- Hemoglobin ≤11.0 g/dL (110 g/L) for men; hemoglobin ≤10.0 g/dL (100 g/L) for women
- Abnormal free thyroxine (FT4) values. Abnormal thyroid stimulating hormone (TSH)
- Contraindications, including but not limited to a history of serious hypersensitivity reaction to saxagliptin, as outlined in the saxagliptin and dapagliflozin Investigator Brochures, the local saxagliptin package insert, or the local metformin package insert
- Use of any antihyperglycemic therapy, other than metformin, for >14 days during the 12 weeks prior to screening
- Previous participation in any SGLT-2 or DPP-4 inhibitor trials
- Subjects with a mean FPG value >270 mg/dL (2 assessments) between Week -10 and Week -2 could not be randomized and was discontinued
- History of diabetes insipidus
- Poorly controlled diabetes (e.g., marked polyuria and polydipsia with >10% weigh loss within 3 months prior screening)
- History of diabetic ketoacidosis or hyperosmolar nonketotic coma
- History of bariatric surgery or lap-band procedure within 12 months
- Any unstable endocrine, psychiatric or rheumatic disorders
- At risk for dehydration or volume depletion, and concomitant use of loop diuretics
- Currently abusing alcohol or other drugs or has done so within the last 6 months

The inclusion and exclusion criteria for this trial were acceptable, but select out a relatively healthy diabetic population for participation. Additionally, the diagnostic criteria for T2D were not described in the clinical protocol or Clinical Study Report (CSR).

Study Treatments:

Subjects were randomized (1:1 treatment allocation) to:

- Saxagliptin 5 mg tablet administered once daily prior to morning meal
  OR
- Placebo tablet matching saxagliptin 5 mg administered once daily prior to morning meal

Open-label medication:

- Dapagliflozin 10 mg tablet administered once daily prior to morning meal
- Metformin 500 mg IR tablets administered twice daily with food

Rationale for Dose Selection:

The Applicant notes that the saxagliptin 5 mg is the maximum recommended daily dose, as well as the usual daily dose of this product for approximately 86% of patients.[(1)] Similarly, dapagliflozin 10 mg is the maximum recommended daily dose in patients tolerating 5 mg once daily who require additional glycemic control. The 10 mg dose accounts for 61% of dapagliflozin prescriptions.[(1)] Although a saxagliptin 2.5 mg dose is available, and currently recommended for patients with an eGFR <45 mL/min/1.73 m^2, dapagliflozin is not recommended for patients with an eGFR <60 mL/min/1.73 m^2. Therefore the study of the 2.5 mg saxagliptin dose would not have been informative. (b) (4)

Assignment to Treatments:

Subjects were randomized to saxagliptin and placebo treatment arms using a 1:1 treatment allocation. Randomization was stratified by site. Randomization schedules for subject treatment and containers were generated and kept by the Randomization Center (i.e., located at BMS and stored in a secure location with restricted access). The Clinical Event Committee (CEC) members, responsible for adjudication of events of interest, remained blinded to the randomization codes throughout the entire trial.

[(1)] Applicant's Clinical Overview (pages 10-11 of 60), available at: \\cdsesub1\evsprod\nda209091\0000\m2\25-clin-over\clinical-overview.pdf.

Blinding:

Study medication, Saxagliptin 5 mg tablets and matching placebo tablets, were supplied by BMS as identical plain, (b) (4) biconvex, round film-coated tablets. The investigational site personnel, BMS and (b) (4) study personnel, and study subjects remained blinded to treatment assignments throughout the 24-week, blinded treatment period. Additionally, HbA1c and plasma glucose results were blinded to investigators or BMS, and were not provided to investigators following study completion. In accordance with local regulations, Pharmacovigilance from BMS was permitted to unblind data for Expedited Safety Reports. Additionally, investigators were permitted to break the blind in the event of a medical emergency or pregnancy, for which knowledge of the treatment assignment was essential.

Dose Modifications of Study Medications:

Dose titration of blinded study medication was not permitted at any time during the study. Additionally, open-label metformin doses remained unchanged during the double-blind treatment period.

Administrative Structure:

Trial CV181168 was conducted at 79 clinical sites across nine countries. The clinical statistical analysis and programming were performed by BMS, with additional clinical programming performed by (b) (4) The trial was sponsored and monitored by BMS. Suspected serious cardiovascular (CV) and hepatic adverse events were adjudicated by a blinded, independent Clinical Event Committee (CEC), and a Hepatic Adjudication Committee, respectively. These committees conducted all of their operations in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Adjudication was performed in a blinded fashion, and CEC members remained blinded to randomization codes throughout the adjudication process.

Procedures and Schedule:

A schedule of trial procedures for the ST double-blind treatment period and the LT treatment period is presented in Table 35 and Table 36, respectively.

Dietary Restrictions/Instructions:

Starting at the Open-label treatment period (i.e., Week -16), all subjects received counseling on dietary and life-style modifications in accordance with the ADA or similar local guidelines, and were expected to make every attempt to adhere to the diet and exercise counseling. A registered dietitian, registered nurse, physician, certified diabetes educator (CDE), nutritionist, or other qualified member of the research team provided the counseling. Subjects also were

asked to consume an adequate daily intake of minerals and vitamins, in accordance with the National Academy of Sciences or other similar local guidelines.

Concurrent Medications:

At screening, subjects receiving metformin IR or XR tablets were switched to the nearest multiple of metformin IR 500 mg tablets. The use of any other antihyperglycemic therapy, other than metformin, and initiation of systemic corticosteroids (>5 days) and potent cytochrome P450 3A4/5 inhibitors was not allowed. Medications commonly used by diabetic patients or recommended as standard of medical care (e.g., angiotensin receptor blockers [ARBs], angiotensin converting enzyme inhibitors [ACEIs], antihypertensive medications, diuretics, stable doses of weight loss medications) were allowed. Non-trial medications were coded using the World Health Organization (WHO) dictionary, and start and stop dates collected on the Case Report Form (CRF).

Adherence to Study Treatment:

The importance of adherence to the investigational treatment regimen was reinforced every time study medication was dispensed to subjects, and assessed through subject interviews and tablet counts of returned investigational product. Subjects were considered to be compliant with the treatment regimen if their study medication adherence was between ≥80% and ≤120%.

Rescue Medication:

Subjects with inadequate glycemic control during the ST, double-blind treatment period were eligible to receive open-label rescue medication based on the criteria presented in Table 4. These criteria are consistent with the 2008 Diabetes Guidance.[71] Subjects who met any of the criteria were required to complete a rescue visit, and subsequently prescribed open-label antidiabetic rescue medication (except GLP-1 analogs, other DPP-4/SGLT- inhibitors, or metformin) at the lowest starting dose and titrated according to approved product labeling. Subjects were asked to continue with the planned study visits as described in in Table 35. In the LT treatment period, subjects were eligible to receive open-label rescue therapy in addition to their study medication based on HbA1c criteria. These subjects also were required to complete a rescue visit, and continue with their scheduled follow-up visits (Table 36). At the Type A End of Review Meeting for NDA (b) (4) (dated December 17, 2015), the Agency reiterated to the Applicant that the primary efficacy analysis should use all HbA1c data from all subjects randomized, regardless of treatment adherence and rescue status.

Table 4: Criteria for Initiation of Antihyperglycemic Rescue Therapy

Study Visits	Rescue Laboratory Criteria (Central Lab)
ST Treatment Period	
Week 6	FPG >270 mg/dL
After Week 6 to Week 12	FPG >240 mg/dL
Weeks 12-24	FPG >200 mg/dL
LT Treatment Period	
After Week 24 to Week 52 (excluding Week 52)	HbA1c >8%

Source: Adapted from the Applicant's CV181168 ST Clinical Study Report (labeled as Table 3.1-1, page 52 of 3639) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168\cv181168-clinical-study-report.pdf, and CV181168 ST+LT Clinical Study Report (labeled as Table 3.1.1, page 30 of 3270) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf
Abbreviations: FPG, fasting plasma glucose, and HbA1c, hemoglobin A1c.

Subject Completion, Discontinuation, or Withdrawal:

Subjects were discontinued from study medication for the following reasons:

- Withdrawal of informed consent
- Clinical adverse events (AEs), laboratory abnormalities, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation would not be in the best interest of the subject
- Pregnancy
- Termination of the trial
- Loss of ability to freely provide consent (e.g., incarceration)
- eGFR <60 mL/min/1.73m^2 for 12-16 weeks
- Protocol-defined major hypoglycemia episode or recurrent hypoglycemia episodes (e.g., fingerstick blood glucose ≤54 mg/dL and/or hypoglycemia symptoms)

In cases where a decision was made to discontinue investigational product, subjects were to be followed until resolution/stabilization. Subjects would complete an early termination visit, and be asked to continue in the study for the scheduled follow-up visits. Subjects prematurely discontinuing the trial could be contacted for collection of vital status information. The sample

size estimate assumes that 5% of subjects would not have a post-baseline assessment, and therefore these subjects were not replaced.

Study Endpoints

Primary Efficacy Endpoint:

- Mean change in HbA1c from baseline to Week 24

The primary efficacy endpoint for Study CV181168 was the change from baseline (randomization) in HbA1c (%) after 24 weeks of treatment (i.e., saxagliptin or placebo). 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.[72]
- 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%.[73,74]
- HbA1c has excellent reliability, predicts some of the diabetes-specific complications, and provides a basis for treatment decisions in patients with T2D.[75,76]
- Lowering HbA1c reduces microvascular complications in patients with T1D and T2D,[10,17,18] and may lower macrovascular complications in patients with T1D.[12]

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."[71] All scheduled measurements of HbA1c used for eligibility criteria, efficacy analyses, and need for glycemic rescue, were performed at a Central Laboratory.

Key Secondary Efficacy Endpoints:

The following key secondary endpoints were to be evaluated using a hierarchical testing strategy in the order presented below:

1. Mean change from baseline to Week 24 in the 2-hour PPG during a MMT
2. Mean change from baseline to Week 24 in FPG
3. The proportion of subjects achieving an HbA1c <7%

These endpoints are considered supportive measures of efficacy in Phase 3 trials.[71] The analyses also were based on measurements performed by a Central Laboratory.

Other Relevant Endpoints:

- The proportion of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period
- Mean change from baseline to Week 24 in AUC glucose during the MTT
- Mean percent change from baseline to Week 24 in the following fasting serum lipids: total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)
- Safety: Adverse events (AEs), and clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examination findings

Statistical Analysis Plan

For the analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to Week 24), the Applicant used a longitudinal repeated measures analysis to compare the triple combination of saxagliptin+dapagliflozin+metformin treatment arm to dual therapy with placebo + dapagliflozin+metformin. The model included terms for baseline HbA1c value, treatment group, time, the interaction of treatment group and time, and the interaction of baseline value and time. The analysis population consisted of all randomized subjects that received at least one dose of study medication during the double-blind treatment period. Any HbA1c data collected following glycemic rescue or discontinuation of study medication was not included in the primary efficacy analysis. A 2-sided, p-value of <0.05 was considered to indicate statistical significance for the primary analysis. Assuming a standard deviation of 1%, the Applicant estimated that inclusion of 133 subjects per treatment arm would have 90% power to detect a difference in mean HbA1c of 0.4% between treatment groups. To account for the possibility that 5% of subjects would not have a post-baseline assessment, a total of 280 subjects (i.e., 140 subjects per arm) would need to be randomized.

A repeated measures model also was used to assess change from baseline in specified key secondary endpoints. The study-wise type I error rate related to the primary and secondary efficacy endpoints was controlled at the two-sided 0.05 level by using a hierarchical closed testing procedure (i.e., statistical testing proceeded to each subsequent secondary endpoint only if the two-sided p-value was <0.05 for all previous endpoint analyses). The Applicant used measurements taken prior to starting glycemic rescue for both primary and secondary

endpoints (i.e., these analyses excluded subjects who had inadequate glycemic control on their randomized treatment regimen).

Dr. Anna Kettermann was the Statistical Reviewer for this Application. In her review, she expressed concern with the exclusion of post-discontinuation HbA1c data (e.g., after glycemic rescue therapy) by the Applicant for their primary efficacy analysis, as this result may not reflect the actual efficacy findings should all of the subjects who participated in the trial have been included in the analysis. Therefore, she reanalyzed the primary efficacy endpoint using all available data, including HbA1c data measurements collected after rescue or discontinuation. Further, to evaluate the robustness of the Applicant's conclusions, she performed additional analyses using a multiple imputation approach that imputed data for subjects without Week 24 HbA1c measurements, as well as several sensitivity (i.e., Jump to Reference, Copy Reference, Tipping point analysis, MMRM) and subgroup (i.e., sex, race, age, geographic region) analyses. For a more detailed discussion of the Statistical Analysis Plan (SAP) and the statistical approach used by Dr. Kettermann, please refer to her Statistical Review (dated January 5, 2017).

Protocol Amendments

The original clinical protocol issue date for Trial CV181168 was April 24, 2012. A site-specific amendment (Amendment #1) also was issued on this same date to allow for collection/storage of blood samples for exploratory pharmacogenetic research. On August 13, 2013, a second protocol amendment was submitted, which consisted primarily of technical corrections, as well as clarifications related to Section 8.0 (i.e., Statistical Considerations) of the protocol. One of the statistical clarifications addressed the follow-up of subjects who received glycemic rescue therapy or discontinues treatment early included the following:

> "Subjects may discontinue study drug but continue in the study. Generally, data collected during the study treatment period will be used for analysis. Additional analyses may be performed incorporating data collected after discontinuation of study drug where indicated."

It is noted that HbA1c data obtained following treatment discontinuation were excluded from the Applicant's primary efficacy analysis (i.e., placebo-subtracted HbA1c change from baseline).

Data Quality and Integrity: Sponsor's Assurance

Representatives from BMS, the original holders of IND 118840 (i.e., the saxagliptin/dapagliflozin FCDP), periodically monitored the participating study sites to assess data quality and study integrity. They reviewed study records and source documents, discussed conduct of the trial with investigators, and verified that the study site remains acceptable. In her Statistical Review, Dr. Kettermann felt that the quality of the data was reasonable.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report for Trial CV181168 states that this study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Financial Disclosure

The Applicant also submitted a Form FDA 3454 for each covered study, certifying they have not entered into a financial arrangement with any of the clinical investigators participating in the respective studies that could affect the outcome of the study. See Section 13.3 below for details.

Patient Disposition

In total, 857 subjects were enrolled into Trial CV181168, of which 484 entered the open-label treatment period, and 353 were randomized into the ST, double-blind treatment period (Table 5). The most common reasons for not entering (n=353) and not completing (n=18) the open-label treatment period was 'no longer meeting eligibility criteria'. Of the 431 subjects completing the open-label period, 315 subjects were randomized and treated (i.e., 153 saxagliptin-treated and 162 placebo-treated subjects). The most common reason for not entering the double-blind treatment period was 'no longer meeting study criteria' (primarily due to HbA1c <7% for 106 subjects). Overall, relatively few subjects (n=17) discontinued study during the ST, double-blind treatment period, and included 11 (7.2%) subjects receiving saxagliptin and 6 (3.7%) randomized to placebo. More than 92% of subjects completed the ST treatment period in both arms. The most common reasons for not completing treatment were 'subject withdrew consent' and 'lost to follow-up'. Of the 11 subjects randomized to saxagliptin who discontinued study prematurely, the following AE events were reported in six subjects while in the open-label (OL) or ST, double-blind treatment phase:

1. **CV181168-** (b) (6) **('withdrew consent')**: Hemoglobin decreased (mild/Grade 1; OL period)
2. **CV181168-** (b) (6) **('withdrew consent'):** Hepatic cancer (severe/Grade 3; ST period)
3. **CV181168-** (b) (6) **('withdrew consent'):** Urinary tract infection (mild/Grade 1; OL period); Depression (moderate/Grade 2; OL period); Peripheral neuropathy (moderate/Grade 2; OL period)

4. **CV181168-[(b) (6)] ('lost to follow-up'):** Vomiting (mild/Grade 1; OL period)
5. **CV181168-[(b) (6)] ('subject no longer meets study criteria'):** Diarrhoea (moderate/Grade 2; ST period); Headache (mild/Grade 1; ST period); Rash (mild/Grade 1; ST period)
6. **CV181168-[(b) (6)] (poor/noncompliance):** Nasopharyngitis (mild/Grade 1; OL period); Nasal congestion (mild/Grade 1; OL period); Rash (moderate/Grade 2; ST period)

Most AEs were mild or moderate in severity, with three subjects experiencing events during the ST, double-blind treatment period, while receiving saxagliptin+dapagliflozin+metformin.

Table 5: Subject Disposition (Randomized Population)*

	Saxa+Dapa+Met	Placebo+Dapa+Met	Total
NUMBER OF SUBJECTS ENROLLED, N=857			
NUMBER OF SUBJECT IN OPEN-LABEL PERIOD, n=484			
COMPLETED THE OPEN-LABEL PERIOD, n=431			
Number of Subjects Randomized and Treated	**153**	**162**	**315**
Completed 24-week, Short-term, Double-blind Period, n (%)	142 (92.8)	156 (96.3)	298 (94.6)
Discontinued	11 (7.2)	6 (3.7)	17 (5.4)
Withdrew Consent	4 (2.6)	2 (1.2)	6 (1.9)
Lost to Follow-up	4 (2.6)	2 (1.2)	6 (1.9)
Poor/Non-compliance	1 (0.7)	1 (0.6)	2 (0.6)
Subject Request to Discontinue treatment	1 (0.7)	0	1 (0.3)
No Longer Meets Study Criteria	1 (0.7)	0	1 (0.3)
Adverse Event	0	1 (0.6)	1 (0.3)
Pregnancy	0	0	0

Source: Adapted from the Applicant's summary of Clinical Efficacy (labeled as Table 4, page 27 of 50), available at: \\cdsesub1\evsprod\nda209091\0000\m2\27-clin-sum\summary-clin-efficacy-saxa-dapa-nda.pdf, and derived from the addm.xpt dataset, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Protocol Violations/Deviations

Prespecified sensitivity analyses, using the Evaluable Subjects dataset, were to be conducted if >10% of subjects had relevant protocol deviations (determined prior to the database lock) in any treatment arm. Relevant protocol deviations were defined as deviations that could potentially affect the interpretability of trial results. The Evaluable Subjects dataset, a subset of the Randomized Subjects dataset (i.e., the dataset used for the primary efficacy analysis), excludes primary efficacy data which may have been affected by relevant protocol deviations.

A summary listing of the relevant protocol deviations reported in Trial CV181168 is presented in Table 6. Across both treatment arms, relevant protocol deviations were reported for 19 (6.0%) subjects, of which seven of these individuals were excluded from the Evaluable Subjects analysis population. The proportion of subjects with relevant protocol deviations represented <10% of subjects in either treatment arm. Thus, the Randomized Subjects datasets (which included all data from the 315 subjects), were used for the primary efficacy analyses, and a sensitivity analysis using the Evaluable Subjects dataset was not performed. It is unlikely that the limited number of subjects with relevant deviations would alter the interpretation of the efficacy findings.

Table 6: Relevant Protocol Deviations (Randomized Population)*

Relevant Protocol Deviations	Saxa+Dapa+Met (n=153)	Placebo+Dapa+Met (n=162)	Total (N=315)
Description of Deviation — no. (%)	**8 (5.2)**	**11 (6.8)**	**19 (6.0)**
Took no dose of dapagliflozin or dose outside of dose range for ≥2 consecutive weeks in OL or ST treatment period	6 (3.9)	4 (2.5)	10 (1.2)
Took no dose of metformin or dose outside of dose range for ≥2 consecutive weeks in OL or ST treatment period	4 (2.6)	4 (2.5)	8 (0.9)
Received no double-blind medication for ≥2 consecutive weeks	3 (2.0)	2 (1.2)	5 (0.6)
Treated with any systemic corticosteroid for ≥5 consecutive days initiated or changed during the OL or ST treatment period	1 (0.7)	4 (2.5)	5 (0.6)
Subjects excluded from the Evaluable Subjects Population — no. (%)	**3 (2.0)**	**4 (2.5)**	**7 (2.2)**

Source: Adapted from the Applicant's CV181168 ST Clinical Study Report (labeled as Table 4.3-1, page 76/3639), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168\cv181168-clinical-study-report.pdf.
Abbreviations: no., number; OL, open-label; and ST, short-term.
*All subjects randomized who received ≥1 dose of investigational product during the ST, double-blind treatment period.

Table of Demographic Characteristics

in trial CV181168, 315 subjects were randomized to saxagliptin or placebo added to open-label dapagliflozin+metformin. The baseline demographics (Table 7) and clinical characteristics (Table 8) of the randomized groups are summarized below. Treatment groups at baseline appeared to be well-balanced for demographics and clinical characteristics. Overall, the trial population was predominantly White (88%), and relatively young (mean age of 55 years). Only five subjects were over 75 years of age. The trial was conducted worldwide; with the majority of randomized subjects residing in the North American region (52%), of which 40% were from the U.S.

Table 7: Demographics (Randomized Population)*

	Saxa+Dapa+Met (n=153)	Placebo+Dapa+Met (n=162)	Total (N=315)
DEMOGRAPHICS			
Age, mean ± SD — yr	54.7 ± 9.8	54.5 ± 9.3	54.6 ± 9.6
<65 yr — no. (%)	132 (86.3)	140 (86.4)	272 (86.3)
≥65 yr — no. (%)	21 (13.7)	22 (13.6)	43 (13.7)
≥75 yr — no. (%)	2 (1.3)	3 (1.9)	5 (1.6)
Female sex — no. (%)	80 (52.3)	86 (53.1)	166 (52.7)
Race — no. (%)			
White	136 (88.9)	141 (87.0)	277 (87.9)
Black/African American	11 (7.2)	9 (5.6)	20 (6.3)
Asian	5 (3.3)	8 (4.9)	13 (4.1)
Other	1 (0.7)	4 (2.5)	5 (1.6)
Ethnic Group (Hispanic/Latino) — no. (%)	75 (50.0)	83 (52.5)	73 (23.2)
Not Hispanic/Latino	27 (17.6)	29 (17.9)	56 (17.8)
Not Reported	91 (59.5)	95 (58.6)	186 (59.0)
Region — no. (%)			
North America	78 (51.0)	86 (53.1)	164 (52.1)
Europe	55 (35.9)	55 (34.0)	110 (12.8)
Latin America	20 (13.1)	21 (13.0)	41 (13.0)
Asia/Pacific	0	0	0
Country — no. (%)			
United States of America	62 (40.5)	67 (41.4)	129 (40.1)
Russia	28 (18.3)	28 (17.3)	56 (17.8)
Mexico	20 (13.1)	21 (13.0)	41 (4.8)
Canada	15 (9.8)	17 (10.5)	32 (3.7)
Romania	11 (7.2)	9 (5.6)	20 (6.3)
Poland	7 (4.6)	11 (6.8)	18 (5.7)
Czech Republic	5 (3.3)	4 (2.5)	9 (2.9)
Hungary	4 (2.6)	3 (1.9)	7 (2.2)
Puerto Rico	1 (0.7)	2 (1.2)	3 (1.0)

Source: Adapted from the Applicants' Summary of Clinical Efficacy (labeled as Table 6, page 29 of 50), and derived from the addm.xpt dataset, available at:
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: no., number; SD, standard deviation; US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigational product.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Approximately 60% of the population had a body mass index (BMI)>30 kg/m^2. The majority of

subjects (58%) had baseline HbA1c concentrations <8%. The mean duration of diabetes was approximately 8 years, and approximately 30% of subjects had a diagnosis of diabetes for more than 10 years. Since subjects with an eGFR <60 mL/min/1.73m^2 were to be excluded from study participation, few subjects (n=7) had renal impairment below this level of renal function.

Table 8: Baseline Clinical Characteristics (Randomized Population)*

	Saxa+Dapa+Met (n=153)	Saxa+Met (n=162)	Dapa+Met (N=315)
CLINICAL CHARACTERISTICS			
BMI, mg/m^2 — mean ± SD	31.4 ± 5.2	31.3 ± 5.3	31.4 ± 5.3
<30 mg/m^2 — no. (%)	64 (41.8)	62 (38.3)	126 (40.0)
≥30 mg/m^2 — no. (%)	89 (58.2)	100 (61.7)	189 (60.0)
Duration of T2D, mean ± SD — yr	8.1 ± 7.0	7.4 ± 5.8	7.7 ± 6.4
<3 yr — no. (%)	36 (23.5)	36 (22.2)	72 (22.9)
≥3 to ≤10 yr — no. (%)	72 (47.1)	78 (48.1)	150 (47.6)
>10 yr — no. (%)	45 (29.4)	48 (29.6)	93 (29.5)
Glycemic Status			
HbA1c% — mean ± SD	8.0 ± 0.8	7.9 ± 0.9	7.9 ± 0.9
<8% — no. (%)	85 (55.6)	99 (61.1)	184 (58.4)
8 to <9% — no. (%)	50 (32.7)	42 (25.9)	92 (29.2)
≥9% — no. (%)	18 (11.8)	21 (13.0)	39 (12.4)
2-h PPG, mg/dL — mean ± SD	208.5 ± 50.1	206.4 ± 53.1	207.4 ± 51.6
FPG, mg/dL — mean ± SD	163.9 ± 34.4	157.6 ± 34.6	160.7 ± 34.6
C-peptide, ng/mL — mean ± SD	2.4 ± 1.0	2.6 ± 1.2	2.47 ± 1.09
eGFR, mL/min/1.73m^2 — mean ± SD	92.8 ± 21.6	93.88 ± 20.6	93.4 ± 21.1
≥30 to <60 mL/min/1.73m^2 — no. (%)	3 (2.0)	4 (2.5)	7 (2.2)
≥60 to <90 mL/min/1.73m^2 — no. (%)	77 (50.3)	70 (43.2)	147 (46.7)
>90 mL/min/1.73m^2 — no. (%)	73 (47.7)	88 (54.3)	161 (51.1)

Source: Adapted from the Applicants' Summary of Clinical Efficacy (labeled as Table 6, page 29 of 50), and derived from the addm.xpt and adlb2.xpt datasets, available at:
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG

Abbreviations: BMI, body mass index; C-peptide, connecting peptide; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; no., number; PPG, postprandial glucose; SD, standard deviation; T2D, type 2 diabetes mellitus; US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigation product.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Adherence to Study Treatment:

In Trial CV181168, subjects were 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.[39] Additionally, prospective electronic monitoring studies have documented that patients took 67-85% of their oral antihyperglycemic doses as prescribed.[39] Although there is no universally accepted definition for what constitutes adequate adherence, a compliance rate of >80% is reasonable.[43,44,77] During the ST, double-blind treatment period, two placebo-treated subject (i.e., dual therapy) and two saxagliptin-treated subjects (i.e., triple therapy) had compliance rates <80%, while one subject in each group discontinued study prematurely due to poor/noncompliance (please refer to Table 5). It is unlikely that this relatively low rate of nonadherence will affect the interpretation of the primary and key secondary efficacy finding.

Concomitant Medications:

Approximately 85% of subjects used concomitant medications during the ST, double-blind treatment period. As depicted in Table 9, there did not seem to be obvious imbalances between treatment arms for common pharmacologic drug classes prescribed as concomitant medications for patients with T2D.

Table 9: Commonly Used (>10%) Concomitant Medications by Therapeutic Class (Randomized Population)*

Anatomic Class Therapeutic Class	Saxa+Dapa+Met (n=153)	Placebo+Dapa+Met (n=162)	Total (N=315)
TOTAL NUMBER OF SUBJECTS RECEIVING CONCOMITANT MEDICATIONS — NO. (%)	*129 (84.3)*	*143 (88.3)*	**272 (86.30)**
Cardiovascular System	**103 (67.3)**	**107 (66.0)**	**210 (66.7)**
Antihypertensive	93 (60.8)	92 (56.8)	185 (58.7)
Beta-blocking agents	41 (26.8)	38 (23.5)	79 (25.1)
Calcium Channel blockers	21 (13.7)	18 (11.1)	39 (12.4)
Diuretic	26 (17.0)	28 (17.3)	54 (17.1)
Blood/Blood Forming Organ	**70 (45.8)**	**72 (44.4)**	**142 (45.1)**
Serum lipid reducing agents	65 (42.5)	63 (38.9)	128 (40.6)

Anatomic Class Therapeutic Class	Saxa+Dapa+Met (n=153)	Placebo+Dapa+Met (n=162)	Total (N=315)
Nervous System	**65 (42.5)**	**66 (40.7)**	**131 (41.6)**
Analgesic	57 (37.3)	62 (38.3)	119 (37.8)
Alimentary Tract and Metabolism	**30 (19.6)**	**34 (21.0)**	**64 (20.3)**
Vitamins	17 (11.1)	16 (9.9)	33 (10.5)
Antacid medication	13 (8.5)	20 (12.3)	33 (10.5)
Respiratory System	**22 (14.4)**	**16 (9.9)**	**38 (12.1)**
General anti-infective for systemic use	**22 (14.4)**	**26 (16.0)**	**48 (15.2)**

Source: Adapted from the Applicants' CV181168 ST Clinical Study Report (labeled as Table 4.4.1A, pages 212-228 of 3639), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168\cv181168-clinical-study-report.pdf, and confirmed using the adcm.xpt dataset, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.
Abbreviations: no., number; SD, standard deviation; US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigation product.

Rescue Medication Use:

Glycemic rescue criteria were prespecified in Trial CV181168, as described above (Table 4). According to the Applicant, the number of subjects who discontinued study medication for lack of glycemic control or required rescue during the 24-week, double-blind period was lower, but not different between treatment arms (i.e., 2.5% [4/153] in the saxagliptin+dapagliflozin+metformin treatment arm vs. 4.4% [7/162] in the placebo+ dapagliflozin+metformin arm; adjusted percent difference -1.9% (95% CI -5.9, 2.1). The first rescue medication used in all of these subjects was a sulfonylurea (i.e., glimepiride, glipizide, or glyburide). By Week 52, the proportion of subjects favored the triple therapy arm (i.e., 18.6% [29/153] vs. 28.4% [45/162], respectively).

A concern noted by Dr. Kettermann in her review was that the Applicant did not account for the data from subjects who received antihyperglycemic rescue therapy or discontinued the use of study medication prior to completion of the ST efficacy period. This could result in the evaluation of only those subjects who achieved a therapeutic response or tolerated therapy. However, it appears that the number of subjects who were excluded from the efficacy analyses for inadequate glycemic response/rescue was relatively limited during the ST, double-blind treatment period.

Efficacy Results – Primary Endpoint

The results of the primary efficacy analysis (i.e., placebo-subtracted change in HbA1c from baseline to Week 24) performed using a MMRM approach by the Applicant, and reanalyzed by the Agency, are presented in Table 10 below. Compared to use of placebo addition of saxagliptin resulted in modest, but statistically significant reductions in HbA1c, regardless of exclusion (Applicant's analysis) or inclusion (Agency analysis) of HbA1c data collected after glycemic rescue/discontinuation. For product labeling, Dr. Kettermann recommends that the intent-to-treat estimands be used (i.e., based on all available data, regardless of rescue or discontinuation).

Table 10: Analysis of Mean Change in HbA1c from Baseline to Week 24

Analytical Approach	Treatment Comparison	HbA1c Difference (%)	95% CI
MMRM (Applicant)*	Saxa+Dapa+Met vs. Placebo+Dapa+Met	-0.35	(-0.52, -0.18)
MMRM (Agency)¶	Saxa+Dapa+Met vs. Placebo+Dapa+Met	-0.37	(-0.50, -0.17)

Source: Adapted from Dr. Anna Kettermann's Statistical Review (dated January 5, 2015), labeled as Tables 7 and 8, pages 19-20.
Abbreviations: CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin; MMRM, mixed model repeated measures; Saxa, saxagliptin; vs, versus.
* Excludes HbA1c data after glycemic rescue or discontinuation.
¶ Analysis includes HbA1c data after rescue or discontinuation.

Data Quality and Integrity – Reviewers' Assessment

As noted in Section 4.1 above, OSI was not consulted to conduct additional audits/site inspections for this NDA. In her review, Dr. Kettermann felt that the analysis and data quality for the submission were reasonable. Many of the safety analyses performed by the Applicant also were confirmed in this review. This reviewer concurs with Dr. Kettermann's assessment that the data quality was reasonable.

Efficacy Results – Secondary and other relevant endpoints

Key secondary analyses performed by the Applicant are presented in Table 11. Both the 2-hour PPG and FPG analyses failed to show a statistically significant difference between the saxagliptin triple therapy and placebo dual therapy treatment arms. In accordance with the prespecified SAP, hierarchical significance testing for the other key secondary endpoints was stopped once the result of the 2-hour PPG analysis was found to be nonsignificant, and therefore formal statistical testing of these endpoints were not performed. Therefore, inclusion of statistical test results in Section 14 of product labeling should be limited to the primary

efficacy analysis. However, to be consistent with SGLT-2/DPP-4 class labeling, inclusion of descriptive statistics to show the "known" proportion of subjects who achieve an HbA1c <7% (i.e., to indicate that formal statistical testing was not performed) would be reasonable, as recommended by Dr. Kettermann.

Table 11: Analysis Secondary Endpoints (Change from Baseline to Week 24)

Efficacy Endpoint*	Treatment Comparison	Difference	95% CI
2-h PPG (mg/dL)	Saxa+Dapa+Met vs. Placebo+Dapa+Met	-5.9	(-14.9, 3.1)
FPG (mg/dL)	Saxa+Dapa+Met vs. Placebo+Dapa+Met	-3.7	(-11.0, 3.6)
Subjects with HbA1c <7% (%)	Saxa+Dapa+Met vs. Placebo+Dapa+Met	12	(3, 21)

Source: Adapted from Dr. Anna Kettermann's Statistical Review (dated January 5, 2015), labeled as Tables 9 and 10, pages 20-22.
Abbreviations: 2-h PPG, 2 hour postprandial glucose; CI, confidence interval; Dapa, dapagliflozin; FPG, fasting plasma glucose; HbA1c, hemoglobin HbA1c; Met, metformin; MMRM, mixed model repeated measures; and Saxa, saxagliptin.
* All analyses did not include data after rescue or discontinuation.

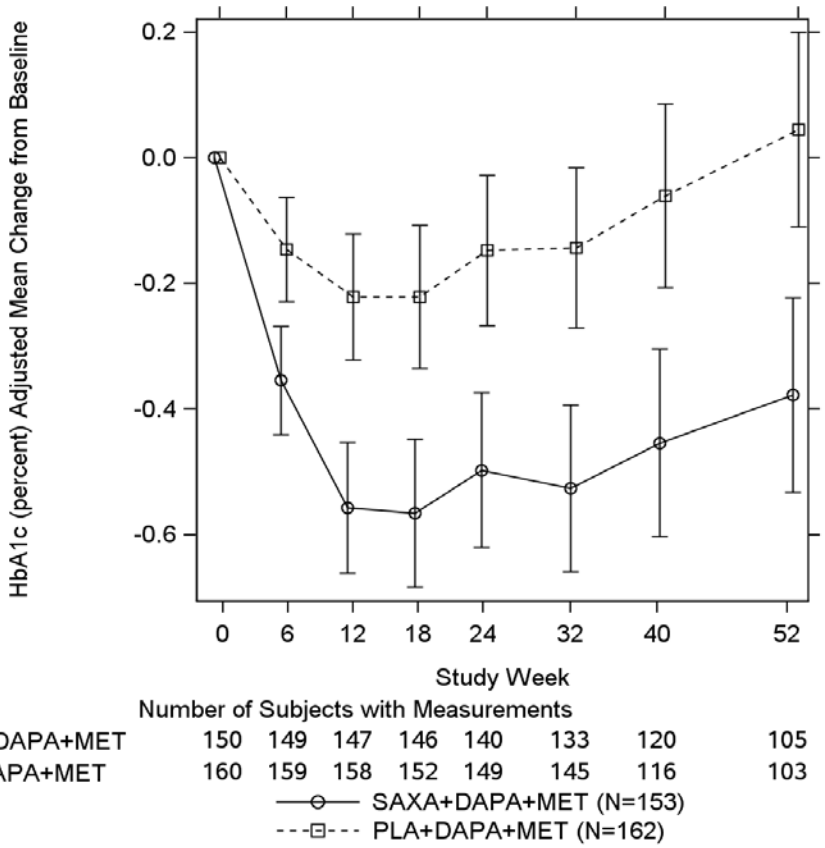
Dose/Dose Response

The Applicant only submitted data to support a single tablet formulation for QTERN (i.e., saxagliptin 5 mg/dapagliflozin 10 mg), and therefore assessments of dose and dose response were not provided.

Durability of Response

Following completion of the 24-week double-blind treatment period, subjects were eligible to participate in a 28-week site- and subject- blind LT treatment period, with efficacy endpoints assessed at Week 52. Of 297 subjects entering the LT extension phase, 280 subjects (i.e., 133 in the saxagliptin triple therapy arm and 147 in the placebo dual therapy arm) completed the trial. The Applicant conducted a MMRM analysis, with treatment, baseline HbA1c value, week, week-by-treatment interaction, and week-by-baseline interaction as independent variables. Based on this analysis, greater HbA1c reduction was observed throughout the 52-week treatment period (Figure 2). In their published report of this study, the Applicant acknowledged that this analysis should be considered exploratory.[78]

Figure 2: Longitudinal Adjusted Mean Changes in HbA1c (Baseline to Week 52)*



Source: Reproduced from the Applicant's CV181168 ST+LT Clinical Study Report (labeled as Figure 7.2.1-1, page 59 of 3279, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf
Abbreviations: DAPA, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin; PLA, placebo; and SAXA, saxagliptin.
*Data after rescue is excluded.

Persistence of Effect

Not applicable. Both saxagliptin and dapagliflozin have relatively short half-lives (i.e., 2.5 and 12.9 hours, respectively). Therefore, following treatment discontinuation, persistence of the antihyperglycemic effects of these study medications would not be expected.

Additional Analyses Conducted on the Individual Trial

Dr. Kettermann also conducted sensitivity analyses of the primary efficacy endpoint using a multiple imputation approach, and Jump to Reference, Copy Reference, and Tipping point

statistical methodologies. All sensitivity analyses were supportive (i.e., resulted in similar point estimates and CIs [data not shown]). She also performed subgroup analyses based on the following intrinsic factors: sex, race, age, and geographic region. The saxagliptin triple therapy arm remained superior to the placebo dual therapy arm, regardless of sex and age, while HbA1c results by race were less informative, potentially due to limited number of non-White subjects randomized in the trial (i.e., n=33). The placebo-subtracted mean HbA1c reductions reported for the North American region (i.e., -0.25%; 95% CI, -0.48 to -0.01) were less than those observed for the primary efficacy analysis. A similar finding was also observed for the Applicant's supporting Phase 3 trials (i.e., CV181169 and MB102129).

Please refer to Dr. Kettermann's Statistical Review for detailed discussion of the sensitivity and subgroup analyses performed to support the findings of the primary efficacy analysis.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The Applicant intends to label only Trial CV181168. Additionally, the study designs of the three submitted Phase 3 trials (i.e., CV181168, CV181169, and MB102129) were diverse (please refer to Table 3). Similar to the design of Trial CV181168, MB102129 was a stepwise add-on study; however, in this trial, dapagliflozin was added to background saxagliptin+metformin therapy and not vice versa (as in CV181168). Trial MB102129 also was submitted primarily to support safety. In Trial CV181169, saxagliptin + dapagliflozin dual therapy was added to metformin and compared to the individual components. Thus, an integrated analysis of the primary efficacy endpoint across the three Phase 3 trials was not performed. Nevertheless, to better understand the contribution of each of the individual components to this FCDP; it is helpful to show 24-week HbA1c changes from baseline to Week 24 in each trial. Dr. Kettermann reanalyzed the data from all three trials using a MMRM model that included data after rescue (Table 12). All trials achieved statistically significant HbA1c reductions.

Table 12: Agency Analysis of Mean Change in HbA1c from Baseline to Week 24 – Trials CV181168, CV181169, and MB102129 (Data after Rescue/Discontinuation Included)

Trial	Saxa+Dapa+Met vs.	HbA1c Difference (%)	95% CI
CV181168	Placebo+Dapa+Met	-0.37	(-0.50, -0.17)
CV181169	Placebo+Dapa+Met	-0.28	(-0.50, -0.07)
	Placebo+Saxa+Met	-0.52	(-0.73, -0.07)
MB102129	Placebo+Saxa+Met	-0.65	(-0.83, -0.47)

Source: Adapted from Dr. Anna Kettermann's Statistical Review (dated January 5, 2015), labeled as Table 8, page 20.
Abbreviations: CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; Met, metformin; MMRM, mixed model repeated measures; and Saxa, saxagliptin.
* Excludes HbA1c data after glycemic rescue or discontinuation.
¶ Analysis includes HbA1c data after rescue or discontinuation.

7.1.2. Secondary and Other Endpoints

Please refer to Dr. Kettermann's review for evaluation of secondary endpoints for each of the three Phase 3 trials.

7.1.3. Subpopulations

Dr. Kettermann performed subgroup analyses of each Phase 3 trial. Please refer to her review for detailed information.

7.1.4. Dose and Dose-Response

Not applicable. In all three Phase 3 trials, only the saxagliptin 5 mg and dapagliflozin 10 mg doses were evaluated.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Since HbA1c reflects mean glycemic control over two to three months, efficacy is typically assessed after at least 24 weeks of antihyperglycemic therapy. All three Phase 3 clinical trials included a 24-week double-blind treatment period. Please refer to Section 6.1.2 above for discussion related to the duration and durability of glycemic efficacy related to Trial CV181168.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the saxagliptin/dapagliflozin Phase 3 clinical development program, only four subjects ≥75 years of age and 86 non-White subjects were exposed to saxagliptin + dapagliflozin. Clinical exposure from the individual saxagliptin and dapagliflozin development programs provides some supporting safety and efficacy data for the use of the mono-components of the FCDP in these patient subsets. However the therapeutic experience with combination therapy is limited at this time, making interpretation and generalizability of efficacy findings in these patient populations difficult.

Only a single dosage strength is proposed for QTERN (i.e., saxagliptin 5 mg/dapagliflozin 10 mg), and these dose strengths were the only doses evaluated in the three Phase 3 clinical trials submitted to this Application. The Applicant proposes that use of their FCDP be restricted to patients tolerating dapagliflozin 10 mg/day. The approved doses of saxagliptin are 2.5 mg and 5 mg once daily, with the 2.5 mg tablet strength recommended for patients with renal impairment (creatinine clearance ≤50 mL/min), as well as patients receiving strong CYP450 3A4/5 inhibitors. Currently, approximately 13% of saxagliptin prescriptions are for the 2.5 mg tablet strength.[(2)] Since neither dapagliflozin (5 mg or 10 mg) or saxagliptin 5 mg would be recommended in patients with a creatinine clearance of ≤50

mL/min, the potential use of an FCDP containing saxagliptin 2.5 mg would likely be limited (i.e., patients receiving CYP450 3A4/5 inhibitors). However, according to 2016 drug usage data, approximately 39% of dapagliflozin prescriptions are for the 5 mg tablet strength,[(2)] and the recommended starting dose of dapagliflozin is 5 mg once daily, with the dose increased to 10 mg for patient tolerating the 5 mg dose who require additional glycemic control.[4] Therefore, a significant proportion of the diabetic population, including individuals currently receiving dapagliflozin, would be restricted from the use of this product should it be approved, and there is the potential for off-label use. [(b) (4)]

7.2.2. Other Relevant Benefits

As discussed in more detail in Section 2.2 above, T2D affects more than 29 million people in the U.S., and is a progressive and serious, life-threatening condition. Further, a significant number of patients with T2D do not achieve adequate glycemic control despite the availability of numerous therapeutic options (Table 34), and nonadherence or intolerance to the prescribed treatment regimen is common. Therefore, an oral, once-daily, FCDP that includes two pharmacologic antihyperglycemic drug classes with different mechanisms of action and a relatively low risk of hypoglycemia (e.g., DDP-4 plus SGLT2) could be of benefit to patients and may improve adherence to prescribed therapy.

7.3. Integrated Assessment of Effectiveness

To demonstrate the efficacy of QTERN (i.e., adult T2D patients who tolerate, but have inadequate glycemic control, with dapagliflozin 10 mg/day), the Applicant conducted a Phase 3 trial (i.e., CV181168). This pivotal trial evaluated the stepwise addition of saxagliptin 5 mg/day or placebo in adult patients with T2D who had inadequate glycemic control on maximum tolerated doses of dapagliflozin (i.e., 10 mg/day) and metformin (≥1500 mg/day). Consistent with the 2008 Diabetes Guidance,[71] this trial included a 24-week, randomized, double-blind, placebo-controlled treatment period to assess efficacy, followed by a 28-week extension period to evaluate the durability of glycemic effect and safety of the FCDP. Compared to the placebo dual therapy arm, the saxagliptin triple therapy arm resulted in a modest, but statistically significant, reduction in HbA1c from baseline to Week 24 (-0.37; 95% CI, -0.50 to -0.17). Of the prespecified key secondary glycemic efficacy endpoints (i.e., 2-hour PPG, FPG, and proportion

[(2)] Applicant's Clinical Overview (pages 10-11 of 60), available at: \\cdsesub1\evsprod\nda209091\0000\m2\25-clin-over\clinical-overview.pdf.

of subjects with HbA1c <7%), only the proportion of subjects with HbA1c <7% was supportive. However, based on the Applicant's prespecified hierarchical testing procedure, formal statistical testing of this endpoint was not performed, as testing was stopped after the first comparison (i.e., 2-hour PPG) was nonsignificant.

The Applicant also submitted two additional Phase 3 clinical trials (CV181169 and MB102129) to support efficacy and safety. Trial CV181169 was a 24-week randomized, double-blind, active-controlled, parallel-group trial that compared the addition of saxagliptin 5 mg/day + dapagliflozin 10 mg/day (dual therapy) versus placebo + saxagliptin 5 mg/day and versus placebo + dapagliflozin 10 mg/day, all administered concomitantly to maximum tolerated doses of metformin (≥1500 mg/day) in adults with T2D who had inadequate glycemic control. The saxagliptin+dapagliflozin+metformin arm resulted in greater 24-week HbA1c reductions than the saxagliptin+metformin (-0.52; 95% CI, -0.73 to -0.07) and the dapagliflozin+metformin (-0.28; 95% CI, -0.50 to -0.07) dual therapy arms. The Applicant asserts that this supportive trial fulfils the requirements of 21 CFR 300.50.[6]

Trial MB102129 was a 24-week (with a 28-week LT extension) that evaluated the efficacy and safety of the sequential addition of dapagliflozin 10 mg/day in adult T2D patients who had inadequate glycemic control on the maximum tolerated dose of saxagliptin (5 mg/day) and metformin (≥1500 mg/day). This trial was submitted primarily to support safety. Compared to the placebo dual therapy arm, the dapagliflozin triple therapy arm resulted in a greater reduction in HbA1c from baseline to Week 24 (-0.65; 95% CI, -0.83 to -0.47).

Based on the totality of these data, and in accordance with 21 CFR 314.126(a)(b),[5] I believe that the Applicant has provided sufficient evidence of effectiveness to support approval of this FCDP with an amended indication.

8 Review of Safety

8.1. Safety Review Approach

The safety evaluation for this Application was primarily based on the integrated safety data from the three Phase 3 trials (i.e., CV181168, CV181169, and MB102129), and the data from the three individual Phase 1 trials (i.e., CV181191, CV181341, (b) (4)). Descriptions of the trial designs and populations are provided in Table 3.

The Applicant submitted integrated ST (i.e., a pool of the 24-week trial data) and ST+LT (i.e., a pool of the 52-week data) safety datasets for their three Phase 3 trials. The Applicant states that the rationale for pooling these trials was based on similarity in study designs and the

availability of a larger population to establish safety of their FCDP. It is noted that Trials CV181168 and MB102129 included a 16-week open-label (OL) phase in which subjects were treated with saxagliptin+metformin or dapagliflozin+metformin, respectively. Subjects who met inclusion criteria (HbA1c ≥7 and ≤10.5%) at the end of this phase entered the ST, double-blind treatment phase. Hence, except for rare events, other AEs occurring with comparators during this treatment period were not considered for comparing incidence rates to study drug combinations. For the supplemental NDAs (i.e., sNDA 22350/S-018 and sNDA 200678/S-018), safety data from the single clinical trial CV181168 was reviewed.

The safety evaluation plan for this Application included routine assessments, as well as a focus on potential risks associated with DPP-4 inhibitors and SGLT-2 inhibitors (i.e., adverse events of special interest [AEOSI]). Additionally, clinical study reports and analysis datasets were reviewed for safety. Selected AEs and laboratory abnormalities were crosschecked with those provided with the NDA documents. (b) (4) Applicant was requested to provide updated information (additional analyses and evaluation of postmarketing reports) related to specific safety concerns (i.e., CK elevations, and musculoskeletal and renal AEs), and has provided this information in their 4-Month Safety Update.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database was comprised of all subjects randomized and treated (i.e., took at least one dose of investigational product). A summary of the size of the safety population and duration of exposure to investigational products is presented in Table 13. Overall, 1169 subjects were randomized and treated, of which 492 received saxagliptin+dapagliflozin+metformin. The median duration of exposure was longer in this treatment arm (359 days) compared to the saxagliptin+metformin (176 days) and the dapagliflozin+metformin (176 days) treatment arms, with overall patient-years (p-y) of exposure of 370.2 p-y, 227.6 p-y, and 230.8 p-y, respectively. To account for the differences in treatment exposure, the Applicant also assessed incidence rates per 100 p-y for many of their analyses. On average, 86% (423/492) of subjects in the saxagliptin+dapagliflozin+metformin arm were exposed for at least 168 days (24 weeks), while approximately 48% were exposed for at least 360 days.

Table 13: Integrated Safety Population, Size and Duration of Exposure (ST+LT Pool)

	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Total N=1169
Phase 3 Trials — no. (%)				
CV181168	153 (31.1)	–	162 (47.5)	315 (26.9)
CV181169	179 (36.4)	176 (52.4)	179 (52.5)	534 (45.7)
MB102129	160 (32.5)	160 (47.6)	–	320 (27.4)
Saxagliptin Exposure				
Mean (range) — days	274.6 (1, 396)	248.1 (1, 404)	247.2 (1, 395)	259.0 (1, 404)
Median (IQR) — days	359.0 (169.0, 365.0)	176.0 (169.0, 364.0	176.0 (169.0, 364.0)	223.5 (169.0, 264.0)
>360 Days — no. (%)	235 (47.8)	128 (38.1)	130 (38.1)	493 (42.2)
Dapagliflozin Exposure				
Mean (range) — days	274.5 (1, 396)	247.4 (1, 404)	247.8 (1, 395)	258.9 (1, 404)
Median (IQR) — days	359.0 (169.0, 365.0)	175.5 (169.0, 364.0)	175.5 (169.0, 364.0)	223.0 (169.0, 364.0)
>360 Days — no. (%)	236 (48.0)	128 (38.1)	127 (37.2)	491 (42.0)

Source: Adapted from the Applicant's 4-Month Safety Update (labeled as Table 7, pages 40-41 of 5911), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf.
Abbreviations: Dapa, dapagliflozin; IQR, 25th and 75th interquartile range; Met, metformin; no., number; and Saxa, saxagliptin.

8.2.2. Relevant characteristics of the safety population:

For the safety population, the baseline demographic and clinical characteristics appeared to be reasonably similar across the treatment arms (Table 14). There were similar distributions of males and females, and U.S. and non-U.S. patients. The mean baseline HbA1c was approximately 8.5%, and average duration of diabetes was 7.6 years. Overall, the population tended to be less than 65 years of age; were mostly white; had a BMI above 30 kg/m^2, and normal renal function (i.e., eGFR >90 $mL/min/1.73m^2$). Similar to the demographics for Trial CV181168, the safety population included limited numbers of subjects who were ≥75 years of age, and non-White participants represented only 20% of randomized/treated subjects.

Table 14: Demographics and Clinical Characteristics (Safety Population)*

	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Total (N=1169)
DEMOGRAPHICS				
Age, mean ± SD — yr	54.4± 9.5	54.8 ± 9.6	54.0 ± 9.5	54.4 ± 9.5
<65 yr — no. (%)	429 (87.2)	280 (83.3)	298 (87.4)	1007 (86.1)
≥65 yr — no. (%)	63 (12.8)	56 (16.7)	43 (12.6)	162 (13.9)
≥75 yr — no. (%)	4 (0.8)	1 (0.3)	4 (1.2)	9 (0.8)

	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Total (N=1169)
Female sex — no. (%)	264 (53.7)	166 (49.4)	176 (51.6)	606 (51.8)
Race — no. (%)				
White	406 (82.5)	268 (79.8)	272 (79.8)	946 (80.9)
Black/African American	41 (8.3)	32 (9.5)	25 (7.3)	98 (8.4)
Asian	18 (3.7)	12 (3.6)	18 (5.3)	48 (4.1)
Other	27 (5.5)	24 (7.1)	26 (7.6)	77 (6.6)
Region — no. (%)				
North America	231 (47.0)	147 (43.8)	186 (54.5)	564 (48.2)
Europe	146 (29.7)	97 (28.9)	95 (27.9)	338 (28.9)
Latin America	113 (23.0)	89 (26.5)	59 (17.3)	261 (22.3)
Asia/Pacific	2 (0.4)	3 (0.9)	1 (0.3)	6 (0.5)
Country — no. (%)				
United States of America	203 (41.3)	136 (40.5)	160 (46.9)	499 (42.7)
Mexico	113 (23.0)	89 (26.5)	59 (17.3)	261 (22.3)
Russia	56 (11.4)	38 (11.3)	28 (8.2)	122 (10.4)
Romania	36 (7.3)	20 (6.0)	29 (8.5)	85 (7.3)
Canada	23 (4.7)	6 (1.8)	22 (6.5)	51 (4.4)
Poland	17 (3.5)	11 (3.3)	17 (5.0)	45 (3.8)
Czech Republic	9 (1.8)	8 (2.4)	4 (1.2)	21 (1.8)
Puerto Rico	5 (1.0)	5 (1.5)	4 (1.2)	14 (1.2)
Hungary	4 (0.8)	0 (0.0)	3 (0.9)	7 (0.6)
CLINICAL CHARACTERISTICS				
BMI, mg/m^2 — mean ± SD	31.5 ± 5.0	32.0 ± 5.2	31.4 ± 5.3	31.6 ± 5.1
<30 mg/m^2 — no. (%)	201 (40.9)	124 (36.9)	139 (40.8)	464 (39.7)
≥30 mg/m^2 — no. (%)	291 (59.1)	212 (63.1)	202 (59.2)	705 (60.3)
Duration of T2D, mean ± SD — yr	7.5 ± 5.9	8.0 ± 6.0	7.4 ± 5.6	7.6 ± 5.9
<3 yr — no. (%)	113 (23.0)	64 (19.0)	75 (22.0)	252 (21.6)
≥3 to ≤10 yr — no. (%)	243 (49.4)	170 (50.6)	168 (49.3)	581 (49.7)
>10 yr — no. (%)	134 (27.2)	102 (30.4)	98 (28.7)	334 (28.6)
Glycemic Status				
HbA1c% — mean ± SD	8.4 ± 1.1	8.6 ± 1.1	8.4 ± 1.2	8.5 ± 1.1
<8% — no. (%)	195 (39.6)	105 (31.3)	140 (41.1)	440 (37.6)
8 to <9% — no. (%)	160 (32.5)	115 (34.2)	103 (30.2)	378 (32.3)
≥9% — no. (%)	137 (27.8)	116 (34.5)	98 (28.7)	351 (30.0)
2-h PPG, mg/dL — mean ± SD	231.6 ± 57.4	249.8 ± 60.1	227.1 ± 59.7	235.5 ± 59.6
FPG, mg/dL — mean ± SD	174.9 ± 44.1	184.5 ± 46.4	172.0 ± 44.5	176.8 ± 45.1
C-peptide, ng/mL — mean ± SD	2.3 ± 1.0	2.4 ± 1.0	2.4 ± 1.1	2.4 ± 1.1

	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Total (N=1169)
eGFR, mL/min/1.73m^2 — mean ± SD	94.4 ± 20.6	92.0 ± 21.2	93.9 ± 20.2	93.6 ± 20.7
≥30 to <60 mL/min/1.73m^2 — no. (%)	13 (2.6)	9 (2.7)	6 (1.8)	28 (2.4)
≥60 to <90 mL/min/1.73m^2 — no. (%)	220 (44.7)	167 (49.7)	145 (42.5)	532 (45.5)
>90 mL/min/1.73m^2 — no. (%)	259 (52.6)	160 (47.6)	190 (55.7)	609 (52.1)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 8, pages 42-43 of 5911), and derived from the addm.xpt dataset, available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: BMI, body mass index; C-peptide, connecting peptide; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; no., number; PPG, postprandial glucose; SD, standard deviation; T2D, type 2 diabetes mellitus; US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigational product.

8.2.3. Adequacy of the safety database:

At the time of the original submission for NDA (b) (4) only 73% and 60% of subjects, had completed the ST+LT portions of Trials CV181168 and MB10219, respectively, and the overall saxagliptin+dapagliflozin+metformin arm included 272 p-y of exposure. (b) (4) Applicant was informed that (b) (4) they submit updated integrated safety analyses that include the completed long-term data from Trials CV181168 and MB102129. The Applicant has complied with this recommendation for the current Application, and submitted the additional data (i.e., ST+LT datasets) from these completed trials, which now includes a total exposure of 370.2 p-y in the saxagliptin+dapagliflozin+metformin treatment arm. I feel that the additional exposure and safety data provided is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Safety was evaluated based on the following: treatment-emergent adverse events (TEAEs), clinical laboratory assessments, changes in vital signs, ECGs findings, and physical examinations. The quality of the overall submission was adequate. The frequency of safety assessments for the ST and the ST+LT treatment periods are presented Table 35 and Table 36, respectively (please refer to Appendix 13.4), and were adequate to evaluate safety for this Application. Additionally, many of the key safety findings reported in this Application were reproduced and confirmed using the ST and ST+LT integrated datasets. Based on these analyses, there were no obvious issues related to data quality.

8.3.2. **Categorization of Adverse Events**

The integrated analyses were conducted using the Randomized and Treated Subjects Dataset (i.e., all subjects who received ≥1 dose of double-blind study medication). Safety analyses were performed by the Applicant on all data regardless of rescue (unless specified otherwise) for the double-blind treatment period. Adverse events in the CSR for Trial CV181168 were classified by System Organ Class (SOC) and/or Preferred Term (PT), and coded based on Medical Dictionary for Regulatory Activities (MedDRA) versions 17.0. For the Integrated ST safety pool, MedDRA version 17.0 was used, while for the ST+LT pool, version 17.1 was used.

An adverse event (AE) was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an investigational (medicinal) product, and that did not necessarily have a causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs occurring from Day 1 of the ST treatment period up to 4 days and up to 30 days after the last dose of study medication during the ST+LT treatment period for non-serious AEs and SAEs, respectively. Adverse event occurrence was identified based on information volunteered by the subject or by general questioning and examination of subjects at each visit. The AE information obtained and documented in the electronic case report form (eCRF) included: the event, onset and resolution dates, intensity (mild, moderate, severe, or very severe), action taken, treatment required, outcome, and the Investigator's opinion regarding the relationship to study treatment. The intensity of AEs was graded using the following definitions:

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

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

- Resulted in death
- Was life-threatening (defined as an event in which the subject was at risk of death at the time of the event
- Required inpatient hospitalization or caused prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require

intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above)

All nonserious and serious AEs were to be followed until resolution or stabilization.

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 Case Report Form [CRF] text and analysis datasets) provided by the investigators and the MedDRA PTs for which these AEs were coded. The classifications of these data appeared appropriate.

The Applicant also created Custom MedDRA Queries (CMQs) for identifying adverse events of special interest (AEOSI) from lists of prespecified PTs (identified prior to unblinding Trials CV181168, CV181169, and MB102129) or Standardized MedDRA Queries (SMQs). These AEOSI were related to safety findings in the saxagliptin and dapagliflozin nonclinical and clinical programs, and known safety signals/theoretical concerns (e.g., related to mechanisms of action) associated with other DPP-4 inhibitors and SGLT-2 inhibitors. For the integrated safety assessment AEOSI included: bladder neoplasm; breast neoplasm; cardiac failure; confirmed adjudicated cardiovascular (CV) events; confirmed adjudicated hepatic events; decreased lymphocyte count; decreased thrombocyte count; fractures; genital infections; hypoglycemia, infections, malignancies (including pancreatic cancer); opportunistic infection, pancreatitis; renal failure/impairment; severe cutaneous adverse reactions (including Stevens-Johnson syndrome); severe hypersensitivity (anaphylaxis, angioedema and urticaria related events); volume depletion (including hypotension, dehydration, and hypovolemia); and urinary tract infections. Pancreatic cancer and hypovolemia were added post data-base lock for study CV181169, and cardiac failure was added as an AEOSI for Trials CV181168 and MB102129.

For completeness, my safety evaluation also included 'Broad' Custom MedDRA Queries (CMQs) that were derived using existing SMQs and PTs for AEOSI from other DPP-4 inhibitor and SGLT-2 inhibitor clinical programs, including new/evolving safety issues identified for these products. These CMQs and associated PTs (which also included the Applicant's list of PTs for respective CMQs) are presented in Appendix 13.5. Assessments for AEOSIs will be described in more detail in the relevant sections.

8.3.3. **Routine Clinical Tests**

The frequency of clinical laboratory safety assessments for Trial CV181168 is described in Appendix 13.4 Schedule of Trial Procedures. Blood and urine samples were obtained for evaluation of standard safety laboratory panels (chemistry, hematology, and urinalysis) at Weeks -18, -16, -10, -2, 0 (Day 1), 6, 12, 18, 24, 32, 40, and 52/termination, and at the time of rescue or early treatment discontinuation. Laboratory assessments for the integrated safety

datasets were also provided at these same time points from Weeks 0-52. Blood specimens for evaluation of lipid and glycemic parameters were collected under fasted conditions. The laboratory data were evaluated based on changes from baseline and marked abnormalities (MAs). A listing of the MAs by relevant laboratory parameter, and the numbers/proportions (%) of subjects with these abnormalities, is discussed in more detail in Section 8.4.6. The safety laboratory panels and the frequency of assessments were adequate, based on the known toxicity profiles of saxagliptin and dapagliflozin, the patient population studied, and the proposed indication.

Vital signs were evaluated based on changes from baseline at the same time points as described above. The normality or abnormality of ECG findings (as determined by the investigator at baseline, and Weeks 24 and 52) were summarized in frequency tables.

8.4. Safety Results

A summary of the AEs reported in the integrated ST and ST+LT safety pools of this Application is presented in Table 15. Overall, more than 50% of subjects in all treatment arms for the ST+LT treatment period experienced at least one AE. However, SAEs and hypoglycemic events were observed in relatively fewer subjects (approximately 3-4% and 1-2%, respectively), and the proportions of subjects with these events were similar across treatment arms. There were only two deaths reported during the ST+LT treatment period; both occurring during the LT treatment period, of which one had been randomized to the saxagliptin+dapagliflozin+metformin arm (Section8.4.1). As noted in Section 8.2.1, the safety data for the saxagliptin+dapagliflozin+metformin treatment arm included longer treatment exposures (i.e., 139 p-y) than the other treatment arms, and these differences should be considered when reviewing event counts for the ST+LT treatment period.

Table 15: Summary of Adverse Events (Integrated ST and ST+LT Safety Pools)

	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Event — no. (%)						
At least one AE	250 (50.8)	187 (55.7)	157 (46.0)	282 (57.3)	207 (61.6)	181 (53.1)
At least one hypoglycemia	6 (1.2)	3 (0.9)	6 (1.8)	8 (1.6)	4 (1.2)	7 (2.1)
Deaths	0	0	0	1 (0.2)	0	1 (0.3)
At least one SAE	12 (2.4)	9 (2.7)	7 (2.1)	16 (3.3)	10 (3.0)	13 (3.8)

	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
SAE leading to D/C of study medication	3 (0.6)	2 (0.6)	0	5 (1.0	2 (0.6)	1 (0.3)
AE leading to D/C of study medication				13 (2.6)	3 (0.9)	6 (1.8)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 10, pages 47 of 5911), and derived from the addm.xpt dataset, available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: AE, adverse event; Dapa, dapagliflozin; D/C, discontinuation; Met, metformin; SAE, serious adverse event; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.4.1. Deaths

In Trial CV181168, one subject (CV181168-(b) (6)) died prior to receiving study medications, and one subject (CV181168-(b) (6)) died of a pulmonary embolism during the open-label treatment period (dapagliflozin+metformin; study day not reported). There were only two deaths reported for this Application during the ST+LT treatment period, one in the saxagliptin + dapagliflozin + placebo arm (i.e., SAEs of acute myocardial infarction [MI] and cardiac failure acute), and a second in the dapagliflozin+metformin arm (i.e., SAE of MI). Additionally, in Trial CV181169, one subject (CV181169-(b) (6)) died six months after discontinuing study medications and post database lock. Brief narrative summaries for the three relevant cases are provided as follows:

Saxagliptin plus dapagliflozin plus metformin arm:

- **Subject MB102129-**(b) (6): a 69-year-old Caucasian male died of an acute MI and acute heart failure on Study Day 353. The subject had a medical history that included steatohepatosis, atrial fibrillation, New York Heart Association (NYHA) class II heart failure, hypertension, diabetic neuropathy, coronary artery disease (including MI), and obesity. Prior and concomitant medications included metformin, vildagliptin (Days -988 to -50), dabigatran, bisoprolol, digoxin, isorbide dinitrate, and spironolactone. The subject was hospitalized on Study Day 341 with an SAE of unstable angina, had coronary artery bypass grafting (CABG) performed four days later, and was reported as recovered from the event the same day (Day 345). Study medications were stopped on Day 344. Given the prior history of coronary artery disease (CAD), preceding SAE of unstable angina, and other comorbidities, a causal association to study medications is unlikely.

- **Subject CV181169-(b) (6):** a 73-year-old White male, was diagnosed with an SAE of chronic pancreatitis on Day 101. His medical history included cholecystectomy, hyperlipidemia and obesity. A computed tomography (CT) scan of the abdomen and pelvis was significant for chronic pancreatitis and three small non calcified lung nodules. The reason for the CT scan is not reported. Evidence for acute pancreatitis was not found. Based on CT findings, the event was graded mild in intensity. No action was taken with regards to study medications. On Day 137 the subject was diagnosed with a nonmalignant gastric neoplasm, found during incidental radiography. The Investigator reported a nonserious AE of dysphagia, graded mild in intensity, which was reported as resolved on Day 166. The subject completed the study and received the last doses of metformin on Day 169, and saxagliptin + dapagliflozin on Day 170. Three months after completion of the study, the subject underwent gastroscopy which showed a gastric mass. On Day 297, laboratory test results revealed positive carcinoembryonic antigen. On Day 351, six months after completion of study medications, the subject died due to gastric neoplasm. There was an apparent delay in diagnosis between Day 137 and 3-months post-study. Given the short duration of exposure (<5 months), a causal association with study medications is not likely. However, the potential for study medications to promote tumor growth is unknown.

Dapagliflozin plus metformin arm:

- **Subject CV181168-(b) (6):** a 66-year-old Caucasian female died of an SAE of MI, complicated by pericardial tamponade, acute circulatory arrest and acute respiratory distress on Study Day 203, two days following the last dose of study medications (Day 201). Her relevant medical history included hypertension, which was treated with indapamide, bisoprolol, and ramipril.

8.4.2. Serious Adverse Events

The occurrence of SAE in both the ST and the ST+LT treatment periods were relatively limited (i.e., approximately 2-4% of subjects), with similar proportions of subjects experiencing these events across treatment arms (Table 16). During the ST+LT treatment period, the SOC with the highest number of subjects with SAEs in the saxagliptin+dapagliflozin+metformin treatment arm was cardiac disorders, which included four subjects; of which one subject (MB102129-(b) (6) (b) (6)) with an SAE of acute MI died (described in Section 8.4.1). This treatment arm also included three neoplasms (i.e., hepatic cancer [CV181168-(b) (6)], invasive ductal breast carcinoma [MB102129-(b) (6)], and gastric neoplasm [CV181169-(b) (6); resulted in death]), which all occurred during the ST treatment period; latencies between 59-137 days), and a single case each of rhabdomyolysis (CV181168-(b) (6); Day 280), thrombocytopenia (MB102129-(b) (6); Day 127), and pyelonephritis (CV181168-(b) (6); Day 307). These events were all reported during the original NDA review of NDA (b) (6), and will be discussed further in Section 8.5. The

SAEs of thrombocytopenia and pyelonephritis were considered by the investigators to be treatment-related. Although other SOCs had numerically more subjects with SAEs in the saxagliptin+dapagliflozin+metformin treatment arm compared to the other trial arms, the numbers were limited. Additionally, there were more subjects with SAEs of infection in the treatment arms that included saxagliptin (a labeled adverse reaction), but again the numbers of events (n=5) were inadequate to draw meaningful conclusions, and none were associated with opportunistic infections.

Table 16: Summary of Serious Adverse Events by System Organ Class (Integrated ST and ST+LT Safety Pools)

System Organ Class — no. (%) MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
TOTAL SUBJECTS WITH SAES	**12 (2.4)**	**9 (2.7)**	**7 (2.1)**	**16 (3.3)**	**10 (3.0)**	**13 (3.8)**
CARDIAC DISORDERS	**3 (0.6)**	**0**	**1 (0.3)**	**4 (0.8)**	**0**	**3 (0.9)**
Acute myocardial infarction	1 (0.2)	0	0	2 (0.4)	0	0
Atrial fibrillation	0	0	1 (0.2)	1 (0.2)	0	1 (0.3)
Cardiac failure	1 (0.2)	0	0	1 (0.2)	0	0
Cardiac failure acute	0	0	0	1 (0.2)	0	0
Ventricular tachycardia	1 (0.2)	0	0	1 (0.2)	0	0
Angina unstable	0	0	0	1 (0.2)	0	0
Myocardial infarction	0	0	0	0	0	1 (0.3)
Angina pectoris	0	0	0	0	0	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**3 (0.6)**	**0**	**0**	**3 (0.6)**	**0**	**0**
Hepatic cancer	1 (0.2)	0	0	1 (0.2)	0	0
Invasive ductal breast carcinoma	1 (0.2)	0	0	1 (0.2)	0	0
Gastric neoplasm	1 (0.2)	0	0	1 (0.2)	0	0
INFECTIONS AND INFESTATIONS	**0**	**2 (0.6)**	**0**	**3 (0.6)**	**2 (0.6)**	**0**
Postoperative wound infection	0	0	0	1 (0.2)	0	0
Pyelonephritis	0	0	0	1 (0.2)	0	0
Appendicitis	0	0	0	1 (0.2)	0	0
Gangrene	0	1 (0.3)	0	0	1 (0.3)	0
Tooth infection	0	1 (0.3)	0	0	1 (0.3)	0
Abscess limb	0	1 (0.3)	0	0	1 (0.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2 (0.4)**	**0**	**0**	**2 (0.4)**	**0**	**0**
Skin ulcer	1 (0.2)	0	0	1 (0.2)	0	0
Diabetic foot	1 (0.2)	0	0	1 (0.2)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**2 (0.4)**	**1 (0.3)**	**1 (0.3)**	**2 (0.4)**	**1 (0.3)**	**1 (0.3)**

System Organ Class — no. (%) MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Pulmonary embolism	1 (0.2)	1 (0.3)	0	1 (0.2)	1 (0.3)	0
Chronic obstructive pulmonary disease	1 (0.2)	0	0	1 (0.2)	0	0
Asthma	0	0	1 (0.3)	0	0	1 (0.3)
VASCULAR DISORDERS	**1 (0.2)**	**1 (0.3)**	**0**	**2 (0.4)**	**1 (0.3)**	**0**
Peripheral vascular disorder	0	0	0	1 (0.2)	0	0
Peripheral artery thrombosis	1 (0.2)	0	0	1 (0.2)	0	0
Deep vein thrombosis	0	1 (0.3)	0	0	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	**0**	**0**	**1 (0.3)**	**1 (0.2)**	**0**	**1 (0.3)**
Syncope	0	0	0	1 (0.2)	0	0
Transient ischaemic attack	0	0	1 (0.3)	0	0	1 (0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1 (0.2)**	**0**	**0**	**1 (0.2)**	**0**	**0**
Thrombocytopenia	1 (0.2)	0	0	1 (0.2)	0	0
GASTROINTESTINAL DISORDERS	**1 (0.2)**	**2 (0.6)**	**1 (0.3)**	**1 (0.2)**	**2 (0.6)**	**1 (0.3)**
Pancreatitis chronic	1 (0.2)	0	0	1 (0.2)	0	0
Umbilical hernia	0	1 (0.3)	0	0	1 (0.3)	0
Colitis	0	0	1 (0.3)	0	0	1 (0.3)
Gastritis	0	0	1 (0.3)	0	0	1 (0.3)
Gastric ulcer	0	1 (0.3)	0	0	1 (0.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**0**	**1 (0.3)**	**0**	**1 (0.2)**	**1 (0.3)**	**0**
Rhabdomyolysis	0	0	0	1 (0.2)	0	0
Arthritis	0	1 (0.3)	0	0	1 (0.3)	0
HEPATOBILIARY DISORDERS	**1 (0.2)**	**0**	**0**	**1 (0.2)**	**0**	**0**
Cholelithiasis	1 (0.2)	0	0	1 (0.2)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0**	**2 (0.6)**	**1 (0.3)**	**0**	**2 (0.6)**	**1 (0.3)**
Patella fracture	0	1 (0.3)	0	0	1 (0.3)	0
Fall	0	0	1 (0.3)	0	0	1 (0.3)
Ankle fracture	0	1 (0.3)	0	0	1 (0.3)	0
INVESTIGATIONS	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Staphylococcus test positive	0	0	0	0	0	1 (0.3)
Liver function test abnormal	0	0	0	0	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	**0**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**0**
Hyperkalaemia	0	1 (0.3)	0	0	1 (0.3)	0
EYE DISORDERS	**0**	**0**	**0**	**0**	**0**	**1 (0.3)**
Retinal detachment	0	0	0	0	0	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**0**	**0**	**1 (0.3)**	**0**	**0**	**2 (0.6)**
Uterine haemorrhage	0	0	0	0	0	1 (0.3)

System Organ Class — no. (%) MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Benign prostatic hyperplasia	0	0	1 (0.3)	0	0	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0**	**1 (0.3)**	**1 (0.3)**	**0**	**1 (0.3)**	**3 (0.9)**
Chest pain	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)
Non-cardiac chest pain	0	0	0	0	0	1 (0.3)
Hernia	0	0	0	0	0	1 (0.3)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 13, pages 53-56 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; SAE, serious adverse event; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs during the ST and ST+LT treatment periods were few (<3%; Table 17). There were numerically more subjects who discontinued study medications due to AEs in the saxagliptin+dapagliflozin+metformin treatment arm during both periods, with events related to renal function/impairment more common in this treatment group (i.e., glomerular filtration rate decreased, pollakiuria, renal impairment, and urine albumin/creatinine ratio increased). However, the numbers of subjects were insufficient to adequately evaluate trends in events, even by MedDRA hierarchy (i.e., High Level Terms [HLTs], High Level Group Terms [HLGTs] or SOCs). Additionally, four subjects from the treatment arms that included dapagliflozin, discontinued study early due to a decrease in eGFR (i.e., levels fell below prespecified protocol withdrawal criteria of sustained eGFR <60 mL/min/1.73 m^2 for ≥12-16 weeks).

Table 17: Summary of Discontinuations Due to Adverse Events (Integrated ST and ST+LT Safety Pools)

Discontinuations Due to AEs MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
TOTAL SUBJECTS D/C	**10 (2.0)**	**2 (0.6)**	**4 (1.2)**	**13 (2.6)**	**3 (0.9)**	**6 (1.8)**
Glomerular filtration rate decreased	2 (0.4)	0	1 (0.3)	2 (0.4)	0	2 (0.6)
Pollakiuria	2 (0.4)	0	0	2 (0.4)*	0	0
Urinary tract infection	1 (0.2)	0	0	2 (0.4)	0	0
Cardiac failure	1 (0.2)	0	0	1 (0.2)	0	0

Discontinuations Due to AEs MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Dental caries	1 (0.2)	0	0	1 (0.2)	0	0
Invasive ductal breast carcinoma	1 (0.2)	0	0	1 (0.2)	0	0
Pleural effusion	1 (0.2)	0	0	1 (0.2)	0	0
Renal impairment	1 (0.2)	0	0	1 (0.2)	0	0
Thrombocytopenia	1 (0.2)	0	0	1 (0.2)	0	0
Transaminases increased	1 (0.2)	0	0	1 (0.2)	0	0
Vaginal haemorrhage	1 (0.2)	0	0	1 (0.2)	0	0
Vulvovaginal mycotic infection	1 (0.2)	0	0	1 (0.2)	0	0
Hepatic steatosis	0	0	0	1 (0.2)	1 (0.3)	0
Urine albumin/creatinine ratio increased	0	0	0	1 (0.2)	0	0
Pyelonephritis	0	0	0	1 (0.2)	0	0
Angina unstable	0	0	0	1 (0.2)	0	0
Alanine aminotransferase increased	0	0	1 (0.3)	0	0	1 (0.3)
Myocardial infarction	0	0	0	0	0	1 (0.3)
Hepatic cirrhosis	0	0	0	0	1 (0.3)	0
Liver function test abnormal	0	0	0	0	1 (0.3)	0
Ankle fracture	0	1 (0.3)	0	0	1 (0.3)	0
Ascites	0	0	1 (0.3)	0	0	1 (0.3)
Diabetic foot	0	1 (0.3)	0	0	1 (0.3)*	0
Drug intolerance	0	0	1 (0.3)	0	0	1 (0.3)
Gangrene	0	1 (0.3)	0	0	1 (0.3)*	0

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 14, pages 61-62 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
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url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: AE, adverse event; Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; No., number; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.
*Events of 'diabetic foot' and 'gangrene' for Subject MB102129-(b) (6) and 'pollakiuria' for Subjects MB102129-(b) (6) and MB102129-(b) (6) were derived from the adae.xpt dataset (i.e., numbers differ from the Applicant's table for the ST+LT treatment period).

8.4.4. Significant Adverse Events

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

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of all TEAEs reported in ≥2% of subjects during the ST and the ST+LT treatment periods, regardless of treatment allocation, is presented in Table 18. During the ST treatment period, common TEAEs in the saxagliptin+dapagliflozin+metformin arm occurring in a higher proportion of subjects compared to the other two treatment arms included nasopharyngitis, back pain, and arthralgia, while during the ST+LT period, diarrhea and arthralgia were reported more often. Following a review of MedDRA HLTs, common (≥2%) HLTs that were reported more often in the saxagliptin+dapagliflozin+metformin arm included: diarrhoea (3.7%; 18/492); bladder and urethral symptoms (3.3%; 16/492); joint related signs and symptoms (2.4%; 12/492); and gastrointestinal and abdominal pains (2.2%; 11/492). By SOC only 'Nervous System Disorders' occurred in a higher proportion of subjects receiving triple therapy (8.7%; 43/492) than in the other two treatment arms at an incidence of ≥2%.

Table 18: Summary of Common TEAEs (Integrated ST and ST+LT Safety Pools)

TEAEs (≥2% of Subjects) MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
TOTAL SUBJECTS WITH AEs	**250 (50.8)**	**187 (55.7)**	**157 (46.0)**	**282 (57.3)**	**207 (61.6)**	**181 (53.1)**
Urinary tract infection	17 (3.5)	18 (5.4)	13 (3.8)	27 (5.5)	24 (7.1)	18 (5.3)
Headache	17 (3.5)	14 (4.2)	10 (2.9)	21 (4.3)	18 (5.4)	14 (4.1)
Nasopharyngitis	18 (3.7)	12 (3.6)	10 (2.9)	21 (4.3)	16 (4.8)	15 (4.4)
Diarrhoea	11 (2.2)	11 (3.3)	6 (1.8)	18 (3.7)	12 (3.6)	8 (2.3)
Influenza	14 (2.8)	15 (4.5)	11 (3.2)	18 (3.7)	19 (5.7)	12 (3.5)
Back pain	13 (2.6)	8 (2.4)	6 (1.8)	16 (3.3)	12 (3.6)	8 (2.3)
Hypertriglyceridaemia	11 (2.2)	13 (3.9)	9 (2.6)	13 (2.6)	14 (4.2)	9 (2.6)
Arthralgia	12 (2.4)	4 (1.2)	3 (0.9)	12 (2.4)	4 (1.2)	3 (0.9)
Dyslipidaemia	11(2.2)	8 (2.4)	7 (2.1)	12 (2.4)	8 (2.4)	7 (2.1)
Upper respiratory tract infection	8 (1.6)	7 (2.1)	9 (2.6)	11 (2.2)	8 (2.4)	11 (3.2)
Vulvovaginal mycotic infection	7(1.4)	1 (0.3)	8 (2.3)	10 (2.0)	1 (0.3)	9 (2.6)
Cough	0	0	0	8 (1.6)	7 (2.1)	6 (1.8)
Nausea	8 (1.6)	9 (2.7)	5 (1.5)	8 (1.6)	11 (3.3)	6 (1.8)
Pain in extremity	0	0	0	5 (1.0)	7 (2.1)	6 (1.8)
Dyspepsia	0	0	0	4 (0.8)	8 (2.4)	5 (1.5)
Depression	0	0	0	3 (0.6)	7 (2.1)	2 (0.6)
Muscle spasms	0	0	0	3 (0.6)	7 (2.1)	2 (0.6)
Hyperuricaemia	0	0	0	1 (0.2)	7 (2.1)	2 (0.6)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table11, pages 49-50 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:

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url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG

Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period; TEAE, treatment-emergent adverse event.

8.4.6. Laboratory Findings

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

Marked Laboratory Abnormalities

A summary table of prespecified marked laboratory abnormalities reported during the ST+LT treatment period is presented in Table 19. Generally, the numbers of subjects with these laboratory changes were limited. However, compared to the other two treatment arms, the saxagliptin+dapagliflozin+metformin treatment group included higher proportions of subjects with marked abnormalities of low serum sodium, phosphorus, and glucose, and high serum potassium, calcium, and CK concentrations. Although a higher proportion of subjects had marked laboratory abnormalities of hyperkalemia (2.9%; 14/492) in the saxagliptin+dapagliflozin+metformin treatment arm, no subjects discontinued study due to these events, and none were coded as SAEs.

Marked CK elevations were noted during the original review of NDA (b) (4) for this FCDP. Please refer to Dr. Suchitra Balakrishnan's Clinical Review (dated September 15, 2015) and the Cross-Discipline Team Leader Memorandum (dated October 7, 2015) for additional discussion of the findings from this submission. With an additional 100 p-y of exposure to the combination of saxagliptin+dapagliflozin+metformin, there have been no additional cases identified from the completed Phase 3 trials included in the Applicant's safety database. Further discussion of these laboratory abnormalities will be discussed in Section 8.5.15 (Myopathy/Rhabdomyolysis). A summary of the mean changes in serum CK from baseline to Week 52 of the ST+LT treatment period also is presented in the Clinical Chemistry Section below in Table 21.

Table 19: Summary of Marked Laboratory Abnormalities (ST+LT Safety Pool)

Laboratory Parameter	Saxa+Dapa+Met (N=492)			Saxa+Met (N=336)			Dapa+Met (N=341)		
	N	Low	High	N	Low	High	N	Low	High
Hematology									
Hemoglobin (<6 G/DL, >18 G/DL)	487	0	4 (0.8)	333	0	1 (0.3)	333	0	3 (0.9)
Hemoglobin (>20 G/DL)	487	NE	0	333	NE	0	333	NE	0
Hematocrit (<20%, >55%)	487	0	6 (1.2)	333	0	4 (1.2)	333	0	5 (1.5)
Hematocrit (>60%)	487	NE	0	333	NE	1 (0.3)	333	NE	0

Laboratory Parameter	Saxa+Dapa+Met (N=492)			Saxa+Met (N=336)			Dapa+Met (N=341)		
	N	Low	High	N	Low	High	N	Low	High
Serum Renal Function Tests									
Creatinine (>=1.5 x BSL)	486	NE	5 (1.0)	334	NE	6 (1.8)	334	NE	5 (1.5)
Creatinine (>=2.5 mg/dL)	486	NE	1 (0.2)	334	NE	0	334	NE	1 (0.3)
Serum Electrolytes									
Sodium (<130, >150 mEq/L)	486	1 (0.2)	15 (3.1)	334	0	9 (2.7)	334	0	11 (3.3)
Sodium (<120 mEq/L)	486	0	NE	334	0	NE	334	0	NE
Potassium (≤2.5, ≥6.0 mEq/L)	486	0	14 (2.9)	334	0	9 (2.7)	334	0	8 (2.4)
Calcium, total	486	6 (1.2)	5 (1.0)	334	4 (1.2)	0	334	1 (0.3)	3 (0.9)
Phosphorus, inorganic	486	2 (0.4)	6 (1.2)	334	0	1 (0.3)	334	0	7 (2.1)
Magnesium (<1 mEq/L, >4 mEq/L)	486	0	0	334	3 (0.9)	0	334		0
Cardiac tests									
Creatine kinase (>5x ULN)	**486**	**NE**	**7 (1.4)***	**334**	**NE**	**0**	**334**	**NE**	**1 (0.3)**
Creatine kinase (>10x ULN)	**486**	**NE**	**5 (1.0)***	**334**	**NE**	**0**	**334**	**NE**	**1 (0.3)**
Plasma Glucose									
Glucose (<54, >350 mg/dL)	486	4 (0.8)	4 (0.8)	333	0	9 (2.7)	333	0	1 (0.3)
Serum Protein									
Protein, total (>10 G/dL)	486	NE	0	334	NE	0	334	NE	0
Quantitative Urine Chemistry									
Albumin/Creatinine Ratio (>1800 mg/G)	486	NE	4 (0.8)	331	NE	2 (0.6)	333	NE	3(0.9)

Source: Adapted from the Applicants' Summary of Clinical Safety (labeled as Table 22, pages 77-79 of 92) available at: \\cdsesub1\evsprod\nda209091\0000\m2\27-clin-sum\summary-clin-safety.pdf.

Abbreviations: Dapa, dapagliflozin; Met, metformin; N, sample size; Saxa, saxagliptin; ST+LT, short-term plus long-term treatment period; and UNL, upper normal limit.

* An additional case was added to include a subject with marked CK elevations which were not measured at the central lab, but were >10x UNL.

Hematology

Dapagliflozin and other SGLT-2 inhibitors are associated with small increases in hematocrit (0.2-3.0%),[4,79,80] which has been attributed to osmotic diuresis. Because of the potential risks associated with volume depletion and hemoconcentration, such as viscosity-mediated embolic events,[81,82] the Applicant assessed changes in hemoglobin and hematocrit throughout the treatment period. Small increases in both laboratory parameters were observed at 24 and 52 weeks in the treatment arms that included dapagliflozin (Table 20). Although marked increases in hemoglobin (i.e., >18 g/dL) and hematocrit (i.e., >55%) were reported in 4 subjects and 6 subjects in the saxagliptin+dapagliflozin+metformin arm, respectively, these events were not coded as either AEs or SAEs (Table 19), and none were associated with thromboembolic events.

Table 20: Mean Changes from Baseline in Hemoglobin and Hematocrit (ST+LT Safety Pool)

			Baseline Value		Value at Visit		Change from Baseline			
Lab Parameter	**Week**	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Median**	**95% CI**
Hemoglobin (g/dL)										
SAXA+DAPA+MET	0	492			13.9	1.4				
	6	480	13.9	1.4	14.2	1.4	0.3	0.8	0.3	(0.22, 0.35)
	12	473	13.9	1.4	14.3	1.4	0.4	0.8	0.4	(0.29, 0.44)
	18	467	13.9	1.4	14.3	1.5	0.4	0.9	0.4	(0.36, 0.52)
	24	**449**	**13.9**	**1.4**	**14.2**	**1.4**	**0.3**	**0.8**	**0.3**	**(0.25, 0.41)**
	32	283	14.1	1.3	14.3	1.3	0.3	0.9	0.3	(0.19, 0.40)
	40	277	14.0	1.3	14.4	1.4	0.4	0.9	0.3	(0.25, 0.46)
	52	**260**	**14.1**	**1.3**	**14.4**	**1.3**	**0.3**	**0.9**	**0.3**	**(0.23, 0.44)**
SAXA+MET	0	336			13.8	1.3				
	6	333	13.8	1.3	13.8	1.4	0.0	0.7	0.0	(-0.10, 0.04)
	12	318	13.8	1.3	13.8	1.3	-0.1	0.8	0.0	(-0.13, 0.04)
	18	315	13.8	1.3	13.8	1.4	0.0	0.8	0.0	(-0.09, 0.09)
	24	**306**	**13.8**	**1.3**	**13.8**	**1.3**	**0.0**	**0.8**	**0.0**	**(-0.13, 0.04)**
	32	146	13.9	1.2	13.8	1.3	-0.1	0.7	-0.1	(-0.21, 0.04)
	40	143	13.9	1.2	13.7	1.3	-0.1	0.7	-0.1	(-0.24, 0.00)
	52	**133**	**13.8**	**1.2**	**13.8**	**1.2**	**0.0**	**0.7**	**0.0**	**(-0.13, 0.13)**
DAPA+MET	0	341			14.0	1.5				
	6	327	14.0	1.5	14.2	1.5	0.3	0.7	0.3	(0.19, 0.35)
	12	322	14.0	1.5	14.3	1.5	0.4	0.8	0.3	(0.27, 0.45)
	18	316	14.0	1.5	14.3	1.6	0.3	0.9	0.3	(0.23, 0.42)
	24	**310**	**14.0**	**1.5**	**14.2**	**1.6**	**0.2**	**0.9**	**0.2**	**(0.11, 0.31)**
	32	153	14.3	1.4	14.3	1.4	0.1	0.9	0.0	(-0.06, 0.24)
	40	150	14.2	1.4	14.3	1.4	0.1	1.0	0.0	(-0.08, 0.24)
	52	**142**	**14.2**	**1.4**	**14.4**	**1.5**	**0.1**	**0.9**	**0.0**	**(-0.02, 0.29)**
Hematocrit (%)										
SAXA+DAPA+MET	0	492			42.6	4.1				
	6	462	42.7	4.1	43.8	4.2	1.1	2.6	1.1	(0.85, 1.33)
	12	456	42.6	4.1	44.0	4.2	1.3	2.8	1.4	(1.06, 1.58)
	18	450	42.7	4.1	44.2	4.4	1.5	2.9	1.5	(1.25, 1.80)
	24	424	42.7	4.2	43.9	4.0	1.2	2.8	1.2	(0.93, 1.46)
	32	270	43.1	4.0	44.2	3.7	1.1	3.1	1.0	(0.69, 1.43)
	40	268	43.1	4.0	44.4	4.1	1.3	3.2	1.3	(0.90, 1.67)
	52	251	43.3	4.0	44.4	3.9	1.1	3.1	1.1	(0.76, 1.52)
SAXA+MET	0	336			42.4	4.0				
	6	325	42.4	4.0	42.4	4.1	0.0	2.2	0.0	(-0.26, 0.22)
	12	308	42.4	4.1	42.2	4.1	-0.2	2.4	-0.2	(-0.42, 0.12)
	18	308	42.4	4.0	42.4	4.1	0.0	2.5	0.2	(-0.28, 0.29)
	24	286	42.4	4.1	42.3	4.0	-0.1	2.5	-0.1	(-0.41, 0.18)
	32	142	42.2	3.7	42.3	3.8	0.0	2.4	0.1	(-0.37, 0.44)
	40	142	42.3	3.6	42.2	3.9	-0.1	2.4	-0.1	(-0.53, 0.27)
	52	126	42.2	3.5	42.6	3.7	0.4	2.6	0.5	(-0.02, 0.90)
DAPA+MET	0	341								
	6	322	43.0	4.5	44.0	4.4	1.0	2.5	0.9	(0.71, 1.26)
	12	321	43.2	4.5	44.1	4.4	1.0	2.7	0.7	(0.70, 1.28)
	18	308	43.0	4.5	44.0	4.7	0.9	2.9	0.8	(0.61, 1.26)

			Baseline Value		Value at Visit		Change from Baseline			
Lab Parameter	**Week**	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Median**	**95% CI**
	24	302	43.1	4.5	43.6	4.6	0.6	3.0	0.3	(0.21, 0.89)
	32	149	44.0	4.2	44.1	4.1	0.1	3.0	-0.3	(-0.38, 0.59)
	40	148	44.0	4.1	44.1	4.0	0.1	3.2	-0.2	(-0.46, 0.59)
	52	136	44.1	4.2	44.4	4.3	0.3	2.9	-0.1	(-0.15, 0.82)

Source: Adapted from the Applicant's 4-Month Safety Update (labeled as Table 1.5.3.1, pages 805-808 of 5911) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf.

Abbreviations: Dapa, dapagliflozin; Met, metformin; N, sample size; Saxa, saxagliptin; SD, standard deviation; and ST+LT, short-term plus long-term treatment period.

Clinical Chemistry

No clinically relevant mean changes from baseline to Weeks 24 and 52 were reported for electrolytes, minerals (calcium, magnesium, and phosphorus), or total protein (data not shown), and generally results from measurements of these analytes remained within the laboratory normal reference limits.

Diabetic patients have an increased fracture risk, in part due to decreases in mineralized surface area, rate of mineral apposition, osteoid surface, osteoblast activity, and numbers of osteoclasts.[83] Additionally, these patients may have increased urinary excretion of calcium and magnesium, accumulation of glycation end products, and oxidative stress potentially leading to altered bone strength, metabolism and structure.[83] Dapagliflozin and other SGLT-2 inhibitors further alter renal tubular transport of several minerals (e.g., phosphorus, calcium and magnesium), and may be associated with increases in parathyroid hormone concentrations and decreases in 1,25-dihydroxyvitamin D concentrations.[84] In FARXIGA product labeling, the Applicant reported a mean increase from baseline to Week 24 in the serum phosphorus of 0.13 mg/dL in subjects exposed to dapagliflozin, with higher proportions of subjects experiencing marked laboratory abnormalities of hyperphosphatemia in the dapagliflozin treatment arm compared to placebo-treated subjects (i.e., 1.7% vs. 0.9%).[4] In the QTERN integrated safety population, mean (SD) increases in phosphorus concentrations reported in the saxagliptin+dapagliflozin+metformin arms at Weeks 24 and 52 were 0.08 ± 0.54 and 0.03 ± 0.60 mg/dL, respectively. The proportions of subjects with marked abnormalities of hyperphosphatemia for the three arms were: 1.2% (6/492) in the saxagliptin+dapagliflozin+ metformin arm vs. 0.3% (1/334) in the saxagliptin+metformin arm vs. 2.1% (7/334) in the dapagliflozin+metformin arm. There also were mean increases from baseline to Week 24 in serum calcium (0.05 ± 0.46 mg/dL) and magnesium (0.10 ± 0.14 mg/dL) concentrations in subjects receiving saxagliptin+dapagliflozin+metformin. None of the cases of marked elevations of phosphorus or calcium were coded as SAEs or AEs, and there were no discontinuations from study due to hyperphosphatemia, hypercalcemia or hypermagnesemia. The long-term clinical implications of these laboratory changes on bone metabolism and fracture risk are unknown. The Applicant does not intend to include information related to changes in the mineral panel in

product labeling. Additionally, mean changes in minerals reported in FARXIGA labeling will not be included in QTERN labeling.

Although marked laboratory abnormalities of elevated CK concentrations were observed in individual subjects enrolled in the QTERN clinical program (Table 19), mean changes from baseline through week 52 of the three clinical trials were similar across treatment arms (Table 21). Further discussion is provided in Section 8.5.

Table 21: Mean Changes from Baseline in Serum Creatine Kinase (ST+LT Safety Pool)

			Baseline Value		Value at Visit		Change from Baseline			
Lab Parameter	**Week**	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Median**	**95% CI**
Creatine Kinase (U/L)										
SAXA+DAPA+MET	0	492			110.6	134.34				
	6	481	110.8	135.50	101.3	71.31	-9.5	112.26	-2.0	(-19.5, 0.6)
	12	472	109.9	136.02	104.4	94.98	-5.5	126.56	-1.0	(-16.9, 6.0)
	18	466	110.7	136.82	118.4	222.46	7.7	238.49	-1.5	(-14.0, 29.4)
	24	**448**	**111.1**	**139.35**	**110.7**	**174.26**	**-0.4**	**196.89**	**-1.0**	**(-18.7, 17.9)**
	32	285	111.3	143.88	105.4	78.39	-5.9	118.77	0.0	(-19.7, 8.0)
	40	279	112.4	145.17	105.9	77.28	-6.5	126.93	0.0	(-21.5, 8.4)
	52	**267**	**112.8**	**147.96**	**106.1**	**78.11**	**-6.7**	**126.66**	**-1.0**	**(-22.0, 8.5)**
SAXA+MET	0	336			112.9	95.79				
	6	331	113.1	96.44	110.7	79.21	-2.4	85.39	1.0	(-11.6, 6.9)
	12	319	111.7	95.55	112.5	82.01	0.7	93.90	1.0	(-9.6, 11.1)
	18	315	111.7	95.63	113.6	71.12	1.9	80.65	4.0	(-7.1, 10.8)
	24	**305**	**112.7**	**97.20**	**114.3**	**75.96**	**1.6**	**93.90**	**5.0**	**(-9.0, 12.2)**
	32	146	111.5	114.19	111.6	70.40	0.1	112.33	3.5	(-18.3, 18.4)
	40	143	112.0	115.18	99.5	50.37	-12.5	106.42	0.0	(-30.1, 5.0)
	52	**137**	**112.5**	**117.34**	**108.5**	**81.70**	**-4.0**	**129.21**	**2.0**	**(-25.8, 17.9)**
DAPA+MET	0	341			103.4	73.4				
	6	331	103.7	73.62	98.8	62.51	-4.9	64.71	-3.0	(-11.9, 2.1)
	12	322	103.7	72.84	100.3	62.85	-3.4	57.52	-2.0	(-9.7, 2.9)
	18	314	103.3	73.65	101.1	66.16	-2.2	62.65	-1.0	(-9.2, 4.8)
	24	**308**	**103.5**	**70.16**	**101.4**	**65.91**	**-2.1**	**58.07**	**-2.0**	**(-8.6, 4.4)**
	32	153	99.6	68.19	103.8	73.96	4.2	65.13	-1.0	(-6.2, 14.6)
	40	149	98.6	67.56	124.6	246.23	26.0	253.21	1.0	(-15.0, 67.0)
	52	**144**	**98.1**	**68.04**	**98.5**	**59.83**	**0.4**	**57.52**	**0.0**	**(-9.1, 9.9)**

Source: Adapted from the Applicant's 4-Month Safety Update (labeled as Table 1.5.4.1, pages 839-840 of 5911) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf.
Abbreviations: Dapa, dapagliflozin; Met, metformin; N, sample size; Saxa, saxagliptin; SD, standard deviation; and ST+LT, and short-term plus long-term treatment period;

Renal Function Tests

Sodium-glucose cotransport 2 inhibitors have been associated with postmarketing reports of acute kidney injury (AKI). On June 14, 2016, the FDA strengthened the existing warning about

the risk of acute kidney injury for canagliflozin and dapagliflozin.[85] Proposed mechanisms for these events have included osmotic diuresis, resulting in hyperosmolarity and dehydration, uricosuria-mediated tubular injury, and stimulation of chemokines, local inflammation and tubular injury.[86]

In the QTERN Phase 3 clinical program, the mean and median changes in serum creatinine were small across all three treatment arms at Weeks 24 and 52. The mean change from baseline in eGFR at Week 24 (ST, double-blind period) was -1.17 ml/min/1.73m^2 in the saxagliptin+dapagliflozin+metformin arm vs. -0.46 ml/min/1.73m^2 in the saxagliptin+metformin arm vs. 0.81 ml/min/1.73m2 in the dapagliflozin+metformin arm (Table 22). At Week 52 (EOS), changes from baseline in eGFR were -0.92 mL/min/1.73m^2, -1.93 mL/min/1.73m^2, and -1.28 mL/min/1.73m^2, respectively. In the saxagliptin+dapagliflozin+metformin arm, marked abnormalities of serum creatinine >2.5 mg/dL and >1.5 x baseline were reported in 1 and 5 subjects, respectively; however, none of these cases were coded as SAEs. It is important to note that the baseline eGFR was approximately 94 mL/min/1.73m^2 across all three treatment groups, and therefore the modest effects on renal function observed in the QTERN clinical program, which enrolled subjects with mostly normal renal function, may not be generalizable to the entire diabetic population that would be exposed to QTERN should it be approved. Additionally, Farxiga labeling,[4] and published findings from 12 double-blind, placebo-controlled, randomized clinical trials that compared dapagliflozin to placebo,[87] report increased renal adverse events in subjects ages 65 years and over. The QTERN integrated safety population only randomized 63 subjects ≥65 years of age (of which only four were ≥75 years old) to the saxagliptin+dapagliflozin+metformin arm.

Acute kidney injury and impairment in renal function is currently included in the WARNINGS AND PRECAUTIONS section of FARXIGA product labeling, with eGFR changes of -4.2 to -7.3 mL/min/1.73m^2 observed following 52 weeks of exposure to dapagliflozin.[4] Although these findings are not currently reported in proposed QTERN labeling, these data are informative and should be included.

Table 22: Mean Changes from Baseline in Serum Creatinine and eGFR (ST+LT Safety Pool)

			Baseline Value		Value at Visit		Change from Baseline			
Lab Parameter	**Week**	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Median**	**95% CI**
Creatinine (mg/dL)										
SAXA+DAPA+MET	0.0	492			0.8	0.2				
	6.0	482	0.8	0.2	0.8	0.3	0.0	0.2	0.0	(0.010, 0.054)
	12.0	472	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.009, 0.026)
	18.0	467	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.010, 0.029)
	24.0	**452**	**0.8**	**0.2**	**0.8**	**0.2**	**0.0**	**0.1**	**0.0**	**(0.005, 0.025)**
	32.0	286	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.001, 0.025)
	40.0	280	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.010, 0.034)
	52.0	**267**	**0.8**	**0.2**	**0.8**	**0.2**	**0.0**	**0.1**	**0.0**	**(-0.004, 0.021)**

			Baseline Value		Value at Visit		Change from Baseline			
Lab Parameter	**Week**	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Median**	**95% CI**
SAXA+MET	0.0	336			0.8	0.3				
	6.0	331	0.8	0.3	0.8	0.2	0.0	0.3	0.0	(-0.040, 0.015)
	12.0	319	0.8	0.3	0.8	0.2	0.0	0.3	0.0	(-0.038, 0.018)
	18.0	315	0.8	0.3	0.8	0.2	0.0	0.3	0.0	(-0.042, 0.017)
	24.0	**307**	**0.8**	**0.3**	**0.8**	**0.2**	**0.0**	**0.3**	**0.0**	**(-0.044, 0.016)**
	32.0	146	0.8	0.4	0.8	0.2	0.0	0.4	0.0	(-0.093, 0.026)
	40.0	143	0.8	0.4	0.8	0.2	0.0	0.4	0.0	(-0.094, 0.035)
	52.0	**137**	**0.8**	**0.4**	**0.8**	**0.2**	**0.0**	**0.4**	**0.0**	**(-0.079, 0.050)**
DAPA+MET	0.0	341			0.8	0.2				
	6.0	331	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.010, 0.029)
	12.0	323	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(0.009, 0.042)
	18.0	314	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(-0.005, 0.018)
	24.0	**311**	**0.8**	**0.2**	**0.8**	**0.2**	**0.0**	**0.1**	**0.0**	**(-0.016, 0.006)**
	32.0	153	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(-0.009, 0.024)
	40.0	149	0.8	0.2	0.8	0.2	0.0	0.1	0.0	(-0.007, 0.021)
	52.0	**144**	**0.8**	**0.2**	**0.8**	**0.2**	**0.0**	**0.1**	**0.0**	**(-0.005, 0.027)**
eGFR (mL/min/1.73 m^2										
SAXA+DAPA+MET	0	492			94.4	20.6				
	6	482	94.4	20.6	92.0	22.0	-2.4	13.3	-2.8	(-3.617, -1.240)
	12	472	94.6	20.5	93.1	22.7	-1.5	13.7	-1.9	(-2.786, -0.300)
	18	467	94.5	20.6	92.9	23.2	-1.6	14.7	-3.0	(-2.974, -0.297)
	24	**452**	**94.3**	**20.6**	**93.1**	**22.3**	**-1.2**	**13.8**	**-2.0**	**(-2.445, 0.100)**
	32	286	92.9	21.1	92.0	22.7	-1.0	12.6	-2.7	(-2.433, 0.505)
	40	280	92.9	21.0	90.5	21.7	-2.5	12.9	-3.6	(-3.988, -0.959)
	52	**267**	**93.2**	**21.0**	**92.3**	**21.9**	**-0.9**	**13.8**	**-2.6**	**(-2.584, 0.746)**
SAXA+MET	0	336			92.0	21.2				
	6	331	91.9	20.9	91.6	19.5	-0.3	12.4	0.0	(-1.676, 1.010)
	12	319	92.0	21.1	91.3	19.6	-0.7	13.1	-1.1	(-2.148, 0.747)
	18	315	92.0	21.0	91.9	20.1	0.0	13.3	-0.1	(-1.518, 1.432)
	24	**307**	**91.8**	**21.2**	**91.3**	**19.8**	**-0.5**	**15.4**	**-0.9**	**(-2.193, 1.277)**
	32	146	91.2	22.9	91.3	19.5	0.1	13.6	-0.4	(-2.088, 2.364)
	40	143	90.5	22.1	91.3	22.1	0.8	15.3	-0.2	(-1.705, 3.353)
	52	**137**	**90.6**	**22.3**	**88.6**	**19.9**	**-1.9**	**15.5**	**-0.4**	**(-4.539, 0.687)**
DAPA+MET	0	341			93.9	20.2				
	6	331	94.0	20.3	91.8	21.0	-2.2	12.1	-1.8	(-3.492, -0.880)
	12	323	94.0	20.2	91.8	20.9	-2.2	13.2	-0.3	(-3.682, -0.794)
	18	314	93.8	19.9	93.2	20.4	-0.7	14.1	-1.2	(-2.247, 0.889)
	24	**311**	**93.8**	**19.8**	**94.6**	**20.7**	**0.8**	**13.1**	**0.6**	**(-0.643, 2.270)**
	32	153	94.3	20.8	93.6	22.3	-0.7	14.1	-1.5	(-2.909, 1.600)
	40	149	94.5	20.4	93.2	20.3	-1.3	12.3	-1.2	(-3.315, 0.654)
	52	**144**	**94.9**	**20.5**	**93.6**	**22.4**	**-1.3**	**13.3**	**-1.7**	**(-3.466, 0.905)**

Source: Adapted from the Applicant's 4-Month Safety Update (labeled as Table 1.5.3.1, pages 805-808 of 5911) available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf.

Abbreviations: Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; Met, metformin; N, sample size; Saxa, saxagliptin; SD, standard deviation; ST+LT, short-term plus long-term treatment period.

Lipid Panel

Small, possibly dose-related, increases in mean low-density lipoprotein cholesterol (LDL-C) concentrations have been reported with the use of SGLT-2 inhibitors, which are described in product labeling of all three approved products.[4,88,89] Long-term CV risks associated with these changes are unknown.

In their three Phase 3 clinical trials, the Applicant reported AEs associated dyslipidemia (i.e., 'hypertriglyceridaemia, 'dyslipdaemia', 'hypercholesterolaemia', and 'hyperlipidaemia') in 5.1% (25/492) of subjects in the saxagliptin+dapagliflozin+metformin treatment arm compared with 6.8% (23/336) and 5% (17/341) of subjects randomized to the saxagliptin+metformin and dapagliflozin+metformin arms, respectively. There also did not appear to be clinically meaningful changes from baseline reported for the following fasting serum lipids: total cholesterol (Total-C), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Overall, the mean percent changes from baseline to Weeks 24 and 52 (Table 23) were relatively small for many of these lipid parameters and similar across treatment arms. However, in the saxagliptin+dapagliflozin+metformin arm, the mean LDL-C changes from baseline to Week 24 ranged from -0.7% up to 4.5%, and from 2.1 to 6.9% from baseline to Week 52. Increased LDL-C is included in the WARNINGS AND PRECAUTIONS section of FARXIGA labeling,[4] as well as the proposed labeling for QTERN.

Table 23: Mean Changes from Baseline to End-of-Study in Fasting Lipid Parameters – Trials CV181168, CV181169, MB102129 (ST and ST+LT Safety Pools)

Lipid Parameter Trial	ST Pool (Baseline to Week 24)			ST+LT Pool (Baseline to Week 52)		
	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341)	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341
Total-C, mg/dL – mean ± SD						
CV181168 Baseline EOS (Weeks 24 and 52) Adj. percent change from BSL – mean (95% CI)	N=143 190.9 ± 44.2 190.3 ± 43.6 -0.7 (-3.4, 2.1)	—	N=150 194.9 ± 51.1 195.1 ± 42.1 1.1 (-1.6, 3.9)	N=135 190.9 ± 44.2 192.7 ± 46.0 -0.8 (-2.5, 4.3)	—	N=144 194.9 ± 51.1 192.6 ± 46.9 -0.6 (-3.8, 2.7)
CV181169 Baseline EOS (Weeks 24 and 52) Adj. percent change from BSL – mean (95% CI)	N=164 187.7 ± 41.4 188.6 ± 43.2 0.4 (-1.8, 2.7)	N=159 193.2 ± 46.9 187.6 ± 41.4 -1.9 (-4.2, 0.3)	N=155 181.8 ± 35.6 191.2 ± 45.6 3.8 (1.5, 6.3)			—
MB102129 Baseline EOS (Weeks 24 and 52) Adj. percent change from BSL – mean (95% CI)	N=144 195.9 ± 41.6 201.7 ± 42.9 3.0 (0.5, 5.6)	N=148 187.7 ± 42.1 192.6 ± 42.0 1.8 (-0.6, 4.3)		N=132 195.9 ± 41.6 204.1 ± 48.5 3.7 (0.9, 6.7)	N=140 187.7 ± 42.1 192.3 ± 41.5 1.8 (-1.0, 4.6)	—

Lipid Parameter Trial	ST Pool (Baseline to Week 24)			ST+LT Pool (Baseline to Week 52)		
	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341)	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341
LDL-C, mg/dL – mean ± SD						
CV181168	N=143		N=150	N=135		N=143
Baseline	105.9 ± 37.7		108.3 ± 35.2	105.9 ± 37.7		108.3 ± 35.2
EOS (Weeks 24 and 52)	105.2 ± 36.3	—	108.7 ± 35.1	107.7 ± 38.2	—	106.8 ± 38.0
Adj. percent change from BSL – mean (95% CI)	-0.7 (-4.8, 3.6)		1.2 (-2.8, 5.5)	2.1 (-3.1, 7.5)		-1.8 (-6.7, 3.3)
CV181169	N=161	N=158	N=153			
Baseline	102.2 ± 36.4	102.7 ± 35.4	98.1± 30.4			
EOS (Weeks 24 and 52)	105.5± 39.0	100.4 ± 34.4	102.0 ± 33.2	—	—	—
Adj. percent change from BSL – mean (95% CI)	3.7 (-09, 8.6)	-0.6 (-5.1, 4.1)	1.5 (-3.1, 6.4)			
MB102129	N=143	N=147		N=130	N=140	
Baseline	109.1 ± 32.5	103.8 ± 34.9		109.1 ± 32.5	103.8 ± 34.9	
EOS (Weeks 24 and 52)	114.3 ± 36.8	107.0 ± 35.7	—	116.5 ± 36.9	107.2 ± 34.0	—
Adj. percent change from BSL – mean (95% CI)	4.5 (0.7, 8.3)	2.2 (-1.4, 5.9)		6.9 (2.6, 11.4)	2.9 (-1.1, 7.1)	
HDL-C, mg/dL – mean ± SD						
CV181168	N=143		N=150	N=135		N=144
Baseline	48.1 ± 12.5		48.2 ± 12.1	48.1 ± 12.5		48.2 ± 12.1
EOS (Weeks 24 and 52)	48.7 ± 12.5	—	48.2 ± 12.1	50.0 ± 14.2	—	48.5 ± 12.9
Adj. percent change from BSL – mean (95% CI)	1.5 (-0.9, 3.9)		0.04 (-2.3, 2.4)	2.3 (-0.4, 5.1)		1.0 (-1.6, 3.6)
CV181169	N=164	N=159	N=155			
Baseline	45.3 ± 11.0	45.2 ± 11.14	43.2 ± 10.1			
EOS (Weeks 24 and 52)	47.6± 11.5	45.7 ± 11.9	46.9 ± 11.9		—	—
Adj. percent change from BSL – mean (95% CI)	5.4 (3.0, 7.8)	0.9 (-1.4, 3.3)	7.7 (5.2, 10.2)			
MB102129						
Baseline	N=143	N=148		N=130	N=140	
EOS (Weeks 24 and 52)	45.3 ± 11.8	46.5 ± 11.0		45.3 ± 11.8	46.5 ± 11.0	—
Adj. percent change from BSL – mean (95% CI)	48.3 ± 13.4	47.4 ± 11.8		47.7 ± 12.8	47.0 ± 11.9	
	6.0 (3.3, 8.8)	2.6 (0.02, 5.2)		5.2 (1.9, 8.6)	0.2 (-2.8, 3.3)	
TG, mg/dL – mean ± SD						
CV181168	N=143		N=150	N=135		N=143
Baseline	193.8 ± 108.6		206.0 ± 208.3	193.8 ± 108.6		206.0 ± 208.3
EOS (Weeks 24 and 52)	192.1 ± 116.1	—	200.6 ± 138.7	187.5 ± 131.0	—	196.7± 165.3
Adj. percent change from BSL – mean (95% CI)	-1.7 (-7.3, 4.4)		1.6 (-4.2, 7.7)	-3.9 (-9.8, 2.3)		-1.7 (-7.5, 4.5)
CV181169	N=163	N=159	N=155			
Baseline	220.5 ± 193.9	248.2 ± 302.2	215.5 ± 166.4			
EOS (Weeks 24 and 52)	191.2 ± 133.1	223.5 ± 179.8	226.6 ± 318.4	—	—	—
Adj. percent change from BSL – mean (95% CI)	-10.8 (-16.0, -5.4)	-3.7 (-9.4, 2.2)	-2.5 (-8.3, 3.6)			
MB102129	N=144	N=148		N=132	N=140	
Baseline	217.4 ± 132.5	200.1 ± 112.4		217.4 ± 132.5	200.1 ± 112.4	
EOS (Weeks 24 and 52)	210.8 ± 128.4	203.5 ± 129.9	—	214.7 ± 137.1	201.0 ± 125.9	—
Adj. percent change from BSL – mean (95% CI)	-3.1 (-9.0, 3.2)	-1.4 (-7.3, 4.8)		-3.0 (-9.1, 3.6)	-2.6 (-8.6, 3.7)	

Source: Adapted from the Applicant's Clinical Study Reports for CV181168 (labeled as Table S.7.52, pages 421-424 of 3279), CV181169 (labeled as Table S.7.22, pages 451-454 of 3186), and MB102129 (labeled as Table S.7.25, pages 409-412 of 3483), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181169\cv181169-clinical-study-report.pdf \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\mb102129-st-lt\mb102129-st-lt-clinical-study-report.pdf.
Abbreviations: BSL, baseline; Dapa, dapagliflozin; EOS, end-of-study (Weeks 24 and 52); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, sample size; SD, standard deviation; SE, standard error; ST, short-term treatment period; ST+LT, short-term plus long-term treatment period; TG, triglycerides; and Total-C, total cholesterol.
*Longitudinal repeated measures analysis conducted by the Applicant.

Hepatic Panel

During the review of NDA 202293 (dapagliflozin), a single case of apparent dapagliflozin-induced liver injury was observed, which was subsequently reclassified as autoimmune hepatitis. In the QTERN clinical development program, hepatic-related effects (i.e., based on measured laboratory values and/or AEs of hepatic disorder) were considered AEOSI.

In the integrated safety population, mean changes from baseline to Weeks 24 and 52 for serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBL), and alkaline phosphatase (ALP) did not appear to be clinically meaningful in all three treatment arms (data not shown). A summary of the proportions of subjects with clinically relevant changes in hepatic laboratory parameters is presented in Table 24. In the saxagliptin+dapagliflozin+metformin treatment arm, a single subject (CV181168-(b) (6)) had an ALT >7x ULN with a TBL >59x ULN and ALP >5x ULN. This event was adjudicated as cholestatic liver injury secondary to bile duct obstruction, and is discussed further in Section 8.5.3 below. Additionally, other possible or probable adjudicated and confirmed cases of potential drug-induced liver injury also discussed in this section.

Table 24: Subjects with Elevated Liver Laboratory Tests (ST and ST+LT Safety Pools)

Hepatic Laboratory Test Abnormalities	ST+LT Pool		
	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341)
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS — No. (%)	16 (3.3)	15 (4.5)	8 (2.4)
ALT elevation			
>3x ULN	7 (1.4)	7 (2.1)	2 (0.6)
>5x ULN	4 (0.8)	4 (1.2)	0
>10x ULN	0	1 (0.3)	0
>20x ULN	0	1 (0.3)	0
AST elevation			
>3x ULN	5 (1.0)	5 (1.5)	0
>5x ULN	1 (0.2)	5 (1.5)	0

Hepatic Laboratory Test Abnormalities	ST+LT Pool		
	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341)
>10x ULN	0	1 (0.3)	0
>20x ULN	0	1 (0.3)	0
ALT or AST elevation			
>3x ULN	10 (2.1)	9 (2.7)	2 (0.6)
>5x ULN	5 (1.0)	4 (1.2)	0
>10x ULN	0	1 (0.3)	0
>20x ULN	0	1 (0.3)	0
Total bilirubin (TBL)			
>1.5x ULN	1 (0.2)	3 (0.9)	1 (0.3)
>3x ULN	1 (0.2)	1 (0.3)	0
Aminotransferase or Total Bilirubin (TBL) elevation			
ALT or AST >3x ULN and TBL >1.5x ULN*	1 (0.2)	1 (0.3)	0
ALT or AST >3x ULN and TBL >2x ULN*	1 (0.2)	1 (0.3)	0
ALT or AST >3x ULN and TBL >2x ULN* and ALP <2x ULN*	0	0	0
ALP			
>1.5x ULN	8 (1.6)	5 (1.5)	6 (1.8)
>3x ULN	1 (0.2)	0	0

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.5.5.3, pages 877-878 of 5911), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Dapa, dapagliflozin; Met, metformin; N, sample size; No., number; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; ST+LT, short-term plus long-term treatment period; TBL, total bilirubin; and ULN, upper limit of normal.

*Event occurred within 14 days on or after aminotransferase elevation.

8.4.1. Vital Signs

Since the SGLT-2 pharmacologic class is associated with diuresis and volume depletion, assessments of vital signs were performed throughout the ST and ST+LT treatment periods (Appendix 13.4). Changes from baseline to Weeks 24 and 52 are presented in Table 25. Baseline vital signs were similar across treatment arms, and heart rate and blood pressure changes were relatively small during the ST and the ST+LT treatment periods. Additionally, only a single non-serious TEAE of hypotension was reported in a subject from the dapagliflozin+metformin arm.

Table 25: Mean Changes from Baseline to End-of-Study in Vital Signs (ST and ST+LT Safety Pools)

Vital Sign	ST Pool (Baseline to Week 24)			ST+LT Pool (Baseline to Week 52)		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
SBP, mmHg – mean ± SD						
Baseline	127.7 ± 12.9	127.3 ± 12.9	128.7± 12.8	127.7 ± 12.9	127.3 ± 12.9	128.7± 12.8
Number of subjects	N=492	N=336	N=341	N=492	N=336	N=341
EOS	126.4± 13.6	128.7 ± 13.0	126.7± 13.2	126.0 ± 13.6	128.7 ± 13.0	127.6± 13.2
Number of subjects	N=457	N=310	N=312	N=268	N=138	N=144
Change from baseline	-1.3 ± 12.3	1.2 ± 11.4	-1.7 ± 12.2	-1.3 ± 11.8	2.9 ± 11.5	0.8 ± 10.0
DBP (mmHg) – mean ± SD						
Baseline	77.7 ± 8.5	77.7 ± 8.3	78.5 ± 8.1	77.7 ± 8.5	77.7 ± 8.3	78.5 ± 8.1
Number of subjects	N=492	N=336	N=341	N=492	N=336	N=341
EOS	76.7 ± 9.2	77.9 ± 8.2	77.2 ± 8.7	77.5 ± 8.4	77.8 ± 8.2	78.4 ± 8.6
Number of subjects	N=457	N=310	N=312	N=268	N=138	N=144
Change from baseline	-1.2 ± 8.2	-0.1 ± 7.6	-1.2 ± 7.7	-0.6 ± 7.7	0.5 ± 7.8	0.3 ± 7.0
Heart rate (bpm) – mean ± SD						
Baseline	74.9 ± 8.8	76.0 ± 10.4	75.3 ± 9.4	74.9 ± 8.8	76.0 ± 10.4	75.3 ± 9.4
Number of subjects	N=492	N=336	N=341	N=492	N=336	N=341
EOS	74.0 ± 9.0	75.7 ± 9.6	73.5 ± 9.5	73.7 ± 9.0	74.2 ± 9.2	74.4 ± 9.6
Number of subjects	N=457	N=310	N=312	N=268	N=138	N=144
Change from baseline	-1.0 ± 8.2	-0.5 ± 8.5	-1.8 ± 8.2	-1.1 ± 7.6	-1.5 ± 7.8	-0.7 ± 9.1

Source: Modified from the Applicant's 4-Month Update (labeled as Table 1.6.1, pages 440-442 of 5911, and Table 1.6.1, pages 886-891 of 5911).
Abbreviations: BPM, beats per minute; Dapa, dapagliflozin; EOS, end-of-study (Weeks 24 or 52); Met, metformin; N, sample size; SD, standard deviation; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.4.2. Electrocardiograms (ECGs)

The Applicant reported no "clinically meaningful" adverse findings related to ECG findings. According to the CSRs for CV181168, CV181169, and MB102129, the majority of subjects randomized to the saxagliptin+dapagliflozin+metformin treatment arm who had normal ECGs at baseline also had normal ECGs at Weeks 24 (89-92%) and 52 (89-96%). The following TEAEs of abnormal rhythm/conduction were reported during the ST+LT treatment period for this treatment arm: 'atrial fibrillation' 1.0% (5/492); 'bundle branch block left' 0.2% (1/492); 'electrocardiogram QT prolonged' 0.2% (1/492); 'sinus bradycardia' 0.2% (1/492); 'sinus

tachycardia' 0.2% (1/492); 'tachycardia' 0.2% (1/492); 'ventricular extrasystoles' 0.2% (1/492); and 'ventricular tachycardia' 0.2% (1/492). No clear imbalances were observed between treatment arms for these events.

8.4.3. **QT**

A Thorough QT (TQT) study was not conducted for this Application. During the ST treatment period, TEAEs of 'electrocardiogram QT prolonged' were reported for one subject each in the saxagliptin+dapagliflozin+metformin and the dapagliflozin+metformin treatment arms. According to FARXIGA product labeling, dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended maximum dose) in a study of healthy subjects.[4] In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended maximum dose) of dapagliflozin in healthy subjects. Similarly, ONGLYZA product labeling states that once-daily, orally-administered saxagliptin in healthy subjects at doses up to 400 mg daily for two weeks (80 times the recommended maximum dose) had no clinically meaningful effect on QTc interval or heart rate.[3]

8.4.4. **Immunogenicity**

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

8.5. **Analysis of Submission-Specific Safety Issues**

The Applicant searched for AEOSI related to safety findings in the saxagliptin and dapagliflozin nonclinical and clinical programs, as well as known safety concerns associated with other DPP-4 inhibitors and SGLT-2 inhibitors. These AEOSI included the following: bladder neoplasm; breast neoplasm; cardiac failure; cardiovascular (CV) events; hepatic events; decreased lymphocyte count; decreased thrombocyte count; fractures; genital infections; hypoglycemia, infections, malignancies (including pancreatic cancer); opportunistic infection, pancreatitis; renal failure/impairment; severe cutaneous adverse reactions (including Stevens-Johnson syndrome); severe hypersensitivity (anaphylaxis, angioedema and urticaria related events); volume depletion (including hypotension, dehydration, and hypovolemia); urinary tract infections, and hypovolemia.

8.5.1. **Malignancies**

A broad CMQ search was performed that included additional PTs of premalignant conditions (Appendix 13.5). Results from this CMQ are presented in Table 26. The Applicant reported SAEs of malignancies for three subjects (i.e., gastric neoplasm, pancreatic cancer with hepatic metastases, and invasive ductal breast carcinoma) in the saxagliptin+dapaflozin+metformin treatment arms. The latency between exposure and diagnosis for all three cases ranged from 54 to 137 days. Brief narrative summaries of these cases are described below.

Saxagliptin plus dapagliflozin plus metformin arm:

- **Subject CV181169-**(b) (6)**:** a 73-year-old White male, was diagnosed with a nonmalignant gastric neoplasm on Day 137, found during incidental radiography. On Day 351, six months after completion of study medications, the subject died due to gastric neoplasm. This case is described in greater detail in Section 8.4.2 (Serious Adverse Events).

- **Subject MB102129-**(b) (6)**:** a 60-year-old White female had an SAE of invasive ductal breast carcinoma on Study Day 59. Her relevant medical history included breast pain and breast lumps (b) (6) On Day 54, a digital bilateral mammogram showed a high-density oval mass in the right breast. On Day 100, the subject underwent excisional lumpectomy and the event of invasive ductal breast carcinoma was considered as resolved. Study medication was discontinued because of this event.

- **Subject CV181168-**(b) (6)**:** a 50-year-old White male an SAE reported as Grade 3 hepatic cancer (Day 113) following routine abdominal ultrasound, which showed multiple hepatic metastases. The subject remained on study medications, but an investigational antineoplastic agent was started. He received his last dose of study medication on Day 152. The SAE was adjudicated as hepatic adenocarcinoma (resulting from pancreatic carcinoma that metastasized to the liver), and felt to be unrelated to study medications.

All three events were reviewed by Dr. Balakrishnan for NDA (b) (4) who felt that an association with study medications was unlikely due to the relatively short durations of exposure (i.e., 54 to 137 days). However she noted that the possibility of tumor promoting activity related to investigational therapy could not be ruled out. I concur with this assessment.

Based on the broad CMQ (Appendix 13.5) that I performed, two additional cases in the saxagliptin+dapagliflozin+metformin treatment arm were identified and reviewed that included the PTs of 'infected neoplasm' (Subject MB102129-(b) (6)) and 'renal neoplasm' (Subject

CV181168-(b) (6)).

- **Subject MB102129-(b) (6):** a 56-year-old White female had a Grade II AE of 'infected neoplasm' (reported term 'infected lipoma') on Day 90. Antibiotic treatment was required (sulfamethoxazole/trimethoprim; Day 96), with resolution by Day 163. The subject remained on study medications (last dose Day 363).

- **Subject CV181168-(b) (6):** a 53 year-old White male, had an AE reported of dysuria on Day -75 (i.e., during the open-label treatment period), and two AEs reported for hematuria (Days -70, and 170). Both AEs of hematuria were considered related to study medication by the investigator and mild in intensity. No treatment was required and no action was taken. After the last event of hematuria, follow-up laboratory results indicated a normal urine culture. The subject also had an ultrasound of the abdomen with findings of an enlarged liver and a renal neoplasm in the form of cysts on the right kidney, reported as AEs by the investigator (Day 239). No treatment was required and no action was taken. The last dose of study medication was on Day 364.

For Subject MB102129-(b) (6), superficial lipomas are common benign soft-tissue neoplasms, and unlikely to be associated to investigation product. For Subject CV181168-(b) (6), AEs of dysuria and hematuria prior to initiating randomized treatment make an association with study medication and renal cysts unlikely. These two additional cases do not alter my assessment of the risk for malignancy.

In the dapagliflozin clinical development program (NDA 202293), newly diagnosed cases of bladder cancer were reported in 10/6045 subjects (0.17%) treated with dapagliflozin and 1/3512 subjects (0.03%) treated with placebo/comparator.[4] After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were four cases with FARXIGA and no cases with placebo/comparator.[4] Because of the uncertain risk of bladder cancer, microscopic urinalysis was performed at a central laboratory to identify the presence of hematuria (defined as ≥3 red blood cells/high-power field [RBC/HPF]) during the screening visit, and at Weeks 12, 24, 40 and 52 in the QTERN Phase 3 clinical program. Based on these assessments, microscopic hematuria was reported in 7.5% (36/477), 6.1% (20/2326), and 7.9% (26/329) of subjects randomized to the saxagliptin+dapagliflozin+metformin, saxagliptin+metformin, and dapagliflozin+metformin treatment arms, respectively. None of these events were associated with bladder cancer.

Table 26: Summary of Malignancies and Premalignant Conditions (ST and ST+LT Safety Pools)

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**5 (1.0)**	**0**	**3 (0.9)**	**7 (1.4)**	**0**	**3 (0.9)**
Rectal Polyp	1 (0.2)	0	0	2 (0.4)	0	0
Gastric Neoplasm*	1 (0.2)	0	0	1 (0.2)	0	0
Hepatic Cancer*	1 (0.2)	0	0	1 (0.2)	0	0
Infected Neoplasm	1 (0.2)	0	0	1 (0.2)	0	0
Invasive Ductal Breast* Carcinoma	1 (0.2)	0	0	1 (0.2)	0	0
Large Intestine Polyp	0	0	1 (0.3)	1 (0.2)	0	1 (0.3)
Renal Neoplasm	0	0	0	1 (0.2)	0	0
Leukostasis Syndrome	0	0	1 (0.3)	0	0	1 (0.3)
Thyroid Neoplasm	0	0	1 (0.3)	0	0	1 (0.3)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table11, pages 49-50 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period; TEAE, treatment-emergent adverse event.
*Malignancies reported by the Applicant.

8.5.2. Cardiovascular Events

A summary table of adjudicated cardiovascular (CV) events is presented in Table 27. The numbers of events were few for all treatment arms, and consistent with the types of events expected in a T2D patient population.[90] Most events occurred during the ST treatment period, and obvious trends were not observed. In the saxagliptin cardiovascular outcomes trial (CVOT) (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; SAVOR), the Applicant reported that saxagliptin was not associated with an increase or decrease in the rate to first major adverse cardiovascular events (MACE), which included CV death, nonfatal myocardial infarction (MI), and/or nonfatal ischemic stroke.[3,91] Additionally, in a published meta-analysis report of the 21 Phase 2b/3 dapagliflozin clinical trials, dapagliflozin was not associated with an increase in CV risk.[92] The Applicant's dapagliflozin CVOT (i.e., Dapagliflozin Effect on CardiovascuLAR Events; DECLARE) is ongoing at the time of this review.[93]

In the SAVOR trial, an increase in the risk of hospitalization for heart failure was observed in the saxagliptin treatment arm (hazard ratio [HR] 1.27; 95% CI, 1.07, 1.51).[3,94] The Applicant assessed heart failure events as AEOSI in the QTERN Phase 3 clinical program. Based on their SMQ (cardiac failure, broad), heart failure events were reported in 1.2% (6/492), 2.4% (8/336),

and 1.2% (4/341) of subjects in the saxagliptin+dapagliflozin+metformin, saxagliptin+metformin, and dapagliflozin+metformin treatment arms, respectively. No additional cases were identified using the broad CMQ search described in Appendix 13.5. A single SAE of adjudicated and confirmed heart failure (Subject MB102129-(b) (6)) was reported in the saxagliptin+dapagliflozin+metformin treatment arm (Table 27). The narrative summary of this case is provided below. An additional subject (MB102129-(b) (6)) in the saxagliptin+dapagliflozin+metformin arm died due to SAEs of MI and cardiac failure. Please refer to Section 8.4.4 for further discussion of this subject.

- **Subject MB102129-(b) (6):** a 53-year-old White male had an SAE of cardiac failure on Day 112. His medical history included a history of systolic murmur (right second intercostal space). On Day 22, an echocardiogram was performed to evaluate symptoms of dyspnea and orthopnea, and showed an ejection fraction of 50% and bicuspid aortic valve with moderate aortic stenosis, reported as an AE of moderate intensity. The subject experienced AEs of dyspnea and orthopnea on Day 99, and an ECG revealed left bundle branch block, and he was subsequently referred to a cardiologist. Cardiac catheterization on Day 112 revealed severe bicuspid valve aortic stenosis with valve calcification and a reduced ejection fraction (approximately 20-25%) with global hypokinesis. On Day 114, a CT scan showed moderate to large right pleural effusion (reported as a non-serious AE of moderate intensity), and he underwent an ultrasound-guided right thoracentesis. He was treated with diuretics (furosemide), angiotensin converting enzyme inhibitors (ACEIs; lisinopril), and beta blockers (carvedilol). The subject underwent cardiopulmonary bypass surgery with aortic valve replacement (Day 119). The SAE of severe heart failure was considered resolved on Day 130. Study medication was discontinued because of this event (last dose on Day 112).

This case was previously reviewed by Dr. Balakrishnan for NDA (b) (4) who felt that an association to study medication was unlikely given the history of severe aortic stenosis. I agree with this assessment. However, whether the study regimen, that included saxagliptin, may have contributed to the clinical manifestations of this condition is unknown.

Table 27: Summary of Adjudicated Cardiovascular Events (ST and ST+LT Safety Pools)

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**4 (0.8)**	**2 (0.6)**	**2 (0.6)**	**5 (1.0)**	**2 (0.6)**	**3 (0.9)**
Angina unstable	1 (0.2)	0	0	2 (0.4)	0	0
Acute myocardial infarction	1 (0.2)	0	0	1 (0.2)	0	0
Atrial fibrillation	0	0	1 (0.3)	1 (0.2)	0	1 (0.3)
Cardiac failure	1 (0.2)	0	0	1 (0.2)	0	0

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Coronary artery disease	1 (0.2)	0	0	1 (0.2)	0	0
Pulmonary embolism	1 (0.2)	1 (0.3)	0	1 (0.2)	1 (0.3)	0
Ventricular tachycardia	1 (0.2)	0 (0.0)	0	1 (0.2)	0	0
Silent myocardial infarction	0	1 (0.3)	0	0	1 (0.3)	0
Myocardial infarction	0	0	0	0	0	1 (0.3)
Transient ischaemic attack	0	0	1 (0.3)	0	0	1 (0.3)
Deep vein thrombosis	0	1 (0.3)	0	0	1 (0.3)	0

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table11, pages 49-50 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.
*Malignancies reported by the Applicant.

The limited data from the QTERN development program do not demonstrate any clear evidence of increased cardiovascular risk.

8.5.3. Confirmed Adjudicated Hepatic Events

Potential AEs of drug-induced liver injury were adjudicated by an independent committee (i.e., Hepatic Adjudication Committee) blinded to treatment allocation. Of 14 possible events identified for adjudication, the relationship to investigational therapy was adjudicated as 'probable' or 'possible' for five events, of which two cases involved subjects randomized to the saxagliptin+dapagliflozin+metformin treatment arm, two occurred in subjects receiving saxagliptin+metformin, and one occurred in a subject receiving dapagliflozin+metformin. Brief narrative summaries for the two cases randomized to the saxagliptin+dapagliflozin+metformin arm are as follows:

Saxagliptin plus dapagliflozin plus metformin arm:

- **Subject CV181169-** (b) (6): a 33-year-old White male with a history of elevated liver enzymes, fatty liver disease, abdominal pain, hypertension, gout, and dyslipidemia had an elevated ALT >5x ULN while receiving study treatment (Day 85). Concomitant medications included hydrochlorothiazide, hydroxyzine, and losartan. Baseline liver tests were normal except for elevated ALT concentrations of 85 and 75 U/L (normal range 0-41 U/L). On Day 38 an abdominal ultrasound was performed, which showed mild hepatomegaly with hyperechoic pattern which was felt to be compatible with

fatty infiltration. On Day 85 his ALT was reported as 179 U/L, and remained between 162-193 U/L until Day 106, when his ALT and AST concentrations were 213 U/L and 89 U/L (normal range 0-37 U/L), respectively. Due to the ALT elevation of >5x ULN, the event was sent for independent adjudication. The ALT concentration subsequently decreased to 172 U/L by Day 110 and remained between 125-187 U/L for the remainder of the trial. Hepatitis serology was negative, and no treatment was required or action taken regarding study medication (Day 169 was his last dose). Based on follow-up consultation with a gastroenterologist, it was felt that the subject had chronic nonalcoholic liver disease. On Day 213, a CT scan of the abdomen showed diffuse fatty infiltration of the liver with borderline enlargement. On Day 272, the event of increased ALT was considered resolved (ALT 75 U/L and AST 29 U/L). The Independent Hepatic Adjudication Committee assessed the event as probably related to study medication.

- **Subject MB102129-(b) (6)**: a 51-year-old female with a medical history of gastritis had an elevated ALT >5x ULN (166 U/L; normal range 0-33 U/L) and an AST of 104 U/L (normal range 0-33) on Day 277, which were both reported to be resolved by Day 306 (i.e., AST 12 U/L, and ALT 16 U/L). No treatment was required and the subject continued study medications through completion of the trial (last dose was on Day 361). The Hepatic Adjudication Committee considered these events to be possibly related to study medication.

The event for Subject CV181169-(b) (6) was previously evaluated by Dr. Suchitra Balakrishnan during her review of NDA (b) (4). Based on her assessment, she felt that significant confounding from underlying medical conditions made an association to study treatment unlikely. I concur with this assessment. A preexisting medical history of nonalcoholic fatty liver disease, previous elevations in transaminase concentrations, resolution with continued treatment, and the unknown contribution of concomitant medications (i.e., hydrochlorothiazide,[95,96] and losartan[97]) make it difficult to attribute a direct causal relationship to study medications. For Subject MB102129-(b) (6), resolution of laboratory tests abnormalities without interruption in investigational therapy is not supportive of a causal association.

In addition, a 66-year-old White male (**Subject CV181168-(b) (6)**) randomized to the saxagliptin+dapagliflozin+metformin treatment arm, was hospitalized for an SAE of cholelithiasis (Day 21), which was considered to be recurrent choledocholithiasis. Laboratory test results showed ALT of 219 U/L (normal range NA-30 U/L), AST of 101 U/L (normal range NA-37 U/L), TBL 17.9 mg/dL (normal range NA-0.3 mg/dL), and ALP of 755 U/L (normal range

NA-129). The event was adjudicated as Grade 3 cholestatic liver injury secondary to common bile duct obstruction, and a causal relationship to blinded study medication was excluded. Based on his preexisting medical history, I concur with this assessment. Further, since the subject's ALP was >2x ULN, he did not meet criteria for biochemical Hy's Law.[98]

The limited data from the QTERN development program do not demonstrate an increased risk for liver injury.

8.5.4. **Decreased Lymphocyte and Platelet Counts**

Reductions in absolute lymphocyte counts and a single case of thrombocytopenia are reported in Section 6.1 of Onglyza product labeling.[3] In the QTERN safety population, no subjects in any treatment arm had AEs or SAEs of 'decreased lymphocyte count' or 'lymphopenia'. However, in the saxagliptin+dapagliflozin+metformin arm one subject (MB102129-(b) (6)) had an SAE of thrombocytopenia. An additional subject (MB102129-(b) (6)) had mild (Grade I) thrombocytopenia on Days -54, -7, and 164. Overall, the mean change from baseline to Week 52 (ST+LT treatment period) in platelet counts was 4600/µL in the saxagliptin+dapagliflozin+metformin arm.

- **Subject MB102129-**(b) (6): a 45-year-old White female had an SAE of thrombocytopenia on Day 127. She had no relevant medical history and was not taking any other medications. Her platelet counts decreased from 216,000 µL (Day 85; normal range 140,000-450,000/µL) to 61,000/µL (Day 127), with further reductions to 49,000/µL on Day 145, 41,000/µL on Day 169, and 31,000/µL on Day 174 (refer to Appendix 13.6 for the graphical patient profile). She was asymptomatic with no signs of bleeding. Although study medication was discontinued on Day 173, her platelet count remained at 31,000/µL seven days later (Day 180). In consultation with a hematologist (Day 181), it was felt that this subject had either immune thrombocytopenia or drug-induced thrombocytopenia, and she was started on prednisone 20 mg three times daily. Laboratory examination of the peripheral smear revealed some large platelets, and tests for helicobacter and hepatitis C (associated with secondary idiopathic thrombocytopenic purpura) were negative. A bone marrow biopsy was not performed. Within seven days of starting corticosteroid therapy, her platelet count returned to normal (257,000/µL). The hematologist commented that the event was probably idiopathic thrombocytopenic purpura given the rapid response to corticosteroids, although he was not completely certain. The platelet count on Day 279 remained within the normal range (244, 000/µL). Based on this, the prednisone dose was decreased from 15 mg daily to 10 mg daily. The SAE was considered related to the study medication and severe in intensity (Grade III) by the Investigator.

The Applicant felt that given the continued drop in platelet counts following study drug discontinuation for this subject, and normalization in response to corticosteroid therapy; the etiology of thrombocytopenia is likely to be of autoimmune nature and unlikely to be drug-induced. However, a positive challenge, lack of relevant medical history or concomitant medications, and stabilization of platelet counts off of study medication, make it difficult to completely rule out a possible association. A single case of thrombocytopenia is currently reported in saxagliptin product labeling;[3] however, it is not included in the proposed labeling for QTERN. This event and the case observed in the QTERN safety population were consistent with idiopathic thrombocytopenic purpura, and therefore I do not feel that inclusion of this case in labeling is necessary at this time.

8.5.5. **Fractures**

The SGLT-2 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.[84] 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 SGLT-2 inhibitor class, including dapagliflozin and empagliflozin, would continue to be evaluated to determine if additional label changes or studies are needed.[99]

In the QTERN Phase 3 clinical program, fractures were reported for three subjects (0.6%) in the saxagliptin+dapagliflozin+metformin arm (foot, humerus, and patella); four subjects (1.2%) in the saxagliptin+metformin arm (foot, patella, ankle, and rib); and two subjects (0.6%) in the dapagliflozin+metformin arm (hand, and radius). None of these events were associated with concurrent volume depletion-related adverse events. Additionally, for the three subjects in the saxagliptin+dapagliflozin+metformin arm, none of the fracture events were coded as SAEs. Brief narrative summaries of these three cases are as follows:

- **Subject CV181168-(b) (6):** a 66-year-old White female had an AE of humerus fracture reported on Day 156. The subject reported she stumbled and fell. The subject remained in the study, and treatment was required.

- **Subject CV181168-(b) (6):** a 63-year-old White male had an AE of right patella fracture reported on Day 245. The subject fell on his own and per the investigator, there were no relevant factors contributing to the fall.

- **Subject CV181168-(b) (6):** a 50-year-old White male had an AE of a right foot fracture reported on Day 328. The subject lost his balance and fell at home, and, per the investigator, there were no relevant factors contributing to the fall.

All three fracture cases reported in the saxagliptin+dapagliflozin+metformin treatment arm involved falls, which were not associated with hypoglycemic, nocturia, or volume depletion-related AEs; making an association with study medication less likely. Reports of fractures in patients with moderate renal impairment (i.e., eGFR 30 to <60 mL/min/1.73 m2) are included in Section 6 (Adverse Reactions) of FARXIGA (dapagliflozin) product labeling,[4] but not in the proposed QTERN labeling. However, QTERN is not recommended for use in this patient population.

8.5.6. 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.[100] Further, SGLT-2 inhibitors appear to increase this risk,[101-103] possibly mediated through glucosuria. The risk of genital infections is included in both Farxiga[4] and proposed QTERN labeling.

In the Qtern Phase 3 clinical program AEs of genital infection were reported in higher proportions of subjects in the treatment arms that included dapagliflozin for both the ST and ST+LT treatment periods (Table 28). Vulvovaginal mycotic infection was the most common PT for the saxagliptin+dapagliflozin+metformin and the dapagliflozin+metformin treatment arms. For all three arms, none of the events were coded as SAEs, and the majority of subjects had a single event. In the saxagliptin+dapagliflozin+metformin arm, one subject (MB102129-6-1) had recurrent events (3 events of vulvovaginal mycotic infection), and a second subject (MB102129-6-1) discontinued study medication due to recurrent genital and urinary tract infections (described below).

- **Subject MB102129-(b) (6):** a 70-year-old White female had AEs of UTI and vulvovaginal mycotic infection on Study Days 115 and 118, respectively. Both AEs were considered related to treatment and moderate in intensity by the Investigator. The subject also had nonserious AEs of vulvovaginal mycotic infection of moderate intensity on Study Days 40 and 108. Study drug was discontinued because of recurrent AEs of vulvovaginal mycotic infection and UTI.

Using the broad CMQ search (Appendix 13.5), the following additional PTs were reported for the saxagliptin+dapagliflozin+metformin arm during the ST+LT treatment period: 'vulvovaginal pruritus' 0.6% (3/492); and 'phimosis' 0.2% (1/492).

Table 28: Summary of Genital Infections (ST and ST+LT Safety Pools)

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**8 (1.6)**	**1 (0.3)**	**14 (4.1)**	**15 (3.0)**	**3 (0.9)**	**20 (5.9)**
Vulvovaginal mycotic infection	7 (1.4	1 (0.3)	8 (2.3)	10 (2.0)	1 (0.3)	9 (2.6)
Balanoposthitis	0	0	1 (0.3)	2 (0.4)	0	2 (0.6)
Genital infection fungal	0	0	0	1 (0.2)	0	2 (0.6)
Vaginal infection	1 (0.2)	0	1 (0.3)	1 (0.2)	1 (0.3)	2 (0.6)
Vulvovaginitis	0	0	0	1 (0.2)	0	0
Bacterial vaginosis	0	0	1 (0.3)	0	0	2 (0.6)
Genital candidiasis	0	1 (0.3)	0	0	1 (0.3)	0
Vulval abscess	0	0	1 (0.3)	0	0	1 (0.3)
Vulvovaginal candidiasis	0	0	3 (0.9)	0	0	3 (0.9)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.4.11.2, pages 372 and 757 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.5.7. Urinary Tract Infections

As previously noted with genital infections, T2D patients receiving SGLT-2 inhibitors are also at increased risk for urinary tract infections (UTIs),[101,102] and warnings related to this risk are included in both Farxiga[4] and proposed QTERN labeling.

In the Qtern safety population, the proportions of subjects with urinary tract infections were similar across treatment arms for both the ST and ST+LT treatment periods, of which 81% (58/72) were female. In the saxagliptin+dapagliflozin+metformin treatment arm, 22 of the 28 subjects with UTIs were female, seven had a recurrent infection, and one (MB102129-(b) (6)) had four infections. Additionally, in this treatment arm, one subject discontinued due to recurrent UTIs (MB102129-(b) (6); described in Section 8.5.6), and a second subject (CV181168-(b) (6)) with obstructive uropathy experienced an SAE of pyelonephritis (please refer to Appendix 13.7 for further discussion of this case).

Table 29: Summary of Urinary Tract Infections (ST and ST+LT Safety Pools)

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**17 (3.5)**	**19 (5.7)**	**13 (3.8)**	**28 (5.7)**	**25 (7.4)**	**19 (5.6)**
Urinary tract infection	17 (3.5)	18 (5.4)	13 (3.8)	27 (5.5)	24 (7.1)	18 (5.3)
Pyelonephritis	0	0	0	1 (0.2)	0	0
Prostatitis	0	0	0	1 (0.2)	0	0
Escherichia urinary tract infection	0	0	0	1 (0.2)	0	0
Cystitis	0	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.6)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.4.11.14.1, pages 384 and 769 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.5.8. Infections

Section 6 (Adverse Reactions) of Onglyza (saxagliptin) product labeling describes cases of infections in the Applicant's saxagliptin development program,[3] and proposed Qtern labeling will include information on respiratory tract infection, urinary tract infections and genital infections.

In the ST+LT safety pool, infections were reported in 26.4% (130/492), 30.1% (101/341), and 29.3% (100/341) of subjects in the saxagliptin+dapagliflozin+metformin, saxagliptin+metformin, and dapagliflozin+metformin treatment arms, respectively (data not shown). In the saxagliptin+dapagliflozin+metformin treatment arm, the most common reported PTs (≥2% of subjects) included 'urinary tract infection' (5.5%; 27/492); 'nasopharyngitis' (4.3%; 21/492); 'influenza' (3.7%; 18/492); 'upper respiratory tract infection' (2.2%; 11/492); and 'vulvovaginal mycotic infection' (2%; 10/492). Except for vulvovaginal mycotic infection, which was only reported in one subject in the saxagliptin+metformin arm, these AEs were common to all three treatment arms. No subjects had AEs of opportunistic infections.

8.5.9. Hypoglycemia

As anticipated based on the pharmacodynamics of the study medications and the patient population studied, the numbers of subjects experiencing hypoglycemic events were limited and relatively similar across treatment arms. In the saxagliptin+dapagliflozin+metformin arm, 1.6% (8/492) had at least one hypoglycemic event, regardless of glycemic rescue therapy. No

subject experienced a major episode of hypoglycemia (i.e., requiring third party assistance, blood glucose <54 mg/dL, and prompt recovery following glucose or glucagon) in any treatment arm.

Table 30: Summary of Hypoglycemic Events (ST and ST+LT Safety Pools)*

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals Subjects with Hypoglycemia	**6 (1.2)**	**3 (0.9)**	**6 (1.8)**	**8 (1.6)**	**4 (1.2)**	**7 (2.1)**
Major episode[¶]	0	0	0	0	0	0
Minor episode[†]	2 (0.4)	2 (0.6)	3 (0.9)	3 (0.6)	2 (0.6)	4 (1.2)
Other[‡]	4 (0.8)	2 (0.6)	4 (1.2)	6 (1.2)	3 (0.9)	4 (1.2)
Total Events of Hypoglycemia	**11**	**5**	**10**	**22**	**6**	**24**
Major episode	0	0	0	0	0	0
Minor episode	4 (36.4)	2 (40.0)	6 (60.0)	5 (22.7)	2 (33.3)	20 (83.3)
Other‡	7 (63.6)	3 (60.0)	4 (40.0)	17 (77.3)	4 (66.7)	4 (16.7)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.4.11.17.4, pages 393 and 778 of 5911), and derived from the adhs.xpt dataset, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.
***Includes event data after rescue.**
[¶]**Major episode**: defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.
[†]**Minor episode**: defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL, regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.
[‡]**Other episode:** defined as suggestive episode reported but not meeting the criteria for major or minor episodes.

8.5.10. Pancreatitis

In March of 2013, the Agency issued a Drug Safety Communication of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for T2D.[104] Subsequently, in the Applicant's saxagliptin CVOT (SAVOR), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) of subjects receiving saxagliptin compared to 9 of 8173 (0.1%) receiving placebo.[3,105] Both Onglyza labeling[3] and the proposed Qtern labeling include pancreatitis in Section 5 (Warnings and Precautions).

In the QTERN safety population, only a single AE of chronic pancreatitis was reported in a subject (CV181169-[redacted]) randomized to the saxagliptin+dapagliflozin+metformin arm. This subject had a history of chronic pancreatitis. The narrative summary for this case is presented in Section 8.4.1.

8.5.11. Renal Failure/Impairment

As previously mentioned in Section 8.4.6, Qtern labeling will include acute kidney injury and impairment of renal function in Section 5 (Warnings and Precautions).

In the pooled safety analysis of the ST+LT treatment period, AEs of renal impairment/failure were reported in 2% (10/492), 1.8% (6/336), and 0.6% (2/341) of subjects in the saxagliptin+dapagliflozin+metformin, saxagliptin+metformin, and dapagliflozin+metformin treatment arms, respectively (Table 31). Meaningful trends were not obvious with the relatively low event rate. Three subjects (CV181169-[(b) (6)], MB102129-[(b) (6)], and MB102129-[(b) (6)]) in the saxagliptin+dapagliflozin+metformin arm discontinued study medication due to reductions in eGFR to levels below protocol-specified criteria (<60 mL/min/1.73 m^2). The Applicant reported that subjects with AEs of renal impairment/failure had lower mean eGFR values at baseline compared to the overall safety population (i.e., 62 mL/min/1.73 m^2 vs. 94 mL/min/1.73 m^2).

Additionally, review of the PTs identified using the broad CMQ (Appendix 13.5) did not reveal additional cases.

Table 31: Renal Impairment/Failure

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**7 (1.4)**	**6 (1.8)**	**2 (0.6)**	**10 (2.0)**	**6 (1.8)**	**2 (0.6)**
Glomerular Filtration Rate Decreased	5 (1.0)	1 (0.3)	2 (0.60	5 (1.0)	1 (0.3)	2 (0.6)
Renal Impairment	2 (0.4)	1 (0.3)	0	2 (0.4)	1 (0.3)	0
Blood Creatinine Increased	0	1 (0.3)	0	1 (0.2)	1 (0.3)	0
Renal Failure Acute	0	0	0	1 (0.2)	0	0
Urine Output Decreased	0	0	0	1 (0.2)	0	0
Renal Failure	0	1 (0.3)	0	0	1 (0.3)	0
Renal Failure Chronic	0	3 (0.9)	0	0	3 (0.9)	0

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.4.11.1, pages 371and 756 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.5.12. Severe Cutaneous Adverse Reactions

No severe cutaneous adverse reactions were reported in subjects randomized to the saxagliptin+dapagliflozin+metformin arm. There was two AEs of 'skin exfoliation' (both rated as mild/Grade I) reported. One was reported in a 62-year-old White female (Subject CV181169-(b) (6)) in the saxagliptin+metformin arm on Day 24, and described as fine scaling over the left plantar foot with no ulceration. The second was in a 41-year-old White male (Subject CV181168-(b) (6)) in the dapagliflozin+metformin arm on Day 106, and described as bilateral scaly feet. For these two cases, no action was taken and no treatment provided.

8.5.13. Severe Hypersensitivity Reactions

No severe hypersensitivity adverse reactions were reported in subjects randomized to the saxagliptin+dapagliflozin+metformin arm. Two subjects, CV181168-(b) (6) (38-year-old White female) and CV181168-(b) (6) (57-year-old White female), both randomized to the dapagliflozin+metformin arm had moderate (Grade II) and mild (Grade I) AEs of hypersensitivity on Days 136 and 75, respectively. These events were coded as nonserious, and neither event resulted in discontinuation of study medication. No additional cases of severe hypersensitivity reactions were identified using the broad CMQ search (Appendix 13.5).

8.5.14. Volume Depletion

The SGLT-2 inhibitors 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).[4,85,89,106]

In the ST+LT safety pool, events associated with volume depletion (e.g., hypotension, dehydration, hypovolemia) were limited (Table 32).

Table 32: Summary of Potential Volume Depletion-Related Adverse Events

MedDRA PTs — no. (%)	ST Pool			ST+LT Pool		
	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)	Saxa+Dapa+Met (n=492)	Saxa+Met (n=336)	Dapa+Met (n=341)
Totals	**0**	**0**	**2 (0.6)**	**2 (0.4)**	**0**	**3 (0.9%)**
Urine output decreased	0	0	0	1 (0.2)	0	0
Syncope	0	0	1 (0.3)	1 (0.2)	0	2 (0.6)
Hypotension	0	0	1 (0.3)	0	0	1 (0.3)

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 1.4.11.16, pages 371and 774 of 5911), and derived from the adae.xpt and adae2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG
Abbreviations: Dapa, dapagliflozin; MedDRA, Medical Dictionary for Regulatory Activities; Met, metformin; PT, preferred term; Saxa, saxagliptin; ST, short-term treatment period; and ST+LT, short-term plus long-term treatment period.

8.5.15. **Myopathy/Rhabdomyolysis**

During the review of NDA (b) (4) the original submission for this FCDP, a safety signal of potential muscle injury was identified. In that Application, there were seven subjects with CK elevations >5x ULN, of which five were >10x ULN, for the combination of saxagliptin+dapagliflozin+metformin compared to none for saxagliptin+metformin and one for dapagliflozin+metformin. The incidence of serum CK elevations >10x ULN (0.4%) was similar to that observed in HMG-CoA reductase inhibitor (statin) development programs. Additionally, a case of rhabdomyolysis occurred in a subject treated with saxagliptin+dapagliflozin+metformin in the LT treatment period of Trial CV181168. This subject was hospitalized for syncope and dehydration, and was diagnosed with rhabdomyolysis with a CK >10x ULN. The subject was treated with intravenous hydration, study medication was stopped, and the subject recovered. Notably, no concomitant lipid-lowering medications (i.e., statins or fibrates) were reported, and no cases were identified in any of the subjects treated with saxagliptin or dapagliflozin alone. Additionally, it was felt that the overall safety database was relatively small and that the long-term safety was incomplete at that time. It was recommended that additional analysis of long-term safety of the combination should be performed and included in a resubmission.

The current submission (NDA 209091) includes an additional 100 p-y of exposure to saxagliptin+dapagliflozin+metformin from the completed Phase 3 clinical trials (i.e., CV181168 and MB102129), which were still ongoing at the time of the first review. This section will summarize this information.

In total, seven subjects who were randomized to the saxagliptin+dapagliflozin+metformin, and an additional subject, randomized to the dapagliflozin+metformin treatment arm, experienced marked elevations in serum CK concentration >5x ULN during the ST+LT treatment periods. Within the saxagliptin+dapagliflozin+metformin arm, the demographics and clinical characteristics of these seven subjects are summarized and compared to subjects without these laboratory abnormalities (Table 33). All seven subjects were male, with six subjects less than <65 years of age, and four of African-American descent. The majority also were overweight, with the duration of diabetes ≤10 years. Each of these cases was previously reviewed for NDA (b) (4). The clinical narratives from the current submission, as well as an assessment of causality, are presented in Appendix 13.7. Two additional cases (Subjects CV181169-(b) (6) and CV181168-(b) (6)) in the saxagliptin+dapagliflozin+metformin arm, and one in the

saxagliptin+metformin arm (MB102129-(b) (6)) were reported prior to randomization (e.g., during the open-label period. These cases also are discussed.

Table 33: Demographics and Clinical Characteristics of Subjects with CK Elevations

Demographics and Clinical Characteristics	Saxa+Dapa+Met With CK >5x ULN (N=7)	Saxa+Dapa+Met Without CK >5x ULN (N=485)
DEMOGRAPHICS		
Age, mean ± SD — yr	51.7 ± 14.7	54.4 ± 9.4
<65 yr — no. (%)	6 (85.7)	423 (87.2)
≥65 yr — no. (%)	1 (14.3)	62 (12.8)
Male sex — no. (%)	7 (100.0)	221 (45.6)
Race — no. (%)		
White	3 (42.9)	403 (83.1)
Black/African American	4 (57.1)	37 (7.6)
Asian	0	18 (3.7)
Other	0	9 (1.9)
Country — no. (%)		
United States of America	5 (71.4)	198 (40.8)
Mexico	1 (14.3)	112 (23.1)
Puerto Rico	1 (14.3)	4 (0.8)
Other	0	171 (35.3)
CLINICAL CHARACTERISTICS		
BMI, mg/m^2 — mean ± SD	30.9 ± 4.8	31.5 ± 4.9
<30 mg/m^2 — no. (%)	2 (28.6)	197 (40.6)
≥30 mg/m^2 — no. (%)	5 (71.4)	288 (59.4)
Duration of Exposure, mean ± SD — yr	0.9 ± 0.2	0.8 ± 0.3
Duration of T2D, mean ± SD — yr	6.1 ± 4.2	7.5 ± 5.9
<3 yr — no. (%)	2 (28.6)	111 (22.9)
≥3 to ≤10 yr — no. (%)	4 (57.1)	239 (49.3)
>10 yr — no. (%)	1 (14.3)	133 (27.4)
Glycemic Status		
HbA1c% — mean ± SD	8.3 ± 1.7	8.4 ± 1.1
eGFR, $mL/min/1.73m^2$ — mean ± SD	91.6 ± 16.4	94.4 ± 20.6

Source: Adapted from the Applicants' 4-Month Safety Update (labeled as Table 37, page 132 of 5911), and derived from the addm.xpt, adlb2.xpt datasets, available at:
\\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; no., number; SD, standard deviation; T2D, type 2 diabetes mellitus; ULN, upper limit of normal; US, United States; and yr, years.
*All subjects randomized who received ≥1 dose of investigational product.

To further investigate the datasets for other potential cases, a broad CMQ search for MedDRA PTs (Appendix 13.5) associated with myopathy also was performed. This search also included marked laboratory abnormalities. The results are presented in Table 37. Based on this search, a total of 49 (10%), 38 (11.3), and 24 (7.0%) subjects were identified with musculoskeletal-related PTs and/or laboratory changes from the saxagliptin+dapagliflozin+metformin, saxagliptin+metformin, and dapagliflozin+metformin treatment arms, respectively. A thorough review of the 49 subjects in the triple therapy arm did not reveal any additional cases of concern.

Additionally, the FDA Adverse Event Reporting System (FAERS) database was searched using Empirica Signal™ and Mercado Drug Safety Analytics to identify expedited safety reports of rhabdomyolysis associated with saxagliptin, and/or dapagliflozin. As of February 2017, there were six expedited safety reports of rhabdomyolysis that included saxagliptin and five cases associated with dapagliflozin (Table 38). The saxagliptin reports involved mostly males (n=5), the ages ranged from 56-71 years, and events occurred following 42-147 days of exposure. Three cases included other suspect medications, such as ciprofloxacin (n=1) or statins (n=2). Reported outcomes included hospitalizations (n=3), other serious outcomes (n=6), life-threatening (n=1), and death (n=1). From the available information reported for the five cases associated with dapagliflozin, all reports listed dapagliflozin as the primary suspect drug, four involved females, two used other DPP-4 inhibitors (i.e., vildagliptin and teneligliptin), and one received statins. The reported outcomes included: hospitalization (n=3), and other serious outcomes (n=3), and disability (n=1). One event was associated with a positive dechallenge. Two additional cases involved blinded study medications, one with saxagliptin (#9106185) and one with dapagliflozin (9779478/9782299/10450284). A single report (#10156368) involved the use of saxagliptin in combination with dapagliflozin. This case involved the 78-year-old subject (CV181168-(b) (6)) from Trial CV181168, and is described in further detail in Appendix 13.7.
Although several of these expedited reports support a possible temporal relationship (e.g., challenge, dechallenge, and possibly rechallenge), often they did not contain adequate detail to properly evaluate the event and/or possible association with the suspected medication. Further, comorbidities, concomitant medication use, and missing information made it challenging to exclude alternative etiologies.

In summary, there were no additional cases of marked CK elevations identified based on the additional safety data provided from the completed LT treatment phases of Trials CV181168 and MB102129, which included an additional 100 p-y of exposure to saxagliptin+dapagliflozin+metformin. The laboratory abnormalities reported for the existing cases were typically asymptomatic, transient, and did not require discontinuation of therapy. Further, a search of the integrated safety datasets, using a broad CMQ, failed to reveal any

additional cases, and uncertainty exists with the FAERS cases due to the inherent limitations associated with these data. Nevertheless, rhabdomyolysis, in a patient with other comorbidities, was reported for one of five subjects with CK elevations, for whom no other obvious cause was identified. My opinion is that this potential safety signal can be addressed with appropriate labeling.

8.5.16. **Other Adverse Events Associated with DPP-4 Inhibitors and SGLT-2 Inhibitors**

Using broad CMQs, the AE datasets also were queried for other AEOSI associated with DPP-4 Inhibitors and SGLT-2 Inhibitors, which included arthropathies; bone and joint infections; bone disorders; bone, joint and vascular therapeutic procedures; dermal diabetic complications; venous embolic and thrombotic events; ketoacidosis; osmotic diuresis; opportunistic infections; stomatitis/mouth ulceration; and vascular insufficiency. Event counts for many of the CMQs were limited/non-informative, and no trends were readily identified that suggested apparent imbalances between treatment arms for subjects with these AEOSI.

8.6. **Specific Safety Studies/Clinical Trials**

Not applicable.

8.7. **Additional Safety Explorations**

8.7.1. **Human Carcinogenicity or Tumor Development**

No carcinogenicity or genotoxicity studies were performed for the combination of the two drugs in the FCDP. Studies of the individual drugs were deemed to be adequate for assessment of the carcinogenicity and genotoxicity of the combination. However, an imbalance in newly diagnosed cases of bladder cancers was observed across 22 clinical trials in the dapagliflozin (FARXIGA) clinical program, and is labeled as a Warnings and Precaution. For the current NDA, malignancy was reported for three subjects (i.e., gastric neoplasm, pancreatic cancer with hepatic metastases, and invasive ductal breast carcinoma) receiving the FCDP. The latency between exposure and diagnosis for all three cases was relatively short (i.e., 54 to 137 days).

8.7.2. **Human Reproduction and Pregnancy**

Currently, there is limited clinical experience with the use of QTERN, saxagliptin, or dapagliflozin in pregnant or lactating women (b) (4) Although WOCBP were instructed to use contraception, there were three pregnancies reported in the QTERN

development program; all in Trial CV181169. A brief summary is as follows:

Saxagliptin plus dapagliflozin plus metformin arm:

- **Subject CV1891169-(b) (6):** A 41-year-old White female reported a pregnancy following approximately 15 days of drug exposure. Although the trial site contacted the subject following the anticipated due date, she declined follow-up and withdrew consent.

Saxagliptin plus metformin arm:

- A 36-year-old female partner of **Subject CV181169-(b) (6)** reported a positive pregnancy test, which resulted in miscarriage approximately 44 days later.

Dapagliflozin plus metformin arm:

- **Subject CV1891169-(b) (6):** A 39-year-old White female reported a pregnancy following approximately 47 days of drug exposure. The pregnancy resulted in a live birth (~250 days after positive pregnancy testing); but the infant was diagnosed with a congenital cardiac anomaly.

The available data are insufficient to inform the use of QTERN in pregnancy.

8.7.3. *Pediatrics and Assessment of Effects on Growth*

Not applicable. No pediatric subjects were enrolled in the QTERN clinical development program. Further, pediatric clinical trials and/or assessments on growth and development for either of the active components of Qtern (i.e., saxagliptin or dapagliflozin) have not been completed.

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

The Applicant states that there is no data available related to overdose of the combination of saxagliptin + dapagliflozin. Additionally, the FAERS database was searched using Empirical Signal™ and the following MedDRA PTs: 'Accidental overdose'; 'Drug abuse'; 'Intentional overdose'; 'Intentional product misuse'; 'Overdose'; and 'Prescribed overdose'. No postmarketing case reports were identified that included the combination of saxagliptin + dapagliflozin. Although overdose, drug abuse, withdrawal, or rebound would not be anticipated for either active component of QTERN, 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).[107,108] A literature search revealed a single case of persistent hypoglycemia due to misuse of a sulfonylurea in combination with the DPP-4 inhibitor vildagliptin,[109] as well as reports of unintentional and intentional exposures to DPP-4 inhibitors.[110-112] In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite (i.e., 5-

hydroxy saxagliptin) can be removed by hemodialysis (i.e., approximately 23% of the dose over four hours).[3] According to the most recent Periodic Benefit-Risk Evaluation Report (PBRER, dated October 4, 2016) for NDA 022350 (saxagliptin), the following MedDRA preferred terms were listed in the cumulative spontaneous case reports: accidental overdose (n=5; 4 non-serious, 1 serious); intentional overdose (n=5, 1 non-serious, 4 serious); overdose (n=41; 36 non-serious, 5 serious); prescribed overdose (n=9, all non-serious; intentional product misuse (n=29; 28 non-serious, 1 serious).[3]

No published reports associated with dapagliflozin overdose, abuse or misuse were readily identified, and removal of dapagliflozin by hemodialysis has not been studied.[4] However, in the dapagliflozin clinical development program, single doses up to 500 mg (50x MRHD) and multiple doses of up to 100 mg/day (10x MRHD) for two weeks, did not result in obvious/clinically meaningful drug-related AEs or laboratory abnormalities. According to the most recent Periodic Benefit-Risk Evaluation Report (PBRER, dated November 18, 2016) for NDA 202293 (dapagliflozin), the following MedDRA preferred terms were listed in the cumulative spontaneous case reports: accidental overdose (n=2; both non-serious); overdose (n=5; 4 non-serious, 1 serious); and intentional product misuse (n=157; 155 non-serious, 2 serious).[4]

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The FCDP of saxagliptin/dapagliflozin is not approved in any country, and there is no postmarketing experience with this product. While both saxagliptin and dapagliflozin are approved, clinical experience with the use of the combination of the two components outside of the clinical trial setting is limited.

8.8.2. Expectations on Safety in the Postmarket Setting

QTERN is intended for patients with T2D who have not met their glycemic treatment goals with metformin and the maximum recommended dose of dapagliflozin (10 mg). The recommended starting dose of dapagliflozin is 5 mg once daily, with up-titration to the 10 mg dose in patients who are tolerating therapy but require additional glycemic control.[4] With approval of QTERN, there is the potential that this FCDP could be prescribed for patients who are dapagliflozin-naïve and have a predisposition to dose-related AEs, such as volume depletion or acute kidney

[3] ONGLYZA (Saxagliptin) Periodic Benefit-Risk Evaluation Report (PBRER, dated October 4, 2016), available at: \\cdsesub1\evsprod\nda022350\0198\m5\53-clin-stud-rep\536-postmark-exp\pbrer-31-jul-2015-to-30-jul-2016-us.pdf.
[4] FORXIGA/FARXIGA/EDISTRIDE (Dapagliflozin) PBRER (dated December 6, 2016), available at: \\cdsesub1\evsprod\nda202293\0208\m5\53-clin-stud-rep\536-postmark-exp\pbrer-05-oct-2015-to-04-oct-2016-us.pdf.

injury (e.g., elderly, hypovolemic, renal insufficiency, heart failure).

Additionally, older patients with T2D who require additional glycemic control may be placed on QTERN. As discussed above, there is scant data with saxagliptin plus dapagliflozin combination therapy in this population. However, there is some data from the individual components to suggest what might be expected in terms of safety. The ONGLYZA (saxagliptin) product labeling[3] notes that no overall difference in safety was observed between subjects ≥65 years old (which included 1210 saxagliptin-treated subjects ≥75 years old) and younger subjects; while the FARXIGA labeling reports a higher proportion of adverse events of volume depletion and renal impairment or failure in dapagliflozin-treated subjects ≥65 years of age (which included 207 subjects ≥75 years old). As the current proposed population is one already treated with (and presumably tolerating) dapagliflozin, this latter concern is not particularly relevant.

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

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

8.9. Additional Safety Issues From Other Disciplines

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

8.10. Integrated Assessment of Safety

The safety profile of QTERN reflects the safety profile of its components, i.e., saxagliptin and dapagliflozin. The most common adverse reactions (reported in >5% of subjects) were respiratory tract infections (13.6%), urinary tract infections (5.7%), and dyslipidemia (5.1%), which are also common to either saxagliptin and/or dapagliflozin separately. Although antihyperglycemic FCDPs have a potential for an increased risk of hypoglycemia compared to

the individual components, the incidence of hypoglycemia in the pooled safety population was relatively low (1.4%), and no subjects discontinued study medication due to hypoglycemia or experienced major hypoglycemia (defined as a symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration).

A somewhat unique finding in the pooled safety analysis was an imbalance in the number of subjects who experienced markedly elevated serum CK concentrations >10x ULN (a marker of muscle injury/necrosis) in the saxagliptin+dapagliflozin+metformin treatment arms. These marked laboratory changes were reported in seven (1.4%) saxagliptin+dapagliflozin+metformin-treated subjects compared to one subject (0.3%) randomized to dapagliflozin+metformin arm, and no subjects randomized to saxagliptin+metformin arm. Although these laboratory abnormalities were typically asymptomatic, transient (approximately two weeks in duration), and did not require discontinuation of therapy, rhabdomyolysis was reported for one of the five subjects with CK elevations, for whom no other obvious cause was identified. While this safety finding was flagged as a concern in the review of NDA (b) (4), it is reassuring that no further cases were seen with the additional patient-years of exposure in the updated safety database.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. No Advisory Committee was held to discuss this Application.

10 Labeling Recommendations

10.1. Prescribing Information

The proposed labeling for this NDA conforms to the final rule governing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 18, 2006, available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. However, the Applicant proposed the following indication for QTERN: "As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) (b) (4)" the Division recommends the following indication: "As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on dapagliflozin or who are already treated with dapagliflozin and

saxagliptin."

The proposed labeling also is [redacted] (b) (4) to be consistent with class labeling for this second in class SGLT-2 inhibitor/DPP-4 inhibitor FCDP, the description of the product in labeling, as well as the markings on the tablet (i.e., "5/10") should list/reflect the SGLT-2 inhibitor first (i.e., dapagliflozin/saxagliptin, with "10/5" printed on the tablet).

Dr. Ariane Conrad, from the Division of Medication Error Prevention and Analysis (DMEPA), was asked to review the revised commercial container label, professional sample carton labeling, and professional sample blister cards for QTERN to determine if they are acceptable from a mediation error perspective. These revisions were made in response to previous recommendations provided to the Applicant based on recommendations provided for the original FCDP (i.e., NDA [redacted] (b) (4)).

For the efficacy supplements (i.e., sNDA 22350/S-018 for ONGLYZA; and sNDA200678/S-018 KOMBIGLYZE), the Applicant proposes to revise Sections 8.1 (Pregnancy) and 8.2 (Lactation) in accordance with the Pregnancy and Lactation Labeling Rule (PLLR), and to add information related to the efficacy findings from Trial CV181168 to Section 14.1 (Glycemic Efficacy Trials).

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

10.2. Patient Labeling

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

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy is recommended for this product.

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

Not applicable.

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

Not applicable.

11.3. Recommendations on REMS

Not applicable.

12 Postmarketing Requirements and Commitments

I have no recommendations for any postmarketing requirements or commitments.

The Initial Pediatric Study Plan (iPSP) requesting a full waiver was submitted to Module 1.9.1 of the NDA (available at: \\cdsesub1\evsprod\nda209091\0000_m1\us\initial-pediatric-study-plan.pdf). The Applicant's request was based on the following two criteria:

1. According to a survey of prescription trends from available databases, it was felt that FCDPs, in general, would not likely be used by a substantial number of pediatric patients with T2D.
2. The necessary studies would be impossible or highly impractical to complete because the number of available patients for whom participation in such studies would be appropriate is expected to be very small.

The iPSP request for a full waiver was presented to the Pediatric Research Committee (PeRC) on October 5, 2016. The request for a full waiver of pediatric studies was granted.

13 Appendices

13.1. References

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13.2. Antihyperglycemic Products Approved in the United States

Table 34: Summary Table of Approved Antihyperglycemic Products

Trade Name (Established Name)	NDA # (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	**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;

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			plasma concentrations is not feasible because miglitol acts locally. Little information is available on the safety of miglitol in patients with creatinine clearance <25 mL/min. Therefore, treatment of these patients with miglitol is not recommended.	gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[23]
PRECOSE (acarbose)	020482 (September 6, 1995)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. DOSAGE/ADMINISTRATION: • Initial dose: 25 mg orally 3 times daily at the start of each meal. • May increase to 50 mg 3 times daily after 4-8 weeks. • Maximum recommended dose: 100 mg 3 times daily (50 mg 3 times daily for patients ≤60 kg).	**Not recommended if serum creatinine is >2 mg/dL.** • The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given intravenously, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an oral dose was recovered in the urine as active (that is, parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. • Plasma concentrations of acarbose in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. • Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine > 2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with acarbose is not recommended. • Patients with severe renal impairment (CrCl <25 mL/min/1.73m^2) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function.	CONTRAINDICATIONS: • Known hypersensitivity to the drug, diabetic ketoacidosis or cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, predisposition to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine. WARNINGS AND PRECAUTIONS: • Sulfonylurea agents or insulin may cause hypoglycemia. • In long-term studies (up to 12 months, and including PRECOSE doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) above the upper limit of normal (ULN), greater than 1.8 times the ULN, and greater than 3 times the ULN occurred in 14%, 6%, and 3%, respectively, of PRECOSE-treated patients as compared to 7%, 2%, and 1%, respectively, of placebo-treated patients. • When diabetic patients are exposed

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				to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary. **DISADVANTAGES:** • Generally modest HbA1c efficacy; gastrointestinal side effects (e.g., flatulence, diarrhea); and frequent dosing schedule.[23]
Amylin Mimetics				
SYMLIN (pramlintide)	021332 (March 16, 2005)	**INDICATION:** As an adjunctive treatment in patients with T1D or T2D who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy. **DOSAGE/ADMINISTRATION:** • T1D: Start at 15 mcg subcutaneously before major meals. Increase in 15 mcg increments to a maximum premeal dose of 30 or 60 mcg; if not tolerated, reduce to 30 mcg, as tolerated. • T2D: Start at 60 mcg subcutaneously before major meals then increase to 120 mcg before meals, as tolerated.	**No dosage adjustments are provided in product labeling.** • No studies have been conducted in patients with ESRD. • In a single-dose pharmacokinetic study in patients with type 1 diabetes, 60 mcg of pramlintide was administered to 4 patients with normal renal function (CrCl >90 mL/min), 9 patients with mild renal impairment (CrCl 60-89 mL/min), 5 patients with moderate renal impairment (CrCl 30-59 mL/min) and 3 patients with severe renal impairment (CrCl 15-29 mL/min). No statistically significant differences were noted in total (AUC0-∞) and peak (Cmax) exposure of pramlintide for mild, moderate, and severe renal impairment categories in comparison to patients with normal renal function; although, inter-patient variability in pharmacokinetic parameters was high.	**BOXED WARNING:** • Use with insulin has been associated with an increased risk of severe hypoglycemia, particularly in patients with T1D. **CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to pramlintide or its ingredients, confirmed diagnosis of gastroparesis, or hypoglycemia unawareness. **WARNINGS AND PRECAUTIONS:** • Severe hypoglycemia: Increased risk particularly for type 1 diabetes. Upon initiation of SYMLIN, 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

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				as separate injections. • Slows gastric emptying: Administer concomitant oral medications at least 1 hour before or 2 hours after pramlintide if rapid onset or threshold concentration is critical. **DISADVANTAGES:** • Generally modest HbA1c efficacy; gastrointestinal side effects (e.g., nausea, vomiting); hypoglycemia unless insulin dose is simultaneously reduced; injectable; frequent dosing schedule; and training requirements.[23]
Biguanides				
FORTAMET (metformin) **GLUCOPHAGE** (metformin) **RIOMET** (metformin) **GLUCOPHAGE XR** (metformin extended-release) **GLUMETZA** (metformin extended-release)	021574 (April 27, 2004) 020357 (March 3, 1995) 021591 (September 11, 2003) 021202 (October 13, 2000) 021748 (June 3, 2005)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **DOSAGE/ADMINISTRATION:** • Extended-release tablet is 500 to 1000 mg once daily with the evening meal, although 500 mg may be utilized when clinically appropriate. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg (GLUMETZA, GLUCOPHAGE XR) to 2500 mg (FORTAMET) once daily with the evening meal. • Immediate-release tablet or solution: Adults ≥17 years: Initial: 500 mg twice daily or 850 mg once daily; titrate in increments of 500 mg weekly or 850 mg every other week; may also titrate	• 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	**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

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Combination Products **GLUCOVANCE** (glyburide + metformin)	021178 (July 31, 2000)	from 500 mg twice a day to 850 mg twice a day after 2 weeks. If a dose >2,000 mg daily is required, it may be better tolerated in 3 divided doses with meals. Maximum recommended dose: 2,550 mg daily (2000 mg daily in pediatric patients 10-16 years of age). **GLUCOVANCE INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inadequate glycemic control on diet and exercise alone: 1.25 mg/250 mg once daily with a meal; patients with HbA1c >9% or FPG >200 mg/dL may start with 1.25 mg/250 mg twice daily with meals. • Inadequate glycemic control on a sulfonylurea and/or metformin: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals. Dosage may be increased in increments no greater than 5 mg/500 mg; maximum daily dose: 20 mg/2000 mg.	iodinated contrast. Re-evaluate eGFR 48 hours following the imaging procedure; metformin may be reinitiated once renal function is stable. • Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than CrCl, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. • In patients with decreased renal function (based on measured CrCl), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in CrCl.	alcohol intake, and hepatic impairment. **CONTRAINDICATIONS:** • Use is contraindicated in patients with an eGFR <30 mL/minute/1.73 m^2, known hypersensitivity to metformin (or components of combination product), metabolic acidosis, including diabetic ketoacidosis. **WARNINGS AND PRECAUTIONS:** • Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. • Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents (i.e., glyburide or glipizide) can lead to hemolytic anemia. **DISADVANTAGES:** • Gastrointestinal side effects (diarrhea, abdominal cramping); lactic acidosis risk (rare); vitamin B_{12} deficiency; multiple contraindications.[23] *Also refer to Sulfonylureas for sulfonylurea-containing FCDPs and to DPP-4 inhibitors for DPP-4 inhibitor-containing FCDPs.*
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:		

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		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.		
Bile Acid Sequestrants				
WELCHOL (colesevelam)	21176 (January 18, 2008)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. DOSAGE/ADMINISTRATION: • The recommended dose of colesevelam for T2D is 6 tablets (3.75 g) orally once daily or 3 tablets (1.875 g) twice daily. Colesevelam should be taken with a meal and liquid.	**No dosage adjustment necessary; not absorbed from the GI tract.** • Excretion: In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine. • T2D: Of the 2048 patients enrolled in the six diabetes studies, 807 (39%) had mild renal insufficiency (CrCl 50-<80 mL/min), 61 (3%) had moderate renal insufficiency (CrCl 30-<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	CONTRAINDICATIONS: • Colesevelam is contraindicated in patients with a history of bowel obstruction, serum TG concentrations >500 mg/dL, or a history of hypertriglyceridemia-induced pancreatitis. • Postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia. WARNINGS AND PRECAUTIONS: • Can increase TG, particularly when used with insulin or sulfonylureas. • Not recommended in patients at risk of bowel obstruction (e.g., patients with

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			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.	gastroparesis, other gastrointestinal motility disorders or a history of major gastrointestinal surgery). • Reduces gastrointestinal absorption of some drugs. • Oral Suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet. **DISADVANTAGES:** • Generally modest HbA1c efficacy; constipation; increase in triglycerides; and may decrease the absorption of other medications.[23]
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 approximately 2-6% of an oral dose excreted via the urine. • No pharmacokinetic studies have been conducted in patients with renal impairment. Although the kidney is a minor pathway for elimination of bromocriptine, caution should be used in patients with renal impairment.	**CONTRAINDICATIONS:** • Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients. • Patients with syncopal migraine (increases the likelihood of a hypotensive episode) among patients with syncopal migraine. • Women who are nursing their children (may inhibit lactation, and there are postmarketing reports of stroke in this patient population). **WARNINGS AND PRECAUTIONS:** • Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. • May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis.

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				• 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.[23]
DPP-4 Inhibitors				
JANUVIA (sitagliptin) *Combination Products* **JANUMET** (sitagliptin + metformin) **JANUMET XR** (sitagliptin + metformin extended-release)	021995 (October 16, 2006) 022044 (March 30, 2007) 202270 (February 2, 2012)	**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. **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	**FOR SITAGLIPTIN MONOTHERAPY:** **CrCl >50 mL/min: No dosage adjustment necessary.** **CrCl ≥30 to <50 mL/min (approximate serum creatinine of >1.7 to ≤3 mg/dL [males] or >1.5 to ≤2.5 mg/dL [females]): 50 mg once daily.** **CrCl <30 mL/min (approximate serum creatinine >3 mg/dL [males] or >2.5 mg/dL [females]): 25 mg once daily.** **End-stage renal disease requiring hemodialysis or peritoneal dialysis: 25 mg once daily; administer without regard to timing of hemodialysis.** • Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal half-life following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion	**CONTRAINDICATIONS:** • Metabolic acidosis, including diabetic ketoacidosis. • History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to one of the product components. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. • There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. • There is an increased risk of hypoglycemia when added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. • There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients,

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		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.	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.*	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.[23] *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.**	

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		combination product. Dose adjustments should be made at intervals of ≥4 weeks.	**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.**	
NESINA (alogliptin)	022271 (January 25, 2013)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended dose in patients with normal renal function or mild renal impairment is 25 mg orally once daily.	**FOR ALOGLIPTIN MONOTHERAPY:** **CrCl ≥60 mL/min: No dosage adjustment is necessary.** **CrCl ≥30 to <60 mL/min: 12.5 mg once daily.** **CrCl ≥15 to <30 mL/min or ESRD (CrCl <15 mL/min or hemodialysis): 6.25 mg once daily. Administer without regard to the timing of dialysis.** **Peritoneal dialysis: There is no dosage adjustment provided in product labeling (has not been studied).** • The primary route of elimination of [^{14}C] alogliptin-derived radioactivity occurs via renal excretion (76%) with 13% recovered in the feces, achieving a total recovery of 89% of the administered radioactive dose. The renal clearance of alogliptin (9.6 L/hr) indicates some active renal tubular secretion and systemic clearance was 14.0 L/hr. • A single-dose, open-label study was conducted to evaluate the pharmacokinetics of alogliptin 50 mg in patients with chronic renal impairment compared with healthy subjects. In patients with mild renal impairment (creatinine clearance [CrCl] ≥60 to <90 mL/min), an approximate 1.2-fold increase in plasma AUC of alogliptin was observed. Because increases of this magnitude are not considered clinically relevant, dose adjustment for patients with mild renal impairment is not recommended. In patients with moderate renal impairment (CrCl ≥30 to <60 mL/min), an approximate two-fold increase in plasma AUC of	**CONTRAINDICATIONS:** • History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions or severe cutaneous adverse reactions. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis. • Heart failure: consider the risks and benefits of NESINA prior to initiating treatment in patients at risk for heart failure. • There have been postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. • Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. • When an insulin secretagogue (e.g., sulfonylurea) or insulin is used in combination with NESINA, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia.

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			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.	• 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.[23]
Combination Products **KAZANO** (alogliptin + metformin)	203414 (January 25, 2013)	**KAZANO:** • Individualize the starting dose based on the patient's current regimen. • Should be taken twice daily with food. • May adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg alogliptin and 2000 mg metformin HCl.	**FOR KAZANO:** **Prior to initiation, assess renal function with eGFR.** **Do not use in patients with eGFR below 60 mL/min/1.73 m^2.** **CONTRAINDICATION: Severe renal impairment eGFR below 30/mL/min/1.73 m^2.**	
OSENI (alogliptin + pioglitazone)	022426 (January 25, 2013)	**OSENI:** • Individualize the starting dose based on the patient's current regimen and concurrent medical condition but do not exceed a daily dose of alogliptin 25 mg and pioglitazone 45 mg.	**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**	

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		• 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.	**impairment or ESRD requiring dialysis.** *Also refer to Biguanides for metformin-containing FCDPs and to Thiazolidinediones for pioglitazone-containing FCDPs.*	
ONGLYZA (saxagliptin)	022350 (July 31, 2009)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. • 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., 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 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	**CONTRAINDICATIONS:** • History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to ONGLYZA. **WARNINGS AND PRECAUTIONS:** • Acute pancreatitis. • Heart Failure: Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. • When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. • Hypersensitivity-related events (e.g., urticaria, facial edema): More common in patients treated with ONGLYZA than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. • Severe and disabling arthralgia has been reported in patients taking DPP-

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			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 AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.	4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. **DISADVANTAGES:** • Angioedema/urticaria and other immune-mediated dermatological effects; uncertain risk for acute pancreatitis; and uncertain risk for heart failure hospitalizations with the DPP-4 inhibitor pharmacologic class (statistically significant increase incidence observed in the CVOT, SAVOR).[23]
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.	**FOR KOMBIGLYZE XR:** **Do not use in patients with eGFR below 30 mL/min/1.3 m^2.** **Initiation is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.** **Assess risk benefit of continuing if eGFR falls below 45**	

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Do not exceed a daily dosage of 5 mg saxagliptin/2000 mg metformin HCl extended-release. • Swallow whole. Never crush, cut, or chew.	**mL/min/1.73 m^2.** **Limit the saxagliptin component to 2.5 mg daily if eGFR is less than 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls below 30 mL/min/1.73 m^2.** *Also refer to Biguanides for metformin-containing FCDPs.*	
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	**CONTRAINDICATIONS:** • History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperactivity. **WARNINGS AND PRECAUTIONS:** • There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. • When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. • There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin including anaphylaxis, angioedema, and exfoliative skin conditions. • Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. • There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients

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Combination Products JENTADUETO (linagliptin + metformin)	201281 (January 30, 2012)	**JENTADUETO INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both linagliptin and metformin is appropriate. • Individualize the starting dose based on the patient's current regimen. • The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin twice daily. • Should be given twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.	further supported by the results of population pharmacokinetic analyses. **For JENTADUETO and JENTADUETO XR:** **Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).** **Do not use in patients with eGFR below 30 mL/min/1.73 m^2.** **Initiation is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.** **Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls below 30 mL/min/173 m^2.**	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.[23]
JENTADUETO XR (linagliptin + metformin extended-release)	208026 (May 27, 2016)	**JENTADUETO XR INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both linagliptin and metformin is appropriate. • Individualize the starting dose based on the patient's current regimen. • Do not exceed a total daily dose of linagliptin 5 mg and metformin 2000 mg. • Give once daily with a meal. • Swallow whole; do not split, crush, dissolve, or chew.	**FOR GLYXAMBI:**	

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
GLYXAMBI (empagliflozin/linagliptin)	206073 (January 30, 2015)	**GLYXAMBI INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and linagliptin is appropriate. • The recommended dose is 10 mg empagliflozin/5 mg linagliptin orally once daily, taken in the morning with or without food. • Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.	**Assess renal function before initiating.** **Do not initiate Glyxambi if eGFR is below 45 mL/min/1.73 m^2.** **Discontinue if eGFR falls persistently below 45 mL/min/1.73 m^2.** *Also refer to Biguanides for metformin-containing FCDPs and SGLT-2 inhibitors for empagliflozin-containing FCDRs.*	
GLP-1 Receptor Agonists				
ADLYXIN (lixisenatide)	208471 (July 27, 2016)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 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, mean terminal half-life was approximately 3 hours and	**CONTRAINDICATIONS:** • Hypersensitivity to lixisenatide or any product components. **WARNINGS AND PRECAUTIONS:** • Anaphylaxis and serious hypersensitivity reactions. • Pancreatitis. • Never share ADLYXIN pen between patients, even if the needle is changed. • Hypoglycemia with concomitant use of sulfonylurea or basal insulin. • Acute kidney injury. • Immunogenicity. **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell
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 inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide. • In patients inadequately controlled on less than 30 units of basal insulin or on		

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		lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily. • In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily. • Inject once a day within the hour prior to the first meal of the day. • Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). • SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. • Use alternative antidiabetic products if patients require a SOLIQUA 100/33 daily dosage below 15 units or over 60 units. • Inject subcutaneously in thigh, upper arm, or abdomen. • Do not administer intravenously, intramuscularly, or by an infusion pump. • Do not dilute or mix with any other insulin products or solutions.	the mean apparent clearance (CL/F) about 35 L/h. • Compared to healthy subjects [CrCl using Cockcroft-Gault] ≥90 mL/min (N=4)], plasma Cmax of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild [CrCl 60–89 mL/min (N=9)], moderate [CrCl 30–59 mL/min (N=11)], and severe [CrCl 15–29 mL/min (N=8)] renal impairment. Plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively. • In patients with mild renal impairment (eGFR: 60–89 mL/min/1.73 m^2) no dose adjustment is required, but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because a higher incidence of hypoglycemia, nausea and vomiting were observed in these patients. • In a cardiovascular outcome study, 655 (22%) lixisenatide treated patients had moderate renal impairment (eGFR: 30 to less than 60 mL/min/1.73 m^2). No dosing adjustment is recommended in patients with moderate renal impairment, but close monitoring for lixisenatide related adverse gastrointestinal reactions 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	hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[23]

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			occurrence of gastrointestinal adverse reactions and for changes in renal function. • There is no therapeutic experience in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use lixisenatide in this population.	
BYDUREON (exenatide extended-release) **BYETTA** (exenatide)	022200 (January 27, 2012) 021773 (April 28, 2005) 021919 (October 30, 2009)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Administer 2 mg by subcutaneous injection once every seven days, at any time of day and with or without meals. • Administer immediately after the dose is prepared. **BYETTA INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately six hours or more apart. • Initiate 5 mcg per dose twice daily; increase to 10 mcg twice daily after one month based on clinical response.	**For BYDUREON:** **CrCl >50 mL/min: No dosage adjustment necessary.** **CrCl 30-50 mL/min: There are no dosage adjustments provided in product labeling; use caution.** **CrCL <30 mL/min or ESRD: Use is not recommended.** **Renal transplantation: Use with caution.** • Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 hours post-dose, whereas following administration of exenatide extended-release, plasma exenatide concentrations generally fall below the minimal detectable concentration of 10 pg/mL approximately 10 weeks after discontinuation of 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-	**BOXED WARNING:** • Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including MTC in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to exenatide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors. • Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. • Hypoglycemia: When used in combination with an insulin secretagogue (e.g., a sulfonylurea) or

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			fold compared to that of subjects with normal renal function.	insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia. • Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Not recommended if patient has severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal impairment. • Severe Gastrointestinal Disease: Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). • Hypersensitivity: Postmarketing reports with exenatide of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema). • Injection-site Reactions: There have been postmarketing reports of serious injection-site reactions with or without subcutaneous nodules. **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.[23]
TANZEUM (albiglutide)	(BLA) 125431 (April 15, 2014)	**INDICATION:** As an adjunct to diet and exercise to	**No dosage adjustment necessary. Use caution when initiating or escalating doses.**	**BOXED WARNING:** • Carcinogenicity of albiglutide could

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		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.	• 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.	not be assessed in rodents, but other GLP-1 receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether albiglutide causes thyroid C-cell tumors, including MTC, in humans. • Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to albiglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors. • Pancreatitis. • Hypoglycemia: Can occur when used in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin. • Hypersensitivity Reactions. • Renal Impairment. **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors

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

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				in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[23]
VICTOZA (liraglutide) *Combination Products* XULTOPHY (insulin degludec/liraglutide)	022341 (January 25, 2010) 208583 (November 21, 2016)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Inject subcutaneously in the abdomen, thigh or upper arm. • Administer once daily at any time of day, independently of meals. • Initiate at 0.6 mg per day for one week then increase to 1.2 mg. • Dose can be increased to 1.8 mg for additional glycemic control **XULTOPHY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily). • Recommended starting dosage is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily. • Administer once daily at same time each day with or without food. • Maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide).	**No dosage adjustments are provided in product labeling; however, use with caution, due to reports of acute renal failure and exacerbation of chronic renal failure and limited experience in patients with severe renal impairment.** • During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration. • The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated CrCl 50-80 mL/min) to severe (estimated CrCl <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to liraglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • Thyroid C-cell tumors in animals. • Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. • Never share the liraglutide pen between patients, even if the needle is changed. • Serious Hypoglycemia: When used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the sulfonylurea

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• XULTOPHY 100/3.6 pen delivers doses from 10 to 50 units with each injection (2.1, 2.2); each XULTOPHY 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide. • Use alternative antidiabetic products if patients require a XULTOPHY 100/3.6 daily dosage: Persistently below 16 units, or over 50 units. • Inject subcutaneously in thigh, upper arm or abdomen. • Do not administer intravenously, intramuscularly, or by an infusion pump. • Do not dilute or mix with any other insulin products or solutions.	disease was on average 35%, 19%, 29% and 30% lower, respectively.	or insulin to reduce the risk of hypoglycemia. • Renal Impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. • Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). **DISADVANTAGES:** • Gastrointestinal side effects (nausea/vomiting/diarrhea); increase in heart rate; uncertain risk for acute pancreatitis; C-cell hyperplasia/medullary thyroid tumors in animals; injectable; and training requirements.[23]
Insulins and Insulin Analogues				
AFREZZA (inhaled insulin human) **APIDRA** (insulin glulisine) **BASAGLAR** (insulin glargine) **HUMALOG** (insulin lispro)	022472 (June 27, 2014) 021629 (April 16, 2004) 205692 (August 18, 2014) 020563 (June 14, 1996)	**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**	**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:[113,114] — CrCl >50 mL/min: No adjustment necessary. — CrCl 10-50 mL/min: Administer at 75% of	**CONTRAINDICATIONS (AFREZZA):** • Patients with chronic lung disease (e.g., asthma, COPD) with inhaled insulin. **DISADVANTAGES:** • Hypoglycemia, weight gain, uncertain mitogenic effects, injectable (except inhaled insulin), patient and provider reluctance, training requirements, pulmonary toxicity (inhaled insulin).[23,24] Spirometry (FEV_1) testing

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
HUMULIN N (insulin isophane) **HUMULIN R** (insulin human) **LANTUS** (insulin glargine) **LEVEMIR** (insulin detemir) **NOVOLIN R** (insulin human) **NOVOLOG** (insulin aspart) **TOUJEO** (insulin glargine) **TRESIBA** (insulin degludec) *Combination Products* **HUMALOG MIX** (insulin lispro protamine + insulin lispro) **NOVOLOG MIX** (insulin aspart protamine + insulin aspart) **RYZODEC**	018781 (October 28, 1982) 018780 (October 28, 1982) 021081 (April 20, 2000) 021536 (June 16, 2005) 019938 (June 25, 1991) 020986 (June 7, 2000) 206538 (February 25, 2015) 203314 (September 25, 2015) 021017 (December 22, 1999) 021018 December 22, 1999 021172 (November 1, 2001) 203313	**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.**[24] ***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).	recommended dose. — CrCl <10 mL/min: Administer at 50% of recommended dose and monitor glucose closely. — Hemodialysis: Because of a large molecular weight (6000 daltons), insulin is not significantly removed by either peritoneal or hemodialysis; supplemental dose is not necessary. — CRRT: Administer at 75% of recommended dose. • Polypeptides and low-molecular proteins, such as insulin, can be actively reabsorbed by the proximal tubules through luminal endocytosis, followed by hydrolysis by the digestive enzymes in the lysosomes to peptide fragments and amino acids. The amino acids are then reabsorbed by a carrier-mediated, energy-dependent transport mechanism. Approximately one-third of the insulin dose may undergo degradation in the kidneys. Azotemia may be associated with a prolonged half-life of insulin, and an increased risk of hypoglycemia. Patients with CKD treated with insulin should closely monitor their blood glucose to minimize this risk, and dose adjustments made as necessary. Initiation of peritoneal dialysis may require an increase in the insulin dosage due to the absorption of glucose from the dialysate through the peritoneal cavity.[115,116]	prior to and after starting inhaled insulin therapy. **WARNINGS AND PRECAUTIONS:** • Never share insulin pen injectors, syringes, or needles • Hyper- or hypoglycemia (e.g., with changes in insulin regimen) • Medication Errors • Hypersensitivity reactions • Hypokalemia • Fluid retention and heart failure with concomitant use of thiazolidinediones • May require a reduction in dose with renal or hepatic impairment

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(insulin degludec + insulin aspart)	(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.	**No dosage adjustment is required with mild to moderate renal impairment. Initiate with a 0.5 mg dose, and subsequently titrate carefully with severe renal impairment.** • Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces. • Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with T2D and normal renal function (CrCl >80 mL/min), mild to moderate renal function impairment (CrCl = 40-80 mL/min), and severe renal function impairment (CrCl = 20-40 mL/min). Both AUC and Cmax of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced 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	**CONTRAINDICATIONS:** • Diabetic ketoacidosis, with or without coma. • T1D. • Co-administration of gemfibrozil. • Known hypersensitivity to the drug or its inactive ingredients. **WARNINGS AND PRECAUTIONS:** • Not indicated for use in combination with NPH-insulin. • All oral antihyperglycemic drugs are capable of producing hypoglycemia. • Use with caution in patients with moderate to severe liver disease because such patients have not been studied. • May need to discontinue and temporarily use insulin if glycemic control deteriorates during periods of stress or if there is decreased intake of fluids and food (e.g., infection, surgery). **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[23] *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		

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		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.	conducted in patients with CrCl <20 mL/min or patients with renal failure requiring hemodialysis. *Also refer to Biguanides for metformin-containing FCDPs.*	
STARLIX (nateglinide)	021204 (December 22, 2000)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Nateglinide should be taken one to 30 minutes prior to meals. • The recommended starting and maintenance dose, alone or in combination with metformin or a thiazolidinedione, is 120 mg three times daily before meals. • The 60-mg dose, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA1C 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	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug or its inactive ingredients. • T1D. • DKA. **WARNINGS AND PRECAUTIONS:** • Not indicated for use in combination with NPH-insulin. • All oral antihyperglycemic drugs are capable of producing hypoglycemia. • May need to discontinue and temporarily use insulin if glycemic control deteriorates during periods of stress or if there is decreased intake of fluids and food (e.g., infection, surgery). **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and frequent dosing schedule.[23]

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			drug exposure. However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.	
SGLT-2 Inhibitors				
FARXIGA (dapagliflozin)	202293 (January 8, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. • Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control.	**FOR DAPAGLIFLOZIN MONOTHERAPY:** **eGFR ≥60 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR 30 to <60 mL/minute/1.73 m^2: Use is not recommended for initiation of therapy or when eGFR is persistently between 30 and <60 mL/minute/1.73 m^2.** **eGFR <30 mL/minute/1.73 m^2, ESRD, or hemodialysis: Use is contraindicated.** • Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose 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 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	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to FARXIGA. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. **WARNINGS AND PRECAUTIONS:** • Hypotension: Before initiating FARXIGA, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. • Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, and glycogen storage disorders).[117] • Acute Kidney Injury and Impairment in Renal Function. • Urosepsis and Pyelonephritis. • Hypoglycemia: In patients taking insulin or an insulin secretagogue with FARXIGA, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. • Genital Mycotic Infections. • Increased LDL-C.

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Combination Products **XIGDUO XR** (dapagliflozin+metformin)	205649 (October 29, 2014)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both dapagliflozin and metformin is appropriate. • Individualize the starting dose based on the patient's current treatment. • Administer once daily in the morning with food. • Swallow whole. Never crush, cut, or chew. • Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release. • Assess renal function before initiating. Do not initiate or continue if eGFR is below 60 mL/min/1.73 m^2. • No dosage adjustment is indicated in patients with mild renal impairment. • XIGDUO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.	higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with T2D and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known. **FOR XIGDUO XR:** **eGFR <60 mL/minute/1.73 m^2, ESRD, ESRD, or dialysis: Use is contraindicated.** *Also refer to Biguanides for metformin-containing FCDPs.*	• Bladder Cancer: An imbalance in bladder cancers was observed in clinical trials. FARXIGA should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer. **DISADVANTAGES:** • Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[23] **XIGDUO XR BOXED WARNING:** • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.

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				Also refer to Biguanides for metformin-containing FCDPs.
INVOKANA (canagliflozin)	204042 (March 29, 2013)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • The recommended starting dose is 100 mg once daily, taken before the first meal of the day. • 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.	**FOR CANAGLIFLOZIN MONOTHERAPY:** **eGFR ≥60 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR 45 to <60 mL/minute/1.73 m^2: Maximum dose: 100 mg once daily. If patient receiving concurrent UDP-glucuronosyl transferase (UGT) enzyme inducers (e.g., rifampin, phenytoin, phenobarbital, ritonavir) and eGFR 45 to <60 mL/minute/1.73 m^2 at baseline, consider the use of another antihyperglycemic agent.** **eGFR ≥30 to <45 mL/minute/1.73 m^2: Use not recommended for initiation of therapy or when eGFR is persistently <45 mL/minute/1.73 m^2.** **eGFR <30 mL/minute/1.73 m^2: Use is contraindicated.** **ESRD: Use is contraindicated.** **Hemodialysis: Use is contraindicated.** • Following administration of a single oral [^{14}C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in feces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible. Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min. Mean systemic clearance of canagliflozin was approximately	**CONTRAINDICATIONS:** • History of serious hypersensitivity reaction to INVOKANA. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. **WARNINGS AND PRECAUTIONS:** • Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. • Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, and glycogen storage disorders).[117] • Acute Kidney Injury and Impairment in Renal Function. • Hyperkalemia. • Urosepsis and Pyelonephritis. • Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with canagliflozin. • Genital mycotic infections. • Hypersensitivity reactions. • Bone fracture: Consider factors that
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 canagliflozin and metformin is appropriate. • Individualize based on the patient's current regimen. • Take one INVOKAMET tablet twice daily with meals, recommended starting dose of canagliflozin is 50 mg twice daily and metformin 500 mg twice daily. • Canagliflozin dose can be increased to		

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INVOKAMET XR (canagliflozin + metformin extended-release)	205879 (September 20, 2016)	150 mg twice daily in patients tolerating canagliflozin 50 mg twice daily who have eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control. Do not exceed a total daily canagliflozin dose of 300 mg. • Gradually escalate metformin dose to reduce the gastrointestinal side effects while not exceeding total daily dose of 2000 mg. • Assess renal function before initiating and periodically thereafter. **INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both canagliflozin and metformin is appropriate. • Individualize based on the patient's current regimen. • Take two tablets once daily with the morning meal. • In patients currently not treated with either canagliflozin or metformin, initiate therapy with two INVOKAMET XR tablets, each tablet containing canagliflozin 50 mg and metformin 500 mg. • In patients already treated with canagliflozin and metformin, switch to two INVOKAMET XR tablets containing the same total daily dose of	192 mL/min in healthy subjects following intravenous administration. • A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects. Renal impairment did not affect the Cmax of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m2), 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 m2, 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. **FOR INVOKAMET AND INVOKAMET XR:** **Contraindicated in patients with an estimated eGFR <45 mL/min/1.73 m^2.** **Limit the dose of canagliflozin component to 50 mg twice daily (INVOKAMET) or to two tablets, each contain 50 mg, once daily (INVOKAMET XR) in patients with an eGFR of 45 to <60 mL/min/1.73 m^2.** **May need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.** *Also refer to Biguanides for metformin-containing FCDPs.*	contribute to fracture risk before initiating INVOKANA. • Increased LDL-C. **DISADVANTAGES:** Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[23] **INVOKAMET AND INVOKAMET XR BOXED WARNING:** • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. *Also refer to Biguanides for metformin-containing FCDPs.*

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		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 while not exceeding a total daily dose of 2000 mg. • Assess renal function before initiating and periodically thereafter • Swallow whole. Never crush, cut, or chew.		
JARDIANCE (empagliflozin)	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. • The recommended dose is 10 mg once daily, taken in the morning, with or without food. • Dose may be increased to 25 mg once daily. • Assess renal function before initiating.	FOR EMPAGLIFLOZIN MONOTHERAPY AND GLYXAMBI: **eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.** **eGFR <45 mL/minute/1.73 m^2: Do not initiate therapy; in patients already taking empagliflozin, discontinue therapy when eGFR is persistently <45 mL/minute/1.73 m^2** **eGFR <30 mL/minute/1.73 m^2: Use is contraindicated. ESRD, dialysis: Use is contraindicated.** • The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population	CONTRAINDICATIONS: • History of serious hypersensitivity reaction to JARDIANCE. • Severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease, or dialysis. WARNINGS AND PRECAUTIONS: • Hypotension: Before initiating JARDIANCE, assess and correct volume status in patients with renal impairment, the elderly, in patients with low SBP, and in patients on diuretics.

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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.	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 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.	• Ketoacidosis (possibly associated with recent use of insulin, reducing caloric intake, alcohol abuse, chronic liver disease, and glycogen storage disorders).[117] • 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. • Genital mycotic infections. • Increased LDL-C. **DISADVANTAGES:** • Genitourinary infections; polyuria; volume depletion/hypotension/ dizziness; increase LDL-C; and increase in serum creatinine (usually transient).[23]
SYNJARDY (empagliflozin + metformin)	206111 (August 26, 2015)	**SYNJARDY INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with	**FOR SYNJARDY:** **eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary.**	

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		T2D who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. • Individualize the starting dose of SYNJARDY based on the patient's current regimen. • The maximum recommended dose is 12.5 mg empagliflozin/1000 mg metformin twice daily. • Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin. • Assess renal function before initiating.	**eGFR <45 mL/minute/1.73 m^2, ESRD, or dialysis: Use is contraindicated.** *Also refer to Biguanides for metformin-containing FCDPs and to DPP-4 inhibitors for linagliptin-containing FCDPs.*	
Sulfonylureas				
DIABINESE (chlorpropamide)	011641 (October 28, 1958)	**INDICATION:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • Initial dose: 250 mg orally daily in mild to moderate diabetes in middle-aged, stable patients. • In debilitated or malnourished patients, the initial dosing should be conservative to avoid hypoglycemic reactions. • After 5-7 days of initiation, subsequent daily dosages may be increased or decreased by 50-125 mg at 3- to 5-day intervals. • The maintenance dose is 100-250 mg	**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.[113]** **eGFR ≤50 mL/min, hemodialysis, peritoneal dialysis, or CRRT: Avoid use.[113]** • 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.	**CONTRAINDICATIONS:** • Known hypersensitivity to any component of this medication. • T1D, and DKA, with or without coma. **WARNINGS AND PRECAUTIONS:** • Hypoglycemia: All sulfonylurea drugs including chlorpropamide are capable of producing severe hypoglycemia, which may result in coma, and may require hospitalization. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur.

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		daily (500 mg/day may be required; avoid doses >750 mg/day).	Within 96 hours, 80% to 90% of a single oral dose is excreted in the urine. However, long-term administration of therapeutic doses does not result in undue accumulation in the blood, since absorption and excretion rates become stabilized in about 5 to 7 days after the initiation of therapy. • Chlorpropamide impairs water excretion. Renal insufficiency also affect the disposition of chlorpropamide and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. The elimination half-life with ESRD may be increased to 50-200 hours, and prolonged hypoglycemia may occur in azotemic patients.	At such times, it may be necessary to discontinue DIABINESE and administer insulin. • Hemolytic Anemia: Treatment of patients with glucose G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Geriatric Use: Chlorpropamide is identified in the Beers Criteria as a potentially inappropriate medication to be avoided in patients 65 years and older (independent of diagnosis or condition) because of its prolonged half-life in older adults, which may cause prolonged hypoglycemia.[118] 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)[18] have not supported an association. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[23]

Trade Name (Established Name)	NDA # (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.**[119] • 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	**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)[18] have not supported an association. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[23]

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			terminal half-life for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III. • A multiple-dose titration study was conducted in 16 patients with T2D and renal impairment using doses ranging from 1 mg to 8 mg daily for 3 months. Baseline CrCl ranged from 10 to 60 mL/min. The pharmacokinetics of glimepiride were evaluated in the multiple-dose titration study and the results were consistent with those observed in patients enrolled in a single-dose study. In both studies, the relative total clearance of glimepiride increased when kidney function was impaired. Both studies also demonstrated that the elimination of the two major metabolites was reduced in patients with renal impairment. *Also refer to thiazolidinediones for TZD-containing FCDPs.*	
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.	**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,[119] and a 50% reduction in dose has been suggested with an eGFR ≤50 mL/min.[113]** **Avoidance of the sustained-release formulation has also been suggested.[120]** • The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are	**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)[18] have not supported an association.

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. • The maximum recommended total daily dose is 40 mg.	inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). • The pharmacokinetics of glipizide has not been evaluated in patients with varying degree of renal impairment. Limited data indicates that glipizide biotransformation products may remain in circulation for a longer time in subjects with renal impairment than that seen in subjects with normal renal function. *Also refer to Biguanides for metformin-containing FCDPs.*	• Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with 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)

Trade Name (Established Name)	NDA # (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.		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.[23] **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)[18] have not supported an association.
GLYNASE (glyburide)	020051 (March 4, 1992)	**INDICATION:** As an adjunct to diet and exercise to	**FOR GLYBURIDE MONOTHERAPY:** **There are no specific dosage adjustments provided in**	**CONTRAINDICATIONS:** • Known hypersensitivity to the drug.

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		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.	**product labeling; however, use in patients with eGFR <60 mL/minute is not recommended.[119]** • 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.*	• 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)[18] have not supported an association. • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue 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

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[23]
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. **DIABETA WARNINGS AND PRECAUTIONS:**

Trade Name (Established Name)	NDA # (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.		• 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)[18] have not supported an association. • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue 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

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				nonsteroidal anti-inflammatory agents, ACE inhibitors, disopyramide, fluoxetine, clarithromycin, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. • Nonteratogenic effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.
(Tolazamide)	A070259¶ (November 7, 1986)	INDICATION: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • 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	**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	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)[18] have not supported an association. • Hypoglycemia: All sulfonylurea drugs are capable of producing severe

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		100 mg once a day.	assessment of renal function.	hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin. • Hemolytic anemia: Treatment of patients with G6PD deficiency with sulfonylurea agents can lead to hemolytic anemia. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency. • Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, 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

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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.[23]
(Tolbutamide)	A086445[†] (April 10, 1979)	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 are 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)[18] have not supported an association. • Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. • Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur.

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				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 more frequently with the use of agents with prolonged half-lives. **DISADVANTAGES:** • Hypoglycemia; increased weight; possibly blunts myocardial ischemic preconditioning; and low durability.[23]
Thiazolidinediones				

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
ACTOS (pioglitazone) *Combination Products* **ACTOPLUS MET** (pioglitazone + metformin) **ACTOPLUS MET XR** (pioglitazone + metformin extended-release) **DUETACT** (pioglitazone + glimepiride) **OSENI** (pioglitazone + alogliptin)	021073 (July 15, 1999) 021842 (August 29, 2005) 022024 (May 12, 2009) 021925 (July 28, 2006) 022426 (January 25, 2013)		**FOR PIOGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/h. • The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance [CrCl] 30 to 50 mL/min) and severe (CrCl <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required with pioglitazone monotherapy. • In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related. In postmarketing experience, reports of new onset or 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	**DISADVANTAGES:** • Increased weight; edema/heart failure; bone fractures; and possible risk for bladder cancer.[23]

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			overload. *Also refer to Biguanides for metformin-containing FCDPs, DPP-4 inhibitors for alogliptin-containing FCDPs, and Sulfonylureas for glimepiride-containing FCDPs.*	
AVANDIA (rosiglitazone) *Combination Products* **AVANDAMET** (rosiglitazone + metformin) **AVANDARYL** (rosiglitazone + glimepiride)	021071 (May 25, 1999) 021410 (October 10, 2002) 021700 (November 23, 2005)		**FOR ROSIGLITAZONE MONOTHERAPY:** **No dosage adjustment necessary with renal impairment.** • Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C] related material ranged from 103 to 158 hours. • There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving rosiglitazone monotherapy. • Rosiglitazone should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone should be used with caution in patients at risk for heart failure. 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	**DISADVANTAGES:** • Increased weight; edema/heart failure; bone fractures; increase in LDL-C; and uncertain risk for MI.[23]

Trade Name (Established Name)	NDA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
			T2D, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose related. Patients with ongoing edema were more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone. *Also refer to Biguanides for metformin-containing FCDPs and Sulfonylureas for glimepiride-containing FCDPs.*	

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; AUC, area under the concentration-time curve; AUCτ,ss, area under concentration-time curve during dosing interval at steady-state; 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; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FBG, fasting blood glucose; FCDP, fixed combination drug product; min, minute; G6PD, 6-phosphate dehydrogenase; GI, gastrointestinal; h, hour; HbA1c, hemoglobin A1c (glycated hemoglobin); JDRF, Juvenile Diabetes Research Foundation; L, liter; MDRD, Modification of Diet in Renal Disease; MEN 2, Multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; NDA, New Drug Application; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; SGLT-2, sodium-glucose Cotransporter-2; SIADH, syndrome of inappropriate antidiuretic hormone secretion; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; TG, triglyceride; TZD, thiazolidinediones;.
*Original date of approval.
†Dosing guidelines for the mono-component of the FCDP, except in the case of JUVISYNC (sitagliptin + simvastatin).
¶Reference Listed Drug (RLD); approved under an Abbreviated New Drug Application (ANDA).
‡Contraindications and Warnings and Precautions relate to the mono-component of the FCDP unless specified otherwise.

13.3. Financial Disclosure

In accordance with 21 CFR 54.2(e), the Applicant included financial disclosure information for all covered clinical studies (i.e., CV181168; CV181169; CV181191; CV181341; and MB102129). Form FDA 3454 was completed and signed for each study on February 16, 2016. The Applicant attests that no investigator in any study had financial interests or arrangements to disclose. Below is the financial disclosure information for the three Phase 3 trials used to support efficacy and safety of the proposed FCDP.

Covered Clinical Study (Name and/or Number): CV181168: *Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo.*

Trial CV181168 is a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group, 24-week trial designed to evaluate the efficacy and safety of the sequential addition of saxagliptin 5 mg to dapagliflozin 10 mg and metformin (≥1500 mg) compared with the addition of placebo to dapagliflozin and metformin in subjects with T2D who had inadequate glycemic control on dapagliflozin and metformin. This trial included a 28-week, long-term, treatment period to evaluate safety and tolerability.

The Applicant has submitted a list of 271 investigators that participated in study CV181168, and four Adjudication Committee Members.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 271 (59 Principal Investigators and 212 Sub-Investigators); as well as 4 Adjudication Committee Members		
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 S Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Source: Derived from the Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454) for CV181168, available at: \\cdsesub1\evsprod\nda209091\0000\m1\us\financial-cert-disclosure-cv181168.pdf.

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

Trial CV181169 was a Phase 3 multicenter, randomized, double-blind, active-controlled, parallel- group, 24-week trial designed to evaluate the efficacy and safety of the addition of saxagliptin 5 mg plus dapagliflozin 10 mg versus placebo plus saxagliptin 5 mg and versus placebo plus dapagliflozin 10 mg when administered concomitantly to metformin (≥1500 mg) in adults with T2D who had inadequate glycemic control on a stable dose of metformin monotherapy.

The Applicant has submitted a list of 628 investigators that participated in study CV181169.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 628 (144 Principal Investigators and 484 Sub-Investigators); as well as 8 Independent Review Committee Members		
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 S Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Source: Derived from the Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454) for CV181169, available at: \\cdsesub1\evsprod\nda209091\0000\m1\us\financial-cert-disclosure-cv181169.pdf.

Covered Clinical Study (Name and/or Number): MB102129: *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin.*

Trial MB102129 is a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel- group, 24-week trial designed to evaluate the efficacy and safety of the addition of dapagliflozin 10 mg to saxagliptin 5 mg and metformin (≥1500 mg) compared with the addition of placebo to saxagliptin and metformin in subjects with T2D who had inadequate glycemic control on saxagliptin and metformin. This trial included a 28-week, long-term, treatment period to evaluate safety and tolerability.

The Applicant has submitted a list of 374 investigators that participated in study MB102129, as well as 4 Adjudication Committee Members.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 374 (82 Principal Investigators and 292 Sub-Investigators); as well as 4 Adjudication Committee Members		
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 S Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Source: Derived from the Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454) for MB102129, available at: \\cdsesub1\evsprod\nda209091\0000\m1\us\financial-cert-disclosure-mb102129.pdf.

The Applicant also provided a list of investigators for the two supporting Phase 1 biopharmaceutics/clinical pharmacology studies (i.e., CV181341 and CV181191, which included 4 and 5 investigators, respectively).

13.4. Schedule of Trial Procedures

Table 35: Schedule of Trial Procedures for the Short-Term Treatment Period

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Eligibility Assessments											The Wk-16 visit cannot be performed until all laboratory results from the screening period have been received and reviewed to confirm eligibility. Once eligibility is confirmed, Wk-16 can be performed within 2 weeks of Wk-18
Obtain Informed Consent	X										
Review Medical History	X										

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Review Eligibility Criteria	X										
Review Randomization Criteria					X						
General Procedures											
Brief Physical Examination				X	X	X	X	X			
Complete Physical Examination	X								X	X	
Body Weight	X	X	X	X	X	X	X	X	X	X	
Blood Pressure and Heart Rate	X	X	X	X	X	X	X	X	X	X	

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Height	X										
Body Mass Index (BMI)	X										
Waist Circumference		X			X				X	X	
12-Lead ECG					X				X*	X*	*Only 2 ECGs performed/subject in the short-term period. ECG is not required at Wk 24 if subject has been rescued or discontinued from treatment prior to Wk 24
Waist Circumference											

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Review Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X	X	
Contact IVR system	X	X	X		X	X	X	X	X*	X**	* Call to register study termination only ** Call at Rescue/ETD/visit only if drug re-supply required.
Provide Diet and Exercise Counseling		X	X	X	X	X	X	X	X	X	
Provide Glucose Meter and Supplies / Instructions		X	X	X	X	X	X	X	X	X	
Provide logs / Instructions		X	X	X	X	X	X	X	X	X	

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Review study logs			X	X	X	X	X	X	X	X	
Safety Assessment											
Assess Adverse Events, Hypoglycemia Episodes		X	X	X	X	X	X	X	X	X	
Central Laboratory											
Pregnancy Test (urine) WOCBP only	X	X	X	X	X	X	X	X	X	X	Home pregnancy test kits sent home with WOCBP subjects to perform pregnancy test between visits and record result in log book
Blood & Urine Standard Safety Laboratory Panel	X	X	X	X	X	X	X	X	X	X	

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Dipstick Urinalysis	X	X*									* Positive dipstick at Wk -16 will require repeat test with microscopy prior to randomization (see App. 3)
Microscopic Urinalysis	X	X*					X		X	X	*Microscopic urinalysis only performed at Wk -16 if dipstick test is positive (see App. 3)
Spot Urine Glucose Quantification and glucose:creatinine ratio	X				X		X		X	X	
HbA1c	X			X	X	X	X	X	X	X	
FPG	X	X	X*	X*	X	X	X	X	X	X	* FPG must be < 270 mg/dL (see inclusion/exclusion criteria section for more details)

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Assess FPG for Rescue						X	X	X	X	X	
Fasting C-peptide	X										
MTT (Glucose)					X				X*	X*	Subject must be fasted for at least 8 hrs prior to the MTT. Subject must abstain from tobacco, alcohol and caffeine for at least 8 hrs prior to the MTT. *Maximum of 2 MTTs performed/subject. MTT not conducted at Wk 24 if subject has been rescued or discontinued from treatment prior to Wk 24.

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
eGFR (MDRD) and Serum Creatinine (SCr)	X		X	X	X	X	X	X	X	X	
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)					X				X	X	
Hepatitis Screen Panel and TSH	X										
Drug Dispensing											
Dispense Blinded Study Medication					X	X	X	X	X	X*	* Only if needed
Dispense Open-Label Study Medication		X	X		X	X	X	X	X	X*	* Only if needed

Short-Term Procedural Outline CV181168 (Screening, Open-Label Treatment and Short-Term Treatment Periods)											
Procedure	Screening Period (Period A)	Open-Label Treatment Period (Period B) (visit windows ± 2 days)			Short-Term Double-Blind Treatment Period (Period C) (visit windows ± 5 days)						Notes
	WK (-18)	WK (-16)	WK (-10)	WK (-2)	Day 1	WK 6	WK 12	WK 18	WK 24 / Termination	Rescue / Early Treatment Discontinuation	
Dispense Open-Label rescue medication, as needed (if applicable)						X	X	X	X	X	
Review Study Medication Compliance				X	X	X	X	X	X	X	

Sources: Adapted from the Applicant's Clinical Study Report (labeled as Table 5.1-1, pages 463-469 of 3279), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf

Abbreviations: BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ETD, early treatment discontinuation; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IVR, Interactive Voice Response; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification in Diet and Renal Disease; MTT, meal tolerance test; Scr, serum creatinine: TG, triglycerides; Total-C, total cholesterol; TSH, thyroid-stimulating hormone; Wk, week; and WOCBP, women of childbearing potential.

Table 36: Schedule of Trial Procedures for the Long-Term Treatment Period

Long-Term Procedural Outline CV181168 (Long-Term Treatment Period)					
Procedure	Long-Term Site and Subject Blind Treatment Period (Period D) (visit windows ± 5 days)				Notes
	Wk 32	Wk 40	Wk 52 / Termination	Rescue / Early Treatment Discontinuation	
General Procedures					
Brief Physical Examination	X	X			
Complete Physical Examination			X	X	
Body Weight	X	X	X	X	
Blood Pressure and Heart Rate	X	X	X	X	
Waist Circumference			X	X	
12-Lead ECG			X*	X*	*Only 1 ECG performed/subject in the site and subject blinded period. ECG is not required at Wk 52 if subject has been rescued or discontinued from treatment prior to Wk 52.
Review Concomitant Medications / Procedures	X	X	X	X	
Contact IVR system	X	X	X*	X**	* Call to register study termination only ** Call at Rescue/ETD/visit only if drug re-supply required.
Provide Diet and Exercise Counseling	X	X			

Long-Term Procedural Outline CV181168 (Long-Term Treatment Period)					
Procedure	Long-Term Site and Subject Blind Treatment Period (Period D) (visit windows ± 5 days)				Notes
	Wk 32	Wk 40	Wk 52 / Termination	Rescue / Early Treatment Discontinuation	
Dispense Glucose Meter and Supplies / Provide Instructions	X	X			
Dispense logs / Provide Instructions	X	X			
Review study logs	X	X	X	X	
Safety Assessment					
Assess Adverse Events, Hypoglycemia Episodes	X	X	X	X	
Pregnancy Test (urine) WOCBP only	X	X	X	X	
Blood & Urine Standard Safety Laboratory Panel	X	X	X	X	
Microscopic Urinalysis		X	X	X	
Spot Urine Glucose Quantification and glucose:creatinine ratio	X	X	X	X	
HbA1c	X	X	X	X	
Assess HbA1c for Rescue Criteria	X	X			

Long-Term Procedural Outline CV181168 (Long-Term Treatment Period)					
Procedure	Long-Term Site and Subject Blind Treatment Period (Period D) (visit windows ± 5 days)				Notes
	Wk 32	Wk 40	Wk 52 / Termination	Rescue / Early Treatment Discontinuation	
FPG	X	X	X	X	
eGRF (MDRD) and Serum Creatinine (SCr)	X	X	X	X	
Fasting Serum Lipids (Total-C, LDL-C, HDL-C, TG)			X	X	
Drug Dispensing					
Dispense Blinded Study Medication	X	X			
Dispense Open-Label Study Medication	X	X			
Dispense Open-Label rescue medication, as needed (if applicable)	X	X			
Review Study Medication Compliance	X	X	X	X	

Sources: Adapted from the Applicant's Clinical Study Report (labeled as Table 5.1-1, pages 470-472 of 3279), available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\cv181168-st-lt\cv181168-clinical-study-report-lt.pdf
Abbreviations: electrocardiogram; eGFR, estimated glomerular filtration rate; ETD, early treatment discontinuation; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IVR, Interactive Voice Response; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification in Diet and Renal Disease; Scr, serum creatinine: TG, triglycerides; Total-C, total cholesterol; Wk, week; and WOCBP, women of childbearing potential.

13.5. SGLT2 Inhibitor & DPP-4 Inhibitor Adverse Events of Special Interest (System/Custom MedDRA Queries)

Note: MedDRA v17.1 was used, and SMQs/CMQs were derived from existing MedDRA SMQs and/or from SGLT2 inhibitor and/or DPP-4 inhibitor Applications

ACUTE KIDNEY INJURY AND CHRONIC RENAL FAILURE

MedDRA PTs: Acquired cystic kidney disease; Acute phosphate nephropathy; Acute prerenal failure; Albumin urine present; Albuminuria; Aluminium overload; Anuria; Artificial kidney device user; 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; Blood urea nitrogen/creatinine ratio decreased; Blood urea nitrogen/creatinine ratio increased; Bloody peritoneal effluent; Bone cyst; Calcification of muscle; Calciphylaxis; Cerebrohepatorenal syndrome; Chronic allograft nephropathy; Chronic autoimmune glomerulonephritis; Coma uraemic; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Diabetic end stage renal disease; Diabetic nephropathy; Dialysis; Dialysis amyloidosis; Dialysis device insertion; Dialysis disequilibrium syndrome; Dialysis related complication; Diffuse mesangial sclerosis; Effective peritoneal surface area increased; Encephalopathy; Eosinophils urine present; Extensive interdialytic weight gain; Fibrillary glomerulonephritis; Focal segmental glomerulosclerosis; Fractional excretion of sodium; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Glomerulonephritis; Glomerulonephritis acute; Glomerulonephritis chronic; Glomerulonephritis membranoproliferative; Glomerulonephritis membranous; Glomerulonephritis minimal lesion; Glomerulonephritis proliferative; Glomerulonephritis rapidly progressive; Glomerulonephropathy; Glomerulosclerosis; Goodpasture's syndrome; Haemodialysis; Haemodialysis complication; Haemodialysis-induced symptom; Haemofiltration; Haemolytic uraemic syndrome; Haemorrhagic diathesis; Haemorrhagic fever with renal syndrome; Hepatitis virus-associated nephropathy; Hepatorenal failure; Hepatorenal syndrome; High turnover osteopathy; HIV associated nephropathy; Hypercalcaemic nephropathy; Hypercreatininaemia; Hyperkalaemia; Hyperparathyroidism; Hyperparathyroidism secondary; Hyperphosphataemia; Hypertensive nephropathy; Hypervolaemia; Hypoalbuminaemia; Hypocalcaemia; Hyponatraemia; IgA nephropathy; Immunotactoid glomerulonephritis; 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; Oedema due to renal disease; Oliguria; Osteomalacia; Pancreatorenal 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; Post infection glomerulonephritis; Post streptococcal glomerulonephritis; Postoperative renal failure; Postrenal failure; 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 chronic; Renal failure neonatal; Renal function test abnormal; Renal impairment; Renal impairment neonatal; Renal injury; Renal osteodystrophy; Renal papillary necrosis; Renal replacement therapy; Renal rickets; Renal transplant; Renal tubular atrophy; Renal tubular disorder; Renal tubular necrosis; Secondary hypertension; Tubulointerstitial nephritis; Ultrafiltration failure; Ultrasound kidney abnormal; Uraemia odour; Uraemic acidosis; Uraemic encephalopathy; Uraemic gastropathy; Uraemic 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; Caplan's syndrome; Carcinomatous polyarthritis; Chondrocalcinosis; Chondrocalcinosis pyrophosphate; Chondromalacia; Crystal arthropathy; Epidemic polyarthritis; Facet joint syndrome; Felty's syndrome; Gout; Gouty arthritis; Gouty tophus; Haemophilic arthropathy; Hip arthroplasty; Injection site joint effusion; 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 destruction; Joint effusion; Joint fluid drainage; Joint range of motion decreased; Joint stiffness; Joint swelling; Joint warmth; Juvenile idiopathic arthritis; Knee arthroplasty; Laryngeal rheumatoid arthritis; Monarthritis; Musculoskeletal stiffness; Neck pain; Neuropathic arthropathy; Nodal osteoarthritis; Osteoarthritis; Osteoarthropathy; Palindromic rheumatism; Patellofemoral pain syndrome; Periarthritis; Periarthritis calcarea; Periarticular disorder; Polyarthritis; Psoriatic arthropathy; Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome; Rapidly progressive osteoarthritis; Reiter's syndrome; Rheumatic disorder; Rheumatic fever; Rheumatoid arthritis; Rheumatoid nodule removal; Sacroiliitis; Senile ankylosing vertebral hyperostosis; Septic arthritis haemophilus; Septic arthritis neisserial; Septic arthritis staphylococcal; Septic arthritis streptobacillus; Septic arthritis streptococcal; Seronegative arthritis; Shoulder arthroplasty; SLE arthritis; Spinal osteoarthritis; Spinal pain; Spondylitis; Spondyloarthropathy; Still's disease adult onset; Synovectomy; Synovial fluid analysis abnormal; Synovial fluid crystal present; Synovial fluid protein present; Synovial fluid red blood cells positive; Synovial fluid white blood cells positive; Synoviorthesis; Synovitis; Temporomandibular joint syndrome; Traumatic arthritis; Traumatic arthropathy

Bone and Joint Infections

MedDRA PTs: Abscess jaw; Arthritis infective; Bone abscess; Bone tuberculosis; Bursitis infective; Bursitis infective staphylococcal; Candida osteomyelitis; Infected bunion; Infective chondritis; Infective periostitis; Infective spondylitis; Injection site joint infection; Intervertebral discitis; Joint abscess; Joint tuberculosis; 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; Yaws of bone

Bone, Joint and Vascular Therapeutic Procedures

MedDRA PTs: Amputation; Arm amputation; Arterial bypass operation; Arterial graft; Arterial stent insertion; Arterial therapeutic procedure; Calcanectomy; Debridement; Finger amputation; Finger repair operation; Foot amputation; Foot operation; Hand amputation; Hand repair operation; Hip disarticulation; Interscapulothoracic amputation; 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; Talipes correction; Toe amputation; Toe operation; Trapezectomy

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; Eagles 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 jaw; Osteoradionecrosis; Osteorrhagia; Osteosclerosis; Osteosis; Pain in jaw; Periostitis;

Periostitis hypertrophic; Periprosthetic osteolysis; Post transplant distal limb syndrome; Post-traumatic osteoporosis; Primary sequestrum; Pubic pain; Radiation osteitis; Secondary sequestrum; Skeletal injury; Spinal column injury; Spinal disorder; Spinal pain; Sternal injury; Tertiary sequestrum; Vertebral column mass; Vertebral lesion; Vertebral wedging

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

Dermal Diabetic Complications

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

Venous Embolic and Thrombotic Events

MedDRA PTs: Axillary vein thrombosis; Budd-Chiari syndrome; Catheterisation venous; Cavernous sinus thrombosis; Central venous catheterisation; Cerebral venous thrombosis; Compression stockings application; Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Hepatic vein occlusion; Hepatic vein thrombosis; Homans' sign positive; Iliac vein occlusion; Inferior vena cava syndrome; Inferior vena caval occlusion; Intracranial venous sinus thrombosis; Jugular vein 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; 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 occlusion; Venous operation; Venous recanalisation; Venous repair; Venous stent insertion; Venous thrombosis; Venous thrombosis in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal

Genital Infections

MedDRA PTs: Acquired phimosis; Bacterial prostatitis; Bacterial vaginosis; 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; 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 inflammation; Vaginal lesion; Vaginal odour; Vaginitis bacterial; 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 mycotic infection; Vulvovaginal pain; Vulvovaginal pruritus; Vulvovaginal swelling; Vulvovaginal ulceration; Vulvovaginitis; Vulvovaginitis streptococcal

Heart Failure/Cardiomyopathy

MedDRA PTs: Acquired cardiac septal defect; Acute left ventricular failure; Acute pulmonary oedema; Acute right ventricular failure; Alcohol septal ablation; Allergic myocarditis; Arrhythmia; Arrhythmia supraventricular; Arrhythmogenic right ventricular dysplasia; Artificial heart implant; Ascites; Atrial hypertrophy; Atrial natriuretic peptide abnormal; Atrial natriuretic peptide increased; Atrial pressure increased; Atrial septal defect acquired; Autoimmune myocarditis; 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; Brain natriuretic peptide abnormal; Brain natriuretic peptide increased; Cardiac amyloidosis; Cardiac aneurysm; Cardiac arrest; Cardiac asthma; Cardiac cirrhosis; 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 disorder; 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; Cheyne-Stokes respiration; 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; Ischaemic cardiomyopathy; Jugular vein distension; Kearns-Sayre syndrome; Labile blood pressure; Left atrial dilatation; Left ventricular dysfunction; Left ventricular end-diastolic pressure decreased; Left ventricular failure; Left ventricular heave; Low cardiac output syndrome; 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; 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; Pulmonary arterial wedge pressure increased; Pulmonary congestion; Pulmonary oedema; Pulmonary oedema neonatal; Reduction ventriculoplasty; Respiration abnormal; Respiratory tract congestion; Restrictive cardiomyopathy; Right atrial dilatation; Right atrial pressure increased; Right ventricle outflow tract obstruction; Right ventricular dysfunction; Right ventricular failure; Right ventricular heave; Right ventricular systolic pressure decreased; Scan myocardial perfusion abnormal; Stress cardiomyopathy; Stroke volume decreased; Sudden cardiac death; Sudden death; Syncope; Systolic dysfunction; Tachycardia induced cardiomyopathy; Thyrotoxic cardiomyopathy; Ultrasound Doppler abnormal; Vascular resistance pulmonary increased; Venous pressure increased; Venous pressure jugular abnormal; Venous pressure jugular increased; Ventricular arrhythmia; Ventricular assist device insertion; Ventricular dysfunction; Ventricular dyskinesia; Ventricular dyssynchrony; Ventricular failure; Ventricular hyperkinesia; Ventricular hypertrophy; Ventricular hypokinesia; Ventricular hypoplasia; Ventricular remodelling; Ventricular septal defect acquired; Viral cardiomyopathy; Viral myocarditis

Hepatotoxicity

MedDRA PTs: 5'nucleotidase increased; Accessory liver lobe; Acquired antithrombin III deficiency; Acquired protein S deficiency; Acute fatty liver of pregnancy; Acute graft versus host disease in liver; Acute hepatic failure; Acute hepatitis B; Acute hepatitis C; Acute 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; Antithrombin III decreased; Ascites; Aspartate aminotransferase abnormal; Aspartate aminotransferase increased; Asterixis; Asymptomatic viral hepatitis; Autoimmune hepatitis; Bacterascites; Benign hepatic 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; 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 increased; Cholaemia; 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; 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 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 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 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 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; Hepatolenticular 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; 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 disorder; Liver function test abnormal; Liver induration; Liver injury; Liver iron concentration abnormal; Liver iron concentration increased; Liver operation; Liver palpable subcostal; Liver sarcoidosis; Liver scan abnormal; Liver tenderness; Liver transplant; Lupoid hepatic cirrhosis; Lupus hepatitis; Mitochondrial aspartate aminotransferase increased; Mixed hepatocellular cholangiocarcinoma; Mixed liver injury; Molar ratio of total branched-chain amino acid to tyrosine; Neonatal cholestasis; Neonatal hepatomegaly; Nodular regenerative hyperplasia; Non-alcoholic steatohepatitis; Ocular icterus; Oedema due to hepatic disease; Oesophageal varices haemorrhage; Parenteral nutrition associated liver disease; Perihepatic discomfort; Peripancreatic varices; Periportal oedema; Peritoneal fluid protein abnormal; Peritoneal fluid protein decreased; Peritoneal fluid protein increased; Peritoneovenous shunt; Pneumobilia; Polycystic liver disease; Porphyria acute; Porphyria non-acute; Portal fibrosis; Portal hypertension; Portal hypertensive enteropathy; Portal hypertensive gastropathy; Portal pyaemia; Portal shunt; Portal 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; Stomal varices; Subacute hepatic failure; Thrombin time abnormal; Thrombin time prolonged; Total bile acids increased; Transaminases abnormal; Transaminases increased; Ultrasound liver abnormal; Urine bilirubin increased; Urobilinogen urine decreased; Urobilinogen urine increased; Varices oesophageal; Varicose veins of abdominal wall; X-ray hepatobiliary abnormal; Yellow skin

Hypersensitivity/Anaphylactic Reaction/Angioedema

MedDRA PTs: Acute generalised exanthematous pustulosis; Acute respiratory failure; Administration site eczema; Administration site hypersensitivity; Administration site rash; Administration site urticaria; Airway remodelling; Allergic bronchitis; Allergic colitis; Allergic cough; Allergic cystitis; Allergic eosinophilia; Allergic gastroenteritis; Allergic granulomatous angiitis; Allergic hepatitis; Allergic keratitis; Allergic myocarditis; Allergic oedema; Allergic otitis externa; Allergic otitis media; Allergic pharyngitis; Allergic respiratory disease; Allergic respiratory symptom; Allergic sinusitis; Allergic transfusion reaction; Allergy test positive; Allergy to chemicals; Allergy to fermented products; Allergy to immunoglobulin therapy; 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 urticaria; Arthritis allergic; Aspirin-exacerbated respiratory disease; Asthma; Asthma late onset; Asthmatic crisis;

Atopy; Auricular swelling; Blepharitis allergic; Blister; Blood immunoglobulin A abnormal; Blood immunoglobulin A increased; Blood immunoglobulin D increased; Blood immunoglobulin E abnormal; Blood immunoglobulin E increased; Blood immunoglobulin G abnormal; Blood immunoglobulin G increased; Blood immunoglobulin M abnormal; Blood immunoglobulin M increased; Blood pressure decreased; Bromoderma; Bronchial hyperreactivity; Bronchial oedema; Bronchospasm; Bullous impetigo; Caffeine allergy; Capillaritis; Cardiac arrest; Cardio-respiratory arrest; Cardio-respiratory distress; Cardiovascular insufficiency; Catheter site dermatitis; Catheter site eczema; Catheter site hypersensitivity; Catheter site rash; Catheter site urticaria; Catheter site vasculitis; Charcot-Leyden crystals; Choking; Choking sensation; Chronic eosinophilic rhinosinusitis; Chronic hyperplastic eosinophilic sinusitis; Circulatory collapse; Circumoral oedema; Complement factor C1 decreased; Complement factor C1 increased; Complement factor C2 decreased; Complement factor C2 increased; Complement factor C3 decreased; Complement factor C3 increased; Complement factor C4 decreased; Complement factor C4 increased; Complement factor decreased; Complement factor increased; Complement fixation abnormal; Complement fixation test positive; Conjunctival oedema; Conjunctivitis; Conjunctivitis allergic; Contact stomatitis; Contrast media allergy; Contrast media reaction; Corneal exfoliation; Corneal oedema; Cross sensitivity reaction; 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; Diastolic hypotension; Diffuse vasculitis; Distributive shock; Documented hypersensitivity to administered drug; Drug eruption; Drug hypersensitivity; Drug provocation test; Drug reaction with eosinophilia and systemic symptoms; Dyspnoea; Ear swelling; Eczema; Eczema infantile; Eczema nummular; Eczema vaccinatum; Eczema vesicular; Eczema weeping; Encephalitis allergic; Encephalopathy allergic; Endotracheal intubation; Eosinophil count abnormal; Eosinophil count increased; Eosinophil percentage abnormal; Eosinophil percentage increased; Eosinophilia; Eosinophilia myalgia syndrome; Eosinophilic bronchitis; Eosinophilic oesophagitis; Eosinophilic pneumonia; Eosinophilic pneumonia acute; Eosinophilic pneumonia chronic; Epidermal necrosis; Epidermolysis; Epidermolysis bullosa; Epiglottic oedema; Erythema; Erythema multiforme; Erythema nodosum; Exfoliative rash; Eye allergy; Eye oedema; Eye pruritus; Eye swelling; Eyelid oedema; Face oedema; 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; Haemorrhagic vasculitis; 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; 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 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; Iodine allergy; Kaposi's varicelliform eruption; Kounis syndrome; Laryngeal dyspnoea; Laryngeal obstruction; Laryngeal oedema; Laryngitis allergic; Laryngospasm; Laryngotracheal oedema; Leukotriene increased; Limbal swelling; Lip exfoliation; Lip oedema; Lip swelling; Local swelling; Localised oedema; Mast cell degranulation test; Mechanical urticaria; Medical device site reaction; Mesenteric panniculitis; Mouth swelling; Mouth ulceration; Mucocutaneous rash; Mucosa vesicle; Mucosal erosion; Mucosal exfoliation; Mucosal necrosis; Mucosal ulceration; Multiple allergies; Nasal obstruction; Nasal oedema; Necrotising panniculitis; Nephritis allergic; Neurodermatitis; Neutralising antibodies positive; Nikolsky's sign; Nipple oedema; Nipple swelling; Noninfective conjunctivitis; Non-neutralising antibodies positive; Obstructive airways disorder; Occupational asthma; Occupational dermatitis; Ocular hyperaemia; Oculomucocutaneous syndrome; Oculorespiratory syndrome; Oedema; Oedema genital; Oedema mouth; Oedema mucosal; Oedema neonatal; Oedema peripheral; Oral allergy syndrome; Oral mucosal exfoliation; Orbital oedema; Oropharyngeal blistering; Oropharyngeal spasm; Oropharyngeal swelling; Palatal oedema; Palatal swelling; Palisaded neutrophilic granulomatous dermatitis; Palpable purpura; Panniculitis; Pathergy reaction; Penile exfoliation; Penile oedema; Penile swelling; Perineal rash; 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; Recall phenomenon; 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; Skin erosion; Skin exfoliation; Skin necrosis; Skin oedema; Skin reaction; Skin swelling; Skin test positive; Small bowel angioedema; Sneezing; Solar urticaria; Solvent sensitivity; Status asthmaticus; Stevens-Johnson syndrome; Stoma site hypersensitivity; Stoma site rash; Stomatitis; Streptokinase antibody increased; Stridor; Suffocation feeling; Swelling; Swelling face; Swollen tongue; Tachypnoea; Throat tightness; Tongue exfoliation; Tongue oedema; Toxic epidermal necrolysis; Toxic skin eruption; Tracheal obstruction; Tracheal oedema; Tracheostomy; Transplantation associated food allergy; Type I hypersensitivity; Type II hypersensitivity; Type III immune complex mediated reaction; Type IV hypersensitivity reaction; Upper airway obstruction; Urticaria; Urticaria cholinergic; Urticaria chronic; Urticaria contact; Urticaria papular; Urticaria physical; Urticaria pigmentosa; Urticaria vesiculosa; Vaccination site dermatitis; Vaccination site erythema; Vaccination site exfoliation; Vaccination site hypersensitivity; Vaccination site rash; Vaccination site urticaria; Vaccination site vesicles; Vaginal exfoliation; Vaginal oedema; Vaginal ulceration; Vasculitic rash; Vasculitis; Vasculitis necrotising; Vessel puncture site reaction; Visceral oedema; Vulval oedema; Vulval ulceration; Vulvovaginal rash; Vulvovaginal swelling; Vulvovaginal ulceration; Wheezing

Hypoglycemia

MedDRA PTs: Blood glucose decreased; 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 osmolarity abnormal; Blood osmolarity 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; Hypoosmolar state; Ketoacidosis; Ketonuria; Ketosis; Kussmaul respiration; Lactic acidosis; Metabolic acidosis; Organic acid analysis abnormal; Osmolar gap abnormal; PCO2 abnormal; PCO2 decreased; Respiratory alkalosis; Urine ketone body; Urine ketone body present; Urine lactic acid increased

Lymphopenia

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

Malignancies & Premalignant Conditions

MedDRA PTs: 5q minus syndrome; Abdominal neoplasm; 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 megakaryocytic leukaemia; Acute megakaryocytic leukaemia (in remission); Acute monocytic leukaemia; Acute monocytic leukaemia (in remission); Acute myeloid leukaemia; Acute myeloid leukaemia (in remission); Acute myeloid leukaemia recurrent; Acute myelomonocytic leukaemia; Acute promyelocytic leukaemia; Acute undifferentiated leukaemia; Adenocarcinoma; Adenocarcinoma gastric; Adenocarcinoma of appendix; Adenocarcinoma of colon; Adenocarcinoma of salivary gland; Adenocarcinoma of the cervix; Adenocarcinoma pancreas; Adenoid cystic carcinoma; Adenoid cystic carcinoma of salivary gland; Adenomatous polyposis coli; Adenosquamous carcinoma of the cervix; Adenosquamous carcinoma of vagina; Adenosquamous cell carcinoma; Adenosquamous cell lung cancer; Adenosquamous cell lung cancer recurrent; Adenosquamous cell lung cancer stage 0; Adenosquamous cell lung cancer stage I; Adenosquamous cell lung cancer stage II; Adenosquamous cell lung

cancer stage III; Adenosquamous cell lung cancer stage IV; Adrenal gland cancer; Adrenal gland cancer metastatic; Adrenal neoplasm; Adrenocortical carcinoma; Adult T-cell lymphoma/leukaemia; Adult T-cell lymphoma/leukaemia recurrent; Adult T-cell lymphoma/leukaemia refractory; Adult T-cell lymphoma/leukaemia stage I; Adult T-cell lymphoma/leukaemia stage II; Adult T-cell lymphoma/leukaemia stage III; Adult T-cell lymphoma/leukaemia stage IV; Aesthesioneuroblastoma; Alcoholisation procedure; Aleukaemic leukaemia; Alpha 1 foetoprotein abnormal; Alpha 1 foetoprotein increased; Alpha interferon therapy; Alveolar rhabdomyosarcoma; Alveolar soft part sarcoma; Alveolar soft part sarcoma metastatic; Alveolar soft part sarcoma recurrent; Amputation of penis; Anal cancer; Anal cancer metastatic; Anal cancer recurrent; Anal cancer stage 0; Anal cancer stage I; Anal cancer stage II; Anal cancer stage III; Anal cancer stage IV; Anal leukoplakia; Anal neoplasm; Anal polyp; Anal polypectomy; Anal squamous cell carcinoma; Anaplastic astrocytoma; Anaplastic large cell lymphoma T- and null-cell types; Anaplastic large cell lymphoma T- and null-cell types recurrent; Anaplastic large cell lymphoma T- and null-cell types refractory; Anaplastic large cell lymphoma T- and null-cell types stage I; Anaplastic large cell lymphoma T- and null-cell types stage II; Anaplastic large cell lymphoma T- and null-cell types stage III; Anaplastic large cell lymphoma T- and null-cell types stage IV; Anaplastic large-cell lymphoma; Anaplastic lymphoma kinase gene and nucleophosmin gene fusion overexpression; Anaplastic meningioma; Anaplastic oligodendroglioma; Anaplastic thyroid cancer; Androgen therapy; Angiocentric glioma; Angiocentric lymphoma; Angiocentric lymphoma recurrent; Angiocentric lymphoma refractory; Angiocentric lymphoma stage I; Angiocentric lymphoma stage II; Angiocentric lymphoma stage III; Angiocentric lymphoma stage IV; Angiogenesis biomarker increased; Angioimmunoblastic T-cell lymphoma; Angioimmunoblastic T-cell lymphoma recurrent; Angioimmunoblastic T-cell lymphoma refractory; Angioimmunoblastic T-cell lymphoma stage I; Angioimmunoblastic T-cell lymphoma stage II; Angioimmunoblastic T-cell lymphoma stage III; Angioimmunoblastic T-cell lymphoma stage IV; Angiosarcoma; Angiosarcoma metastatic; Angiosarcoma non-metastatic; Angiosarcoma recurrent; Anogenital dysplasia; Antiandrogen therapy; Anti-androgen withdrawal syndrome; Anti-NMDA antibody positive; Antioestrogen therapy; Anti-VGCC antibody positive; Apocrine breast carcinoma; Appendix cancer; APUDoma; Arsenical keratosis; Aspiration bone marrow abnormal; Astrocytoma; Astrocytoma malignant; Atypical fibroxanthoma; Atypical teratoid/rhabdoid tumour of CNS; Autologous bone marrow transplantation therapy; B precursor type acute leukaemia; Barrett's oesophagus; Basal cell carcinoma; Basosquamous carcinoma; Basosquamous carcinoma of skin; B-cell lymphoma; B-cell lymphoma recurrent; B-cell lymphoma refractory; B-cell lymphoma stage I; B-cell lymphoma stage II; B-cell lymphoma stage III; B-cell lymphoma stage IV; B-cell prolymphocytic leukaemia; B-cell small lymphocytic lymphoma; B-cell small lymphocytic lymphoma recurrent; B-cell small lymphocytic lymphoma refractory; B-cell small lymphocytic lymphoma stage I; B-cell small lymphocytic lymphoma stage II; B-cell small lymphocytic lymphoma stage III; B-cell small lymphocytic lymphoma stage IV; B-cell type acute leukaemia; B-cell unclassifiable lymphoma high grade; B-cell unclassifiable lymphoma low grade; Benign hydatidiform mole; Beta interferon therapy; Bile duct adenocarcinoma; Bile duct adenosquamous carcinoma; Bile duct cancer; Bile duct cancer recurrent; Bile duct cancer stage 0; Bile duct cancer stage I; Bile duct cancer stage II; Bile duct cancer stage III; Bile duct cancer stage IV; Bile duct squamous cell carcinoma; Biliary cancer metastatic; Biliary neoplasm; Biopsy abdominal wall abnormal; Biopsy adrenal gland abnormal; Biopsy anus abnormal; Biopsy artery abnormal; Biopsy bile duct abnormal; Biopsy bladder abnormal; Biopsy blood vessel abnormal; Biopsy bone abnormal; Biopsy bone marrow abnormal; Biopsy brain abnormal; Biopsy breast abnormal; Biopsy bronchus abnormal; Biopsy cartilage abnormal; Biopsy cervix abnormal; Biopsy chest wall abnormal; Biopsy chorionic villous abnormal; Biopsy colon abnormal; Biopsy conjunctiva abnormal; Biopsy cornea abnormal; Biopsy diaphragm abnormal; Biopsy ear abnormal; Biopsy endometrium abnormal; Biopsy epididymis abnormal; Biopsy eyelid abnormal; Biopsy fallopian tube abnormal; Biopsy foetal abnormal; Biopsy heart abnormal; Biopsy intestine abnormal; Biopsy kidney abnormal; Biopsy larynx abnormal; Biopsy ligament abnormal; Biopsy lip abnormal; Biopsy liver abnormal; Biopsy lung abnormal; Biopsy lymph gland abnormal; Biopsy mucosa abnormal; Biopsy muscle abnormal; Biopsy oesophagus abnormal; Biopsy ovary abnormal; Biopsy palate abnormal; Biopsy pancreas abnormal; Biopsy parathyroid gland abnormal; Biopsy penis abnormal; Biopsy pericardium abnormal; Biopsy peripheral nerve abnormal; Biopsy peritoneum abnormal; Biopsy pharynx abnormal; Biopsy pleura abnormal; Biopsy prostate abnormal; Biopsy rectum abnormal; Biopsy retina abnormal; Biopsy salivary gland abnormal; Biopsy sclera abnormal; Biopsy seminal vesicle abnormal; Biopsy site unspecified abnormal; Biopsy skin abnormal; Biopsy small intestine abnormal; Biopsy spinal cord abnormal; Biopsy spleen abnormal; Biopsy stomach abnormal; Biopsy tendon abnormal; Biopsy testes abnormal; Biopsy thymus gland abnormal; Biopsy thyroid gland abnormal; Biopsy tongue abnormal; Biopsy trachea abnormal; Biopsy urethra abnormal; Biopsy uterus abnormal; Biopsy vagina abnormal; Biopsy vocal cord abnormal; Biopsy vulva abnormal; Biotherapy; Biphasic mesothelioma; Bladder adenocarcinoma recurrent; Bladder adenocarcinoma stage 0; Bladder adenocarcinoma stage I; Bladder adenocarcinoma stage II; Bladder adenocarcinoma stage III; Bladder adenocarcinoma stage IV; Bladder adenocarcinoma stage unspecified; Bladder cancer; Bladder cancer recurrent; Bladder cancer stage 0, with cancer in situ; Bladder cancer stage 0, without cancer in situ; Bladder cancer stage I,

with cancer in situ; Bladder cancer stage I, without cancer in situ; Bladder cancer stage II; Bladder cancer stage III; Bladder cancer stage IV; Bladder dysplasia; Bladder leukoplakia; Bladder neck resection; Bladder neoplasm; Bladder neoplasm surgery; Bladder polypectomy; Bladder squamous cell carcinoma recurrent; Bladder squamous cell carcinoma stage 0; Bladder squamous cell carcinoma stage I; Bladder squamous cell carcinoma stage II; Bladder squamous cell carcinoma stage III; Bladder squamous cell carcinoma stage IV; Bladder squamous cell carcinoma stage unspecified; Bladder transitional cell carcinoma; Bladder transitional cell carcinoma metastatic; Bladder transitional cell carcinoma recurrent; Bladder transitional cell carcinoma stage 0; Bladder transitional cell carcinoma stage I; Bladder transitional cell carcinoma stage II; Bladder transitional cell carcinoma stage III; Bladder transitional cell carcinoma stage IV; Blast cell count increased; Blast cell crisis; Blast cell proliferation; Blast cells present; Blast crisis in myelogenous leukaemia; Blood chromogranin A increased; Bone cancer; Bone cancer metastatic; Bone giant cell tumour; Bone giant cell tumour malignant; Bone marrow infiltration; Bone marrow leukaemic cell infiltration; Bone marrow reticulin fibrosis; Bone marrow tumour cell infiltration; Bone neoplasm; Bone sarcoma; Bone scan abnormal; Borderline mucinous tumour of ovary; Borderline ovarian tumour; Borderline serous tumour of ovary; Bowenoid papulosis; Bowen's disease; Brachytherapy; 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 dysplasia; Breast neoplasm; Breast prosthesis implantation; Breast reconstruction; Breast sarcoma; Breast sarcoma metastatic; Breast sarcoma recurrent; Brenner tumour; Bronchial carcinoma; Bronchial neoplasm; Bronchioloalveolar carcinoma; Burkitt's leukaemia; Burkitt's lymphoma; Burkitt's lymphoma recurrent; Burkitt's lymphoma refractory; Burkitt's lymphoma stage I; Burkitt's lymphoma stage II; Burkitt's lymphoma stage III; Burkitt's lymphoma stage IV; Buschke-Lowenstein's tumour; Cancer hormonal therapy; Cancer in remission; Cancer pain; Cancer surgery; Carbohydrate antigen 125 increased; Carbohydrate antigen 15-3 increased; Carbohydrate antigen 19-9 increased; Carbohydrate antigen 27.29 increased; Carbohydrate antigen 549 increased; Carcinoembryonic antigen decreased; Carcinoembryonic antigen increased; Carcinogenicity; Carcinoid crisis; Carcinoid heart disease; Carcinoid syndrome; Carcinoid tumour; Carcinoid tumour of the appendix; Carcinoid tumour of the caecum; Carcinoid tumour of the duodenum; Carcinoid tumour of the gastrointestinal tract; Carcinoid tumour of the pancreas; Carcinoid tumour of the prostate; Carcinoid tumour of the small bowel; Carcinoid tumour of the stomach; Carcinoid tumour pulmonary; Carcinoma 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; Cell marker increased; Cementoplasty; Central nervous system leukaemia; Central nervous system lymphoma; 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; 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); Clear cell carcinoma of cervix; Clear cell endometrial carcinoma; Clear cell renal cell carcinoma; Clear cell sarcoma of soft tissue; Clear cell sarcoma of the kidney; Clonal evolution; CNS germinoma; Colectomy; Colectomy total; Colon adenoma; Colon cancer; Colon cancer metastatic; Colon cancer recurrent; Colon cancer stage 0; Colon cancer stage I; Colon cancer stage II; Colon cancer stage III; Colon cancer stage IV; Colon dysplasia; Colon neoplasm; Colony stimulating factor therapy; Colorectal adenocarcinoma; Colorectal cancer; Colorectal cancer metastatic; Colorectal cancer recurrent; Colorectal cancer stage I; Colorectal cancer stage II; Colorectal cancer stage III; Colorectal cancer stage IV; Colorectal carcinoma stage 0; Composite lymphoma; Computerised tomogram breast abnormal; Congenital fibrosarcoma; Congenital malignant neoplasm; Congenital melanocytic naevus; Congenital retinoblastoma; Congenital teratoma; Conjunctival melanoma; Conjunctival neoplasm; Conjunctival primary

acquired melanosis; Connective tissue neoplasm; Corneoconjunctival intraepithelial neoplasia; Crohn's disease; Cronkhite-Canada syndrome; CSF lymphocyte count abnormal; CSF lymphocyte count increased; Cyclotron therapy; Cystadenocarcinoma ovary; Cystoprostatectomy; Cytokeratin 18 increased; Dedifferentiated liposarcoma; Dermatofibrosarcoma protuberans; Dermatofibrosarcoma protuberans metastatic; Desmoplastic melanoma; Desmoplastic mesothelioma; Desmoplastic small round cell tumour; Diaphragm neoplasm; Diffuse large B-cell lymphoma; Diffuse large B-cell lymphoma recurrent; Diffuse large B-cell lymphoma refractory; Diffuse large B-cell lymphoma stage I; Diffuse large B-cell lymphoma stage II; Diffuse large B-cell lymphoma stage III; Diffuse large B-cell lymphoma stage IV; Disseminated large cell lymphoma; Ductal adenocarcinoma of pancreas; Duodenal neoplasm; Duodenal polyp; Duodenectomy; Dysplasia; Dysplastic naevus; Dysplastic naevus syndrome; Ear neoplasm; Ear neoplasm malignant; Eastern Cooperative Oncology Group performance status improved; Eastern Cooperative Oncology Group performance status worsened; Eccrine carcinoma; Ectopic ACTH syndrome; Ectopic aldosterone secretion; Ectopic antidiuretic hormone secretion; Ectopic calcitonin production; Ectopic chorionic gonadotrophin secretion; Ectopic growth hormone secretion; Ectopic hormone secretion; Ectopic parathyroid hormone production; Ectopic prolactin secretion; Ectopic renin secretion; Electron radiation therapy; Electron radiation therapy to bladder; Electron radiation therapy to blood; Electron radiation therapy to bone; Electron radiation therapy to brain; Electron radiation therapy to breast; Electron radiation therapy to colon; Electron radiation therapy to ear, nose, or throat; Electron radiation therapy to liver; Electron radiation therapy to lung; Electron radiation therapy to pancreas; Electron radiation therapy to prostate; Electron radiation therapy to skin; Electron radiation therapy to soft tissue; Electron radiation therapy to uterus; Elephantiasis nostras verrucosa; Embryonal rhabdomyosarcoma; Endocrine neoplasm; Endocrine neoplasm malignant; Endometrial adenocarcinoma; Endometrial cancer; Endometrial cancer metastatic; Endometrial cancer recurrent; Endometrial cancer stage 0; Endometrial cancer stage I; Endometrial cancer stage II; Endometrial cancer stage III; Endometrial cancer stage IV; Endometrial dysplasia; Endometrial hyperplasia; Endometrial neoplasm; Endometrial sarcoma; Endometrial sarcoma metastatic; Endometrial sarcoma recurrent; Endometrial stromal sarcoma; Enteropathy-associated T-cell lymphoma; Eosinophilic leukaemia; Ependymoma; Ependymoma malignant; Epidermodysplasia verruciformis; Epididymal cancer; Epididymal neoplasm; Epiglottic carcinoma; Epiglottidectomy; Epithelioid mesothelioma; Epithelioid sarcoma; Epithelioid sarcoma metastatic; Epithelioid sarcoma recurrent; Epstein-Barr virus associated lymphoma; Epstein-Barr virus associated lymphoproliferative disorder; Erythraemic myelosis (in remission); Erythroleukaemia; Erythroplasia; Erythroplasia of lip; Erythroplasia of penis; Erythroplasia of vulva; Essential thrombocythaemia; Ewing's sarcoma; Ewing's sarcoma metastatic; Ewing's sarcoma recurrent; Ex vivo gene therapy; Exploratory operation; Extended radical mastectomy; Extradural neoplasm; Extragonadal primary embryonal carcinoma; Extragonadal primary germ cell tumour; Extragonadal primary germ cell tumour mixed; Extragonadal primary germ cell tumour mixed stage I; Extragonadal primary germ cell tumour mixed stage II; Extragonadal primary germ cell tumour mixed stage III; Extragonadal primary malignant teratoma; Extragonadal primary non-seminoma; Extragonadal primary non-seminoma stage I; Extragonadal primary non-seminoma stage II; Extragonadal primary non-seminoma stage III; Extragonadal primary non-seminoma stage IV; Extragonadal primary seminoma (pure); Extragonadal primary seminoma (pure) stage I; Extragonadal primary seminoma (pure) stage II; Extragonadal primary seminoma (pure) stage III; Extragonadal primary seminoma (pure) stage IV; Extramammary Paget's disease; Extranodal marginal zone B-cell lymphoma (MALT type); Extranodal marginal zone B-cell lymphoma (MALT type) recurrent; Extranodal marginal zone B-cell lymphoma (MALT type) refractory; Extranodal marginal zone B-cell lymphoma (MALT type) stage I; Extranodal marginal zone B-cell lymphoma (MALT type) stage II; Extranodal marginal zone B-cell lymphoma (MALT type) stage III; Extranodal marginal zone B-cell lymphoma (MALT type) stage IV; Extraocular retinoblastoma; Extra-osseous Ewing's sarcoma; Extra-osseous Ewing's sarcoma metastatic; Extra-osseous Ewing's sarcoma recurrent; Extraskeletal chondrosarcoma metastatic; Extraskeletal chondrosarcoma recurrent; Extraskeletal myxoid chondrosarcoma; Extraskeletal osteosarcoma; Extraskeletal osteosarcoma metastatic; Extraskeletal osteosarcoma recurrent; Eyelid tumour; Fallopian tube cancer; Fallopian tube cancer metastatic; Fallopian tube cancer stage I; Fallopian tube cancer stage II; Fallopian tube cancer stage III; Fallopian tube cancer stage IV; Fallopian tube neoplasm; Familial medullary thyroid cancer; Female reproductive neoplasm; Female reproductive tract carcinoma in situ; Fibrosarcoma; Fibrosarcoma excision; Fibrosarcoma metastatic; 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 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; Ganglioglioma; Ganglioneuroblastoma; 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; Gastrinoma; Gastrinoma malignant; Gastrointestinal cancer metastatic; Gastrointestinal carcinoma; Gastrointestinal carcinoma in situ; Gastrointestinal dysplasia; 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 tract neoplasm; Germ cell cancer; Germ cell cancer metastatic; Germ cell neoplasm; Gestational trophoblastic tumour; Gingival cancer; Glioblastoma; Glioblastoma multiforme; Glioma; Gliomatosis cerebri; Glioneuronal tumour; Gliosarcoma; Glossectomy; Glottis carcinoma; Glucagonoma; Granular cell tumour; Growth hormone-producing pituitary tumour; Haemangiopericytoma; Haemangiopericytoma of meninges; Haematological malignancy; Haematopoietic neoplasm; Haemorrhagic tumour necrosis; Hairy cell leukaemia; 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; Histiocytic medullary reticulosis; 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 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; Hypercalcaemia of malignancy; Hypergammaglobulinaemia benign monoclonal;

Hyperthermia therapy; Hypopharyngeal cancer; Hypopharyngeal cancer recurrent; Hypopharyngeal cancer stage 0; Hypopharyngeal cancer stage I; Hypopharyngeal cancer stage II; Hypopharyngeal cancer stage III; Hypopharyngeal cancer stage IV; Hypopharyngeal neoplasm; Hypophysectomy; Hysterectomy; Hysterosalpingectomy; Hysterosalpingo-oophorectomy; Ileectomy; Ileocolectomy; Immune enhancement therapy; Immune reconstitution inflammatory syndrome associated Kaposi's sarcoma; Immunoblastic lymphoma; 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 ductal breast carcinoma; Invasive lobular breast carcinoma; Invasive papillary breast carcinoma; Iris melanoma; Iris neoplasm; Jejunectomy; Juvenile chronic myelomonocytic leukaemia; Kaposi's sarcoma; Kaposi's sarcoma AIDS related; Kaposi's sarcoma classical type; Keratinising squamous cell carcinoma of nasopharynx; Keratoacanthoma; Lacrimal duct neoplasm; Langerhans' cell histiocytosis; Large cell lung cancer; Large cell lung cancer metastatic; Large cell lung cancer recurrent; Large cell lung cancer stage 0; Large cell lung cancer stage I; Large cell lung cancer stage II; Large cell lung cancer stage III; Large cell lung cancer stage IV; Large granular lymphocytosis; Large intestinal polypectomy; Large intestine polyp; Laryngeal cancer; Laryngeal cancer metastatic; Laryngeal cancer recurrent; Laryngeal cancer stage 0; Laryngeal cancer stage I; Laryngeal cancer stage II; Laryngeal cancer stage III; Laryngeal cancer stage IV; Laryngeal dysplasia; Laryngeal leukoplakia; Laryngeal neoplasm; Laryngeal polypectomy; Laryngeal squamous cell carcinoma; Laryngopharyngectomy; Leiomyosarcoma; Leiomyosarcoma metastatic; Leiomyosarcoma recurrent; Lentigo maligna; Lentigo maligna recurrent; Lentigo maligna stage I; Lentigo maligna stage II; Lentigo maligna stage III; Lentigo maligna stage IV; Leukaemia; Leukaemia basophilic; Leukaemia cutis; Leukaemia granulocytic; Leukaemia in remission; Leukaemia monocytic; Leukaemia recurrent; Leukaemic infiltration; Leukaemic infiltration extramedullary; Leukaemic infiltration gingiva; Leukaemic infiltration hepatic; Leukaemic infiltration pulmonary; Leukaemic infiltration renal; Leukaemic lymphoma; Leukaemic retinopathy; Leukoplakia; Leukoplakia oesophageal; Leukoplakia of penis; Leukoplakia oral; Leukostasis syndrome; Leydig cell tumour of the testis; Linitis plastica; Lip and/or oral cavity cancer; Lip and/or oral cavity cancer recurrent; Lip and/or oral cavity cancer stage 0; Lip and/or oral cavity cancer stage I; Lip and/or oral cavity cancer stage II; Lip and/or oral cavity cancer stage III; Lip and/or oral cavity cancer stage IV; Lip neoplasm; Lip neoplasm malignant stage unspecified; Lip squamous cell carcinoma; Liposarcoma; Liposarcoma metastatic; Liposarcoma recurrent; Liver ablation; Liver carcinoma ruptured; Liver scan abnormal; Lobular breast carcinoma in situ; Lung adenocarcinoma; Lung adenocarcinoma metastatic; Lung adenocarcinoma recurrent; Lung adenocarcinoma stage 0; Lung adenocarcinoma stage I; Lung adenocarcinoma stage II; Lung adenocarcinoma stage III; Lung adenocarcinoma stage IV; Lung cancer metastatic; Lung carcinoma cell type unspecified recurrent; Lung carcinoma cell type unspecified stage 0; Lung carcinoma cell type unspecified stage I; Lung carcinoma cell type unspecified stage II; Lung carcinoma cell type unspecified stage III; Lung carcinoma cell type unspecified stage IV; Lung infiltration malignant; Lung lobectomy; Lung neoplasm; Lung neoplasm malignant; Lung neoplasm surgery; Lung squamous cell carcinoma metastatic; Lung squamous cell carcinoma recurrent; Lung squamous cell carcinoma stage 0; Lung squamous cell carcinoma stage I; Lung squamous cell carcinoma stage II; Lung squamous cell carcinoma stage III; Lung squamous cell carcinoma stage IV; Lymph nodes scan abnormal; Lymphadenectomy; Lymphangiosarcoma; Lymphangiosis carcinomatosa; Lymphatic mapping; Lymphatic system neoplasm; Lymphocyte adoptive therapy; Lymphocyte morphology abnormal; Lymphocytic leukaemia; Lymphocytic lymphoma; Lymphoid leukaemia (in remission); Lymphoid tissue operation; Lymphoma; Lymphoma AIDS related; Lymphoma cutis; Lymphoma operation; Lymphoma transformation; Lymphoplasmacytoid lymphoma/immunocytoma; Lymphoplasmacytoid lymphoma/immunocytoma recurrent; Lymphoplasmacytoid lymphoma/immunocytoma refractory; Lymphoplasmacytoid lymphoma/immunocytoma stage I; Lymphoplasmacytoid lymphoma/immunocytoma stage II; Lymphoplasmacytoid lymphoma/immunocytoma stage III; Lymphoplasmacytoid lymphoma/immunocytoma stage IV; Lymphoproliferative disorder; Lymphoproliferative disorder in remission; Male reproductive tract neoplasm; Malignant anorectal neoplasm; Malignant ascites; Malignant blue naevus; Malignant connective tissue neoplasm; Malignant cranial nerve neoplasm; Malignant dysphagia; Malignant exophthalmos; Malignant fibrous histiocytoma; Malignant fibrous histiocytoma metastatic; Malignant fibrous histiocytoma of bone; Malignant fibrous histiocytoma recurrent; Malignant genitourinary tract neoplasm; Malignant giant cell fibrous histiocytoma; Malignant glioma; Malignant haemangiopericytoma;

Malignant haemangiopericytoma metastatic; Malignant haemangiopericytoma recurrent; Malignant histiocytosis; Malignant hydatidiform mole; Malignant lymphoid neoplasm; Malignant lymphoma unclassifiable high grade; Malignant lymphoma unclassifiable low grade; Malignant mast cell neoplasm; Malignant mediastinal neoplasm; Malignant melanoma; Malignant melanoma in situ; Malignant melanoma of eyelid; Malignant melanoma of sites other than skin; Malignant melanoma stage I; Malignant melanoma stage II; Malignant melanoma stage III; Malignant melanoma stage IV; Malignant 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 unknown primary site; Malignant neoplasm of uterine adnexa; Malignant neoplasm progression; Malignant nervous system neoplasm; Malignant nipple neoplasm; Malignant nipple neoplasm female; Malignant nipple neoplasm male; Malignant oligodendroglioma; Malignant ovarian cyst; Malignant palate neoplasm; Malignant pericardial neoplasm; Malignant peritoneal neoplasm; Malignant pituitary tumour; Malignant pleural effusion; Malignant respiratory tract neoplasm; Malignant splenic neoplasm; Malignant sweat gland neoplasm; Malignant transformation; Malignant urinary tract neoplasm; Mantle cell lymphoma; Mantle cell lymphoma recurrent; Mantle cell lymphoma refractory; Mantle cell lymphoma stage I; Mantle cell lymphoma stage II; Mantle cell lymphoma stage III; Mantle cell lymphoma stage IV; Mastectomy; Mastocytic leukaemia; Mastoidectomy; Mature B-cell type acute leukaemia; Maxillofacial sinus neoplasm; Mediastinal biopsy abnormal; Mediastinum neoplasm; Medullary carcinoma of breast; Medullary thyroid cancer; Medulloblastoma; Medulloblastoma recurrent; Megaloblasts increased; Meigs' syndrome; Melanoma recurrent; Melanoplakia oral; Meningeal neoplasm; Meningioma malignant; Mesenteric neoplasm; Mesothelioma; Mesothelioma malignant; Mesothelioma malignant recurrent; Metaplastic breast carcinoma; Metastases to abdominal cavity; Metastases to abdominal wall; Metastases to adrenals; Metastases to biliary tract; Metastases to bladder; Metastases to bone; Metastases to bone marrow; Metastases to breast; Metastases to central nervous system; Metastases to chest wall; Metastases to diaphragm; Metastases to Eustachian tube; Metastases to eye; Metastases to fallopian tube; Metastases to gallbladder; Metastases to gastrointestinal tract; Metastases to heart; Metastases to kidney; Metastases to large intestine; Metastases to larynx; Metastases to liver; Metastases to lung; Metastases to lymph nodes; Metastases to meninges; Metastases to mouth; Metastases to muscle; Metastases to nasal sinuses; Metastases to neck; Metastases to nervous system; Metastases to oesophagus; Metastases to ovary; Metastases to pancreas; Metastases to pelvis; Metastases to penis; Metastases to perineum; Metastases to peripheral nervous system; Metastases to peripheral vascular system; Metastases to peritoneum; Metastases to pharynx; Metastases to pituitary gland; Metastases to placenta; Metastases to pleura; Metastases to prostate; Metastases to rectum; Metastases to reproductive organ; Metastases to retroperitoneum; Metastases to salivary gland; Metastases to skin; Metastases to small intestine; Metastases to soft tissue; Metastases to spine; Metastases to spleen; Metastases to stomach; Metastases to testicle; Metastases to the mediastinum; Metastases to the respiratory system; Metastases to thorax; Metastases to thyroid; Metastases to trachea; Metastases to urinary tract; Metastases to uterus; 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 ocular melanoma; Metastatic pulmonary embolism; Metastatic renal cell carcinoma; Metastatic salivary gland cancer; Metastatic squamous cell carcinoma; Metastatic uterine cancer; Micrographic skin surgery; Mixed hepatocellular cholangiocarcinoma; Mixed-type liposarcoma; Modified radical mastectomy; Monoclonal gammopathy; Monocytic leukaemia in remission; Mucinous adenocarcinoma of appendix; Mucinous breast carcinoma; Mucinous cystadenocarcinoma of pancreas; Mucinous cystadenocarcinoma ovary; Mucinous endometrial carcinoma; Mucoepidermoid carcinoma; Mucoepidermoid carcinoma of salivary gland; Mueller's mixed tumour; Multiple gated acquisition scan abnormal; Muscle neoplasm; Myasthenic syndrome; Mycosis fungoides; Mycosis fungoides recurrent; Mycosis fungoides refractory; Mycosis fungoides stage I; Mycosis fungoides stage II; Mycosis fungoides stage III; Mycosis fungoides stage IV; Myectomy; Myeloblastoma; Myelodysplastic syndrome; Myelodysplastic syndrome transformation; Myelodysplastic syndrome unclassifiable; Myelofibrosis; Myeloid leukaemia; Myeloid leukaemia in remission; Myeloma cast nephropathy; Myxofibrosarcoma; Myxoid liposarcoma; Nasal cavity cancer; Nasal neoplasm; Nasal sinus cancer; Nasopharyngeal cancer; Nasopharyngeal cancer recurrent; Nasopharyngeal cancer stage 0; Nasopharyngeal cancer stage I; Nasopharyngeal cancer stage II; Nasopharyngeal cancer stage III; Nasopharyngeal cancer stage IV; Natural killer-cell leukaemia;

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

IV; Ovarian germ cell teratoma; Ovarian germ cell teratoma stage I; Ovarian germ cell teratoma stage II; Ovarian germ cell teratoma stage III; Ovarian germ cell teratoma stage IV; Ovarian germ cell tumour 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 theca cell tumour; Paget's disease of nipple; Paget's disease of penis; Paget's disease of the vulva; Palliative care; Pancoast's tumour; Pancreastatin abnormal; Pancreastatin increased; Pancreatectomy; Pancreatic carcinoma; Pancreatic carcinoma metastatic; Pancreatic carcinoma recurrent; Pancreatic carcinoma stage 0; Pancreatic carcinoma stage I; Pancreatic carcinoma stage II; Pancreatic carcinoma stage III; Pancreatic carcinoma stage IV; Pancreatic neoplasm; Pancreatic neuroendocrine tumour; Pancreatic neuroendocrine tumour metastatic; Pancreatic sarcoma; Pancreaticoduodenectomy; Pancreaticosplenectomy; Pancreatoblastoma; Papillary serous endometrial carcinoma; Papillary thyroid cancer; Paraganglion neoplasm; Paraganglion neoplasm malignant; Paranasal biopsy abnormal; Paranasal sinus and nasal cavity malignant neoplasm; Paranasal sinus and nasal cavity malignant neoplasm recurrent; Paranasal sinus and nasal cavity malignant neoplasm stage 0; Paranasal sinus and nasal cavity malignant neoplasm stage I; Paranasal sinus and nasal cavity malignant neoplasm stage II; Paranasal sinus and nasal cavity malignant neoplasm stage III; Paranasal sinus and nasal cavity malignant neoplasm stage IV; Paranasal sinus neoplasm; Paraneoplastic dermatomyositis; Paraneoplastic encephalomyelitis; Paraneoplastic neurological syndrome; Paraneoplastic pemphigus; 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; 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; Pineal germinoma; Pineal neoplasm; Pineal parenchymal neoplasm malignant; Pinealoblastoma; Pinealoma; Pituitary cancer metastatic; Pituitary gland radiotherapy; Pituitary neoplasm malignant recurrent; Pituitary tumour; Pituitary tumour recurrent; Placental neoplasm; Plasma cell leukaemia; Plasma cell leukaemia in remission; Plasma cell myeloma; Plasma cell myeloma in remission; Plasma cell myeloma recurrent; Plasmablastic lymphoma; Plasmacytoma; Pleomorphic adenoma; Pleomorphic liposarcoma; Pleomorphic malignant fibrous histiocytoma; Pleural mesothelioma; Pleural mesothelioma malignant; Pleural mesothelioma malignant recurrent; Pleural neoplasm; Pleural sarcoma; Pleurectomy; Pneumonectomy; POEMS syndrome; Polycythaemia vera; Polyneuropathy in malignant disease; Porocarcinoma; 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 effusion lymphoma; Primary mediastinal large B-cell lymphoma; Primary mediastinal large B-

cell lymphoma recurrent; Primary mediastinal large B-cell lymphoma refractory; Primary mediastinal large B-cell lymphoma stage I; Primary mediastinal large B-cell lymphoma stage II; Primary mediastinal large B-cell lymphoma stage III; Primary mediastinal large B-cell lymphoma stage IV; Primitive neuroectodermal tumour; Primitive neuroectodermal tumour metastatic; Proctocolectomy; Progesterone receptor assay positive; Prolactin-producing pituitary tumour; Prolymphocytic leukaemia; Prophylactic chemotherapy; Prostate ablation; Prostate cancer; Prostate cancer metastatic; Prostate cancer recurrent; Prostate cancer stage 0; Prostate cancer stage I; Prostate cancer stage II; Prostate cancer stage III; Prostate cancer stage IV; Prostate cryoablation; Prostate interstitial hyperthermia therapy; Prostatectomy; Prostatic dysplasia; Prostatic specific antigen abnormal; Prostatic specific antigen increased; Pseudoachalasia; Pseudomyxoma peritonei; Pseudosarcoma; 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 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 joint; Radiotherapy to kidney; Radiotherapy to liver; Radiotherapy to lung; Radiotherapy to lymph nodes; Radiotherapy to nose; Radiotherapy to ovary; Radiotherapy to pancreas; Radiotherapy to pleura; Radiotherapy to prostate; Radiotherapy to skin; Radiotherapy to soft tissue; Radiotherapy to spleen; Radiotherapy to stomach; Radiotherapy to throat; Radiotherapy to thymus; Radiotherapy to thyroid; Radiotherapy to urinary bladder; Radiotherapy to uterus; Radiotherapy to vagina; Rectal adenocarcinoma; Rectal cancer; Rectal cancer metastatic; Rectal cancer recurrent; Rectal cancer stage 0; Rectal cancer stage I; Rectal cancer stage II; Rectal cancer stage III; Rectal cancer stage IV; Rectal neoplasm; Rectal polyp; Rectal polypectomy; Rectosigmoid cancer; Rectosigmoid cancer metastatic; Rectosigmoid cancer recurrent; Rectosigmoid cancer stage 0; Rectosigmoid cancer stage I; Rectosigmoid cancer stage II; Rectosigmoid cancer stage III; Rectosigmoid cancer stage IV; Recurrent cancer; Refractory anaemia with an excess of blasts; Refractory anaemia with ringed sideroblasts; Refractory cancer; Refractory cytopenia with multilineage dysplasia; Refractory cytopenia with unilineage dysplasia; Regional chemotherapy; Renal cancer; Renal cancer metastatic; Renal cancer recurrent; Renal cancer stage I; Renal cancer stage II; Renal cancer stage III; Renal cancer stage IV; Renal cell carcinoma; Renal cell carcinoma recurrent; Renal cell carcinoma stage I; Renal cell carcinoma stage II; Renal cell carcinoma stage III; Renal cell carcinoma stage IV; Renal neoplasm; Renal scan abnormal; Renal tumour excision; Respiratory tract carcinoma in situ; Respiratory tract neoplasm; Retinal melanoma; Retinal neoplasm; Retinal tumour excision; Retinoblastoma; Retro-orbital neoplasm; Retroperitoneal cancer; Retroperitoneal neoplasm; Retroperitoneal neoplasm metastatic; Retro-pubic prostatectomy; Rhabdoid tumour; Rhabdoid tumour of the kidney; Rhabdomyosarcoma; Rhabdomyosarcoma recurrent; Richter's syndrome; Round cell liposarcoma; Salivary gland cancer; Salivary gland cancer recurrent; Salivary gland cancer stage 0; Salivary gland cancer stage I; Salivary gland cancer stage II; Salivary gland cancer stage III; Salivary gland cancer stage IV; Salivary gland neoplasm; Salivary gland resection; Salivary gland scan abnormal; Salpingectomy; Salpingo-oophorectomy; Salpingo-oophorectomy bilateral; Salpingo-oophorectomy unilateral; Sarcoma; Sarcoma excision; Sarcoma metastatic; Sarcoma of skin; Sarcoma uterus; Sarcomatoid mesothelioma; Sarcomatosis; Scan abdomen abnormal; Scan abnormal; Scan adrenal gland abnormal; Scan bone marrow abnormal; Scan gallium abnormal; Scan myocardial perfusion abnormal; Scan with contrast abnormal; Scrotal cancer; Sebaceous carcinoma; Sebaceous naevus; Second primary malignancy; Secondary cerebellar degeneration; Secretory adenoma of pituitary; Seminoma; Serous cystadenocarcinoma of pancreas; Serous cystadenocarcinoma ovary; Sertoli cell testicular tumour; Sezary cells increased; Sigmoidectomy; Signet-ring cell carcinoma; Simple mastectomy; Sinus cancer metastatic; Skin angiosarcoma; Skin cancer; Skin cancer metastatic; Skin cryotherapy; Skin neoplasm bleeding; Skin neoplasm excision; Small cell carcinoma; Small cell carcinoma of the cervix; Small cell lung cancer; Small cell lung cancer extensive stage; Small cell lung cancer limited stage; Small cell lung cancer metastatic; Small cell lung cancer recurrent; Small intestinal polypectomy; Small intestinal resection; Small intestine adenocarcinoma; Small intestine carcinoma; Small intestine carcinoma metastatic; Small intestine carcinoma recurrent; Small intestine carcinoma stage 0; Small intestine carcinoma stage I; Small intestine carcinoma stage II; Small intestine carcinoma stage III; Small intestine carcinoma stage IV; Small intestine leiomyosarcoma; Smooth muscle cell neoplasm; Soft tissue neoplasm; Soft tissue sarcoma; Solid pseudopapillary tumour of the pancreas; Somatostatin receptor scan abnormal; Somatostatinoma; Spermatocytic seminoma; Spinal cord neoplasm; Spinal meningioma malignant; Spindle cell sarcoma; Spitzoid melanoma; Spleen scan abnormal; Splenectomy; Splenic marginal zone lymphoma; Splenic marginal zone lymphoma recurrent; Splenic marginal zone lymphoma refractory; Splenic marginal zone lymphoma stage I; Splenic marginal zone lymphoma stage II; Splenic marginal zone lymphoma stage III; Splenic marginal zone lymphoma stage IV; Splenic neoplasm malignancy unspecified; Squamous cell carcinoma; Squamous cell carcinoma of head and neck; Squamous cell carcinoma of lung; Squamous cell carcinoma of pharynx; Squamous cell carcinoma of skin; Squamous cell carcinoma of the cervix; Squamous cell carcinoma of the

hypopharynx; Squamous cell carcinoma of the oral cavity; Squamous cell carcinoma of the tongue; Squamous cell carcinoma of the vagina; Squamous cell carcinoma of the vulva; Squamous endometrial carcinoma; Stauffer's syndrome; Stem cell transplant; Stewart-Treves syndrome; Stomach scan abnormal; Superficial spreading melanoma stage I; Superficial spreading melanoma stage II; Superficial spreading melanoma stage III; Superficial spreading melanoma stage IV; Superficial spreading melanoma stage unspecified; Superior vena cava occlusion; Superior vena cava syndrome; Suprapubic prostatectomy; Synovial sarcoma; Synovial sarcoma metastatic; Synovial sarcoma recurrent; Targeted cancer therapy; T-cell chronic lymphocytic leukaemia; T-cell lymphoma; T-cell lymphoma recurrent; T-cell lymphoma refractory; T-cell lymphoma stage I; T-cell lymphoma stage II; T-cell lymphoma stage III; T-cell lymphoma stage IV; T-cell prolymphocytic leukaemia; T-cell type acute leukaemia; T-cell unclassifiable lymphoma high grade; T-cell unclassifiable lymphoma low grade; Tendon neoplasm; Teratoma; Testicular cancer metastatic; Testicular choriocarcinoma; Testicular choriocarcinoma recurrent; Testicular choriocarcinoma stage I; Testicular choriocarcinoma stage II; Testicular choriocarcinoma stage III; Testicular embryonal carcinoma; Testicular embryonal carcinoma stage I; Testicular embryonal carcinoma stage II; Testicular embryonal carcinoma stage III; Testicular germ cell cancer; Testicular germ cell cancer metastatic; Testicular germ cell tumour 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; 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 urethra; Transurethral bladder resection; Transurethral prostatectomy; Trousseau's syndrome; Tubular breast carcinoma; Tumour associated fever; Tumour cell mobilisation; Tumour compression; Tumour embolism; Tumour excision; Tumour fistulisation; Tumour flare; Tumour haemorrhage; Tumour invasion; Tumour lysis syndrome; Tumour marker increased; Tumour necrosis; Tumour of ampulla of Vater; Tumour pain; Tumour perforation; Tumour rupture; Tumour thrombosis; Tumour ulceration; Tumour vaccine therapy; Ultrasound scan abnormal; Ultrasound scan vagina abnormal; Undifferentiated carcinoma of colon; Undifferentiated nasopharyngeal carcinoma; Undifferentiated sarcoma; Ureteral neoplasm; Ureteric cancer; Ureteric cancer local; Ureteric cancer metastatic; Ureteric cancer recurrent; Ureteric cancer regional; Urethral cancer; Urethral cancer metastatic; Urethral cancer recurrent; Urethral melanoma metastatic; Urethral neoplasm; Urethrectomy; Urinary bladder sarcoma; Urinary cystectomy; Urinary tract carcinoma in situ; Urinary tract neoplasm; Uterine cancer; Uterine carcinoma in situ; Uterine leiomyosarcoma; Uterine neoplasm; Uterine tumour excision; Uvulectomy; Vaginal adenocarcinoma; Vaginal cancer; Vaginal cancer metastatic; Vaginal cancer recurrent; Vaginal cancer stage 0; Vaginal cancer stage I; Vaginal cancer stage II; Vaginal cancer stage III; Vaginal cancer stage IVA; Vaginal cancer stage IVB; Vaginal dysplasia; Vaginal neoplasm; Vaginectomy; Vascular neoplasm; Vipoma; Vocal cord leukoplakia; Vocal cord neoplasm; Vocal cordectomy; Vulval cancer; Vulval cancer metastatic; Vulval cancer recurrent; Vulval cancer stage 0; Vulval cancer stage I; Vulval cancer stage II; Vulval cancer stage III; Vulval cancer stage IV; Vulval neoplasm; Vulval operation; Vulval warts removal; Vulvar adenocarcinoma; Vulvar dysplasia; Vulvectomy; Vulvovaginal adenosis; Waldenstrom's macroglobulinaemia; Waldenstrom's macroglobulinaemia recurrent; Waldenstrom's macroglobulinaemia refractory; Waldenstrom's macroglobulinaemia stage I; Waldenstrom's macroglobulinaemia stage II; Waldenstrom's macroglobulinaemia stage III; Waldenstrom's macroglobulinaemia stage IV; X-ray therapy to bladder; X-ray therapy to blood; X-ray therapy to bone; X-ray therapy to brain; X-ray therapy to breast; X-ray therapy to colon; X-ray therapy to ear, nose, or throat; X-ray therapy to joint; X-ray therapy to liver; X-ray therapy to lung; X-ray therapy to pancreas; X-ray therapy to pleura; X-ray therapy to prostate; X-ray therapy to skin; X-ray therapy to soft tissue; X-ray therapy to thyroid; X-ray therapy to uterus; X-ray treatment; Yolk sac tumour site unspecified

Musculoskeletal and Soft Tissue Investigations

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

Myopathy/Rhabdomyolysis

MedDRA PTs: Acute 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; Compartment syndrome; Creatine urine; Creatine urine abnormal; Creatine urine increased; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Diaphragm muscle weakness; Electromyogram abnormal; Flank pain; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Hypercreatinaemia; Hypocalcaemia; Inflammatory pain; Muscle disorder; Muscle enzyme; Muscle enzyme increased; Muscle fatigue; Muscle haemorrhage; Muscle injury; Muscle necrosis; Muscle rupture; Muscle spasms; Muscle spasticity; Muscular weakness; Musculoskeletal chest pain; Musculoskeletal discomfort; Musculoskeletal disorder; Musculoskeletal injury; Musculoskeletal pain; Musculoskeletal stiffness; Myalgia; Myalgia intercostal; Myoglobin blood; Myoglobin blood increased; Myoglobin blood present; Myoglobin urine; Myoglobin urine present; Myoglobinaemia; Myoglobinuria; Myopathy; Myopathy toxic; Myositis; Myositis-like syndrome; Necrotising myositis; Non-cardiac chest pain; Oliguria; Pain in extremity; Prerenal failure; Renal failure; Renal failure chronic; Renal impairment; Renal tubular necrosis; Rhabdomyolysis; Skeletal muscle enzymes; Tendon discomfort

Opportunistic Infections

MedDRA PTs: Acute pulmonary histoplasmosis; Adrenal gland tuberculosis; Arthritis fungal; Atypical mycobacterial infection; Atypical mycobacterial lymphadenitis; Atypical mycobacterial pneumonia; Atypical mycobacterium pericarditis; Bacillary angiomatosis; Bartonellosis; Biliary tract infection cryptosporidial; Biliary tract infection fungal; Bone tuberculosis; Bovine tuberculosis; Bronchitis fungal; Candida osteomyelitis; Candida pneumonia; Candida sepsis; Cerebral fungal infection; Cerebral toxoplasmosis; Chronic pulmonary histoplasmosis; Coccidioides encephalitis; Coccidioidomycosis; Congenital tuberculosis; Conjunctivitis tuberculous; Cryptococcal cutaneous infection; Cryptococcal fungaemia; Cryptococcosis; Cryptosporidiosis infection; Cutaneous coccidioidomycosis; Cutaneous tuberculosis; Cytomegalovirus chorioretinitis; Cytomegalovirus colitis; Cytomegalovirus duodenitis; Cytomegalovirus enteritis; Cytomegalovirus enterocolitis; Cytomegalovirus gastritis; Cytomegalovirus gastroenteritis; Cytomegalovirus gastrointestinal infection; Cytomegalovirus hepatitis; Cytomegalovirus infection; Cytomegalovirus mononucleosis; Cytomegalovirus mucocutaneous ulcer; Cytomegalovirus myelomeningoradiculitis; Cytomegalovirus myocarditis; Cytomegalovirus oesophagitis; Cytomegalovirus pancreatitis; Cytomegalovirus pericarditis; Cytomegalovirus syndrome; Cytomegalovirus test positive; Cytomegalovirus urinary tract infection; Cytomegalovirus viraemia; Disseminated cryptococcosis; Disseminated cytomegaloviral infection; Disseminated tuberculosis; Ear tuberculosis; Encephalitis cytomegalovirus; Encephalitis fungal; Endocarditis candida; Endocarditis histoplasma; Enterocolitis fungal; Epididymitis tuberculous; Extrapulmonary tuberculosis; Eye infection toxoplasmal; Female genital tract tuberculosis; Fungal abscess central nervous system; Fungal cystitis; Fungal endocarditis; Fungal oesophagitis; Fungal peritonitis; Fungal retinitis; Fungal rhinitis; Fungal sepsis; Gastritis fungal; Gastroenteritis cryptococcal; Gastroenteritis cryptosporidial; Gastrointestinal fungal infection; Hepatic candidiasis; Hepatic infection fungal; Hepatitis toxoplasmal; Herpes oesophagitis; Herpes sepsis; Herpes simplex hepatitis; Herpes simplex visceral; Herpes zoster cutaneous disseminated; Herpes zoster disseminated; Herpes zoster infection neurological; Histoplasmosis; Histoplasmosis cutaneous; Histoplasmosis disseminated; Isosporiasis; JC virus infection; Joint tuberculosis; Listeria encephalitis; Listeria sepsis; Listeriosis; Lower respiratory tract infection fungal; Lymph node tuberculosis; Lymphadenitis fungal; Male genital tract tuberculosis; Meningitis candida; Meningitis coccidioides; Meningitis cryptococcal; Meningitis fungal; Meningitis herpes; Meningitis histoplasma; Meningitis listeria; Meningitis toxoplasmal; Meningitis tuberculous; Mycobacterial infection; Mycobacterium abscessus infection; Mycobacterium avium complex immune restoration disease; Mycobacterium avium complex infection; Mycobacterium chelonae infection; Mycobacterium fortuitum infection; Mycobacterium kansasii infection; Mycobacterium marinum infection; Mycobacterium tuberculosis complex test positive; Mycobacterium ulcerans infection; Myocarditis toxoplasmal; Necrotising fasciitis fungal; Neurocryptococcosis; Oesophageal candidiasis; Oesophageal tuberculosis; Opportunistic infection; Osteomyelitis fungal; Pancreatitis fungal; Pericarditis fungal; Pericarditis histoplasma; Pericarditis tuberculous; Peritoneal tuberculosis; Pneumocystis jirovecii infection; Pneumocystis jirovecii

pneumonia; Pneumonia cryptococcal; Pneumonia cytomegaloviral; Pneumonia fungal; Pneumonia toxoplasmal; Presumed ocular histoplasmosis syndrome; Progressive multifocal leukoencephalopathy; Prostatitis tuberculous; Pulmonary tuberculoma; Pulmonary tuberculosis; Pyelonephritis fungal; Renal tuberculosis; Retinitis histoplasma; Salmonella bacteraemia; Salmonella sepsis; Salpingitis tuberculous; Silicotuberculosis; Sinusitis fungal; Spleen tuberculosis; Splenic infection fungal; Systemic candida; Thyroid tuberculosis; Toxoplasmosis; Tuberculoma of central nervous system; Tuberculosis; Tuberculosis bladder; Tuberculosis gastrointestinal; Tuberculosis liver; Tuberculosis of central nervous system; Tuberculosis of eye; Tuberculosis of genitourinary system; Tuberculosis of intrathoracic lymph nodes; Tuberculosis of peripheral lymph nodes; Tuberculosis ureter; Tuberculous abscess central nervous system; Tuberculous laryngitis; Tuberculous pleurisy; Tuberculous tenosynovitis; Tubo-ovarian abscess

Osmotic Diuresis

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

Pancreatitis

MedDRA PTs: Abdominal compartment syndrome; Abdominal distension; Abdominal pain; Abdominal pain upper; Abdominal rebound tenderness; Abdominal rigidity; Abdominal tenderness; Abdominal X-ray; Acute abdomen; Amylase abnormal; Amylase creatinine clearance ratio abnormal; Amylase increased; Ascites; Autoimmune pancreatitis; Bilirubin conjugated abnormal; Blood bilirubin increased; Blood trypsin increased; Computerised tomogram abdomen; Computerised tomogram abdomen abnormal; Cullen's sign; Cytomegalovirus pancreatitis; Endocrine pancreatic disorder; Endoscopic retrograde cholangiopancreatography; Endoscopic retrograde cholangiopancreatography abnormal; Endoscopic ultrasound; Endoscopic ultrasound abnormal; Exocrine pancreatic function test; Exocrine pancreatic function test abnormal; Faecal elastase concentration abnormal; Faecal elastase concentration decreased; Fat necrosis; Gastrointestinal pain; Gastrointestinal sounds abnormal; Grey Turner's sign; Haemorrhagic ascites; 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 enzyme abnormality; Pancreatic enzymes abnormal; Pancreatic enzymes increased; Pancreatic fibrosis; Pancreatic haemorrhage; Pancreatic injury; Pancreatic insufficiency; Pancreatic necrosis; Pancreatic phlegmon; Pancreatic pseudocyst; Pancreatic pseudocyst drainage; Pancreatitis; Pancreatitis acute; Pancreatitis bacterial; Pancreatitis chronic; Pancreatitis fungal; Pancreatitis haemorrhagic; Pancreatitis helminthic; Pancreatitis mumps; Pancreatitis necrotising; Pancreatitis relapsing; Pancreatitis viral; Pancreatorenal syndrome; Peripancreatic fluid collection; Premenstrual cramps; Secretin test; Secretin test increased; Steatorrhoea; Traumatic pancreatitis; Vomiting; Vomiting projectile

Skin Reaction

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

Stomatitis/Mouth Ulceration

MedDRA PTs: Allergic pharyngitis; 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 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 discomfort; Oropharyngeal pain; Oropharyngeal plaque; Oropharyngeal scar; Oropharyngeal swelling; Palatal disorder; Palatal dysplasia; Palatal oedema; Palatal swelling; Parotid gland haemorrhage; PFAPA syndrome; Pharyngeal disorder; Pharyngeal dyskinesia; Pharyngeal enanthema; Pharyngeal erosion; Pharyngeal oedema; Pharyngeal ulceration; Pyostomatitis vegetans; Radiation mucositis; Stomatitis; Stomatitis haemorrhagic; Stomatitis necrotising; Stomatitis radiation; Swollen tongue; Tongue oedema

Thrombocytopenia

MedDRA PTs: 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 insufficiency; Arterial occlusive disease; Arterial restenosis; Arterial spasm; Arterial stenosis; Arteriosclerosis; Arteriosclerosis Moenckeberg-type; Arteriosclerotic gangrene; Atrophie blanche; Bone infarction; Chest wall necrosis; Chillblains; Choroidal sclerosis; Compartment syndrome; Dependent rubor; Diabetic foot; Diabetic foot infection; Diabetic gangrene; Diabetic

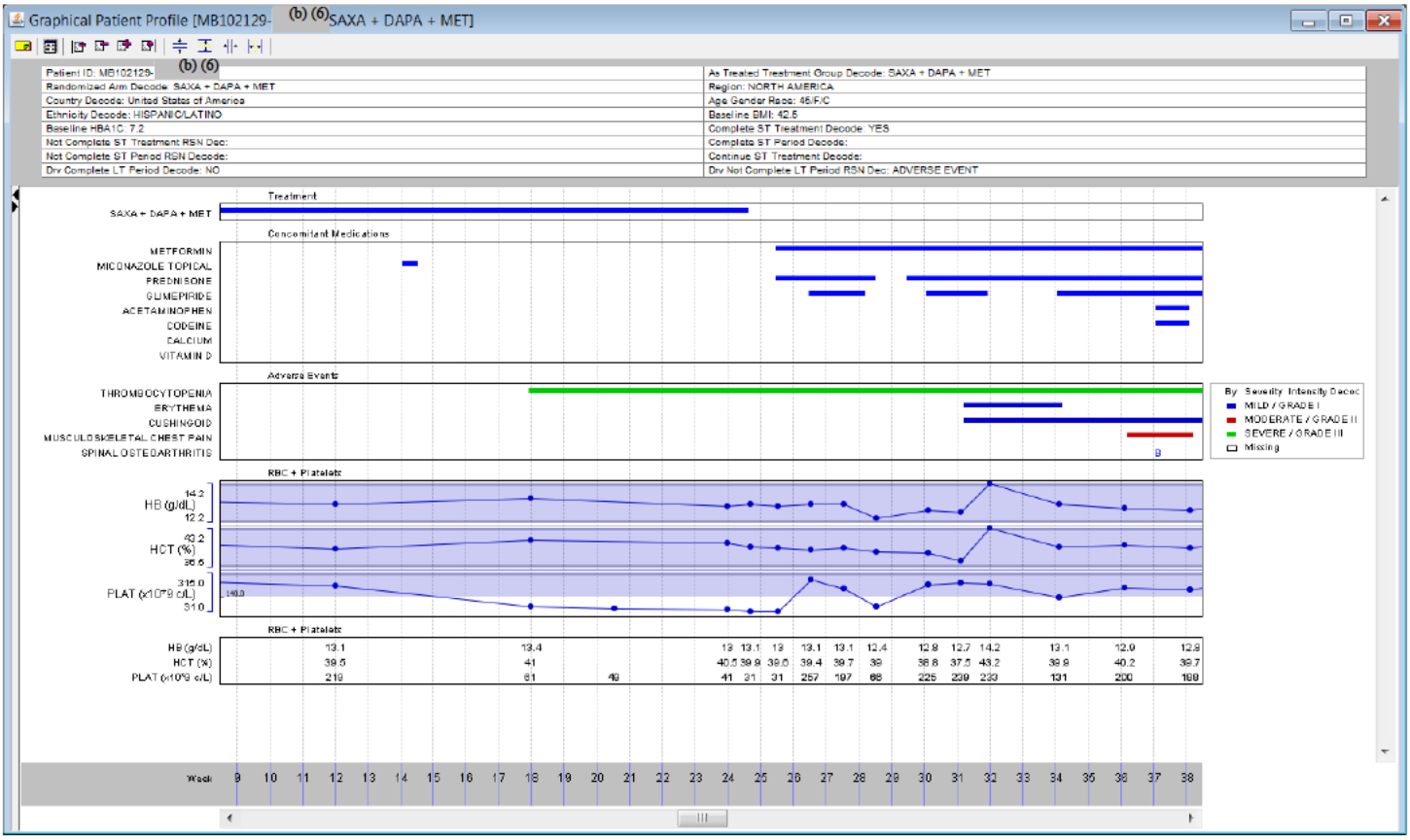
macroangiopathy; Diabetic microangiopathy; Diabetic ulcer; Diabetic vascular disorder; Digital pitting scar; Dry gangrene; Extremity necrosis; Extrinsic iliac vein compression; Fibromuscular dysplasia; Gangrene; Gangrene neonatal; Gas gangrene; Graft ischaemia; Haemorrhagic infarction; Hand-arm vibration syndrome; Iliac artery embolism; Iliac artery occlusion; Iliac vein occlusion; Infarction; Intermittent claudication; Ischaemia; Ischaemic limb pain; Ischaemic neuropathy; Ischaemic ulcer; Malignant atrophic papulosis; Malnutrition-inflammation-atherosclerosis syndrome; Man-in-the-barrel syndrome; May-Thurner syndrome; Mucocutaneous flap necrosis; Necrosis; Necrosis ischaemic; Necrosis of artery; Osteonecrosis; Osteonecrosis of jaw; Osteoradionecrosis; Peripheral arterial occlusive disease; Peripheral arterial reocclusion; Peripheral artery angioplasty; Peripheral artery bypass; Peripheral artery restenosis; Peripheral artery stenosis; Peripheral artery stent insertion; Peripheral artery thrombosis; Peripheral coldness; Peripheral ischaemia; Peripheral vascular disorder; Peripheral venous disease; Phlebosclerosis; Plaque shift; Poor peripheral circulation; Popliteal artery entrapment syndrome; Purple glove syndrome; Raynaud's phenomenon; Scleroderma associated digital ulcer; Scrotal gangrene; Septic necrosis; Skin flap necrosis; Skin ulcer; Soft tissue necrosis; Steal syndrome; Stoma site ischaemia; Strangulated hernia; Subclavian artery occlusion; Subclavian artery stenosis; Subclavian coronary steal syndrome; Subclavian vein thrombosis; Tumour necrosis; Vascular compression; Vascular graft; Vascular graft complication; Vascular graft occlusion; Vascular graft thrombosis; Vascular insufficiency; Vascular occlusion; Vasoconstriction; Vasospasm; Venous occlusion; Venous stenosis; Venous ulcer pain; Visceral arterial ischaemia

Volume Depletion

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

13.6. Thrombocytopenia

Figure 3: Graphical Patient Profile of Subject MB102129-(b) (6)



Source: Derived in JReview using the adae.xpt, adae2.xpt, adcm.xpt, addm.xpt adlb.xpt, adcm.xpt, addm.xpt.

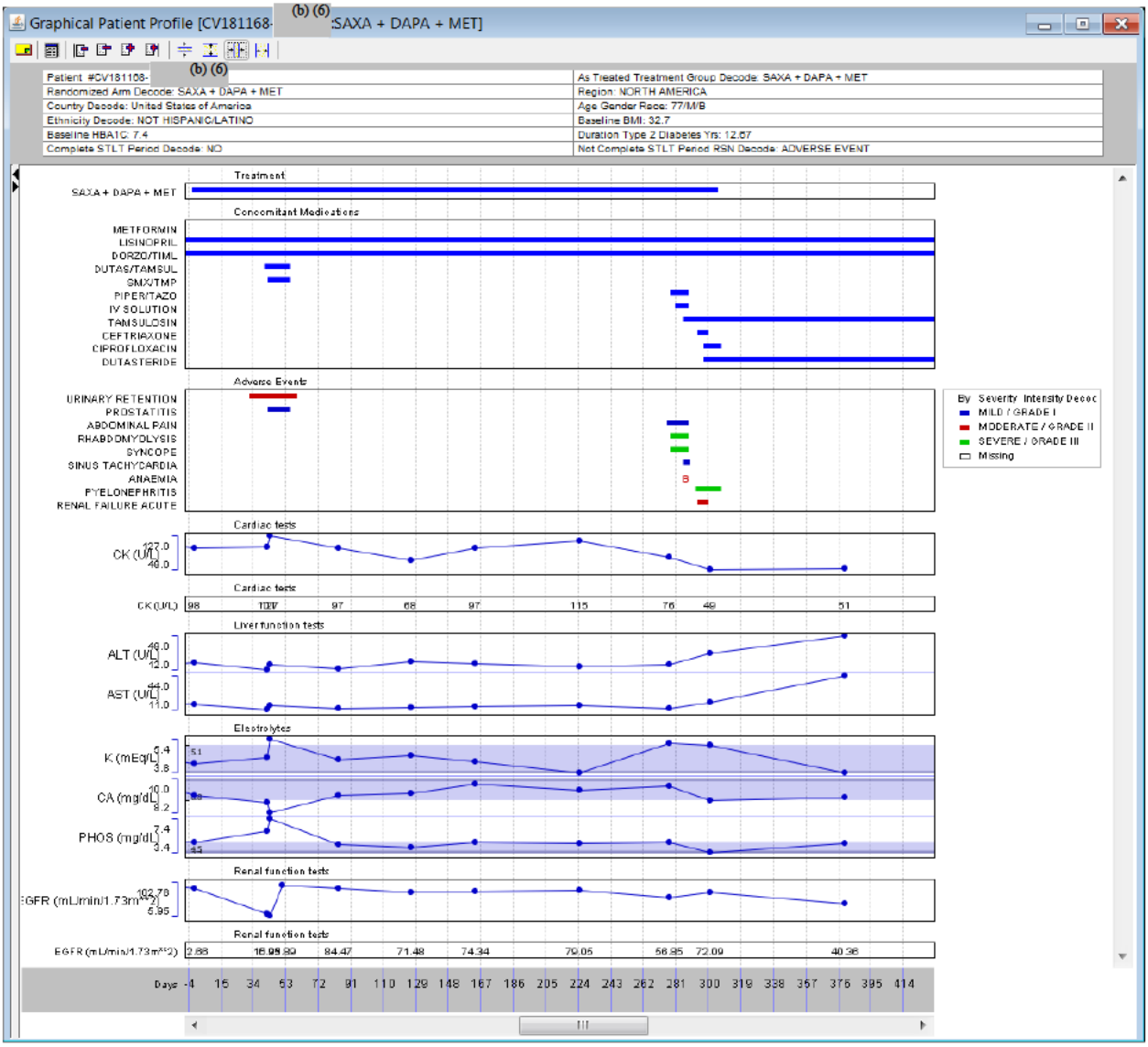
13.7. Marked CK Elevations

The following 12 cases presented in this section include the subjects who experienced marked serum CK elevation (i.e., >5x UNL). Narrative summaries were revised/reproduced from the Applicant's 4-Month Safety Update, pages 97-101, available at: \\cdsesub1\evsprod\nda209091\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\safety-update\5-3-5-3-safety-update.pdf. In addition, selective exploration of the clinical data for the individual cases of marked CK elevations were performed using Graphical Patient Profiles (GPP) with JReview™ in an attempt to better characterize these events.

Subject CV181168- (b) (6): a 77-year-old Black male in the **saxagliptin+dapagliflozin+metformin** treatment arm, experienced SAEs of syncope and rhabdomyolysis on study Day 280 and an SAE of pyelonephritis on study Day 295. His medical history included T2D, hypertension, obesity, benign prostatic hypertrophy, and glaucoma. Concomitant medications included metformin, lisinopril, and dorzolamide/timolol. Relevant baseline central laboratory tests showed CK of 98 U/L (ULN: 203 U/L), serum creatinine of 1.05 mg/dL (normal range: 0.70 to 1.20 mg/dL), and eGFR of 83 mL/min/1.73m^2. During the study treatment period, he experienced an AE of urinary retention on Day 34 and the AE of prostatitis on Day 45, at which time his creatinine was markedly elevated at 10.27 mg/dL. Following treatment with dutasteride/tamsulosin for 12 days and trimethoprim/sulfamethoxazole for 10 days, his creatinine returned to normal on Day 52 (0.94 mg/dL), and the prostatitis and urinary retention were considered resolved by Days 56 and 60, respectively. On Day 278, he experienced an AE of abdominal pain. Central laboratory values on Day 278 included a serum CK of 76 U/L, serum creatinine of 1.45 mg/dL, and eGFR of 56.85 mL/min/ 1.73m^2. On Day 280, the subject had a witnessed syncopal episode when getting out of a taxi. No injuries, seizure activity, or loss of bladder or bowel function was reported. The subject was sent to the hospital for evaluation and the Investigator reported an SAE of syncope. The event of syncope was sent for independent CV adjudication which did not confirm the event of syncope as a true CV event. On this same day, while hospitalized, an SAE of rhabdomyolysis (severe intensity) was reported. Local laboratory tests on Day 280 showed a CK of 6413 U/L, eGFR of 68 mL/min/1.73m^2, prostate specific antigen (PSA) of 65 ng/mL, HbA1c of 10.1%, and urinalysis (white blood cells) of 77 hpf. Following the onset of these events, study medications were interrupted on Day 280. An abdominal CT scan revealed bilateral hydronephrosis and hydroureter, and a Foley catheter was placed. The subject was treated with intravenous fluids and piperacillin/tazobactam and both SAEs resolved 9 days later by Day 288. The subject was also started on treatment with tamsulosin on Day 288. Study drugs were restarted on Day 289. On Day 295 of the study, the subject was found to have a bladder outlet obstruction resulting in acute pyelonephritis and an SAE of pyelonephritis (severe intensity; related to study drugs) was reported. The subject was treated with ciprofloxacin, ceftriaxone, and dutasteride for this event. Following the onset of this event, study drugs were interrupted. On Day 296, the Investigator reported a nonserious event of acute renal failure syndrome (moderate intensity) and an indwelling Foley catheter was placed. Local laboratory tests on Day 296 showed serum creatinine of 2.2 mg/dL, eGFR of 35 mL/min/1.73m^2, large amount of leukocyte esterase, and white blood cell count of 10.1 x10*3 cells/µL. The event of acute renal failure resolved on Day 301 and the event of acute pyelonephritis was resolved on Day 307. The subject was permanently discontinued from study, and his last day of study drug treatment was Day 305. On Day 302, central laboratory test results showed a CK level of 49 U/L, serum creatinine of 1.18 mg/dL, and eGFR of 72.09 mL/min/1.73m^2.

This case was previously reviewed by Dr. Balakrishnan, who felt that the case was confounded due to co-morbidities. However, she noted that the subject was not receiving concomitant antihyperlipidemic medications at the time of the event, and that resolution occurred following discontinuation of study medication. The Applicant felt that a causal relationship of the SAE of rhabdomyolysis to study medication was unlikely due to the following: the presence of a normal CK concentration within two days of the event, no information reported to suggests associated muscle symptoms or myoglobinuria; and possible muscle injury associated with the syncopal episode. While I concur that that preexisting comorbidities, lack of confirmatory laboratory assessments, and limited clinical information make difficult to assess causality for this case, an association between study medication and this event cannot be ruled out based on the available information.

Figure 4: Graphical Profile of Subject CV181168-(b) (6) – Marked Creatine Kinase

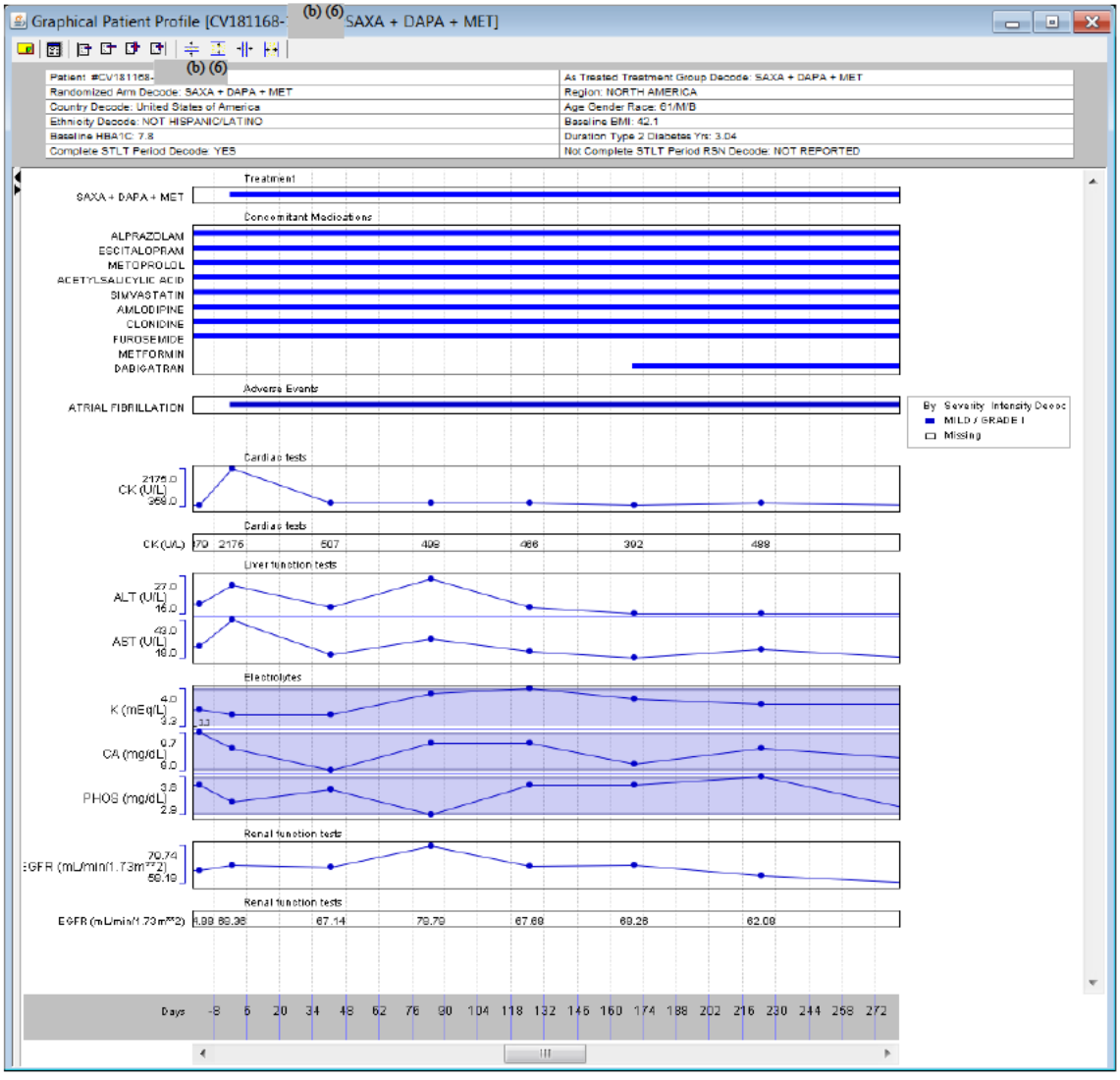


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181168-(b) (6): a 61 year-old Black male in the **saxagliptin+dapagliflozin+metformin** treatment arm had a medical history of hyperlipidemia, spinal stenosis and osteoarthritis, and concomitant medications included simvastatin and escitalopram. Prior to randomization, the subject had elevated CK concentrations, with a CK of 395 U/L on the screening visit (Day -126). On Day 1, during the open-label dapagliflozin treatment period (i.e., prior to randomization), the subject had a marked CK elevation >5x ULN of 2175 U/L. On that day, the subject also had a reported AE of Atrial fibrillation (mild intensity). He continued the study, and entered the double-blind treatment period. On Days 43 and 48, the subject's CK levels decreased to 507 and 498 U/L, respectively. Subsequent laboratory results until the end of the study treatment period were similar, with the last CK level taken on Day 393 of 427 U/L. On Day 393, the AE of Atrial fibrillation was considered resolved. The subject completed the study without interruption to study treatment due to the CK elevations.

Concomitant statin therapy, previous CK elevations prior to receiving study medication, a single event occurring with the first dose of dapagliflozin+metformin, and return to baseline concentrations while receiving study medications, do not suggest a causal relationship.

Figure 5: Graphical Profile of Subject CV181168-(b) (6) – Marked Creatine Kinase

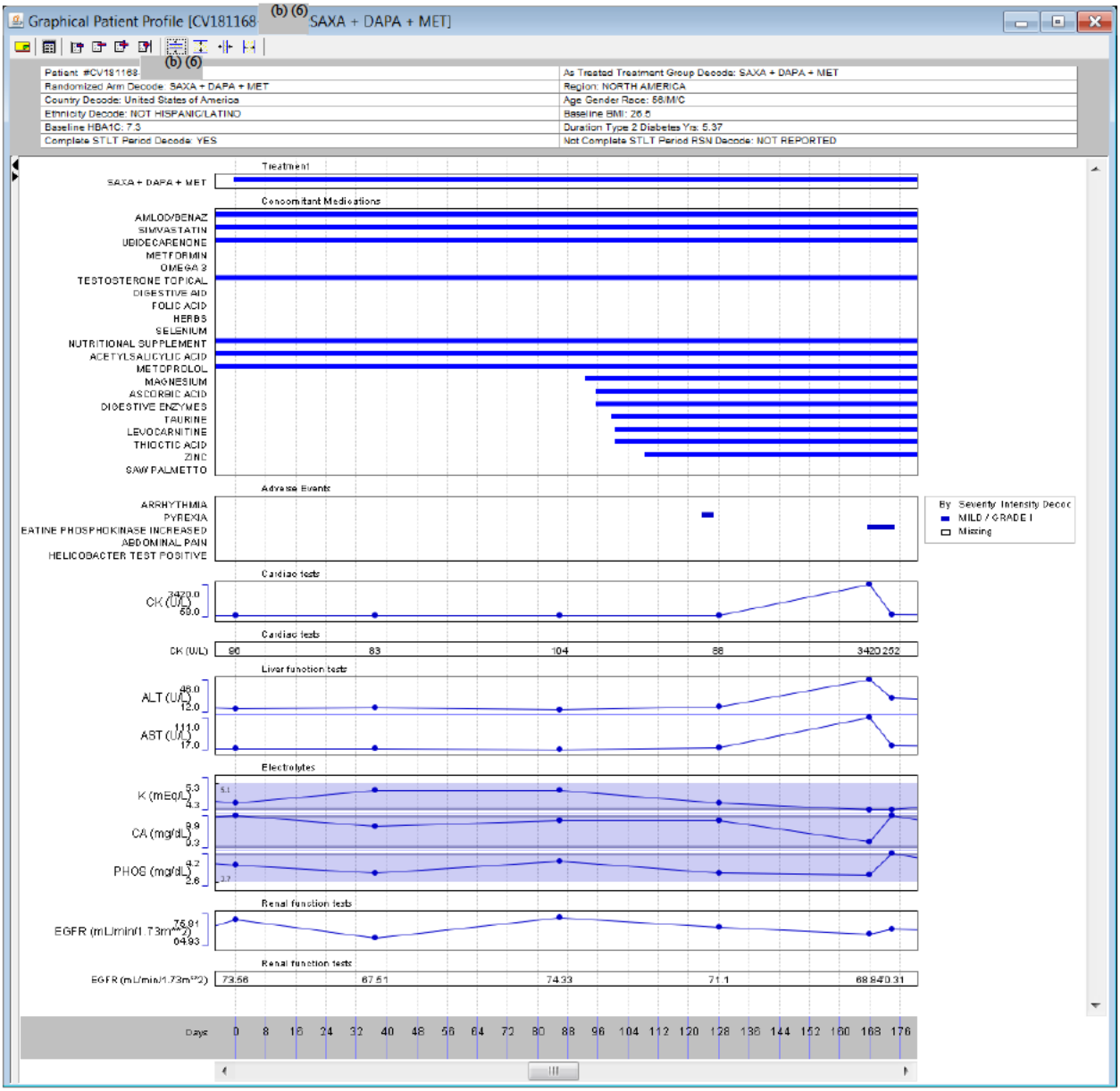


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181168- (b) (6)**:** a 56-year-old White male in the **saxagliptin+dapagliflozin+metformin** treatment arm, with a recent increase in physical activity, had a marked CK elevation >10x ULN at 3420 U/L (ULN 250 U/L) on Day 169. The event was also reported as an AE of 'blood CPK increased' of mild intensity (Grad I). Concomitant medications included simvastatin. On repeat testing, Day 175, CK levels decreased to near normal levels at 252 U/L; the AE was considered resolved while study treatment continued. The Investigator suspected concomitant medication and increased excessive physical activity as possible causes of the event. The subject completed the study without interruption to study treatment.

Concomitant use of statins and dietary supplements, increased physical activity, a single event, and resolution while receiving study medication do not suggest a causal association of study medication with this event.

Figure 6: Graphical Profile of Subject CV181168- (b) (6) **– Marked Creatine Kinase**

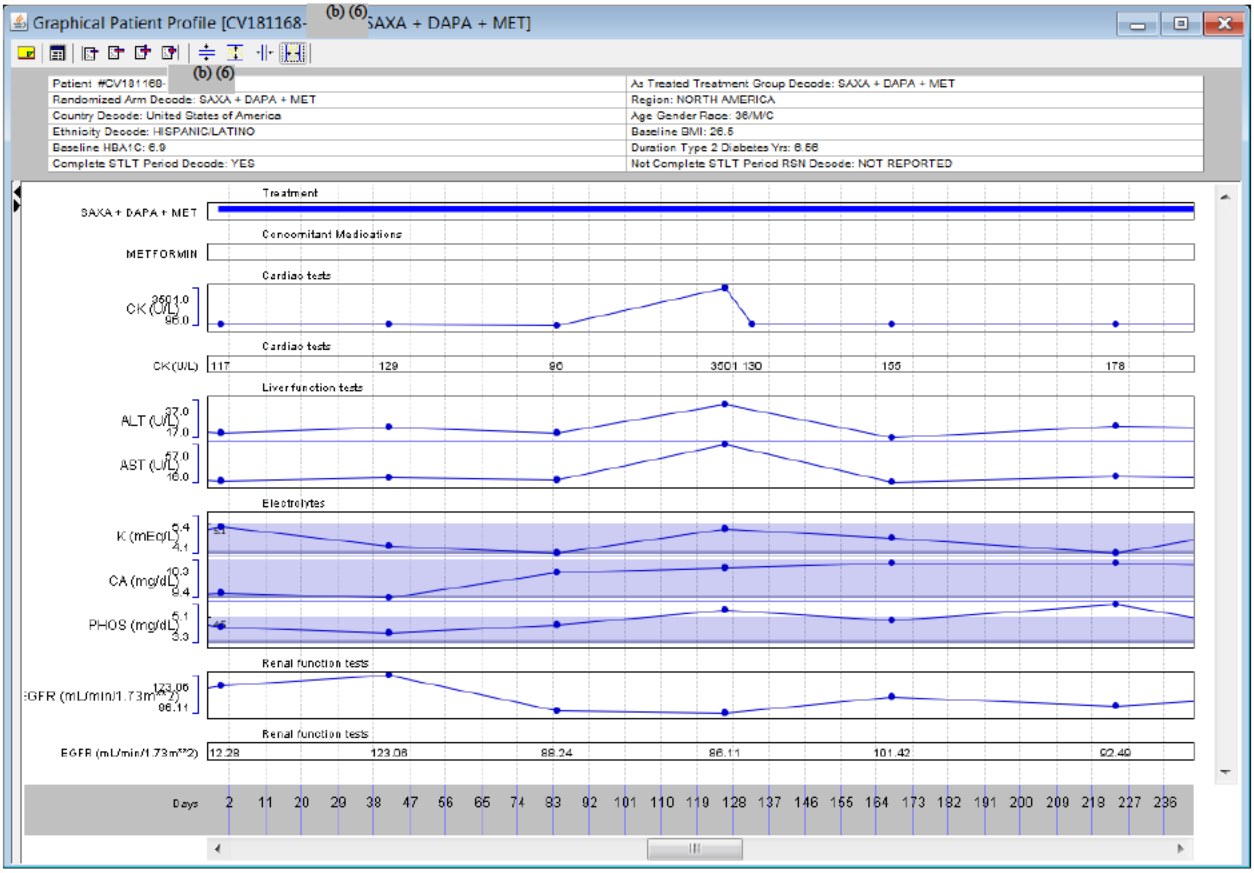


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181168-(b) (6): a 36-year-old White Hispanic/Latino male in the **saxagliptin+dapagliflozin+ metformin** treatment arm experienced a CK elevation of 3501 U/L (>10x ULN; UNL 250 U/L) on Day 127. He had no relevant medical history. Repeat testing on Day 134 showed CK levels had returned to normal at 130 U/L. There were no reported AEs associated with the CK elevation. The subject completed the study without interruption to study treatment.

Although an isolated event that resolved within one week while continuing study medication would not suggest a causal association, the lack of information on the presence of any associated symptoms or changes in physical activity, and the absence of concomitant medications (e.g., statins, fibrates), make it difficult to determine the etiology for this event and rule out a causal association.

Figure 7: Graphical Profile of Subject CV181168-(b) (6) – Marked Creatine Kinase

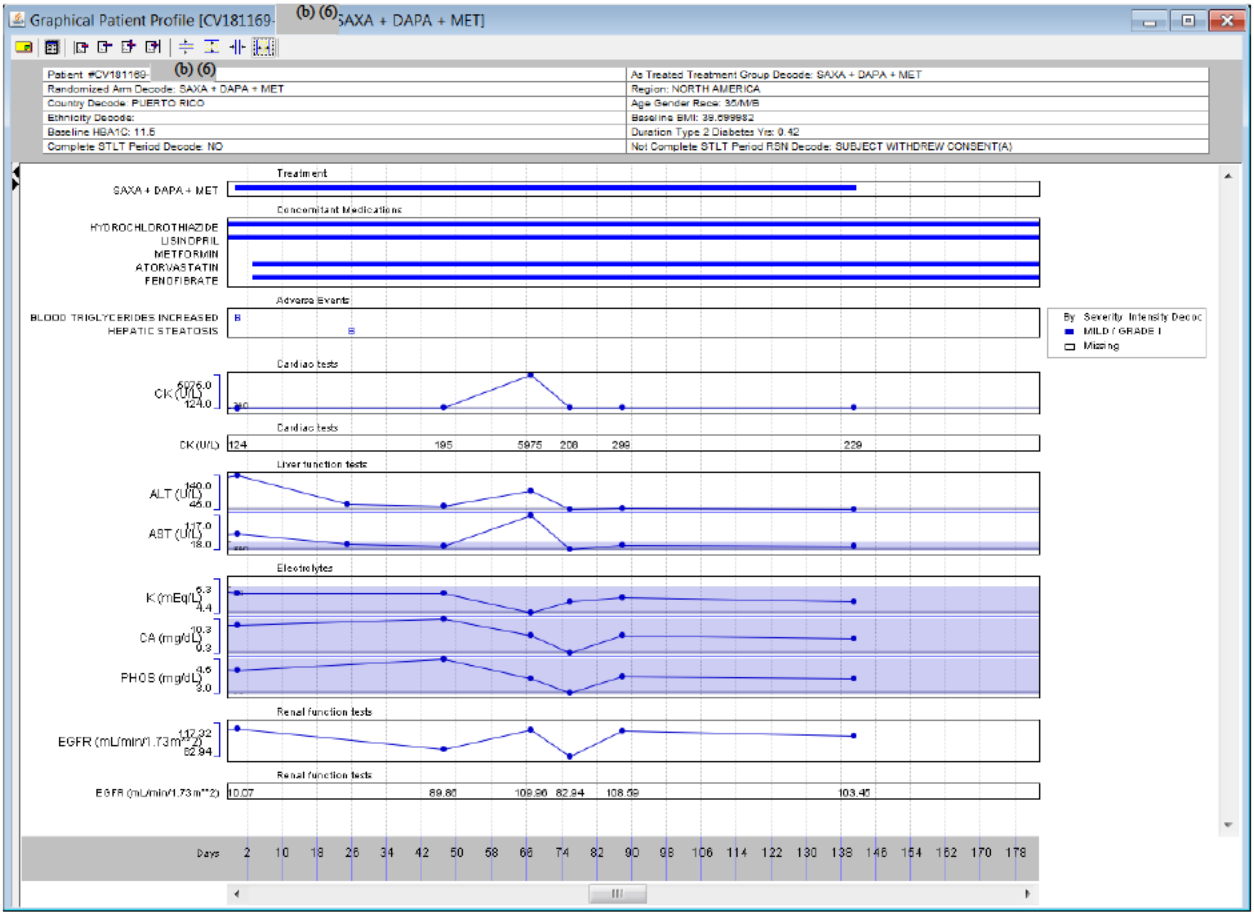


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181169-(b) (6): a 35-year-old Black male in the **saxagliptin+dapagliflozin+metformin** treatment arm had a CK elevation of 5957 U/L (>10x ULN; ULN 250 U/L) on Day 68. Repeat testing on Day 77 showed that the level had returned to 208 U/L. On Day 5, the subject started atorvastatin and fenofibrate, and on Day 27, he had an AE of fatty liver (mild intensity), which the Investigator determined that no intervention was necessary. There were no reported AEs associated with the CK elevation and the study treatment was not interrupted.

This isolated event that also was temporally associated with statin/fibrate therapy, and resolved within two weeks while continuing study treatment, would not suggest a causal association between study medication and the event. Additionally, the possible contribution of nonalcoholic fatty liver disease in this case is unknown.[121]

Figure 8: Graphical Profile of Subject CV181169-(b) (6) – Marked Creatine Kinase

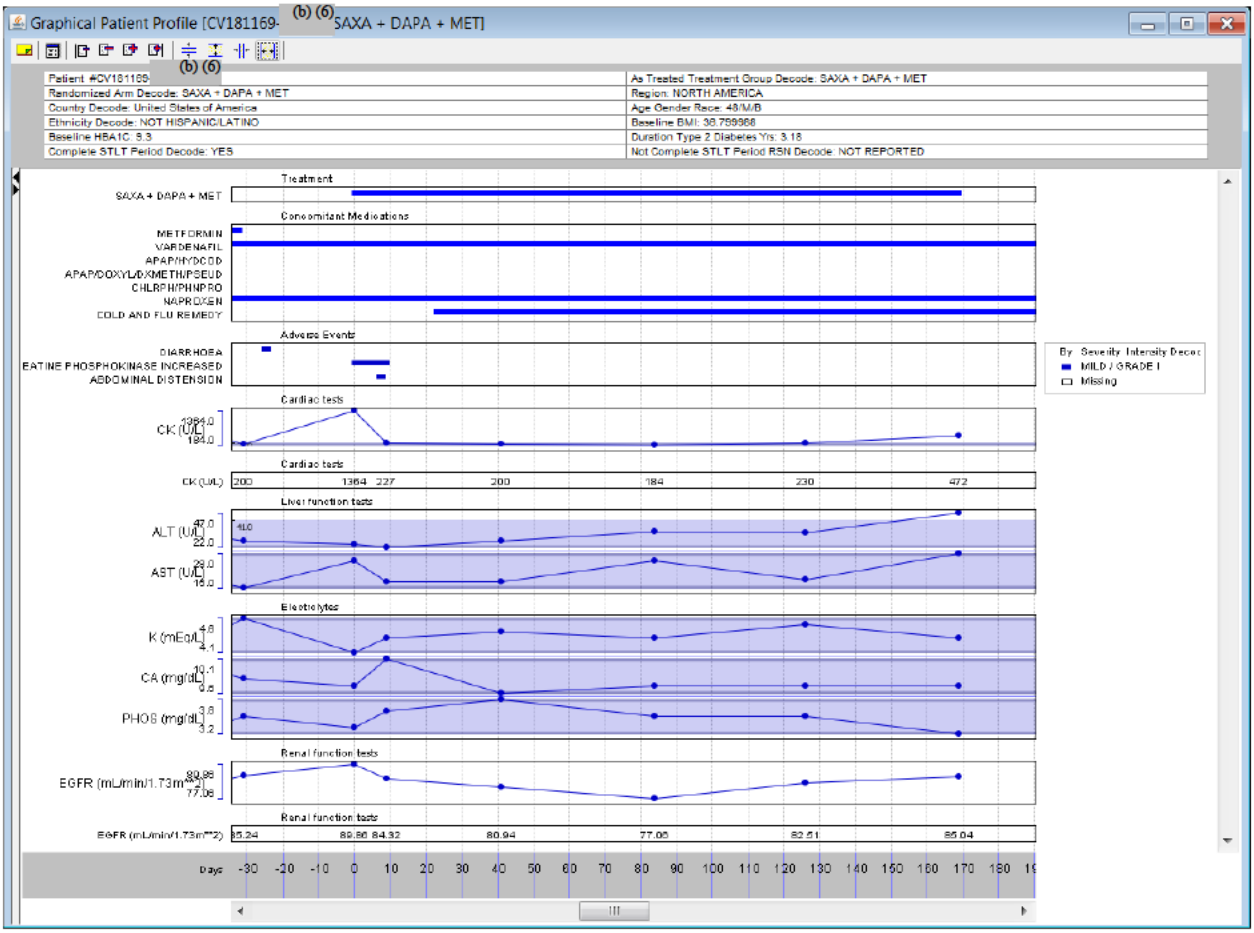


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181169- (b) (6), a 48 year-old Black male in the **saxagliptin+dapagliflozin+metformin** group had a relevant medical history of elevated CK, diabetic neuropathy/nephropathy, and excision of the left foot. Concomitant medications included vardenafil. The subject had a CK elevation of 720 U/L at screening (Day -45; ULN 250 U/L), and on Day 1, during the lead-in metformin treatment period (i.e., prior to randomization), he had a marked CK elevation of 1364 U/L (>5x ULN). On Day 1, the event was also reported as a mild AE (i.e., 'blood creatine phosphokinase increased). The subject continued the study, and entered the double-blind treatment period. On repeat testing, Day 10, CK concentrations decreased to normal levels at 227 U/L, and the AE was considered resolved. The subject completed the study without interruption to study treatment.

An isolated event on Day 1 (during the metformin lead-in treatment period), without associated AEs in a subject with a history of CK elevations, is not suggestive of a causal association between the event and study medications.

Figure 9: Graphical Profile of Subject CV181169- (b) (6) **– Marked Creatine Kinase**

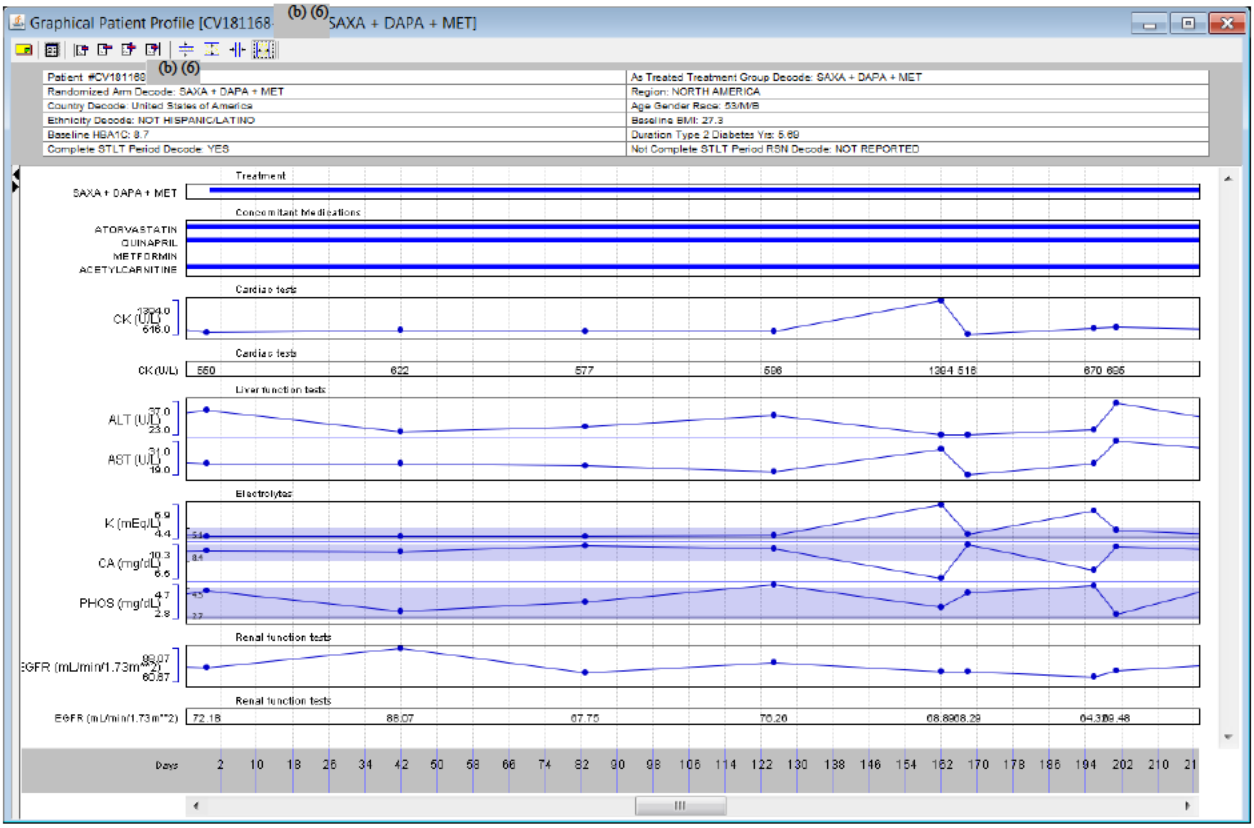


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181168- (b) (6)**:** a 53-year-old Black male in the **saxagliptin+dapagliflozin+metformin** treatment arm had a CK elevation >5x ULN (1394 U/L) on Day 163. Relevant concomitant medications included atorvastatin and acetylcarnitine. His CK levels were elevated (961 U/L; ULN 250 U/L) during the screening visit (Day -126) and remained so until the end of open-label dapagliflozin+metformin treatment period (Day -1) at 550 U/L. Other abnormal laboratory results on Day 163 included elevated serum potassium of 6.9 mEq/L (UNL 5.1 mEq/L) and decreased calcium of 6.5 mg/dL (LLN 8.4 mg/dL). On Day 169, repeat CK concentrations decreased to 516 U/L, and the potassium and calcium concentrations normalized to 4.7 mEq/L and 10.2 mg/dL, respectively. On Day 197, the subject again had a CK elevation of 670 U/L, an elevated potassium concentration of 6.4 mEq/L, and a low calcium concentration of 7.4 mg/dL. On Day 202, the potassium and calcium concentrations returned to normal at 5.0 mEq/L and 10.0 mg/dL, respectively, and remained so until study completion. However, the CK levels remained elevated (>500 U/L) until the end of study treatment on Day 365 at 563 U/L. There were no reported AEs associated with the laboratory abnormalities. The subject completed the study without interruption to study treatment.

Concomitant statin therapy, preexisting CK elevations prior to starting study medications, a lack of associated AEs, and improvement while continuing study medications would not suggest a causal association between study medication and the marked laboratory abnormality. However, a temporal relationship with increases in serum potassium concentrations and reductions in serum calcium concentrations, and continued CK elevations throughout the trial are not inconsistent with a possible myopathy.

Figure 10: Graphical Profile of Subject CV181168- (b) (6) **– Marked Creatine Kinase**

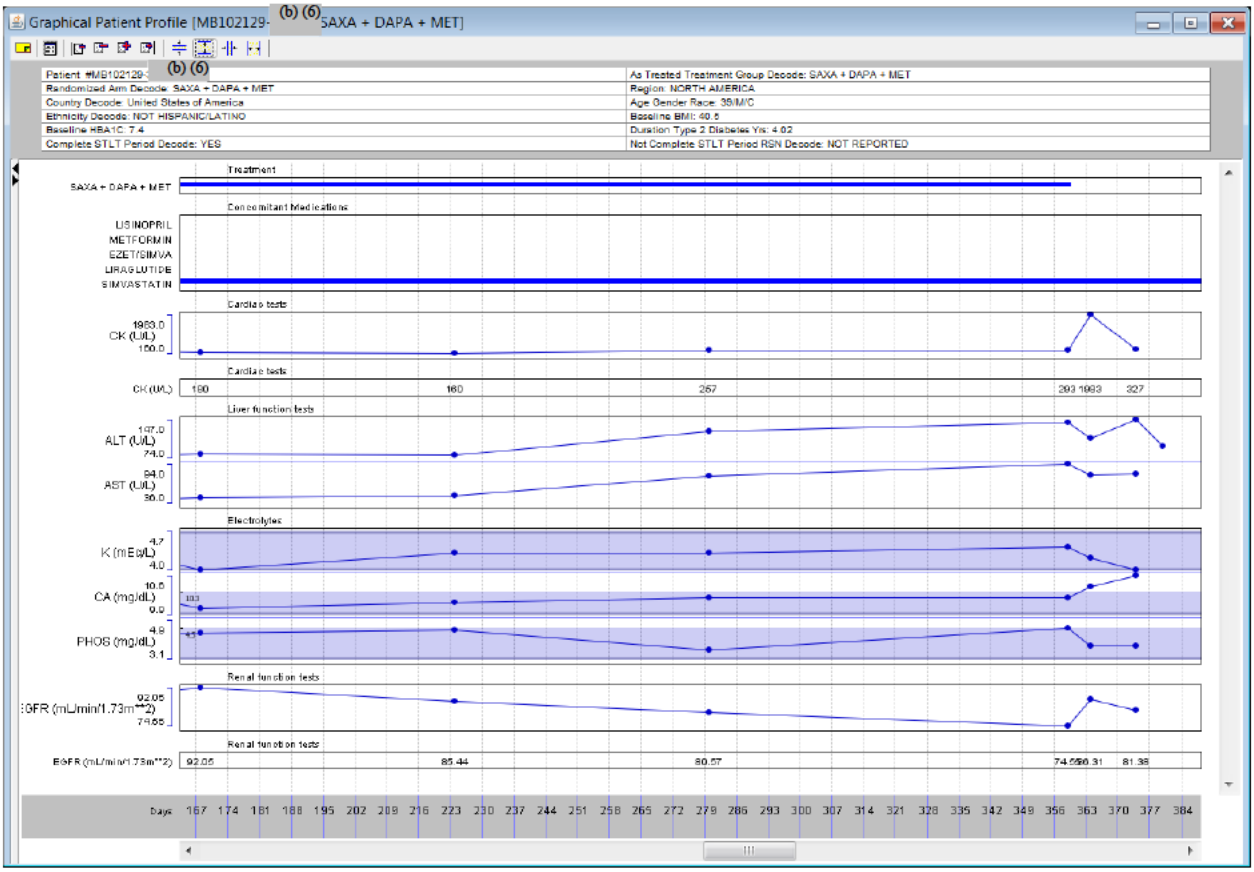


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject MB102129- (b) (6)**:** a 39 year-old White male in the **saxagliptin+dapagliflozin+metformin** group, had a relevant medical history of elevated baseline CK, hypertension (treated with lisinopril) and hyperlipidemia (treated with simvastatin). During the pre-treatment and saxagliptin+metformin open-label periods, his CK was elevated at 278-347 U/L (ULN 250 U/L). While receiving long-term saxagliptin+dapagliflozin+metformin therapy, his CK concentrations were again above the ULN on Days 281 (257 U/L) and 360 (293 U/L; day of last dose). At his post treatment visit (Day 365), is CK was elevated at 1983 U/L (approximately 8x UNL). His CK improved, but remained elevated with repeat testing on Day 375 (327 U/L). There were no associated AEs recorded for this subject at the time of the marked laboratory abnormality.

A preexisting history of CK elevations, concomitant statin use, absence of associated AEs, marked elevation occurring post treatment, and continued elevation reported two weeks off of study medication (half-life of CK ~36 hours)[122] make an association with study medication unlikely.

Figure 11: Graphical Profile of Subject MB102129- (b) (6) **– Marked Creatine Kinase**

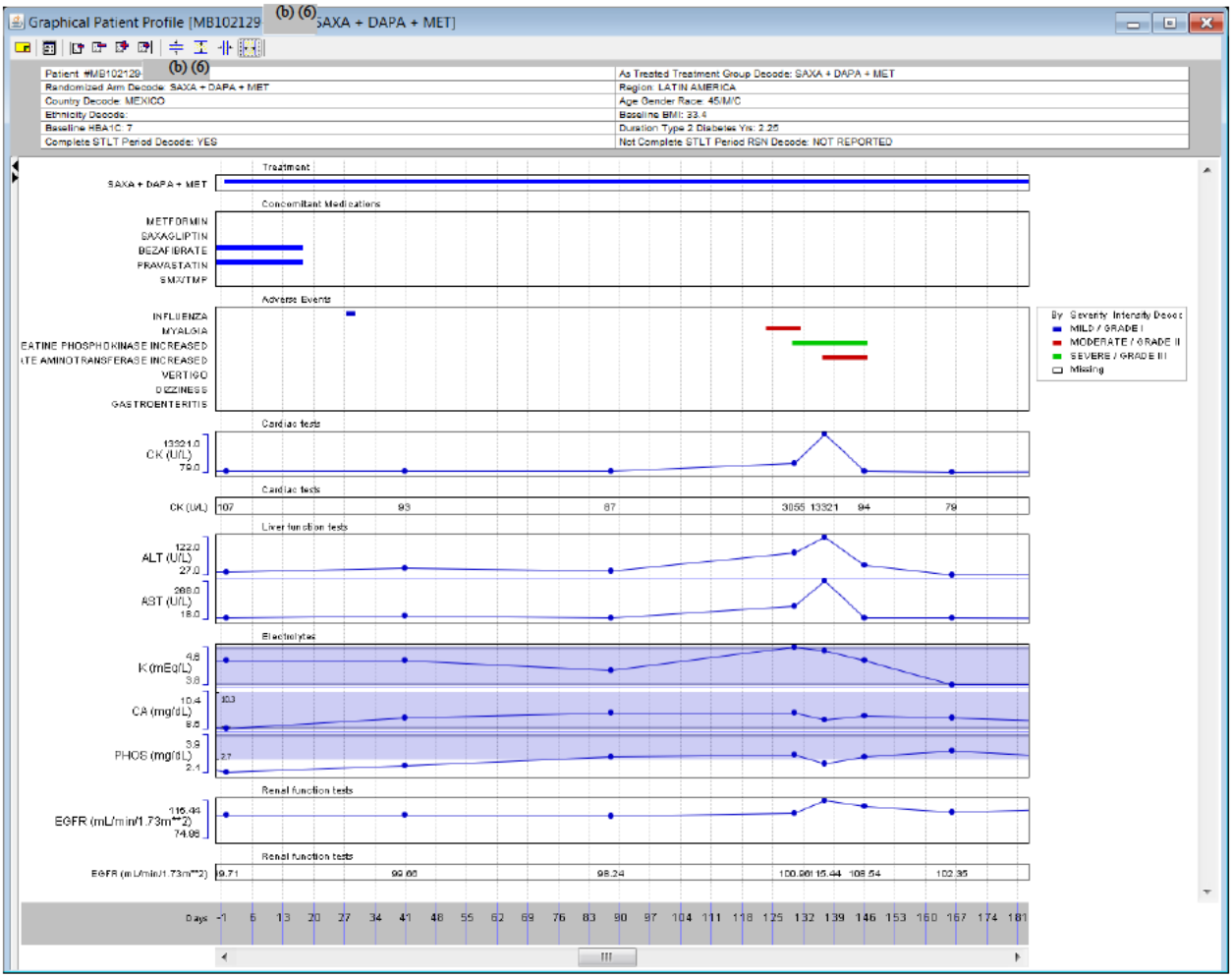


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject MB102129- (b) (6)**:** a 45-year-old White male in the **saxagliptin+dapagliflozin+metformin** treatment group had an AE of myalgia (moderate intensity) on Day 125 considered to be related to the recent start of an exercise program (including weightlifting and "cardio" for 2 hours/day). On Day 131, he had CK levels >10x ULN at 3055 U/L, and it was reported as an AE of 'blood creatine phosphokinase increased' (moderate intensity; Grade II). On repeat testing (Day 138), CK concentrations increased to 13,321 U/L, and the AE of 'creatine phosphokinase increased' (severe intensity; Grade III) was also reported. On study Day 131, laboratory test results also showed an increase in ALT (82 U/L) and AST (100 U/L). On repeat testing, Day 138, ALT and AST increased to 122 U/L and 268 U/L, respectively. Total bilirubin values were normal. The subject had no abdominal pain, fever, jaundice, or other clinical symptoms. The subject was advised to stop exercising. Repeat testing on Day 147 showed all laboratory parameters returned to normal levels. The AEs of myalgia, increased and worsening CPK, and increased AST/ALT concentrations were considered resolved, and did not require any action taken on study treatment. In the opinion of the Hepatic Adjudication Committee, ALT/AST elevation was related to the intensive exercise, and a relationship to study drug was "excluded". The subject completed the study without interruption to study treatment.

Concomitant statin/fibrate therapy, and a temporal association (challenge/dechallenge) of myalgia, and AST/ALT and CK elevations with a daily exercise program[123] make it less likely that the study medications caused this event.

Figure 12: Graphical Profile of Subject MB102129- (b) (6) **– Marked Creatine Kinase**

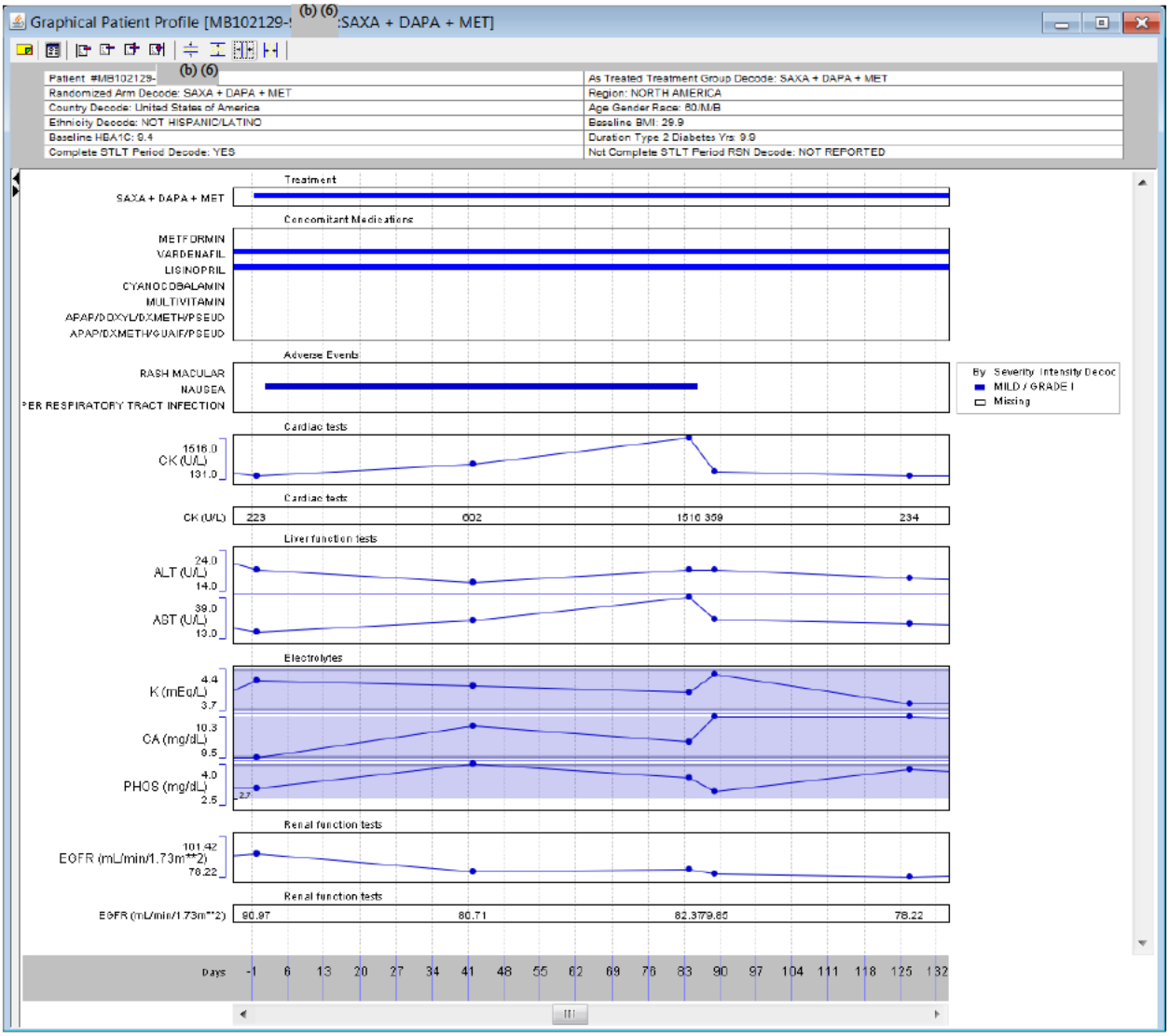


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG

Subject MB102129-(b) (6): a 60-year-old Black male in the **saxagliptin+dapagliflozin+metformin** treatment arm had a CK elevation >5x ULN at 1516 U/L (ULN 250 U/L) on Day 85. Concomitant medications included vardenafil and lisinopril. The subject had CK elevations during the saxagliptin+metformin open-label treatment period, with levels ranging from 322 U/L to 497 U/L. Concentrations on baseline Day 1 were normal (223 U/L). On Days 43 and 85, CK concentrations increased to 602 and 1516 U/L, respectively. Repeat testing results on Day 90 showed CK concentrations decreased to 359 U/L, and on Day 128, CK concentrations returned to normal (234 U/L). There were no reported AEs associated with the CK elevation. The subject completed the study without interruption to study treatment.

The modest CK elevations while receiving open-label saxagliptin+metformin, a lack of associated adverse effects or meaningful laboratory changes, and resolution without an interruption in investigational therapy make a causal association less likely. However, the temporal association and worsening with the combination of saxagliptin+dapagliflozin+metformin, and the absence of other contributing etiologies make it difficult to completely rule out an association.

Figure 13: Graphical Profile of Subject MB102129-(b) (6) – Marked Creatine Kinase

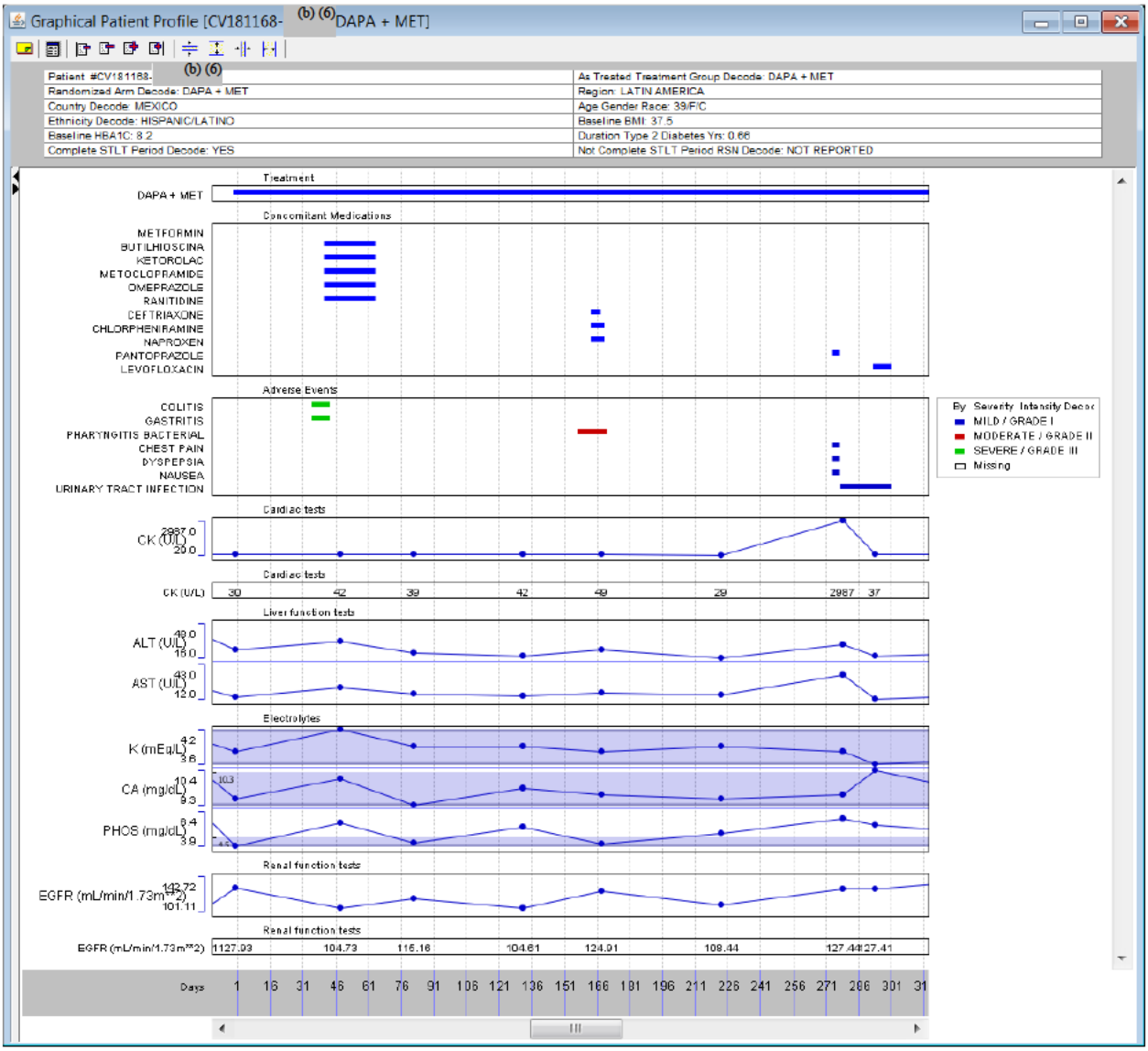


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject CV181168- (b) (6): a 39-year-old White Hispanic female in the **dapagliflozin+metformin** group had a CK elevation >10x ULN at 2987 U/L (ULN 170), a temporally associated AE of UTI (mild in intensity and considered not related to study treatment) on Day 280. On Day 295, the subject was started on levofloxacin for the UTI. On the same day, laboratory test results showed that CK levels returned to normal at 37 U/L. The AE of UTI was considered resolved on Day 301 while the subject continued study treatment. The subject completed the rest of the study without interruption to study treatment.

This single event, with resolution while continuing study treatment, make it unlikely that study medication is causal for the laboratory abnormality. However, acute infection and the presence of gastrointestinal symptoms and chest pain in a diabetic subject with a history of gastritis, make it challenging to assess whether the concurrent symptoms and/or laboratory change may be infectious,[124,125] gastrointestinal, musculoskeletal or cardiac in origin.

Figure 14: Graphical Profile of Subject CV181168- (b) (6) **– Marked Creatine Kinase**

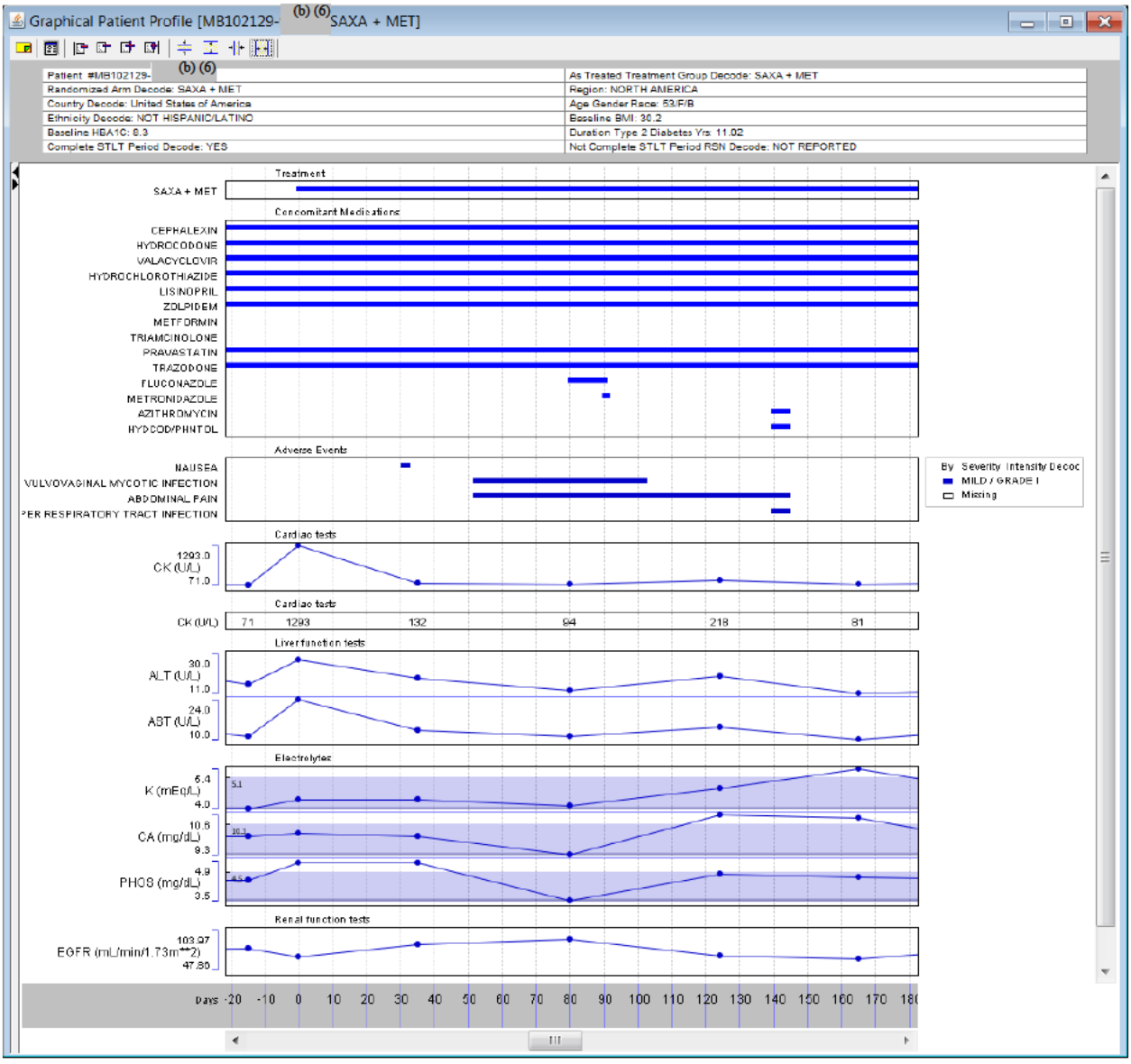


Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Subject MB102129- (b) (6): a 53 year-old Black female in the **saxagliptin+metformin** treatment arm had a relevant medical history of osteoarthritis, vitamin D deficiency, and patellar chrondomalacia, and concomitant medications that included pravastatin. On Day 1, during the open-label saxagliptin treatment period (i.e., prior to randomization), the subject had a marked CK elevation >5x ULN of 1293 U/L. The subject continued the study, and entered the double-blind treatment period. On repeat testing (Day 36), CK concentrations returned to normal at 132 U/L. There were no reported AEs associated with the marked CK elevation and the subject completed the study without interruption to study treatment due to the CK elevation.

Concomitant statin therapy, a lack of associated AEs, and resolution while receiving study medications make a causal association unlikely.

Figure 15: Graphical Profile of Subject MB102129- (b) (6) **– Marked Creatine Kinase**



Source: Derived from the adae.xpt, adcm.xpt, addm.xpt, adex.xpt, adlb2, datasets, available at: url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMjA5MDkxsQeG.

Table 37: Summary of Myopathy/Rhabdomyolysis MedDRA Preferred Terms(ST+LT Safety Pool)

MedDRA PTs/Marked Laboratory Abnormality	ST+LT Pool		
	Saxa+Dapa+Met (N=492)	Saxa+Met (N=336)	Dapa+Met (N=341)
TOTAL SUBJECTS — No. (%)	**49 (10.0)**	**38 (11.3)**	**24 (7.0)**
Back pain	16 (3.3)	12 (3.6)	8 (2.3)
Creatine kinase >3x ULN*	10 (2.0)	4 (1.2)	1 (0.3)
Creatine kinase >5x ULN*	8 (1.6)	0 (0.0)	1 (0.3)
Glomerular filtration rate decreased	5 (1.0)	1 (0.3)	2 (0.6)
Musculoskeletal pain	5 (1.0)	6 (1.8)	2 (0.6)
Pain in extremity	5 (1.0)	7 (2.1)	6 (1.8)
Creatine kinase >10x ULN*	5 (1.0)	0 (0.0)	1 (0.3)
Blood creatine phosphokinase increased	4 (0.8)	1 (0.3)	1 (0.3)
Myalgia	4 (0.8)	1 (0.3)	2 (0.6)
Muscle spasms	3 (0.6)	7 (2.1)	2 (0.6)
Renal impairment	2 (0.4)	1 (0.3)	0 (0.0)
Blood creatinine increased	1 (0.2)	1 (0.3)	0 (0.0)
Flank pain	1 (0.2)	0 (0.0)	0 (0.0)
Muscle fatigue	1 (0.2)	0 (0.0)	0 (0.0)
Rhabdomyolysis	1 (0.2)	0 (0.0)	0 (0.0)
Blood calcium decreased	0 (0.0)	0 (0.0)	1 (0.3)
Chromaturia	0 (0.0)	0 (0.0)	1 (0.3)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (0.3)
Renal failure	0 (0.0)	1 (0.3)	0 (0.0)
Renal failure chronic	0 (0.0)	3 (0.9)	0 (0.0)

Source: Derived from the adae.xpt, addm.xpt, adlb2, datasets, available at:
url:gs:UQAAAAQAAAAAAAAABQEACrEDsQSx4w2DAQAABDAwMDCCsQKDAQEABLEHsQMBAApJbmRpY2F0aW9uAgAEVDJETQAAAQIDAwAGMiA5MDkxsQeG.
Abbreviations: Dapa, dapagliflozin; Met, metformin; N, sample size; No., number; PT, preferred term; Saxa, saxagliptin; ST+LT, short-term plus long-term treatment period; and ULN, upper limit of normal.
***Includes a subject with safety labs determined locally (i.e., not at the Central Laboratory).**

13.8. Expedited Safety Reports – Rhabdomyolysis Associated with Saxagliptin or Dapagliflozin:

The FDA Adverse Event Reporting System (FAERS) database was searched for expedited safety reports of rhabdomyolysis associated with saxagliptin and/or dapagliflozin. In total there were six cases associated with saxagliptin, 5 cases with dapagliflozin, and one with the combination of these two products. The narrative summaries of these cases were copied below (Table 38). It is acknowledged that FAERS data have several limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Table 38: Summary of Expedited Safety Reports of Rhabdomyolysis (Saxagliptin and Dapagliflozin; February 2017)

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
Saxagliptin											
7118418 (Duplicate: 7308831)	**Saxagliptin (Suspect)**	**56**	**Male**	**Japan**	**~81 (off 13 d)**	**HO, OT**	**Resolved**	**—**	**—**	**—**	**Ciprofloxacin (Primary Suspect)**
Narrative:	This case report from a post-marketing study was received on 08-Sep-2009 from the United States, referring to a 56 year-old male. This report was received via [redacted] (b) (4) Concomitant drugs have been given for unknown indication, and unknown indication. For details see section "Concomitant Drugs" at the end of this report. **A clinical investigator reported that a 56-year-old male patient was hospitalized for rhabdomyolysis, urinary tract infection, and sepsis while enrolled in a Phase II Study of saxagliptin in patients with Type 2 Diabetes. The patient started on placebo study therapy** [redacted] (b) (6) **and blinded study medication with saxagliptin or placebo 1 tablet daily starting on** [redacted] (b) (6) **to** [redacted] (b) (6) .On [redacted] (b) (6) the patient experienced urinary tract infection and suspected sepsis 108 days after start of the study medication. The patient experienced pyrexia and due to malaise, the patient was immediately taken to a hospital. On the same day, the patient was diagnosed with sepsis and was hospitalized. Urinary tract infection was suspected as the cause of the sepsis, but this was not for sure. Ciprofloxacin injection was initially administered, but inflammatory findings did not improve and markedly increased blood creatine phosphokinase (CPK) was noted. Myalgia of the upper limb was also noted and the ciprofloxacin was discontinued. Ciprofloxacin was replaced with Meropenem hydrate and the inflammatory findings improved (ciprofloxacin was considered a suspect by BMS). **On** [redacted] (b) (6) **the patient experienced suspected rhabdomyolysis 110 days after start of study medication.** Laboratory results [redacted] (b) (6)										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	revealed aspartate aminotransferase (AST) 183 IU/L, alanine aminotransferase (ALT) 84 IU/L, lactate dehydrogenase (LDH) 355 IU/L, C-reactive protein (CRP) 7.87, creatinine 0.81 mg/dL, **CPK 8691 IU/L**, and white blood cell (WBC) 65 /mm3. Although the CPK level was not completely normalized, the patient was discharged from the hospital (b) (6) and was to be followed up by resting at home. During the hospital stay, prostatic hyperplasia was also pointed out, and (b) (6) the patient was started on tamsulosin hydrochloride. During the hospital stay, blood pressure did not increase and he did not receive valsartan and amlodipine besilate. These drugs were to be reintroduced after he was discharged from the hospital. Laboratory results (b) (6) (b) (6) revealed AST 66 IU/L, ALT 90 IU/L, LDH 209 IU/L, CRP 0.63, **CPK 1194 IU/L**, and WBC 62 /mm3. Laboratory results (b) (6) revealed AST 22U/L, ALT 42U/L, LDH 180 IU/L, CRP 0.16, CPK 282 IU/L, and WBC 60 /rmn3. On (b) (6) the final confirmation was made by a blood test at the outpatient department of the investigational hospital. On the same date the events of urinary tract infection and sepsis were judged as resolved. The outcome of rhabdomyolysis was reported as unknown as of the same day. On (b) (6) the patient visited the investigational hospital for examination at Week 16, and the treatment information was obtained from the patient on this day. The study investigator stated that although diagnosis were made as sepsis and rhabdomyolysis in the diagnostic information obtained from the hospital, urine analysis result suggested urinary tract infection, and the urinary tract infection was suspected to be the cause of the sepsis. However, due to a lack of information for diagnosis, the study investigator assessed the event as suspected sepsis. Although the study medication was discontinued (b) (6) since there were reported cases of urinary tract infection as an adverse drug reaction of the study medication in the past, the study investigator assessed the causal relationship between urinary tract infection and the study medication as unknown at the time of this report. The causal relationship between the study medication and rhabdomyolysis as well as sepsis were reported as unknown. The patient's medical history was significant for hypertension, hyperlipidemia, sleep apnea syndrome, and atrioventricular block first degree. Investigator causality: The investigator assessed the causality as unknown for the events of rhabdomyolysis, urinary tract infection, and sepsis for the blinded study therapy. The events were not assessed for ciprofloxacin. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. Any follow-up information will be provided upon receipt. Follow-up information received from a post-marketing study was received on 28-sep-2009: This information was received on (b) (4) from the clinical investigator, by Bristol-Myers Squibb Company: Information on the administered drugs was updated. The onset date of rhabdomyolysis was corrected to (b) (6) On 28-Aug-2009, the following information was obtained from the hospital: On (b) (6) patient started treatment with Ciprofloxacin, 300 mg/day, for duration of 2 days. - On (b) (6) patient started treatment with Meropenem hydrate, 1,0 mg/day , for duration of 5 weeks 2 days. **On (b) (6) the event of rhabdomyolysis was judged as resolved.** On (b) (6) the patient visited the investigational hospital for follow-up. The follow-up was terminated by the study investigator as of (b) (6) because all of the events were judged as resolved. **The study investigator assessed the event of rhabdomyolysis as unrelated to the study medication (corrected from causality unknown) because of the following reasons: the level of CPK markedly increased after administration of ciprofloxacin; rhabdomyolysis has been reported as a serious adverse drug reaction with ciprofloxacin; and the study medication was completed** (b) (6) On the other hand, the study investigator assessed the events of urinary tract infection and sepsis as related to the study medication (corrected from causality unknown), because urosepsis was reported as a serious adverse event in the Investigators Brochure. Investigator causality: The events of urinary tract infection and sepsis were certainly related to the blinded study therapy. The event of rhabdomyolysis was not related to blinded study medication. Ciprofloxacin was not assessed. BBS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. BBS medical evaluation comment: This patient developed UTI and sepsis approximately 2 weeks after the last dose of blinded study therapy and rhabdomyolysis after the administration of ciprofloxacin for the urosepsis. The events were considered not related to blinded study therapy as diabetes is known to increase the risk of infections including UTI that may lead to sepsis and											

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	rhabdomyolysis due to administration of ciprofloxacin and or urosepsis.										
7308831 (Duplicate: 7118418)	**Saxagliptin 5 mg/d (Primary Suspect)**	**56**	**Male**	**Japan**	**80 (off 13 d)**	**HO**	**Resolved**	**Yes**	**Positive**	**—**	**Ciprofloxacin (Suspect)**
Narrative:	Protocol title NON-BMS/262-08-001: A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, GROUP-COMPARISION STUDY OF OPC-262 IN PATIENTS WITH TYPE 2 DIABETES (DOSE FINDING STUDY (b) (4)) This report was received via (b) (4) A clinical investigator reported that a 56-year-old male patient was hospitalized for rhabdomyolysis, urinary tract infection, and sepsis while enrolled in a Phase II Study of saxagliptin in patients with Type 2 Diabetes. **The patient started on placebo study therapy** (b) (6) **and blinded study medication with saxagliptin or placebo 1 tablet daily starting on** (b) (6) **to** (b) (6) On (b) (6) the patient experienced urinary tract infection and suspected sepsis 108 days after start of the study medication. The patient experienced pyrexia and due to malaise, the patient was immediately taken to a hospital. On the same day, the patient was diagnosed with sepsis and was hospitalized. Urinary tract infection was suspected as the cause of the sepsis, but this was not for sure. Ciprofloxacin injection was initially administered, but inflammatory findings did not improve and markedly increased blood creatine phosphokinase (CPK) was noted. Myalgia of the upper limb was also noted and the ciprofloxacin was discontinued. Ciprofloxacin was replaced with meropenem hydrate and the inflammatory findings improved (ciprofloxacin was considered a suspect by BMS). **On** (b) (6) **the patient experienced suspected rhabdomyolysis 110 days after start of study medication.** Laboratory results (b) (6) revealed aspartate aminotransferase (AST) 183 IU/L, alanine aminotransferase (ALT) 84 IU/L, lactate dehydrogenase (LDH) 355 IU/L, C-reactive protein (CRP) 7.87, creatinine 0.81 mg/dL, **CPK 8691 IU/L**, and white blood cell (WBC) 65 /mm3. Although the CPK level was not completely normalized, the patient was discharged from the hospital (b) (6) and was to be followed up by resting at home. During the hospital stay, prostatic hyperplasia was also pointed out, and on (b) (6) the patient was started on tamsulosin hydrochloride. During the hospital stay, blood pressure did not increase and he did not receive valsartan and amlodipine besilate. These drugs were to be reintroduced after he was discharged from the hospital. Laboratory results (b) (6) revealed AST 66 IU/L, ALT 90 IU/L, LDH 209 IU/L, CRP 0.63, CPK 1194 IU/L, and WBC 62 /mm3. Laboratory results (b) (6) revealed AST 22U/L, ALT 42U/L, LDH 180 IU/L, CRP 0.16, CPK 282 IU/L, and WBC 60 /mm3. On (b) (6) the final confirmation was made by a blood test at the outpatient department of the investigational hospital. On the same date the events of urinary tract infection and sepsis were judged as resolved. The outcome of rhabdomyolysis was reported as unknown as of the same day. On (b) (6) the patient visited the investigational hospital for examination at Week 16, and the treatment information was obtained from the patient on this day. The study investigator stated that although diagnosis were made as sepsis and rhabdomyolysis in the diagnostic information obtained from the hospital, urine analysis result suggested urinary tract infection, and the urinary tract infection was suspected to be the cause of the sepsis. However, due to a lack of information for diagnosis, the study investigator assessed the event as "suspected sepsis." Although the study medication was discontinued (b) (6) since there were reported cases of urinary tract infection as an adverse drug reaction of the study medication in the past, the study investigator assessed the causal relationship between urinary tract infection and the study medication as "unknown' at the time of this report. **The causal relationship between the study medication and rhabdomyolysis as well as sepsis were reported as "unknown."** The patient's medical history was significant for hypertension, hyperlipidemia, sleep apnea syndrome, and atrioventricular block first degree. Investigator causality: The investigator assessed the causality as "unknown" for the events of rhabdomyolysis, urinary tract infection, and sepsis for the blinded study therapy. The events were not assessed for ciprofloxacin. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. Follow-up information received on 26-Aug-2009 from the clinical investigator: Information on relevant test results was updated. The study investigator reported that the patient was urgently taken to the hospital on (b) (6) (b) (6) thus the CPK level before that day had not been measured. The causality assessment between the rhabdomyolysis and the study medication was												

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	reported as unknown since the discontinuation date of ciprofloxacin was unknown at the time of this report. A request letter for diagnostic information had been sent to the hospital, and the causality assessment for the rhabdomyolysis would be judged after the study investigator received a reply from the hospital. The outcome of the three events and causality assessments for all the events by the study investigator and the company remained the same. Investigator causality: The investigator assessed the causality as "unknown" for the events of rhabdomyolysis, urinary tract infection, and sepsis for the blinded study therapy. The events were not assessed for ciprofloxacin. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. 10-Sep-2009, Correction to file for protocol title only: CV181-106, A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, GROUP-COMPARISION STUDY OF OPC-262 IN PATIENTS WITH TYPE 2 DIABETES (DOSE FINDING STUDY- (b) (4) STUDY 262-08-001). Follow-up information received on (b) (4) from the clinical investigator: Information on the administered drugs was updated. **The onset date of rhabdomyolysis was corrected to** (b) (6) (b) (6) On 28-Aug-2009, the following information was obtained from the hospital: On (b) (6) drip infusion of ciprofloxacin (300 mg), once daily, was given. Between (b) (6) and (b) (6), drip infusion of meropenem hydrate (0.5 g), twice daily, was given. On (b) (6), the event of rhabdomyolysis was judged as resolved. On (b) (6), the patient visited the investigational hospital for follow-up. The follow-up was terminated by the study investigator as of (b) (6) because all of the events were judged as resolved. The study investigator assessed the event of rhabdomyolysis as unrelated to the study medication (corrected from causality unknown) because of the following reasons: the level of CPK markedly increased after administration of ciprofloxacin; rhabdomyolysis has been reported as a serious adverse drug reaction with ciprofloxacin; and the study medication was completed (b) (6) On the other hand, the study investigator assessed the events of urinary tract infection and sepsis as related to the study medication (corrected from causality unknown), because urosepsis was reported as a serious adverse event in the Investigators Brochure. Investigator causality: The events of urinary tract infection and sepsis were certainly related to the blinded study therapy. The event of rhabdomyolysis was not related to blinded study medication. Ciprofloxacin was not assessed. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. BMS medical evaluation comment: This patient developed UTI and sepsis approximately 2 weeks after the last dose of blinded study therapy and rhabdomyolysis after the administration of ciprofloxacin for the urosepsis. The events were considered not related to blinded study therapy as diabetes is known to increase the risk of infections including UTI that may lead to sepsis and the rhabdomyolysis was due to administration of ciprofloxacin and or urosepsis. Supplemental information received on 19-Oct-2009 from the clinical investigator: The elevation of AST and ALT were considered accompanying symptoms of rhabdomyolysis and not as separate adverse events. Investigator causality: The events of urinary tract infection and sepsis were certainly related and the event of rhabdomyolysis was not related to blinded study medication. Ciprofloxacin was not assessed. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to blinded study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. **Supplemental information received on 01-Mar-2010 from the clinical investigator: After completion of the study 262-08-001, the randomization code was broken. The subject (b) (6) was on OPC-262.** Investigator causality: The events of urinary tract infection and sepsis were certainly related and the event of rhabdomyolysis was not related to saxagliptin study medication. Ciprofloxacin was not assessed. BMS causality: The events of rhabdomyolysis, urinary tract infection, and sepsis were not related to saxagliptin study therapy. The event of rhabdomyolysis was possibly related; urinary tract infection and sepsis were not related to ciprofloxacin. There are no changes to the BMS comment based on the follow up information.										
7675707 (Duplicate: 7728608)	**Saxagliptin 5 mg/d (Primary Suspect)**	**71**	**Female**	**U.S.**	**? 43 Interrupted**	**HO, OT**	**Recovered**	**Yes**	**Positive**	**? Positive**	**Rosuvastatin (Suspect)**

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
					131						
Narrative:	This report was received from an AstraZeneca Representative. A physician reported that a 71-year-old female patient taking saxagliptin tablets experienced pancreatitis and rhabdomyolysis and the patient was hospitalized. It was reported that her blood sugars were in the 800's. BMS Medical Evaluation Comment: Available information is limited to make a meaningful assessment of this case. Supplemental information received from the physician on 13-Dec-2010 provided the following new information: **The patient received rosuvastatin calcium at a dose of 40 mg for hyperlipidemia that was initiated prior to** (b) (6) **The patient had received oral saxagliptin at a dose of 5 mg for type II diabetes mellitus since** (b) (6) **On** (b) (6) **the patient experienced rhabdomyolysis, hypophosphatemia, hyperglycemia, pancreatitis, nausea with vomiting and dehydration.** The patient was hospitalized as in-patient and she received intravenous (IV) fluids. The patient improved from the events, therapy with insulin glargine was initiated and rosuvastatin calcium, IV fluids, and saxagliptin were stopped. Upon discharge from the hospital, rosuvastatin calcium therapy was restarted and re-challenge was negative. The physician assessed that the events were possibly due to rosuvastatin calcium or viral infection. The patient's medical history included hypertension, gout, swelling and non-alcoholic fatty liver. The patient had no known drug allergies. BMS Medical Evaluation Comment: This patient with hyperlipidemia was diagnosed with pancreatitis, rhabdomyolysis, hypophosphatemia and hyperglycemia while on therapy with saxagliptin and rosuvastatin. **Underlying hyperlipidemia and statin therapy are significant risk factors to develop pancreatitis, considering the negative rechallenge with rosuvastatin, a participatory role of saxagliptin could not be excluded.** Hypophosphatemia could be secondary to rhabdomyolysis which is likely due to rosuvastatin therapy. Diabetic patients are prone to develop hyperglycemia in spite of anti-diabetic medications. **Supplemental information received from physician via AstraZeneca on 20-Dec-2010: It was noted that the onset date of first episode of moderate rhabdomyolysis was prior to** (b) (6) **Therapy with saxagliptin was interrupted on** (b) (6) **and the patient recovered from the event on the same day. Therapy with saxagliptin was restarted. The patient received oral rosuvastatin calcium at a daily dose of 40 mg prior to** (b) (6) **The patient experienced nausea, vomiting and had poor intake but was febrile. Since** (b) (6) **the patient had changes in urine color, muscle weakness, muscle pain and elevated cholesterol. No complications were noted. The event rhabdomyolysis recurred again (2nd episode) on** (b) (6) **Therapy with rosuvastatin calcium was interrupted on** (b) (6) **. Again therapy was saxagliptin was stopped on** (b) (6) **and noted that dechallenge was positive.** Computed tomography of abdomen was normal on (b) (6) It was noted that creatinine kinase was 4735 on (b) (6) after withdrawal of drug it was 800 and on (b) (6) it was 813. On (b) (6) thyroid stimulating hormone was 1.138 and blood sugar was 11.7%. Serum creatinine was 1.69 on (b) (6) and 1.05 on (b) (6) . On (b) (6) , laboratory investigation showed positive urine myoglobin. The patient was treated with insulin and intravenous fluids and noted that the patient was improving. At the time of report, the patient had renal impairment (acute renal failure) since (b) (6) , hypothyroidism, and diabetes were continuing and were considered as risk factors. Therapy with rosuvastatin calcium was restarted. At the time of report, the patient was still hospitalized and considered nausea, vomiting and had poor intake must be from viral infection and still cholesterol was elevated. At the time of report, the patient was recovering from event rhabdomyolysis and had not recovered from pancreatitis. **According to the reporter, the events may have been from (possibly) the saxagliptin therapy (causal relationship).** Her medical history included dehydration, nausea, vomiting and hypophosphatemia. The patient had no known drug allergies. BMS Medical evaluation comment remained unchanged based on the follow up information. Supplemental information received from the physician on (b) (6) included the following: The patient presented to the emergency department with complaint of nausea, vomiting, weakness and hyperglycemia. The patient stated that after working the polls a few days prior to presentation she began to feel like she was coming down with something. She noticed a slight metallic taste in her mouth and decreased appetite. She continued to eat and drink small amounts. She continued to take her medications and went about her business as usual. She continued to feel somewhat ill but remained very functional and still attended to her daily activities until Thursday or Friday prior to admission when she began to feel more nauseous and was really not able to eat or drink very much. The patient continued											

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	to drink small amounts of liquids. By the weekend just prior to admission, the patient began to have some actual vomiting and was unable to keep anything down for a period of a couple of days. She denied any fevers or chills and had no real abdominal pain, just intermittent nausea after she tried to eat something. Her emesis consisted of just food contents, no coffee grounds or hematemesis. She continued to move her bowel normally throughout this time interval. The patient had no melena or hematochezia and no diarrhea. She was not checking her blood sugars during this time. The patient called the day before admission and stated that she was sick and nauseous and had been vomiting. The patient was suggested promethazine hydrochloride suppositories but was told that if she did not get immediate relief she would be required to visit the emergency room for further evaluation. **The patient ended up in the emergency room later that day, presenting with a blood sugar in excess of 700. Her creatine phosphokinase (CPK) was elevated at 4000 with negative cardiac index.** Her lipase was initially mildly elevated at 30, but it then was repeated at a higher level of 80 later. Her lactic acid level was slightly deviated however, her bicarbonate remained relatively normal. Her serum ketones were elevated. She denied any unusual myalgias or arthralgias. She denied any high fevers, chills or night sweats and had no other real constitutional symptoms. The patient's blood urea nitrogen was 52 and her creatinine was 0.24. Her serum phosphorus ended up being extremely low at 0.8. The patient was admitted to the intensive care unit and was seen in consultation by endocrinology and nephrology. She was started on aggressive intravenous replacement and insulin infusion. The patient's blood sugars responded nicely and gradually come down. Her oral hypoglycemic were discontinued as her statin in light of her elevated CPK. The patient's creatinine recovered once her intravascular volume was replaced. The patient was seen in consultation by gastroenterology regarding her possible pancreatitis. Her lipase eventually returned to normal. She was able to be started on a diet which she slowly tolerated. Her initial oral intake was very poor but then this began to improve. She was eventually transitioned to subcutaneously insulin therapy. She was ambulating and feeling better. By (b) (6) plans were made for discharge to home. The patient was instructed to follow up within 1 or 2 weeks. The patient's discharge medications included ciprofloxacin hydrochloride 250mg orally 2 times daily, rosuvastatin calcium 40mg orally at bedtime, insulin glargine 36 units subcutaneously at bedtime, insulin aspart 10 units subcutaneously 3 times daily before meals, pantoprazole sodium 40mg orally daily, levothyroxine sodium 88 microgram orally daily and atenolol 25mg orally daily. The patient's discharge diagnosis included Diabetic hyperosmolar ketosis, uncontrolled diabetes mellitus type 2, acute renal failure, rhabdomyolysis, possible pancreatitis, hypothyroidism, hyperlipidemia, gout, profound hypophosphatemia and methicillin sodium-resistant Staphylococcus epidermitis urinary tract infection. The events of diabetic hyperosmolar ketosis, acute renal failure, methicillin sodium-resistant Staphylococcus epidermitis urinary tract infection were added as additional events and were considered to be medically significant. On 03-Jun-2011, file 15697485 was identified to be a duplicate of this case. All information from file 15697485 has been added to this case. File 15697485 will be voided.										
7728608 (Duplicate: 7675707)	**Saxagliptin (Suspect)**	**71**	**Female**	**U.S.**	**?43 Interrupted 137**	**HO, LT, OT**	**Resolved**	**Yes**	**Positive**	**—**	**Rosuvastatin (Primary Suspect)**
Narrative:	This report was received from an AstraZeneca Representative. A physician reported that a 71-year-old female patient taking saxagliptin tablets experienced pancreatitis and rhabdomyolysis and the patient was hospitalized. It was reported that her blood sugars were in the 800's. BMS Medical Evaluation Comment: Available information is limited to make a meaningful assessment of this case. Supplemental information received from the physician on 13-Dec-2010 provided the following new information: The patient received rosuvastatin calcium at a dose of 40 mg for hyperlipidemia that was initiated prior to (b) (6). The patient had received oral saxagliptin at a dose of 5 mg for type II diabetes mellitus since (b) (6). On (b) (6), the patient experienced rhabdomyolysis, hypophosphatemia, hyperglycemia, pancreatitis, nausea with vomiting and dehydration. The patient was hospitalized as in-patient and she received intravenous (IV) fluids. The patient improved from the events, therapy with insulin glargine was initiated and rosuvastatin calcium, IV fluids, and saxagliptin were stopped. Upon discharge from the hospital, rosuvastatin calcium therapy was restarted and rechallenge was negative. The										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	physician assessed that the events were possibly due to rosuvastatin calcium or viral infection. The patient's medical history included hypertension, gout, swelling and non-alcoholic fatty liver. The patient had no known drug allergies. BMS Medical Evaluation Comment: This patient with hyperlipidemia was diagnosed with pancreatitis, rhabdomyolysis, hypophosphatemia and hyperglycemia while on therapy with saxagliptin and rosuvastatin. Underlying hyperlipidemia and statin therapy are significant risk factors to develop pancreatitis, considering the negative rechallenge with rosuvastatin, a participatory role of saxagliptin could not be excluded. Hypophosphatemia could be secondary to rhabdomyolysis which is likely due to rosuvastatin therapy. Diabetic patients are prone to develop hyperglycemia in spite of anti-diabetic medications. **Supplemental information received from physician via AstraZeneca on 20-Dec-2010: It was noted that the onset date of first episode of moderate rhabdomyolysis was prior to (b) (6) Therapy with saxagliptin was interrupted on (b) (6) and the patient recovered from the event on the same day. Therapy with saxagliptin was restarted.** The patient received oral rosuvastatin calcium at a daily dose of 40 mg prior to (b) (6). The patient experienced nausea, vomiting and had poor intake but was febrile. Since (b) (6) the patient had changes in were noted. The event rhabdomyolysis recurred again (2nd episode) on (b) (6) Therapy with rosuvastatin calcium was interrupted on (b) (6) Again therapy was saxagliptin was stopped on (b) (6) and noted that dechallenge was positive. Computed tomography of abdomen was normal on (b) (6) It was noted that creatinine kinase was 4735 on (b) (6), after withdrawal of drug it was 800 and on (b) (6) it was 813. On (b) (6), thyroid stimulating hormone was 1.138 and blood sugar was 11.7%. Serum creatinine was 1.69 on (b) (6) and 1.05 on (b) (6) On (b) (6) laboratory investigation showed positive urine myoglobin. The patient was treated with insulin and intravenous fluids and noted that the patient was improving. At the time of report, the patient had renal impairment (acute renal failure) since (b) (6), hypothyroidism, and diabetes were continuing and were considered as risk factors. Therapy with rosuvastatin calcium was restarted. At the time of report, the patient was still hospitalized and considered nausea, vomiting and had poor intake must be from viral infection and still cholesterol was elevated. At the time of report, the patient was recovering from event rhabdomyolysis and had not recovered from pancreatitis. According to the reporter, the events may have been from (possibly) the saxagliptin therapy (causal relationship). Her medical history included dehydration, nausea, vomiting and hypophosphatemia. The patient had no known drug allergies. BMS Medical evaluation comment remained unchanged based on the follow up information. Supplemental information received from the physician on (b) (6) included the following: The patient presented to the emergency department with complaint of nausea, vomiting, weakness and hyperglycemia. The patient stated that after working the polls a few days prior to presentation she began to feel like she was coming down with something. She noticed a slight metallic taste in her mouth and decreased appetite. She continued to eat and drink small amounts. She continued to take her medications and went about her business as usual. She continued to feel somewhat ill but remained very functional and still attended to her daily activities until Thursday or Friday prior to admission when she began to feel more nauseous and was really not able to eat or drink very much. The patient continued to drink small amounts of liquids. By the weekend just prior to admission, the patient began to have some actual vomiting and was unable to keep anything down for a period of a couple of days. She denied any fevers or chills and had no real abdominal pain, just intermittent nausea after she tried to eat something. Her emesis consisted of just food contents, no coffee grounds or hematemesis. She continued to move her bowel normally throughout this time interval. The patient had no melena or hematochezia and no diarrhea. She was not checking her blood sugars during this time. The patient called the day before admission and stated that she was sick and nauseous and had been vomiting. The patient was suggested promethazine hydrochloride suppositories but was told that if she did not get immediate relief she would be required to visit the emergency room for further evaluation. The patient ended up in the emergency room later that day, presenting with a blood sugar in excess of 700. Her creatine phosphokinase (CPK) was elevated at 4000 with negative cardiac index. Her lipase was initially mildly elevated at 30, but it then was repeated at a higher level of 80 later. Her lactic acid level was slightly deviated however, her bicarbonate remained relatively normal. Her serum ketones were elevated. She denied any unusual myalgias or arthralgias. She denied any high fevers, chills or night sweats and had no other real constitutional symptoms. The patient's blood urea nitrogen was 52 and										

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	her creatinine was 0.24. Her serum phosphorus ended up being extremely low at 0.8. The patient was admitted to the intensive care unit and was seen in consultation by endocrinology and nephrology. She was started on aggressive intravenous replacement and insulin infusion. The patient's blood sugars responded nicely and gradually come down. Her oral hypoglycemic were discontinued as her statin in light of her elevated CPK. The patient's creatinine recovered once her intravascular volume was replaced. The patient was seen in consultation by gastroenterology regarding her possible pancreatitis. Her lipase eventually returned to normal. She was able to be started on a diet which she slowly tolerated. Her initial oral intake was very poor but then this began to improve. She was eventually transitioned to subcutaneously insulin therapy. She was ambulating and feeling better. By (b) (6), plans were made for discharge to home. The patient was instructed to follow up within 1 or 2 weeks. The patient's discharge medications included ciprofloxacin hydrochloride 250mg orally 2 times daily, rosuvastatin calcium 40mg orally at bedtime, insulin glargine 36 units subcutaneously at bedtime, insulin aspart 10 units subcutaneously 3 times daily before meals, pantoprazole sodium 40mg orally daily, levothyroxine sodium 88 microgram orally daily and atenolol 25mg orally daily. The patient's discharge diagnosis included Diabetic hyperosmolar ketosis, uncontrolled diabetes mellitus type 2, acute renal failure, rhabdomyolysis, possible pancreatitis, hypothyroidism, hyperlipidemia, gout, profound hypophosphatemia and methicillin sodium-resistant Staphylococcus epidermitis urinary tract infection. The events of diabetic hyperosmolar ketosis, acute renal failure, methicillin sodium-resistant Staphylococcus epidermitis urinary tract infection were added as additional events and were considered to be medically significant. On 03-Jun-2011, file 15697485 was identified to be a duplicate of this case. All information from file 15697485 has been added to this case. File 15697485 will be voided. Report received by AstraZeneca from BMS.										
8178403	**Saxagliptin/Metformin XR (Primary Suspect)**	**—**	**Male**	**U.S.**	**—**	**OT**	**—**	**—**	**—**	**—**	**—**
Narrative:	Seriousness criterion: Important medical event This case was received via BMS sales representative. A physician reported that a male patient developed rhabdomyolysis and bone tenderness while on therapy with saxagliptin + metformin hydrochloride.										
9106185	**Saxagliptin or Placebo (Suspect)**	**61**	**Female**	**U.S.**	**742**	**HO**	**Continuing**	**—**	**—**	**—**	**Atorvastatin (Primary Suspect) Metformin (Suspect)**
Narrative:	This is a (b) (4) interventional study report based on information received (b) (4) from Bristol-Myers Squibb company, manufacturer control number (b) (4) This report was received from TIMI study group (Enrollment code: E7865007). A clinical investigator reported that a 61-year-old Black female patient was hospitalized due to mild/grade I dehydration, mild/grade I renal failure and rhabdomyolysis while enrolled in a clinical study involving saxagliptin for type II diabetes mellitus. **The patient was diagnosed with diabetes mellitus in (b) (6), and was initiated with the double blinded study therapy (saxagliptin/placebo) on (b) (6)** She was also on background therapy with insulin glargine at a dose of 80 international units (IU), insulin aspart at a dose of 25 IU and metformin hydrochloride at a dose of 2000 mg. Background therapies were started before randomization and was continuing at the time of this report. On (b) (6), the dose of insulin aspart was decreased to 10 IU and remained ongoing. The onset date of the event dehydration was reported as (b) (6). **On (b) (6), the patient was hospitalized due to dehydration and due to worsening muscle aches for a week. Creatine phosphokinase (CPK) levels were elevated in excess of 14,000. The patient was aggressively hydrated with intravenous fluids with improvement in creatinine. On (b) (6) the patient was diagnosed with acute renal failure secondary to rhabdomyolysis due to statin use.** On (b) (6) the patient had recovered from the event of dehydration and discharged from the hospital on the same day. At the time of this report, the event of renal failure was not resolved. The study therapy was continued, at the time of this report. The events were not related to study procedure. The event of renal failure was considered event of										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	special interest. The patient's serum creatinine level doubled when compared to the baseline. Intervention was required. There were no other medications and no other potential causes that predispose to the occurrence of this event. The patient's medical history included hypertension, dyslipidemia, myocardial infarction on (b) (6), coronary artery bypass graft in 1995 and angina pectoris (angina with moderate exertion). Her additional concomitant medications included angiotensin converting enzyme inhibitor, statin, nitrates, beta blocker, diuretics, calcium antagonist and adenosine diphosphate antagonist. Investigator's causality assessment: The events of dehydration and renal failure were not related to blinded study therapy and background therapy with insulin glargine, insulin aspart and metformin hydrochloride. Causality for the event rhabdomyolysis was not provided. BMS causality assessment: The events of dehydration, renal failure and rhabdomyolysis were not related to blinded study therapy and background therapy with insulin glargine, insulin aspart and metformin hydrochloride. **Supplemental information received on 31Jan2013 and 05Feb2013 from the clinical investigator noted that the patient was also taking atorvastatin calcium. Due to the event rhabdomyolysis, therapy with atorvastatin calcium (statin) was stopped on an unspecified date. At the time of reporting, the patient had not yet recovered from the event rhabdomyolysis.** According to the investigator, the event rhabdomyolysis was related to atorvastatin calcium. Based on the information, atorvastatin calcium was elevated as non-study suspect drug. Investigator's causality assessment: Dehydration and renal failure were not related to blinded study therapy and background therapy with insulin glargine, insulin aspart and metformin hydrochloride. Rhabdomyolysis was not related (previously not assessed) to blinded study therapy and background therapy with insulin glargine, insulin aspart and metformin hydrochloride. Rhabdomyolysis was related to atorvastatin calcium. Causality for the events dehydration and renal failure with atorvastatin calcium were not provided. BMS Medical Comment: Use of statin drug had predisposed this patient to develop rhabdomyolysis which resulted in dehydration and renal failure.										
11537098	**Saxagliptin/Metformin ER 5 mg/1000 mg/d (Primary Suspect)**	**—**	**Male**	**U.S.**	**—**	**OT**	**Continuing**	**Yes**	**No**	**—**	**Exenatide ER (Suspect)**
Narrative:	A report has been received from a nurse concerning a male patient. Medical history of the patient was not reported. There was no information on the concomitant medication. He was taking oral Kombiglyze XR (metformin, saxagliptin) 5/1000 mg daily for type 2 diabetes. **Six-eight weeks ago, he began experiencing myolysis (preferred term: rhabdomyolysis), defined as muscle weakness (preferred term: muscular weakness) and muscle pain (preferred term: myalgia).** The nurse further explained that he had hip pain (preferred term: arthralgia), numbness (preferred term: hypoaesthesia) and tingling (preferred term: paraesthesia), and feelings of neuropathy (preferred term: neuropathy peripheral) like he doesn't have legs (preferred term: hypoaesthesia). His blood glucose levels were also not well controlled on Kombiglyze XR (preferred term: diabetes mellitus inadequate control). On (b) (6) (three weeks ago), his Kombiglyze XR was discontinued and the next day (b) (6) he began subcutaneous Bydureon (exenatide) 2 mg once weekly. The symptoms worsened (preferred term: condition aggravated) upon the switch. He was given a steroid injection last week but it did not improve the symptoms. Treatment with Bydureon was continued. The event of muscle pain and muscle weakness was ongoing, while outcome of the other events was unknown. Company physician considered myolysis and feelings of neuropathy to be medically important and rest of the events to be nonserious.										
12060407	**Saxagliptin 5 mg/d**	**70**	**Male**	**Japan**	**147**	**OT**	**—**	**Yes**	**—**	**—**	**Glimepiride**
Narrative:	A report has been received from a physician via medical representative from Kyowa Hakko Kirin concerning a 70 year old, male patient. Medical history of the patient was not reported. His concomitant medications included glimepiride. On (b) (6) he started treatment with oral Onglyza (saxagliptin) 5 mg daily for type 2 diabetes mellitus. **On (b) (6) his blood creatine phosphokinase increased, rhabdomyolysis (preferred term: rhabdomyolysis) considered. Onglyza was discontinued on (b) (6) The outcome of rhabdomyolysis was unknown.** The reporter considered rhabdomyolysis to be nonserious and not related to Onglyza. According to company physician event term was updated to be medically important. Summary of follow-up										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	information received by AstraZeneca/MedImmune on 10-Feb-2016 from physician: indication and dosing details provided for Onglyza, event start date updated, causality provided, narrative was amended.										
12532127	**Saxagliptin 2.5-5 mg/d**	**68**	**Male**	**Japan**	**94**	**DE, HO, OT**	**Death**	**No**	**—**	**—**	**Atorvastatin**
Narrative:	A report has been received from a Physician concerning a 68 year old, Male subject, Weight: 62.3 Kilograms, enrolled in study ONG01; Onglyza Non-interventional study (Special investigation, Post-Marketing). The patient's concurrent diseases included diabetic neuropathy, renal impairment, hepatic function disorder, cerebral infarction, hepatopathy alcoholic, hypertension, prostatic hypertrophy and insomnia. Patient had drinking habit and no smoking habit. The patient had history of diabetes treatment with sulfonylurea drug, alpha-glucosidase inhibitor, and patient had dietary instructions. No allergic history. Concomitant medications included dutasteride, naftopidil, acetylsalicylic acid, amlodipine, valsartan, and zolpidem tartrate. On an unknown date, the patient was diagnosed with T2D. On an unknown date (before initiation of Onglyza tablets) lab results showed white blood cells 7200/mcl, red blood cells 4880000/mcl, hemoglobin 15 g/dL, platelet 479000/mcl, HbA1c(NGSP) 6.7 %, serum creatinine 1.1 mg/dL, AST(GOT) 24 IU/L, ALT(GPT) 25 IU/L, ALP 161 IU/L, gamma-GTP 51 IU/L, TBL 0.7 mg/dL, LDH 170 IU/L, HDL cholesterol 62 mg/dL, LDL cholesterol 147 mg/dL and triglycerides 198 mg/dL. Blood pressure systolic was 120 mmHg and blood pressure diastolic showed 66 mmHg. On [(b) (6)] treatment with Onglyza (saxagliptin hydrate) tablets 2.5 mg/day was started for type 2 diabetes mellitus. **On an unknown date, Atorvastatin (atorvastatin calcium hydrate) was administered for treatment for hypercholesterolaemia.** On [(b) (6)] the patient experienced high gamma-GT (preferred term: gamma-glutamyltransferase increased). Laboratory results on this day included BUN 17.7mg/dL, Cr 0.99 mg/dl, AST 52 IU/l, ALT 35 IU/L and gamma-GTP 369IU/L. On [(b) (6)], **Onglyza dosage was increased to 5 mg/day. On** [(b) (6)] **the patient developed rhabdomyolysis (preferred term: rhabdomyolysis). CPK revealed 1136 IU/L. The patient fell down (preferred term: fall) due to the difference in level in front of the entrance probably because of his left paresis. He had a bruise in the low back (preferred term: contusion) and became unable to move (preferred term: hypokinesia) and was admitted to the hospital for treatment. The high CPK may be due to the bruise. Treatment with Onglyza tablets was being continued.** On [(b) (6)], the rhabdomyolysis recovered with CPK 39 IU/L. On [(b) (6)] the patient experienced mild renal impairment (preferred term: renal impairment) and mild hepatic function abnormal (preferred term: hepatic function abnormal). Laboratory results showed BUN 26mg/dL, Cr 1.6mg/dl, AST 136IU/l, ALT 82IU/l and gamma-GTP 148IU/l. On [(b) (6)] laboratory results included BUN 21.1mg/dL and Cr 1.1mg/dl. **On** [(b) (6)] **28-day dose of Onglyza was prescribed. The patient experienced death by a disease (cause undetermined)(preferred term: death) which started during** [(b) (6)] On [(b) (6)] the patient was found dead in his home alone two days after his death. The cause of death was unknown and can be captured with alcohol dependence. Autopsy perfumed was unknown. The patient talked to his older sister on the phone half-day before his death and nothing special to be noted. No action was taken with the study drug until patient's death. On an unknown date, administration of Atorvastatin was discontinued due to unspecified reason. At the time of reporting, the event of high gamma-GT was ongoing. At the time of reporting, the event of renal impairment was improving. The outcome of the event of hepatic function disorder, fell down, bruise in the low back and became unable to move were unknown at the time of reporting. The reporting physician considered the event of rhabdomyolysis was serious due to hospitalization. The reporting physician considered the event of death by a disease (cause undetermined) was serious due to death. The reporting physician considered the event of renal impairment was serious.										
Dapagliflozin											
9779478 (Duplicate: 9782299; 10450284)	**Dapagliflozin 10 mg/d or Placebo (Suspect)**	**—**	**—**	**U.S.**	**117**	**HO, OT**	**—**	**—**	**—**	**—**	**Daptomycin (Primary Suspect),**

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
											Rosuvastatin (Suspect), Metformin (Suspect), Liraglutide (Suspect)
Narrative:	A spontaneous case for Cubicin was received on 02-Dec-2013 from an investigator by license partner (AstraZeneca case ID 2013SE86949) via BMS and received at Cubist on 20-Dec-2013. A 53 year old white female (patient id (b) (6)) had developed acute rhabdomyolysis, renal insufficiency, elevated creatine kinase, carpal tunnel decompression, osteomyelitis, systemic inflammatory response syndrome and cellulitis right hand during treatment with Cubicin (daptomycin), **Dapagliflozin (code not broken)**, metformin hydrochloride, Victoza (liraglutide), Novolog (insulin aspart) and **Crestor (rosuvastatin calcium)**. This patient was hospitalized due to moderate/grade II inflammation, complication from carpal tunnel surgery (carpal tunnel surgery) while enrolled in a AstraZeneca clinical study with the Protocol title (D1693C00001): Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes. On an unknown date, the patient started treatment with intravenous infusion of Cubicin (dose and frequency unknown) for an unspecified indication. Relevant medical history included hypertension, diuretic therapy, neuropathy , potassium deficiency, (coagulation disorder), vitamin B deficiency, immune system disorder, pain, tooth extraction, cellulitis, inflammation, myocardial infarction (b) (6) coronary artery bypass grafting (b) (6) vascular disease (angiopathy), retinopathy and congestive heart failure, high cholesterol, kidney disease and type II diabetes mellitus since (b) (6). The patient had been receiving metformin hcl at 500 mg twice per day, orally, liraglutide at 1.8 mg per day and insulin aspart at 60 IU thrice per day were started prior to the initiation of study therapy and was continuing at the time of this report. The patient initiated placebo run in phase on (b) (6) **Blinded study therapy with dapagliflozin 10 mg daily or matching placebo was initiated on** (b) (6) Concomitant medications included, oral carvedilol for hypertension, oral metolazone as a diuretic therapy, oral gabapentin for neuropathy, potassium chloride for potassium deficiency, oral aspirin (acetyl salicylic acid) for blood thinning (coagulation disorder), Metanx (L- methylfolate) for vit. B deficiency, oral vitamin C for unknown indication, oral hydrocodone for pain, oral amoxicillin as antibiotic for tooth extraction, oral clindamycin for cellulitis, IM methylprednisolone for inflammation, SC betamethasone for inflammation, Pneumovax (pneumonia vaccination) for prophylaxis, calcium for calcium deficiency and vitamin D3 for vitamin deficiency. Onset date of the event inflammation complication from carpal tunnel surgery was provided as (b) (6) On (b) (6), the patient had inflammation on her right hand and complications from carpal tunnel surgery. She consulted the physician on (b) (6) and was admitted in hospital for possible infection. The patient had swelling, pain and redness of right wrist and hand. She was treated with intravenous antibiotics. The physician diagnosed the events of carpal tunnel decompression, osteomyelitis, cellulitis of right hand and systemic inflammatory response syndrome by evaluation of X-ray, MRI of right hand and blood work in the hospital. The patient was admitted overnight. Microbiology culture was also done on (b) (6) On (b) (6), magnetic resonance imaging of upper extremity of wrist showed bone marrow edema involving the hook of the hamate with areas of bone destruction involving the hook of the hamate. On (b) (6) erythrocyte sedimentation rate was 111 (reference range 0-20 mm/h); Chest X-ray on (b) (6) showed cardiomegaly, left peripherally inserted central catheter (PICC or PIC line) with tip in superior vena cava (SVC). Causes of cellulitis were not described in records. Toxicology was done on (b) (6) monitoring Vancomycin trough (toxicology) at 15.6 (reference range: 10.0-20.0 ug/dL), immature granulocyte (IG) at 0 percent (reference range: 0-2) and IG number 0.0 k/uL On (b) (6), the patient was given intravenous saline 0.9 percent solution 250ml with total daily dose of 250ml every 12 hours, intravenous vancomycin 1000mg sol 1.25g with total daily dose of1000mg every 12 hours, intravenous										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	sodium chloride with total daily dose of 100ml every 6 hours and intravenous ampicillin sulbactam with total daily dose of 3.0 g every 6 hours for osteomyelitis, oral saccharomyces boulardii 17 at a total daily dose of 250 mg twice daily as probiotic, oral hydrocodone at a total daily dose of 7.5 mg every 6 hours for pain and oral acetaminophen at a total daily dose of 325 mg every 6 hours for pain. The patient was discharged home from the hospital on (b) (6) Final discharge diagnosis was reported to be cellulitis of right hands with tenosynovitis, osteomyelitis of right hand and systemic inflammatory response syndrome due to infectious process without acute organ dysfunction. Action taken with the blinded study drug and other suspect drugs in respect to the events was reported to be dose not changed. **The patient was hospitalized due to acute rhabdomyolysis (Intensity: Severe), elevated creatine kinase level (Intensity: Severe) and renal insufficiency (intensity: moderate) on (b) (6) The events were also reported as medically significant events. Blinded study therapy with dapagliflozin 10 mg daily or matching placebo was interrupted on (b) (6) in regard to the events. The patient had also received non study suspect drugs Cubicin and oral rosuvastatin calcium 5 mg. The patient had been admitted for elevated creatine kinase. The patient had little weakness and denied muscle pain and no other associated symptoms. It was reported that the patient had acute rhabdomyolysis due to daptomycin while she received rosuvastatin calcium. Therapy with rosuvastatin was stopped on (b) (6) per hospital records, and the patient switched Cubicin to intravenous ceftriaxone with sodium chloride, one dose. Creatine kinase was noted at 14772 (Ref: 29-167 IU/L) on (b) (6), 8211 on (b) (6) and 3239 on (b) (6) There were no other labs related to the rhabdomyolysis.** The patient had not described symptoms other than dry mouth. She was assessed at the hospital and discharged on (b) (6) and was treated with change of antibiotics. She was discharged with oral antibiotics cephalexin, but not for the rhabdomyolysis. The patient had not received other treatment for this event. Outcome was unknown at the time of this report because patient was still believed to not be fully recovered. As per medical records, discharge summary stated the patient did not develop renal failure. However the investigator felt that the patient had renal insufficiency caused by rhabdomyolysis per review of records. The patient did not have any symptoms; she was not treated for this specific event. On (b) (6) labs results included, creatnine was noted 1.3 (Ref: 0.6-1.1 mg/dL, BUN was 22.7 (Ref: 9.8-20.1 mg/dL) and BUN/Cr Ratio is 19.6 with no reference range listed, but listed as normal; on (b) (6) BUN was 21.7 (Ref: 9.8-20.1 mg/dL). Urinalysis was performed on the patient with all negative and normal results on (b) (6) eGFR values on (b) (6) was 51 and (b) (6) was 57 with reference rang of [more than/equal to 60] mL/min/1.73 m2. The patient will be coming for follow up at site on 06-Jan-2014. Investigator causality assessment: The event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, acute rhabdomyolysis, elevated creatine kinase level and renal insufficiency were not related to blinded study therapy (dapagliflozin vs Placebo), metformin hcl, liraglutide and insulin aspart. Causality was not provided for daptomycin and oral rosuvastatin calcium. The event inflammation complication from carpal tunnel surgery was considered as event of special interest: cellulitis of right hand with tenosynovitis and osteomyelitis of right hand. Systemic inflammatory response syndrome (SIRS) due to infectious process without acute organ dysfunction was noted. The investigator considered it to be probably related to post-surgical change (history); however, added that osteomyelitis could not be excluded. Thickened synovial tissues within the posterior aspect of the carpal coronal were consistent with synovitis. Inflammatory synovitis or infection could not be excluded. Also, the reporter stated that small fluid collection deep to the flexor profundus tendon was within the carpal tunnel. The reporter considered it as postsurgical fluid collection, cystic synovial fluid, atypical appearing tenosynovitis or small focus of infection/abscess. The investigator also stated that it was flexor tendinopathy versus reactive edema from adjacent synovial process. Mild tendinopathy of the extensor carpi ulnaris with mild synovitis was also reported. Diffuse nonspecific edema, possible cellulitis was described. Wrist joint effusions were also reported. BMS Causality assessment: The event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, acute rhabdomyolysis, elevated creatine kinase level and renal insufficiency were not related to blinded study therapy (dapagliflozin vs Placebo), metformin hcl, liraglutide and insulin aspart. The event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, elevated										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	creatine kinase level and renal insufficiency were not related to daptomycin and oral rosuvastatin calcium 5 mg and acute rhabdomyolysis was possibly related to daptomycin and oral rosuvastatin calcium 5 mg. Company comment: The serious (hospitalization and medically significant) events of rhabdomyolysis, elevated creatine kinase and renal insufficiency are listed whereas serious (hospitalization) events of systemic inflammatory response syndrome, cellulitis, carpal tunnel decompression and osteomyelitis are unlisted in the current CCDS for daptomycin used for the treatment of an unspecified indication. Causality was not provided by the investigator with daptomycin. The investigator felt that the patient had renal insufficiency caused by rhabdomyolysis per review of records. BMS Causality assessment: The event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, acute rhabdomyolysis, elevated creatine kinase level and renal insufficiency were not related to blinded study therapy (dapagliflozin vs Placebo), metformin hcl, liraglutide and insulin aspart. The event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, elevated creatine kinase level and renal insufficiency were not related to daptomycin and oral rosuvastatin calcium 5 mg and acute rhabdomyolysis was possibly related to daptomycin and oral rosuvastatin calcium 5 mg. Cubist considered the events of rhabdomyolysis, elevated creatine kinase and renal insufficiency as possibly related to daptomycin and considered the events of systemic inflammatory response syndrome, cellulitis, carpal tunnel decompression and osteomyelitis as not related to daptomycin. The events of renal insufficiency and CPK increased are considered as a part of rhabdomyolysis but were retained as separate events as reported by BMS. The related events of rhabdomyolysis, with symptoms of elevated creatine kinase and renal insufficiency are considered as listed in the CCDS for daptomycin. The medical history of renal insufficiency, use of multiple medications and specially statin along with daptomycin therapy are confounders for this case.										
9782299 (Duplicate: 9779478; 10450284)	**Dapagliflozin 10 mg/d or Placebo (Suspect)**	**53**	**Female**	**U.S.**	**117**	**HO, OT**	**Recovered**	**Interrupted**	**—**	**—**	**Daptomycin (Primary Suspect), Rosuvastatin (Suspect), Metformin (Suspect), Liraglutide (Suspect)**
Narrative:	Case number PHHY2013US151574, is an initial spontaneous report from an investigator via marketing partner (AstraZeneca case ID: 2013SE86949) via license partner Cubist Pharmaceutical Inc. (Mfr. control number 2013CBST001401) received on (b) (4) and forwarded to Novartis on 24 Dec 2013, with combined follow up reports received from an investigator via marketing partner (AstraZeneca case ID: 2013SE86949) via BMS via license partner (Cubist Pharmaceutical Inc., Mfr. control number 2013CBST001401) on 28 Mar 2014, 03 Apr 2014 and 18 Jun 2014 and forwarded to Novartis on 08 Sep 2014, with a follow up report from an investigator via marketing partner (AstraZeneca case ID: 2013SE86949) via license partner Cubist Pharmaceutical Inc. (Mfr. control number 2013CBST001401) received on 26 Mar 2015 and forwarded to Novartis on 10 Apr 2015. This report refers to a 53 year old female patient who was enrolled in a AstraZeneca clinical study with the Protocol title (D1693C00001): Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double Blind, Placebo Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes. The patient medical history included diuretic therapy, myocardial infarction, coronary artery bypass grafting, tooth extraction and kidney disease. Current conditions included hypertension, neuropathy, potassium deficiency, coagulation disorder,										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	vitamin B deficiency, immune system disorder, pain, cellulitis, inflammation, vascular disease (angiopathy), retinopathy, congestive heart failure, high cholesterol, type II diabetes mellitus and urinary tract infection. This poly-medicated patient had been receiving metformin hydrochloride (manufacturer unknown) orally, for the treatment of type 2 diabetes mellitus from an unknown date at 500 mg twice per day. The patient received Victoza (liraglutide) subcutaneously, for the treatment of type 2 diabetes mellitus from an unknown date at 1.8 mg per day. The patient also received Novolog (insulin aspart) for the treatment of type 2 diabetes mellitus from an unknown date at a dose of 60 IU thrice per day. These drugs were started prior to the initiation of study therapy and treatment was continuing at the time of this report. The patient initiated placebo run in phase on (b) (6) (previously reported as (b) (6)) and interrupted on (b) (6) Patient received blinded study therapy with dapagliflozin (manufacturer unknown) tablet orally, 10 mg daily or matching placebo was initiated on (b) (6) On an unknown date, the patient started treatment with intravenous infusion of Cubicin (daptomycin) (dose and frequency unknown) for the treatment of osteomyelitis (off label use). Onset date of the event inflammation complication from carpal tunnel surgery was provided as (b) (6) On (b) (6) the patient had inflammation on her right hand and complications from carpal tunnel surgery. She consulted the physician on (b) (6), and was admitted in hospital for possible infection. The patient had swelling, pain and redness of right wrist and hand. She was treated with intravenous antibiotics. The physician diagnosed the events of carpal tunnel decompression, osteomyelitis, cellulitis of right hand and systemic inflammatory response syndrome by evaluation of X ray, MRI of right hand and blood work in the hospital. The patient was admitted overnight (b) (6) Microbiology culture was also done on (b) (6) Relevant laboratory were culture negative on (b) (6) On (b) (6) magnetic resonance imaging of upper extremity of wrist showed bone marrow edema involving the hook of the hamate with areas of bone destruction involving the hook of the hamate. On (b) (6) erythrocyte sedimentation rate was 111 (reference range 0 to 20 mm/h); Chest X ray on (b) (6) showed cardiomegaly, left peripherally inserted central catheter (PICC or PIC line) with tip in superior vena cava (SVC). Causes of cellulitis were not described in records. Toxicology was done on (b) (6) monitoring Vancomycin trough (toxicology) at 15.6 (reference range: 10.0 to 20.0 ug/dL), immature granulocyte (IG) at 0 percent (reference range: 0 to 2) and IG number 0.0 k/uL. On (b) (6) the patient was given intravenous saline 0.9 percent solution 250 ml with total daily dose of 250 ml every 12 hours, intravenous vancomycin 1000 mg sol 1.25 g with total daily dose of1000 mg every 12 hours, intravenous sodium chloride with total daily dose of 100 ml every 6 hours and intravenous ampicillin sulbactam with total daily dose of 3.0 g every 6 hours for osteomyelitis, oral saccharomyces boulardii 17 at a total daily dose of 250 mg twice daily as probiotic, oral hydrocodone at a total daily dose of 7.5 mg every 6 hours for pain and oral acetaminophen at a total daily dose of 325 mg every 6 hours for pain. The patient was discharged home from the hospital on (b) (6) Final discharge diagnosis was reported to be cellulitis of right hands with tenosynovitis, osteomyelitis of right hand and systemic inflammatory response syndrome due to infectious process without acute organ dysfunction. Action taken with the blinded study drug and other suspect drugs in respect to the events was reported to be dose not changed. The patient was hospitalized due to acute rhabdomyolysis, elevated creatine kinase level and renal insufficiency on (b) (6) The events were also reported as medically significant events. **Blinded study therapy with dapagliflozin 10 mg daily or matching placebo was interrupted on (b) (6) in regard to the events. The patient had also received non study suspect drugs Cubicin and oral rosuvastatin calcium 5 mg. The patient had been admitted for elevated creatine kinase. The patient had little weakness and denied muscle pain and no other associated symptoms. It was reported that the patient had acute rhabdomyolysis due to daptomycin while she received rosuvastatin calcium. Therapy with rosuvastatin was stopped on (b) (6) per hospital records, and the patient switched Cubicin to intravenous ceftriaxone with sodium chloride, one dose. Creatine kinase was noted at 14772 (Ref: 29 to 167 IU/L) on (b) (6) 8211 on (b) (6) and 3239 on (b) (6). There were no other labs related to the rhabdomyolysis. The patient had not described symptoms other than dry mouth.** On (b) (6), labs results included, creatinine was noted 1.3 (Ref: 0.6 to 1.1 mg/dL, BUN was 22.7 (Ref: 9.8 to 20.1 mg/dL) and BUN/Creat Ratio was 19.6 with no reference range listed, but listed as normal; on (b) (6) BUN was 21.7 (Ref: 9.8 to 20.1 mg/dL). Urinalysis was performed on the patient with all negative and normal results on (b) (6)										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	(b) (6). eGFR values on (b) (6) was 51 and (b) (6) was 57 with reference rang of (more than/equal to 60) mL/min/1.73 m2. She was assessed at the hospital and discharged on (b) (6), and was treated with change of antibiotics. She was discharged with oral antibiotics cephalexin, but not for the rhabdomyolysis. The patient had not received other treatment for this event. Outcome was unknown because patient was still believed to not be fully recovered. As per medical records, discharge summary stated the patient did not develop renal failure. However the investigator felt that the patient had renal insufficiency caused by rhabdomyolysis per review of records. The patient did not have any symptoms; she was not treated for this specific event. The patient would be coming for follow up at site on (b) (6) **The blinded study therapy with dapagliflozin or matching placebo was restarted on (b) (6) A seriousness criterion of the events was reported as serious (medically significant and hospitalization). The outcome of the events systemic inflammatory response syndrome, osteomyelitis, cellulitis right hand, carpal tunnel surgery, acute rhabdomyolysis, elevated creatine kinase was reported as complete recovery on (b) (6) and outcome of the event renal insufficiency was reported as complete recovery on (b) (6). The blinded study therapy with dapagliflozin or matching placebo was stopped on (b) (6)** The investigator stated that the event inflammation complication from carpal tunnel surgery (carpal tunnel surgery), osteomyelitis, cellulitis of right hand, systemic inflammatory response syndrome, acute rhabdomyolysis, elevated creatine kinase level and renal insufficiency were not related to blinded study therapy (dapagliflozin vs Placebo), metformin hydrochloride, liraglutide and insulin aspart. Causality was not provided for daptomycin and oral rosuvastatin calcium. The event inflammation complication from carpal tunnel surgery was considered as event of special interest: cellulitis of right hand with tenosynovitis and osteomyelitis of right hand. Systemic inflammatory response syndrome (SIRS) due to infectious process without acute organ dysfunction was noted. The investigator considered it to be probably related to postsurgical change (history); however, added that osteomyelitis could not be excluded. Thickened synovial tissues within the posterior aspect of the carpal coronal were consistent with synovitis. Inflammatory synovitis or infection could not be excluded. Also, the reporter stated that small fluid collection deep to the flexor profundus tendon was within the carpal tunnel. The reporter considered it as postsurgical fluid collection, cystic synovial fluid, atypical appearing tenosynovitis or small focus of infection/abscess. The investigator also stated that it was flexor tendinopathy versus reactive edema from adjacent synovial process. Mild tendinopathy of the extensor carpi ulnaris with mild synovitis was also reported. Diffuse nonspecific edema, possible cellulitis was described. Wrist joint effusions were also reported. Combined follow up reports received from an investigator via marketing partner (AstraZeneca case ID: 2013SE86949) via BMS via license partner (Cubist Pharmaceutical Inc., Mfr. control number 2013CBST001401) on 28 Mar 2014, 03 Apr 2014 and 18 Jun 2014 and forwarded to Novartis on 08 Sep 2014: Added concomitant medications, medical history (urinary tract infection) and updated information of the event renal insufficiency (outcome). Follow up report received from an investigator via marketing partner (AstraZeneca case ID: 2013SE86949) via BMS via license partner (Cubist Pharmaceutical Inc., Mfr. control number 2013CBST001401) on 26 Mar 2015 and forwarded to Novartis on 10 Apr 2015: updated laboratory data, Cubicin indication (off label use), stop date of Dapagliflozin.										
10336225 (Duplicate:11252812)	**Dapagliflozin 5 mg/d (Primary Suspect)**	**67**	**Female**	**Japan**	**3**	**DS, OT**	**Resolved**	**Yes**	**Positive**	**—**	**Teneligliptin, Pravastatin**
Narrative:	A physician reported that a patient of unspecified age and gender was hospitalized due to pyelonephritis acute, fever and shock while on therapy with dapagliflozin for diabetes mellitus. Two to three weeks before reporting, the patient was started on therapy with dapagliflozin 5 mg once daily at another hospital. Five days after the start of the drug, pyrexia developed, and subsequently acute pyelonephritis occurred. The patient was referred to the reporter's hospital. Shock symptoms also occurred, and the event became quite serious. On an unknown date, dapagliflozin was discontinued. The event gradually resolved. According to the reporter, event pyelonephritis acute was related to dapagliflozin therapy. **Supplemental information received from physician on (b) (4) stated that the 67-year-old female patient had life-threatening acute pyelonephritis, septic shock and suspected rhabdomyolysis on (b) (6) On (b) (6) the therapy with dapagliflozin was started. The Creatine phosphokinase (CPK) on (b) (6) was at 5078 IU/L (b) (6)**										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	the CPK was at 130 IU/L).The therapy with dapagliflozin was stopped on (b) (6).The events acute pyelonephritis, septic shock and suspected rhabdomyolysis resolved on (b) (6) Medical history included hip replacement and concurrent conditions included hypercholesterolaemia, hyperuricaemia and hypertension. Per reporter; the event septic shock was related and event suspected rhabdomyolysis was not assessed. Supplemental information received on 31-Jul-2014 from the physician indicated that "suspected rhabdomyolysis" was deleted from the event. The patient had medically significant acute tubular necrosis, disseminated intravascular coagulation (DIC) and acute lung disorder (lung disorder). The events of "Pyelonephritis acute" and "septic shock" were downgraded to "disability/incapacity" from "life-threatening." The patient had type 2 diabetes mellitus and multiple diabetic complications. The patient had been on oral treatment for diabetes mellitus since (b) (6) but the blood glucose control was poor with HbA1c of 8.0 to 10.0%. On (b) (6) a sodium glucose cotransporter 2 (SGLT2) inhibitor, oral dapagliflozin 5 mg once daily was started by the patient's primary physician. After the start of the drug, the patient experienced physical deconditioning. The patient had pyelonephritis acute on (b) (6) (previously (b) (6)). On (b) (6) the patient felt sick while on the train, and was taken to the previous hospital by ambulance. Pyrexia of 39 degrees Celsius and tendency to somnolence were noted. No neurological abnormality was noted, and acute lesions were unlikely by head computerized tomography (CT). On (b) (6) white blood cells were 4450/mm3 (normal range 4000 to 8500), C-reactive protein was 0.60 mg/dl (normal range 0.00 to 0.20), serum creatinine was 1.95 mg/dl (normal range 0.40 to 0.70), body temperature was 39 c and platelet count was 5.9x104/mm3 (normal range 12.5 to 37.5). Aggravation of renal impairment due to dehydration was considered, oral medications were discontinued and treatment with fluid replacement was given. Urinary tract infection or enterocolitis was suspected as a possible cause of the pyrexia, and ceftriaxone was started. On (b) (6), the patient had septic shock, acute tubular necrosis, DIC and acute lung disorder. On (b) (6), disturbed consciousness improved, but blood test results including white blood cells (WBC) 15980/mcL, CRP 15.61 mg/dL and creatinine 4.72 mg/dL showed aggravation of inflammatory findings and renal function. In addition, creatine kinase was high at 2838 U/L and rhabdomyolysis was suspected. On the same day, the patient was referred to the reporter's hospital as the location was preferable for the patient, and she was urgently admitted to the hospital. Dapagliflozin was discontinued on (b) (6). Findings on admission: Height 147.0cm, weight 70.1kg, body temperature 36.5 degrees Celsius, pulse rate 105bpm and regular, blood pressure 102/54 mmHg, SpO2 92% (on 2L of oxygen) and consciousness clear. In the head and neck area there was no conjunctival rim pallor, no jaundice of the bulbar conjunctiva, pupils were precisely round in shape and equal in size, rapid light reflex, no abnormal eye movement. In the chest the first and second heart sounds were normal, and the third and fourth heart sounds were absent. No murmur, slightly weak breath sounds and no rale. The abdomen findings showed; abdominal distension, soft, no tenderness, no operative scar, weak bowel sounds; Limbs showed oedema was absent. Nail tinea of the foot/feet and hallux valgus were present. Neurological findings showed no abnormal superficial sensation and no symptoms of neurologic deficit. On (b) (6), activated partial thromboplastin time (APTT) was 38.1 (normal range 29.6 to 40.8), prothrombin time 12.8 sec (normal range 10.0 to 13.0); prothrombin time (PT)% was 67.4%; prothrombin time (PT)-international normalized ratio (INR) was 1.19, urine pH was 7.0 (normal range 5 to 6), urinary sugar, urine ketone body, urine bilirubin and urine nitrate were negative; urine protein (qualitative) was 2+, occult blood was 3+, urine urobilinogen was positive and negative; urinary sediment (RBC) was >100 HP, urinary sediment (WBC) was >100 HP and protein urine was 2315.9 mg/dl; albumin was 3.3 g/dl (normal range 4.0 to 5.0), epidermal growth factor receptor (eGFR) was 7.0 ml/min/1.73m2; urea nitrogen was 57.5 mg/dl (normal range 8.0 to 22.0), blood uric acid was 6.7 mg/dl (normal range 2.3 to 7.0), sodium was 140 mEq/L (normal range 138.0 to 146.0), potassium (K) was 4.3 mEq/L (normal range 3.60 to 4.90); chloride (CL) was 103 mEq/l (normal range 98.0 to 109.0) and creatinine in urine was 62.41 mg/dl. Electrocardiogram (ECG) showed heart rate 106 bpm, normal sinus rhythm, normal axis, no ST change. Chest x-ray showed cardio-thoracic ratio unmeasurable, CPA dull, enlargement of gastric air bubbles was noted with raised diaphragm. Chest and abdominal computerized tomography (CT) showed slightly poor study due to poor breath holding. Poor study in the pelvis due to metal artifacts (the patient had probably undergone right hip replacement and left femoral head replacement). Partial poor dilatation in the lungs without obvious abnormalities. A 15 mm										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	sized node in the anterior mediastinum, suggesting a possible lesion stemming from the thymus gland. Mild cardiomegaly was present without pleural effusion. Hepatic steatosis and gallstones were present. The left kidney was larger than the right, which was considered to be right kidney atrophy rather than left kidney enlargement. There was a cloudy adipose tissue in the back of the right kidney. No obvious abnormalities in the pancreas, spleen or adrenal gland. Presence of air-bubbles in the bladder was suspected, but detailed assessment was impossible due to metal artifacts. No significant enlarged lymph nodes were noted. A small amount of ascites was noted. Subcutaneous distended superficial vein was noted in the lower abdomen. Disseminated intravascular coagulation (DIC) was noted with platelets 5.9 x10E4 (6.3 by visual observation) and fibrin degradation products (FDP) 181.4 mcg/mL (DIC score: 7). "Recomodulin" [genetical recombination] 12800 units were administered (until (b) (6)). On arrival to the hospital, SpO2 was maintained at 92% with 2L/min of oxygen by cannula. However, in the middle of the night of the same day, shallow breathing, tachypnea and SpO2 decrease to 87% with 5L/min of oxygen were noted. The symptoms were considered to be transitioning to non-cardiogenic pulmonary oedema due to septic systemic inflammatory response syndrome (SIRS). The oxygen administration was switched to 10 L/min of oxygen by reservoir mask. Pyrexia was absent, blood test results including WBC 19200/mcL and CRP 21.94 mg/dL showed inflammatory findings. CT showed cloudy adipose tissue in the back of the right kidney and pyelonephritis was suspected. CK was high at 5078 IU/L, but the increase was considered not enough to suspect renal failure due to rhabdomyolysis. Therefore, septic shock and acute tubular necrosis (ATN) ascribed to pyelonephritis were diagnosed. Meropenem 0.5 g twice daily and freeze-dried sulfonated human normal immunoglobulin 5 g daily were started. Noradrenaline was also started at 0.07 mcg/kg/min for low blood pressure. On (b) (6) biphasic positive airway pressure (BIPAP) therapy and sivelestat sodium hydrate 300 mg daily were started. The respiratory condition was gradually stabilizing. Continuous hemodiafiltration (CHDF) was started. On (b) (6) BIPAP was switched to nasal continuous positive airway pressure (CPAP). Central venous nutrition (TPN) was performed because the patient was unable to eat. Continuous insulin was also administered for type 2 diabetes mellitus. On (b) (6), CPAP was switched to 5 L of oxygen by mask. On (b) (6), the vital signs gradually stabilized, and noradrenaline was completed. On (b) (6), CHDF was completed, and food intake was resumed. As CRP was also favorably decreasing, the antimicrobial agent was changed to cefazolin sodium from meropenem. Sivelestat sodium hydrate and oxygen administration were discontinued. SpO2 was subsequently maintained at 95% or more with room air. After TPN was completed, insulin had been administered in accordance with blood glucose levels. On (b) (6) after the conditions of septic shock and ATN subsided, amlodipine besilate 5 mg once daily was orally started. Based on blood test results, haemodialysis was performed. On (b) (6) haemodialysis was performed. Blood test results including platelets 18.7 x10E4/mcL and FDP 9.3 mcg/mL showed an improvement of DIC. On (b) (6) haemodialysis was performed. On (b) (6), as increased urine output was noted, it was decided to wait for the renal function to return to normal without haemodialysis thereafter. CRP kept decreasing favorably. Oral 'Trazenta' 5 mg once daily was regularly started for type 2 diabetes mellitus, and insulin administration was discontinued. On (b) (6), blood tests showed that WBC and CRP were stable at 6100/mcL and 0.78 mg/dL, respectively, and the antimicrobial treatment was thus completed on the day. On (b) (6) blood tests showed CRP 0.75 mg/dL. The condition of septic shock was stable, and ATN also showed a tendency of recovery with creatinine 5.82 mg/dL and blood urea nitrogen (BUN) 69.4 mg/dL without subjective symptoms. On (b) (6), the patient was discharged. Medications on discharge included esomeprazole 20 mg one capsule, linagliptin 5 mg one tablet, amlodipine besilate once daily at 5 mg one tablet, febuxostat 20 mg one tablet, pravastatin sodium 10 mg one tablet once daily (after breakfast), and sodium polystyrene sulfonate dry syrup 76% one package twice daily (after breakfast and evening meals). At the time of reporting, oral amlodipine besilate once daily and linagliptin were continuing. The systolic blood pressure was around between 110 and 130 mm Hg. The patient's blood glucose levels were under control with the fasting blood glucose of 100 to 130 mg/dL. The patient's body weight also decreased to 62.6 kg from 70.1 kg by diet therapy with a daily intake of 1200 kcal. The patient was scheduled to start visiting the primary physician of another hospital thereafter. On (b) (6) systolic blood pressure 110 to 130 mmHg and fasting blood sugar level 100 to 130 mg/dL. On (b) (6) the patient had recovered from septic shock, acute tubular necrosis, DIC and acute lung disorder and on the same day the											

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	patient was recovering from pyelonephritis acute. The reporter's comment included as the patient had diabetes mellitus, decreased immunity was suspected first of all. The patient might have had underlying chronic cystitis, which could have progressed to acute pyelonephritis due to increased urinary glucose by administration of dapagliflozin and then become fulminant, possibly causing sepsis. Per reporter the events were related to pyelonephritis acute, septic shock, acute tubular necrosis, DIC and acute lung disorder. The patient had surgical history of endometriosis, uterine operation at age 35, left hip dislocation at age 40, and right hip dislocation at age 50. The patient's chief complaints were feeling poorly and renal impairment. Supplemental information received from physician on 19-Aug-2014, 22-Aug-2014 included the medically significant event rhabdomyolysis. **On (b) (6), the patient had rhabdomyolysis, on the same day patient received last dose of dapagliflozin propylene glycolate hydrate. On (b) (6), the event rhabdomyolysis was resolved. The patient had pyrexia of 39 degrees Celsius on (b) (6) (previously reported as (b) (6)) and was resolved on (b) (6) (previously reported as (b) (6)). The patient had pyelonephritis acute on (b) (6) (previously reported as (b) (6)). The reporter did not assess the events pyrexia of 39 degrees Celsius and rhabdomyolysis. Supplemental information received on 29-Aug-2014 from physician via AstraZeneca provided the following. Rhabdomyolysis might have been caused by sepsis or/and dapagliflozin.** The patient's medical history also included: Overactive bladder, Gastric ulcer, Muscle cramp, Dietary control and drug therapy with glimepiride. The patient had a familial history of having diabetes mellitus in mother, brother and sister.										
10450284 (Duplicates: 9779478; 9782299)	**Dapagliflozin 10 mg/d or Placebo (Suspect)**	**54**	**Female**	**U.S.**	**104**	**HO, OT**	**Recovered**	**Yes**	**Positive**	**—**	**Daptomycin (Primary Suspect), Rosuvastatin (Suspect), Metformin (Suspect), Liraglutide (Suspect)**
Narrative:	A 54-year-old Caucasian female (center id: 6E8078067, patient id: (b) (6)) developed systemic inflammatory response syndrome, inflammation complication from carpal tunnel surgery, osteomyelitis, cellulitis right hand, acute rhabdomyolysis, renal insufficiency and elevated creatine kinase, during off-label treatment with Cubicin (daptomycin) and while on Dapagliflozin (code not broken), metformin hydrochloride, Victoza (liraglutide), Novolog (insulin aspart) and Crestor (rosuvastatin calcium). This patient was hospitalized due to moderate/grade II inflammation, complication from carpal tunnel surgery (carpal tunnel surgery) while enrolled in a AstraZeneca clinical study with the Protocol title (D1693C00001): Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes. Relevant medical history included hypertension, urinary tract infection, diuretic therapy, neuropathy , potassium deficiency, blood thinning (coagulation disorder), vitamin B deficiency, immune system disorder, pain, tooth extraction, cellulitis, inflammation, myocardial infarction (b) (6) coronary artery bypass grafting (b) (6), vascular disease (angiopathy), retinopathy, congestive heart failure, calcium deficiency, vitamin deficiency, high cholesterol, kidney disease and type II diabetes mellitus since (b) (6) Concomitant medications included oral carvedilol for hypertension, oral metolazone as a diuretic therapy, oral gabapentin for neuropathy, oral potassium chloride for potassium deficiency, oral aspirin (acetyl salicylic acid) for blood thinning (coagulation disorder), Metanx (L- methylfolate) for vit. B deficiency, oral hydrocodone for pain, oral amoxicillin as antibiotic for tooth extraction, oral clindamycin for cellulitis, intramuscular methylprednisolone for inflammation, subcutaneous betamethasone for inflammation, Pneumovax (pneumonia vaccination) for prophylaxis, calcium for calcium deficiency, vitamin										

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	D3 for vitamin deficiency, Sulfamethazine(sulfadimidine) for cellulitis, doxycycline for urinary tract infection, atorvastatin and Norco (hydrocodone, paracetamol), vitamin C and atorvastatin for unknown indications. The patient had been receiving metformin HCl at 500 mg twice per day, orally, liraglutide at 1.8 mg per day and insulin aspart at 60 IU three times per day prior to the initiation of study therapy and were ongoing at the time of this report. The patient initiated placebo run in phase on (b) (6). On (b) (6) blinded study therapy with dapagliflozin 10 mg daily or matching placebo was initiated. On an unknown date, the patient started treatment with intravenous infusion of daptomycin (dose and frequency unknown) for osteomyelitis. On (b) (6) carpel-tunnel surgery (Intensity: moderate) was done and the patient had inflammation on her right hand and complications from carpal tunnel surgery. The patient consulted the physician on (b) (6), and was admitted in the hospital for possible infection. The patient had swelling, pain and redness of right wrist and hand. Patient was treated with intravenous antibiotics. The physician diagnosed 'carpal tunnel decompression.' On (b) (6) the events of osteomyelitis (Intensity: moderate), cellulitis of right hand (Intensity: moderate), and systemic inflammatory response syndrome (Intensity: moderate) through evaluation of X-ray, magnetic resonance imaging (MRI) of right hand and blood work in the hospital. The patient was admitted overnight. Microbiology culture was also done on (b) (6) On (b) (6) MRI of upper extremity of wrist showed bone marrow edema involving the hook of the hamate with areas of bone destruction involving the hook of the hamate. On the same day (b) (6) erythrocyte sedimentation rate was 111 (reference range 0-20 mm/h); chest x-ray on (b) (6) showed cardiomegaly and left peripherally inserted central catheter (PICC line) with tip in superior vena cava (SVC). Causes of cellulitis were not described in records. Toxicology was done on (b) (6), monitoring vancomycin trough (toxicology) at 15.6 (reference range: 10.0-20.0 ug/dL), immature granulocyte (IG) at 0 percent (reference range: 0-2) and IG number 0.0 k/uL. On (b) (6), the patient was given intravenous saline 0.9 percent solution 250ml with total daily dose of 250ml every 12 hours, intravenous vancomycin 1000mg sol 1.25g with total daily dose of 1000mg every 12 hours, intravenous sodium chloride with total daily dose of 100ml every 6 hours, intravenous ampicillin sulbactam with total daily dose of 3.0 g every 6 hours for osteomyelitis, oral 'saccharomyces boulardii 17' at a total daily dose of 250 mg twice daily as probiotic, oral hydrocodone at a total daily dose of 7.5 mg every 6 hours for pain, and oral acetaminophen at a total daily dose of 325 mg every 6 hours for pain. The patient was discharged home from the hospital on (b) (6) Final discharge diagnosis was reported to be cellulitis of right hands with tenosynovitis, osteomyelitis of right hand and systemic inflammatory response syndrome due to infectious process without acute organ dysfunction. **On (b) (6) the patient experienced the events of severe acute rhabdomyolysis, severe elevated creatine kinase and renal insufficiency (Intensity: moderate) and was hospitalized for the same. Blinded study therapy with dapagliflozin 10 mg daily or matching placebo was interrupted on (b) (6) in regard to the events. The patient had also received other suspect drugs daptomycin and oral rosuvastatin calcium 5 mg. The patient had been admitted for elevated creatine kinase. The patient had little weakness and denied muscle pain and no other associated symptoms. It was reported that the patient had acute rhabdomyolysis due to daptomycin while she received rosuvastatin calcium. Therapy with rosuvastatin was stopped on (b) (6) per hospital records, and the patient was switched from daptomycin to intravenous ceftriaxone with sodium chloride, one dose. On (b) (6) creatinine was 1.3 (reference range: 0.6-1.1 mg/dL), blood urea nitrogen (BUN) was 22.7 (reference range: 9.8-20.1 mg/dL) and BUN/Creatinine ratio was 19.6 (maximum: 20.1). On the same day (b) (6) creatine kinase was noted at 14772 (reference range: 29-167 IU/L) and on (b) (6) it was 8211. On the same day (b) (6) BUN was 21.7 (reference range: 9.8-20.1 mg/dL) and eGFR values was 51. On (b) (6), eGFR was 57 [reference range: more than 60 mL/min/1.73 sqm] and creatine kinase was 3239. Urinalysis was negative and the results were normal. The patient had not described symptoms other than dry mouth. The patient was assessed at the hospital and discharged on (b) (6) and was treated with change of antibiotics. The patient was discharged with oral antibiotics cephalexin. Patient has had renal insufficiency as a baseline. Patient had acute rhabdomyolysis and was asymptomatic with renal insufficiency. However, lab results showed BUN/Cr of 22.7/1.3 and eGFR of 43. Patient was adequately hydrated. Patient recovered with lab eGFR value of 73 and BUN/Cr 24/0.89. On an unknown date, study therapy was temporarily discontinued.** As per medical records, discharge summary											

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	stated the patient did not develop renal failure. However, the investigator felt that the patient had renal insufficiency caused by rhabdomyolysis per review of records. The patient did not have any symptoms; and was not treated for this specific event. It was reported that, the patient would be coming for follow up at the site on (b) (6) On (b) (6) the patient recovered from the event of acute rhabdomyolysis, inflammation complication from carpal tunnel surgery, osteomyelitis, cellulitis right hand, and systemic inflammatory response syndrome and elevated creatine kinase. On (b) (6) the patient recovered from the event renal insufficiency. The study investigator assessed the event of acute rhabdomyolysis, inflammation complication from carpal tunnel surgery, osteomyelitis, cellulitis right hand, and systemic inflammatory response syndrome and elevated creatine kinase to be serious due to seriousness criteria of hospitalized and important medical event. The study investigator assessed the event of renal insufficiency serious due to seriousness criteria of hospitalized. The study investigator considered the causality between the events of acute rhabdomyolysis, inflammation complication from carpal tunnel surgery, osteomyelitis, cellulitis right hand, and systemic inflammatory response syndrome and elevated creatine kinase, renal insufficiency and study therapy to be not related to dapagliflozin metformin, Victoza (liraglutide) and Novolog (insulin aspart). The investigator did not assess the causality of the events with daptomycin. Systemic inflammatory response syndrome (SIRS) due to infectious process without acute organ dysfunction was noted. The investigator considered it to be probably related to post-surgical change (history); however, added that osteomyelitis could not be excluded. Thickened synovial tissues within the posterior aspect of the carpal coronal were consistent with synovitis. Inflammatory synovitis or infection could not be excluded. Also, the reporter stated that small fluid collection deep to the flexor profundus tendon was within the carpal tunnel. The reporter considered it as postsurgical fluid collection, cystic synovial fluid, atypical appearing tenosynovitis or small focus of infection/abscess. The investigator also stated that it was flexor tendinopathy versus reactive edema from adjacent synovial process. Mild tendinopathy of the extensor carpi ulnaris with mild synovitis was also reported. Diffuse nonspecific edema, possible cellulitis was described. Wrist joint effusions were also reported. Follow-up information was received on 28-Mar-2014, 03-Apr-2014 and 18-Jun-2014 from a clinical investigator via license partner AstraZeneca and received at Cubist on 05-Sep-2014 and the narrative was updated accordingly. Updated event verbatim from carpal tunnel surgery to inflammation complication from carpal tunnel surgery, reaction onset date from (b) (6) to (b) (6) for the event of inflammation complication from carpal tunnel surgery, outcome of event renal insufficiency from unknown to recovered, updated therapy dates for dapagliflozin, added medical history (urinary tract infection), added concomitant medications (atorvastatin, Sulfamethoprim, doxycycline and Norco) and stop date of renal insufficiency (b) (6) Follow-up information was received on 26-Mar-2015 from a clinical investigator via license partner and received at Cubist on 08-Apr-2015 and was incorporated in the narrative: Updated patients age, ethnicity, laboratory data, and concomitant medication. **Updated regimen for dapagliflozin.** Updated the seriousness criteria for the events and event outcome for acute rhabdomyolysis, carpal tunnel surgery, osteomyelitis, cellulitis right hand, systemic inflammatory response syndrome, and renal insufficiency and elevated creatine kinase from unknown to recovered and stop date for events as (b) (6) Updated event stop date of renal insufficiency as (b) (6). Company comment: The serious (hospitalization and medically significant) events of systemic inflammatory response syndrome, carpel tunnel decompression, osteomyelitis and cellulitis are unlisted whereas the serious (hospitalization and medically significant) events of rhabdomyolysis and blood creatine phosphokinase increased and serious (hospitalization) event of renal failure are listed in the current CCDS for daptomycin used for the treatment of osteomyelitis (off-label indication). The investigator felt that the patient had renal insufficiency caused by rhabdomyolysis per review of records. Investigator did not provide the causality for the events in relation to daptomycin. **Given the patient's underlying conditions and medical history, and multiple co-suspect drugs, definitive causality to daptomycin cannot be determined. Crestor can cause rhabdomyolysis, renal failure and increase in creatine kinase; dapagliflozin can cause renal failure and increase in creatine kinase; liraglutide can increase creatine kinase and can cause renal failure; statins use can lead to creatine kinase increase and rhabdomyolysis; all confounders in this case.**											
11237825	**Dapagliflozin 10 mg/d**	**—**	**Female**	**Portugal**	**—**	**HO, OT**	**—**	**—**	**—**	**—**	**Vildagliptin,**

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	(Primary Suspect)										**Metformin**
Narrative:	A spontaneous report has been received from a Physician concerning a, female patient. The patient's medical history included total hysterectomy, unilateral adnexectomy and secondary anemia to metrorrhagia. The patient's concurrent diseases included type I diabetes mellitus, arterial hypertension, obesity grade I and gastritis. Concomitant medications included insulin glargine, insulin lispro, **vildagliptin**, metformin, lansoprazole, candesartan and phospholipids. Patient has started taking oral Forxiga (dapagliflozin) (unknown begin date) 10 mg for type 2 diabetes mellitus. In the meanwhile, patient was hospitalized for a surgery and she had diabetic ketoacidosis (Preferred Term: Diabetic ketoacidosis). **It was also reported that patient had rhabdomyolysis (Preferred Term: Rhabdomyolysis), severe metabolic acidemia (Preferred Term: Metabolic acidosis), hypophosphatemia (Preferred Term: Hypophosphataemia) and iatrogenic hypokalemia (Preferred Term: Hypokalaemia).** Polypneic. No SDR (RDS, Respiratory distress syndrome). Normal Arterial pressure, sinus tachycardia of 115bpmGlycaemia 320, glycosuria and ketonuria. AP (PA, pulmonary auscultation): discrete bibasilar crepitations. Soft and depressible abdomen, with no SIP (PIS, Peritoneal irritation signs). Clean and dry dressing. Apyrexia. GSA (aa): pH 6.88, Bic 1.7 BE30, deficit Bic 870, PCO2 8.9, Lact 2.8GSA (after treatment): pO2: 118.4mmHg, pCO2: 12.8mmHg, pH: 7.224, HCO3: 5.2mmol/L, Glycose:282mg/dL, Na+ corrected: 149mmol/L, K+: 4.46mmol/L, Lactates: 3.79mmol/LBicarbonate deficit: 737mmol Analytically: Hb 12.7, leucocytes 24.9, K+ 6.1, Cr 1.0, PCR 110. Calcium 6.8, albumin 2.4, Ca corrected8.08. **Myoglobin 150, CK 327.** Normal coagulation. Chest X-Ray: no changes. Urinary sediment: proteinuria, glycosuria, ketone bodies and erythrocyturia. She was 2 days in intensive care unit with favorable evolution. In the transference date patient was hemodynamically stable and with no symptoms. With glycaemia 158, ketonemia 3.2 and gasometrically with diabetic ketoacidosis (bicarbonates 15.2) but without acidemia. She was evaluated by Gynecology on 16/05, physical and gynecological exams with no changes, with indication to keep surveillance. Action taken with Forxiga was unknown. At the time of reporting, the event of diabetic ketoacidosis was improving and the outcome of the event of rhabdomyolysis, severe metabolic acidemia, hypophosphatemia and iatrogenic hypokalemia was unknown. The company physician assessed diabetic ketoacidosis, rhabdomyolysis and severe metabolic acidemia to be serious with important medical event and hospitalization. The company physician assessed hypophosphatemia and iatrogenic hypokalemia to be serious with hospitalization. Laboratory values are available. Summary of follow-up information received by AstraZeneca/MedImmune on 17-Aug-2015 from physician via spontaneous source: New serious event Rhabdomyolysis, severe metabolic acidemia, hypophosphatemia and iatrogenic hypokalemia were added. Outcome of event Diabetic ketoacidosis was updated from unknown to recovering. Concomitant Disease and relevant history added. Concomitant drugs added. Lab data added. Narrative updated.										
11252812 (Duplicate:10336225)	**Dapagliflozin 5 mg/d (Primary Suspect)**	**67**	**Female**	**Japan**	**3**	**DS, OT**	**Resolved**	**Yes**	**Positive**	**—**	**Teneligliptin, Pravastatin**
Narrative:	This case was received via AstraZeneca-Japan. A physician reported that a patient of unspecified age and gender was hospitalized due to pyelonephritis acute, fever and shock while on therapy with dapagliflozin for diabetes mellitus. Two to three weeks before reporting, the patient was started on therapy with dapagliflozin 5 mg once daily at another hospital. Five days after the start of the drug, pyrexia developed, and subsequently acute pyelonephritis occurred. The patient was referred to the reporter's hospital. Shock symptoms also occurred, and the event became quite serious. On an unknown date, dapagliflozin was discontinued. The event gradually resolved. **According to the reporter, event pyelonephritis acute was related to dapagliflozin therapy. Supplemental information received from physician on (b) (4) stated that the 67-year-old female patient had life threatening acute pyelonephritis, septic shock and suspected rhabdomyolysis on (b) (4).On (b) (4) the therapy with dapagliflozin was started. The Creatine phosphokinase (CPK) on (b) (4) was at 5078 IU/L (on (b) (4) the CPK was at 130 IU/L).The therapy with dapagliflozin was stopped on (b) (4).The events acute pyelonephritis, septic shock and suspected rhabdomyolysis resolved on (b) (4).** Medical history included hip replacement and concurrent conditions included hypercholesterolaemia, hyperuricaemia and hypertension. Per reporter; the event septic shock was related and event suspected rhabdomyolysis										

FAERS Case #	Primary Suspect/ Suspect Drug(s)	Age (yr)	Sex	Source	Onset (days)	Reported Outcome	Disposition	D/C	Dechallenge	Rechallenge	Relevant Concomitant Medications
	was not assessed. **Supplemental information received on 31-Jul-2014 from the physician indicated that "suspected rhabdomyolysis" was deleted from the event.** The patient had medically significant acute tubular necrosis, disseminated intravascular coagulation (DIC) and acute lung disorder (lung disorder). The events of "Pyelonephritis acute" and "septic shock" were downgraded to "disability/incapacity" from "life-threatening." The patient had type 2 diabetes mellitus and multiple diabetic complications. The patient had been on oral treatment for diabetes mellitus since (b) (6) but the blood glucose control was poor with HbA1c of 8.0 to 10.0**%. On** (b) (6) **a sodium glucose cotransporter 2 (SGLT2) inhibitor, oral dapagliflozin 5 mg once daily was started by the patient's primary physician.** After the start of the drug, the patient experienced physical deconditioning. The patient had pyelonephritis acute on (b) (6) (previously (b) (6)). On (b) (6) the patient felt sick while on the train, and was taken to the previous hospital by ambulance. Pyrexia of 39 degrees Celsius and tendency to somnolence were noted. No neurological abnormality was noted, and acute lesions were unlikely by head computerized tomography (CT). On (b) (6) white blood cells were 4450/mm3 (normal range 4000 to 8500), C-reactive protein was 0.60 mg/dl (normal range 0.00 to 0.20), serum creatinine was 1.95 mg/dl (normal range 0.40 to 0.70), body temperature was 39 c and platelet count was 5.9x104/mm3 (normal range 12.5 to 37.5). Aggravation of renal impairment due to dehydration was considered, oral medications were discontinued and treatment with fluid replacement was given. Urinary tract infection or enterocolitis was suspected as a possible cause of the pyrexia, and ceftriaxone was started. On (b) (6), the patient had septic shock, acute tubular necrosis, DIC and acute lung disorder. On (b) (6) disturbed consciousness improved, but blood test results including white blood cells (WBC) 15980/mcL, CRP 15.61 mg/dL and creatinine 4.72 mg/dL showed aggravation of inflammatory findings and renal function. **In addition, creatine kinase was high at 2838 U/L and rhabdomyolysis was suspected. On the same day, the patient was referred to the reporter's hospital as the location was preferable for the patient, and she was urgently admitted to the hospital. Dapagliflozin was discontinued on** (b) (6)**.** Findings on admission: Height 147.0cm, weight 70.1kg, body temperature 36.5 degrees Celsius, pulse rate 105bpm and regular, blood pressure 102/54 mmHg, SpO2 92% (on 2L of oxygen) and consciousness clear. In the head and neck area there was no conjunctival rim pallor, no jaundice of the bulbar conjunctiva, pupils were precisely round in shape and equal in size, rapid light reflex, no abnormal eye movement. In the chest the first and second heart sounds were normal, and the third and fourth heart sounds were absent. No murmur, slightly weak breath sounds and no rale. The abdomen findings showed; abdominal distension, soft, no tenderness, no operative scar, weak bowel sounds; Limbs showed oedema was absent. Nail tinea of the foot/feet and hallux valgus were present. Neurological findings showed no abnormal superficial sensation and no symptoms of neurologic deficit. On (b) (6) activated partial thromboplastin time (APTT) was 38.1 (normal range 29.6 to 40.8), prothrombin time 12.8 sec (normal range 10.0 to 13.0); prothrombin time (PT)% was 67.4%; prothrombin time (PT)-international normalized ratio (INR) was 1.19, urine pH was 7.0 (normal range 5 to 6), urinary sugar, urine ketone body, urine bilirubin and urine nitrate were negative; urine protein (qualitative) was 2+, occult blood was 3+, urine urobilinogen was positive and negative; urinary sediment (RBC) was >100 HP, urinary sediment (WBC) was >100 HP and protein urine was 2315.9 mg/dl; albumin was 3.3 g/dl (normal range 4.0 to 5.0), epidermal growth factor receptor (eGFR) was 7.0 ml/min/1.73m2; urea nitrogen was 57.5 mg/dl (normal range 8.0 to 22.0), blood uric acid was 6.7 mg/dl (normal range 2.3 to 7.0), sodium was 140 mEq/L (normal range 138.0 to 146.0), potassium (K) was 4.3 mEq/L (normal range 3.60 to 4.90); chloride (CL) was 103 mEq/l (normal range 98.0 to 109.0) and creatinine in urine was 62.41 mg/dl. Electrocardiogram (ECG) showed heart rate 106 bpm, normal sinus rhythm, normal axis, no ST change. Chest x-ray showed cardio-thoracic ratio unmeasurable, CPA dull, enlargement of gastric air bubbles was noted with raised diaphragm. Chest and abdominal computerized tomography (CT) showed slightly poor study due to poor breath holding. Poor study in the pelvis due to metal artifacts (the patient had probably undergone right hip replacement and left femoral head replacement). Partial poor dilatation in the lungs without obvious abnormalities. A 15 mm sized node in the anterior mediastinum, suggesting a possible lesion stemming from the thymus gland. Mild cardiomegaly was present without pleural effusion. Hepatic steatosis and gallstones were present. The left kidney was larger than the right, which was considered to be right kidney atrophy rather than left kidney enlargement. There was a cloudy adipose tissue in the back of the right kidney. No obvious abnormalities in the pancreas, spleen or adrenal											

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	gland. Presence of air-bubbles in the bladder was suspected, but detailed assessment was impossible due to metal artifacts. No significant enlarged lymph nodes were noted. A small amount of ascites was noted. Subcutaneous distended superficial vein was noted in the lower abdomen. Disseminated intravascular coagulation (DIC) was noted with platelets 5.9 x10E4 (6.3 by visual observation) and fibrin degradation products (FDP) 181.4 mcg/mL (DIC score: 7). "Recomodulin" [genetical recombination] 12800 units were administered (until (b) (6)). On arrival to the hospital, SpO2 was maintained at 92% with 2L/min of oxygen by cannula. However, in the middle of the night of the same day, shallow breathing, tachypnoea and SpO2 decrease to 87% with 5L/min of oxygen were noted. The symptoms were considered to be transitioning to non-cardiogenic pulmonary oedema due to septic systemic inflammatory response syndrome (SIRS). The oxygen administration was switched to 10 L/min of oxygen by reservoir mask. Pyrexia was absent, blood test results including WBC 19200/mcL and CRP 21.94 mg/dL showed inflammatory findings. CT showed cloudy adipose tissue in the back of the right kidney and pyelonephritis was suspected. **CK was high at 5078 IU/L, but the increase was considered not enough to suspect renal failure due to rhabdomyolysis.** Therefore, septic shock and acute tubular necrosis (ATN) ascribed to pyelonephritis were diagnosed. Meropenem 0.5 g twice daily and freeze-dried sulfonated human normal immunoglobulin 5 g daily were started. Noradrenaline was also started at 0.07 mcg/kg/min for low blood pressure. On (b) (6), biphasic positive airway pressure (BIPAP) therapy and sivelestat sodium hydrate 300 mg daily were started. The respiratory condition was gradually stabilizing. Continuous hemodiafiltration (CHDF) was started. On (b) (6) BIPAP was switched to nasal continuous positive airway pressure (CPAP). Central venous nutrition (TPN) was performed because the patient was unable to eat. Continuous insulin was also administered for type 2 diabetes mellitus. On (b) (6), CPAP was switched to 5 L of oxygen by mask. On (b) (6), the vital signs gradually stabilized, and noradrenaline was completed. On (b) (6) CHDF was completed, and food intake was resumed. As CRP was also favorably decreasing, the antimicrobial agent was changed to cefazolin sodium from meropenem. Sivelestat sodium hydrate and oxygen administration were discontinued. SpO2 was subsequently maintained at 95% or more with room air. After TPN was completed, insulin had been administered in accordance with blood glucose levels. On (b) (6) after the conditions of septic shock and ATN subsided, amlodipine besilate 5 mg once daily was orally started. Based on blood test results, haemodialysis was performed. On (b) (6) haemodialysis was performed. Blood test results including platelets 18.7 x10E4/mcL and FDP 9.3 mcg/mL showed an improvement of DIC. On (b) (6) haemodialysis was performed. On (b) (6) as increased urine output was noted, it was decided to wait for the renal function to return to normal without haemodialysis thereafter. CRP kept decreasing favorably. Oral ? Trazenta? 5 mg once daily was regularly started for type 2 diabetes mellitus, and insulin administration was discontinued. On (b) (6), blood tests showed that WBC and CRP were stable at 6100/mcL and 0.78 mg/dL, respectively, and the antimicrobial treatment was thus completed on the day. On (b) (6) blood tests showed CRP 0.75 mg/dL. The condition of septic shock was stable, and ATN also showed a tendency of recovery with creatinine 5.82 mg/dL and blood urea nitrogen (BUN) 69.4 mg/dL without subjective symptoms. On (b) (6) the patient was discharged. Medications on discharge included esomeprazole 20 mg one capsule, **linagliptin 5 mg one tablet**, amlodipine besilate once daily at 5 mg one tablet, febuxostat 20 mg one tablet, **pravastatin sodium 10 mg one tablet once daily (after breakfast)**, and sodium polystyrene sulfonate dry syrup 76% one package twice daily (after breakfast and evening meals). **At the time of reporting, oral amlodipine besilate once daily and linagliptin were continuing.** The systolic blood pressure was around between 110 and 130 mm Hg. The patient's blood glucose levels were under control with the fasting blood glucose of 100 to 130 mg/dL. The patient's body weight also decreased to 62.6 kg from 70.1 kg by diet therapy with a daily intake of 1200 kcal. The patient was scheduled to start visiting the primary physician of another hospital thereafter. On (b) (6) systolic blood pressure 110 to 130 mmHg and fasting blood sugar level 100 to 130 mg/dL. On (b) (6), the patient had recovered from septic shock, acute tubular necrosis, DIC and acute lung disorder and on the same day the patient was recovering from pyelonephritis acute. The reporter's comment included as the patient had diabetes mellitus, decreased immunity was suspected first of all. The patient might have had underlying chronic cystitis, which could have progressed to acute pyelonephritis due to increased urinary glucose by administration of dapagliflozin and then become fulminant, possibly causing sepsis. Per reporter the events were related to pyelonephritis acute, septic											

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	shock, acute tubular necrosis, DIC and acute lung disorder. The patient had surgical history of endometriosis, uterine operation at age 35, left hip dislocation at age 40, and right hip dislocation at age 50. The patient's chief complaints were feeling poorly and renal impairment. **Supplemental information received from physician on 19-Aug-2014, 22-Aug-2014 included the medically significant event rhabdomyolysis. On (b) (6), the patient had rhabdomyolysis, on the same day patient received last dose of dapagliflozin propylene glycolate hydrate. On (b) (6) the event rhabdomyolysis was resolved.** The patient had pyrexia of 39 degrees Celsius on (b) (6) (previously reported as (b) (6)) and was resolved on (b) (6) (previously reported as (b) (6)). The patient had pyelonephritis acute on (b) (6) (previously reported as (b) (6)). The reporter did not assess the events pyrexia of 39 degrees Celsius and rhabdomyolysis. Supplemental information received on 29-Aug-2014 from physician via AstraZeneca provided the following. Rhabdomyolysis might have been caused by sepsis or/and dapagliflozin. The patient's medical history also included: Overactive bladder, Gastric ulcer, Muscle cramp, Dietary control and drug therapy with glimepiride. The patient had a familial history of having diabetes mellitus in mother, brother and sister.										
11391388	**Dapagliflozin (Primary Suspect)**	**—**	**Female**	**U.S.**	**—**	**HO**	**—**	**—**	**—**	**—**	**—**
Narrative:	A report has been received from a physician via medical representative concerning a female patient. She had type 2 diabetes. There was no information on the concomitant medication. She was treated with oral Farxiga (dapagliflozin) for type 2 diabetes. Treatment details not specified. **The patient was hospitalized while she was out-of-town for a wedding this past weekend as she experienced increased urination (preferred term: pollakiuria) and dehydration (preferred term: dehydration) and diagnosed with rhabdomyolysis (preferred term: rhabdomyolysis).** She was released from hospital on (b) (6) and she travelled back to Ohio. The patient was okay, and her physician felt that she may have been avoiding drinking fluids while travelling and became dehydrated. The physician was comfortable with continuing the patient on Farxiga, however action taken was unknown. The patient recovered from increased urination and dehydration on an unspecified date, while outcome of rhabdomyolysis was unknown. Company physician considered the events to be serious with hospitalization criterion.										
12195213	**Dapagliflozin 5 mg (Primary Suspect)**	**62**	**Female**	**U.S.**	**33**	**HO**	**—**	**—**	**—**	**—**	**—**
Narrative:	Started Farxiga 6 months ago & developed severe weakness of legs & fatigue requiring help with ambulation at times Progressively worsened over 1 month pd requiring hospitalization for rhabdomyolysis & UTI sp. Laboratory Text: **CPK - 16,000**; TROPONIN - 0.28										
12788807	**Dapagliflozin 5 mg (Primary Suspect)**	**—**	**—**	**U.S.**	**14**	**OT**	**—**	**—**	**—**	**—**	**—**
Narrative:	A report has been received from a Health Professional concerning a patient of unknown age and gender. Concomitant medications, concurrent diseases and medical history were not reported. The patient was receiving oral Farxiga (dapagliflozin).**The patient experienced rhabdomyolysis (preferred term: rhabdomyolysis) with severe muscle cramps and dark urine 2 weeks after starting Farxiga, these are the symptoms, of the event, and nothing to clarify the condition. The outcome of the event of rhabdomyolysis was unknown.** Action taken unknown. According to the company physician the event was considered as serious with the serious criteria of important medical event. PRIMARY SOURCE TELEPHONE: (b) (6) RHABDOMYOLYSIS - MEDICAL CONFIRMATION BY HEALTH PROFESSIONAL: Yes										
Dapagliflozin+Saxagliptin											
10156368 (Subject CV181168-	**Dapagliflozin 10 mg/d (Primary Suspect)**	**78**	**Male**	**U.S.**	**280 (Saxa+**	**HO**	**Resolved**	**Interrupted**	**Positive**	**—**	**Saxagliptin 5 mg/d**

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102-332)					Dapa+ Met)						(Suspect), Metformin 1500 mg/d (Suspect)
	Protocol title (CV181168): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin. A clinical investigator reported that a 78-year-old male patient was hospitalized due to syncope due to dehydration (Severe/grade III) while enrolled in an above mentioned clinical trial with saxagliptin added to dapagliflozin, in combination with metformin compared to therapy with placebo added to dapagliflozin in combination with metformin for the treatment of type 2 diabetes. The patient was diagnosed with type 2 diabetes in 2000. The patient started oral therapies with blinded dapagliflozin/placebo 10 mg orally from (b) (6) open label metformin HCL 1500 mg orally from (b) (6) and blinded saxagliptin/placebo 5 mg orally from (b) (6). The patient witnessed syncope episode when getting out of taxi, no injuries or seizure activities, no loss of bladder or bowel. The patient sent to hospital for evaluation and diagnosed with syncope episode and found to have rhabdomyolysis. The onset date of the event was reported as (b) (6). The patient was admitted and given intravenous fluid. The study therapy was interrupted in response to the event. Laboratory test on (b) (6) revealed hemoglobin A1C at 10.1 mg/dL, creatine phosphokinase (CPK) at 6413, estimated glomerular filtration rate (eGFR) at 40, prostate specific antigen (PSA) at 65 and urinalysis (white blood cell) at 77 hpf. It was reported that the patient recovered from the event on (b) (6). At the time of this report, the patient was continuing the study therapies. The patient concomitantly also received dutasteride/tamsulosin from (b) (6) and was continuing at the time of this report. According to the investigator, the specific cause of the event was unknown at the time of this report. The patient's medical history included glaucoma, elevated prostate specific antigen, hypertension from (b) (6) obesity from (b) (6) and benign prostatic hypertrophy. Investigator causality assessment: Syncope was not related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy) and metformin HCL therapies. BMS causality assessment: Syncope was not related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy) and metformin HCL therapies. Supplemental information received on from the clinical investigator (b) (4), 01-May-2014, 02-May-2014 and 06-May-2014 from the clinical investigator included the following: The event 'syncope due to dehydration' was amended to 'syncope'. It was reported that the therapy with metformin HCL was stopped on (b) (6). On (b) (6), the patient also developed pyelonephritis (Severe/grade III). The patient was on therapy with blinded dapagliflozin/placebo and blinded saxagliptin/placebo at the time of the event. The event led to patient's hospitalization. The patient was found to have a bladder outlet obstruction resulting in acute pyelonephritis. The study therapy was interrupted in response to the event and the patient was treated for the event. The event was resolving at the time of this report. Laboratory test on (b) (6) revealed creatinine at 2.2, estimated glomerular filtration rate (eGFR) at 35, 'leukocyte esterase' was large and white blood cell (WBC) at 10.1. Investigator causality assessment: Syncope was not related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy) and metformin HCL therapies. Pyelonephritis was related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy). Causality for metformin HCL was not provided. BMS causality assessment: Syncope was not related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy) and metformin HCL therapies. Pyelonephritis was not related to dapagliflozin/placebo (blinded study therapy), saxagliptin/placebo (blinded study therapy) and metformin HCL therapies. Supplemental information from the clinical investigator on 07-May-2014 clarified that the rhabdomyolysis was the cause of the syncope however it was not related to the study therapy. Upon internal review on 08-May-2014, the event of pyelonephritis was added to the separate case (CARES#20722880). The event of rhabdomyolysis was elevated as additional serious adverse event. Investigator causality assessment: Syncope was not											

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	related to blinded dapagliflozin/placebo, blinded saxagliptin/placebo and metformin HCL. Rhabdomyolysis was not related to blinded dapagliflozin/placebo, blinded saxagliptin/placebo and metformin HCL BMS causality assessment: Syncope was not related to blinded dapagliflozin/placebo, saxagliptin/placebo and metformin HCL therapies. Rhabdomyolysis was not related to blinded dapagliflozin/placebo, blinded saxagliptin/placebo and metformin HCL.										

Source: Empirica Signal and Mercado Drug Safety Analytics databases, available at: https://esignal.fda.gov/signal/home.jsp; and http://mercado.fda.gov/analytics/saw.dll?Dashboard&portalPath=%2fshared%2fMercado%20Capability%2f_portal%2fPlatform%20Report%20Catalog.

Abbreviations: —, not reported; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIPAP, biphasic positive airway pressure; BMS, Bristol-Myers Squibb; BUN, blood urea nitrogen; CHDF, continuous haemodiafiltration; CPK, creatine phosphokinase; Cr, creatinine; CRP, C-reactive protein; d, day; D/C, discontinued; DE, death; DS, disabled; eGFR, estimated glomerular filtration rate; ER, extended-release; gamma-GT, gamma-glutamyltransferase; HCL, hydrochloride; HO, hospitalization; IG, immature granulocytes; IU, international unit; IV, intravenous; LDH, lactate dehydrogenase; LT, life-threatening; Mfr., manufacturer; OT, other serious outcome; PICC, peripherally inserted central catheter; PSA, prostate specific antigen; T2D, type 2 diabetes mellitus; TBL, total bilirubin; TPN, total parenteral nutrition; U.S., United States; UTI, urinary tract infection; XR, extended-release; WBC, white blood cell.

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/s/

FRANK PUCINO
02/21/2017

WILLIAM H CHONG
02/21/2017