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APPLICATION NUMBER:

205649Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205649
Priority or Standard	Standard
Submit Date(s)	
Received Date(s)	October 29, 2013
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Division / Office	DMEP/Office of New Drugs
Reviewer Name(s)	Kaveeta Vasisht MD, PharmD
Review Completion Date	
Established Name	Dapagliflozin/Metformin Extended Release (XR) Fixed-Dose Combination
(Proposed) Trade Name	Xigduo
Therapeutic Class	Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor + Biguanide
Applicants	AstraZeneca and Bristol-Myers Squibb
Formulation(s)	Oral tablet
Dosing Regimen	Dapagliflozin 5 mg + Metformin XR 500 mg Dapagliflozin 5 mg + Metformin XR 1000mg Dapagliflozin 10 mg + Metformin XR 500 mg Dapagliflozin 10 mg + Metformin XR 1000mg Once daily in the morning with food
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.
Intended Population(s)	Adults with Type 2 Diabetes Mellitus

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the dapagliflozin/metformin fixed-dose combination (FDC) product for the proposed indication for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate. There are adequate data demonstrating the effectiveness of the combination. My rationale for this recommendation is delineated in section 1.2 of this review.

Since other disciplines and signatory authorities are still reviewing this application, the final language may differ from my recommendation.

1.2 Risk Benefit Assessment

Two phase 3 studies compared the efficacy of dapagliflozin (5 mg and 10 mg, respectively) in combination with metformin extended release (XR) to the individual components and are directly related to the proposed dapagliflozin/metformin XR Fixed-dose Combination (FDC). These studies were designed to compare the change from baseline in glycosylated hemoglobin (HbA1c) achieved with dapagliflozin + metformin XR compared with dapagliflozin + placebo, and metformin XR + placebo, after 24 weeks of therapy. Both studies demonstrated statistically significant and clinically relevant reductions in HbA1c from baseline as well as superiority of the combination product over the individual components.

The efficacy assessment of dapagliflozin in combination with metformin was reviewed against the safety profile data from the New Drug Application (NDA) submission and the four month safety update. The overall incidence of serious fatal and nonfatal events was balanced between dapagliflozin plus metformin and placebo plus metformin. Adverse events with an imbalance not in favor of dapagliflozin were for events of: genital infections, urinary tract infections, volume depletion, polyuria and renal impairment. There were small mean increases in hematocrit associated with the combination of dapagliflozin and metformin compared to placebo and metformin treatment. These observed hematocrit increases were likely related to diuretic effect of dapagliflozin and the clinical relevance of these mild changes has not been elucidated. Of note, there was a slight increase in serum creatinine and decrease in estimated glomerular filtration rate (eGFR) with dapagliflozin 10 mg + metformin compared to placebo + metformin. The combination product will be contraindicated in patients with moderate-to-severe renal function and prescribers will be advised to monitor eGFR.

The identified safety concerns with the combination are concordant with the identified safety issues with dapagliflozin monotherapy. Review of the safety data did not identify safety concerns that would preclude the combined use of dapagliflozin with metformin.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Although additional postmarketing risk evaluation and mitigation strategies (REMS) have not been requested for this NDA, a final decision is pending at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

Specific postmarketing requirements and commitments for the dapagliflozin and metformin combination product are not being requested at the time of this review. However, postmarketing studies are required for dapagliflozin (NDA 202293). The sponsor's conducting the following clinical trial as a postmarketing requirement for dapagliflozin under NDA 202993.

- A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.

(b) (4)

They propose that the dapagliflozin pediatric studies (MB102091 and MB102138) to be conducted as a PREA requirement for NDA 202293 will adequately characterize the safety, efficacy, and tolerability of dapagliflozin as add-on to metformin therapy in T2DM patients who are 10 to 17 years of age. The applicants (Bristol-Myers Squibb and AstraZeneca [BMS/AZ]) also previously sought, and were granted, a waiver for the use of dapagliflozin in pediatric patients with T2DM who are less than 10 years of age because T2DM is uncommon in this age group.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor has submitted a 505(b)(2) new drug application for approval of dapagliflozin as a fixed-dose combination (FDC) with metformin HCl extended release (XR). The combination product is intended to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both dapagliflozin and metformin is appropriate.

The applicant referenced information from the dapagliflozin (Farxiga) NDA (202293) and from the metformin (Glucophage) NDA (020357).

The proposed dapagliflozin/metformin (DAPA/MET) FDC doses are:

- 5 mg dapagliflozin + 500 mg metformin XR
- 5 mg dapagliflozin + 1000 mg metformin XR
- 10 mg dapagliflozin + 500 mg metformin XR
- 10 mg dapagliflozin + 1000 mg metformin XR

Dapagliflozin is a selective and reversible inhibitor of the human renal sodium glucose cotransporter (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion.

Metformin is an antihyperglycemic agent of the biguanide class that lowers plasma glucose by increasing insulin sensitivity at peripheral tissues and by decreasing hepatic glucose output and intestinal glucose absorption.

The safety and tolerability of dapagliflozin both as monotherapy and in combination with other therapies for T2DM, including metformin, were documented and evaluated in the initial dapagliflozin New Drug Application (NDA 202-293), the 4-month safety update (4-MSU) submitted April 28,2011 (safety data cut-off, October 15,2010), the major amendment data submitted October 28,2011 (safety data cut-off, July 15,2011), and the 30-month update (30-MU) submitted to the agency on July 11, 2013 (data cut-off November 15, 2012).

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved drug therapies for the management of diabetes are detailed in Table 1.

Table 1: Current Available Antidiabetic Drug Products

Pharmacologic Class	Antidiabetic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-IV INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide, Exenatide; Liraglutide
INSULINS AND INSULIN ANALOGUES	Insulin Aspart; Insulin Detemir; Insulin Glargine; Insulin Glulisine; Insulin Isophane (NPH); Insulin Isophane and Regular; Insulin Lispro; Insulin Regular (human), Pre-mixed (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin, Dapagliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

Source: Adapted from NDA 20293 Dr. Pucino's Clinical Review dated December 22, 2013, Page 16.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substances dapagliflozin and metformin have been approved for the treatment of T2DM in the United States since December 2013 and March 1995, respectively.

2.4 Important Safety Issues with Consideration to Related Drugs

Canagliflozin is the only other SGLT2 inhibitor approved for use in the United States. As described in Dr. Kwon's clinical review of Canagliflozin, dated February 11, 2013, labeled safety concerns with canagliflozin include the following:

- Contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m²), end-stage renal disease, or on dialysis
- Increased hypotension risk in patients with renal impairment, low systolic blood pressure; in the elderly; or if on diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB)
- Impairment in renal function

- Increased hyperkalemia risk in patients with moderate renal impairment taking drugs that interfere with potassium excretion (ACEI or ARB)
- Hypoglycemia with concomitant use with insulin or insulin secretagogues
- Genital mycotic infections
- Hypersensitivity reaction
- Increased low-density lipoprotein cholesterol (LDL-C)
- Urinary tract infections

Labeled safety concerns with metformin include the following:

- Increased risk of lactic acidosis with sepsis, dehydration, excessive alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
- Contraindicated in patients with renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance)
- Potential for acute alteration of renal function when undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures requiring restricted intake of food and fluids.
- Decrease in Vitamin B12 levels
- Hypersensitivity
- Increased risk of hypoglycemia in elderly and debilitated patients when calorie intake is deficient, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 details the presubmission regulatory activity for the dapagliflozin/metformin FDC product.

Table 2: Presubmission Regulatory Activity

Serial No. (SN)/ Date	Type of Interaction	Description
SN0000 (15-Oct-2009) SN0033 (18-May-2011)	Correspondence	Agreement regarding a 3-month combination toxicity study to support submission of the NDA for the dapagliflozin/metformin XR FDC product.
SN0000 (15-Oct-2009), SN0017 (29-Jul-2010), SN0027 (30-Dec-2010) FDA letters dated 7-Jun-2010, 24-Sep-2010, and 16-Mar-2011	Correspondence	Agreement regarding two bioequivalence (BE) evaluations (5 mg dapagliflozin + 500 mg metformin XR FDC tablets and 10 mg dapagliflozin + 1000 mg metformin XR tablets versus their respective individual components) to support the dapagliflozin/metformin XR FDC
SN0000 (15-Oct-2009) FDA letter dated 07-Jun-2010	Correspondence	FDA agreed that the use of 2 x 500 mg GLUCOPHAGE XR as a reference for 1000 mg metformin XR in the FDC was acceptable.

Serial No. (SN)/ Date	Type of Interaction	Description
SN0000 (15-Oct-2009), SN0007 (16-Feb-2010) FDA letters dated 30-Dec-2009 and 25-May-2010	Correspondence	Agreement that Study MB102013 is adequate to support the (b) (4) dosing for the FDC, pending FDA approval of dapagliflozin.
SN0007 (16-Feb-2010) FDA letter dated 30-Dec-2009	Correspondence	FDA agreed the 4 planned FDCs (5 mg dapagliflozin + 500 mg metformin XR FDC, 10 mg dapagliflozin + 500 mg metformin XR FDC, 5 mg dapagliflozin + 1000 mg metformin XR FDC, and 10 mg dapagliflozin + 1000 mg metformin XR FDC) are adequate but noted that the sponsor must present a plan for patients who may be switched to the FDC who are on metformin XR 750 mg tablets.
SN0060 (5-Jul-2012) FDA preNDA feedback letter dated 1-Sep-2012, emails dated 9-December 2012, 30-Jan-2013, 8-Oct-2013, and 9-Oct-2013; Teleconference with the Agency on 28-Feb-2013, and FDA letter dated 19-Apr-2013	Pre-NDA	All pivotal phase 3 clinical trial study reports and datasets that support the DAPA/MET XR FDC NDA will be submitted. Agency granted a waiver from the 4-month safety update for the dapagliflozin/Metformin XR FDC NDA and requested listings and narratives for all serious adverse events, cancer cases and liver cases that occur during the time lapse interval of the cut-off for the NDA and the four month safety update.
April 14, 2014 TCON	Type C Meeting	Discussion regarding FDA's concerns for adverse events regarding the (b) (4) dosing of the FDC. The sponsor resubmitted the FDC label with a new dosing recommendation for AM dosing.

Source: Adapted from NDA 205649, Clinical Overview, Attachment 1: Dapagliflozin/Metformin XR FDC US IND 106,890 Regulatory History, Page 71-74

Abbreviations: NDA = FDC = fixed-dose combination; New Drug Application; SN = serial submission number; TCON = teleconference; XR = extended release

2.6 Other Relevant Background Information

The applicant was asked to clarify how patients on 2000 mg metformin XR will be covered using the DAPA/MET XR FDC product.

Sponsor's response:

The 1000-mg metformin XR strength does not correspond to a marketed Glucophage XR strength, but was developed specifically as part of dapagliflozin fixed-dose combination program to reduce the tablet burden for patients needing a 1000, 1500, or 2000-mg daily dose of metformin XR. The proposed dose strengths for the metformin XR component of the dapagliflozin/metformin XR FDC products directly provide 3 of the 4 recommended doses of Glucophage XR (500, 1000 and 2000 mg QD):

- 1. The recommended usual daily starting dose of 500 mg Glucophage XR: One tablet of 5-mg or 10-mg dapagliflozin /500 mg metformin XR FDC QD*
- 2. The first recommended up-titration dose of Glucophage XR (1000 mg): One tablet of dapagliflozin 5 or 10 mg/ 1000 mg metformin XR FDC QD*

3. *The recommended maximum daily dose of Glucophage XR (2000 mg): Two tablets of dapagliflozin 5 mg/ 1000 mg metformin XR QD*

[REDACTED] (b) (4)

The 5-mg dapagliflozin/2000-mg metformin XR dose can be readily provided as one tablet of 5-mg dapagliflozin/1000-mg metformin XR FDC given with 1000-mg metformin XR/ER QD or with multiple options of Glucophage XR tablets QD.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable.

3.2 Compliance with Good Clinical Practices

All data for safety evaluations were collected and reported according to Good Clinical Practice guidelines.

3.3 Financial Disclosures

Financial Disclosure information was not being provided for the 12 clinical studies supporting the efficacy and safety for dapagliflozin when used with metformin since these were previously submitted to dapagliflozin NDA 202293. Financial Disclosure was provided for five biopharmaceuticals studies. The applicant states that the investigators did not have any information to disclose.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

At the time of this review, several of the other review disciplines had not yet submitted their final reviews. However, significant efficacy or safety issues were not identified by these disciplines at the time of this review that would influence the approval of this NDA.

4.1 Chemistry Manufacturing and Controls

Information regarding dapagliflozin drug substance may be found in NDA 202293.

Information regarding metformin hydrochloride drug substance may be found in [REDACTED] (b) (4) [REDACTED] Type II Drug Master Files, DMF # [REDACTED] (b) (4) site and DMF # [REDACTED]

(b) (4) site. Letters of Authorization for these DMFs can be found in Section 1.4.1, *Letters of Authorization/Access*.

The dapagliflozin/metformin XR FDC program was aimed to develop a reduced mass metformin XR component to decrease the tablet size, and potentially improve patient acceptability. (b) (4)

Dapagliflozin/metformin XR FDC tablets are (b) (4) a (b) (4) tablet configuration using (b) (4) dapagliflozin and metformin (b) (4). The dapagliflozin (b) (4) is formulated for immediate release (IR), whereas the metformin (b) (4) is formulated to provide extended release.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

See relevant review by Dr. Mukesh Summan dated June 11, 2014 for full details.

Dapagliflozin/metformin combination repeat dose oral toxicity studies were conducted in rats for up to 3 months.

There was no evidence of new toxicities or biologically relevant exacerbation of existing dapagliflozin-related effects when administered together with metformin. There were no differences in toxicokinetics or unique or synergistic toxicity outcomes in rats dosed with the coadministration of dapagliflozin and metformin at area under the curve (AUC) multiples up to 52X and 1X the maximum recommended human dose (MRHD) for dapagliflozin and metformin.

There do not appear to be any nonclinical findings that preclude the safe administration of dapagliflozin in combination with metformin at the proposed daily doses up to 10 mg and 2000 mg, respectively.

4.4 Clinical Pharmacology

See relevant review by Dr. Suryanarayana Sista for full details.

The dapagliflozin/metformin XR FDC program consists of five biopharmaceutical studies (three relative bioavailability [BA] and two bioequivalence [BE] studies) that are described in Table 3.

Table 3: Summary of Biopharmaceutical Studies

Study Number	Study Description (Dapagliflozin Dose[s] Used in the Study)
MB102060	Relative bioavailability of a prototype 1000 mg metformin XR tablet FDC core and 2 x 500 mg Glucophage XR tablets (no dapagliflozin dosed in this study)
MB102071	Fasted-state relative bioavailability of two prototype 10 mg dapagliflozin + 500 mg metformin XR FDCs versus the corresponding monocomponent tablets
MB102065	Fasted-state relative bioavailability of two prototype 10 mg dapagliflozin + 1000 mg metformin XR FDCs versus the corresponding monocomponent tablets
MB102092	Fed-state bioequivalence of 5 mg dapagliflozin + 500 mg metformin XR FDC versus the corresponding monocomponent tablets and food effect and steady-state PK characterizations of the 5/500 FDC.
MB102100	Fed-state bioequivalence of 10 mg dapagliflozin + 1000 mg metformin XR FDC versus the corresponding monocomponent tablets and food effect and steady-state PK characterizations of the 10/1000 FDC.

Source: Summary of Clinical Pharmacology: Table 11, Page 9

Abbreviations: FDC = fixed-dose combination; XR = extended release

Results from the BE studies showed that both the 5/500 mg and 10/1000 mg dapagliflozin/metformin XR FDC formulations were bioequivalent to their individual components administered together in the fasted state.

It has been previously established in a clinical drug-drug interaction study that there was no effect of coadministration of dapagliflozin with metformin on either drug's pharmacokinetics.

4.4.1 Mechanism of Action

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose cotransporter (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion.

Metformin is an antihyperglycemic agent of the biguanide class that lowers plasma glucose by increasing insulin sensitivity at peripheral tissues and by decreasing hepatic glucose output and intestinal glucose absorption.

4.4.2 Pharmacodynamics

In patients with T2DM receiving dapagliflozin, approximately 70 grams of glucose may be excreted in the urine per day following 10 mg daily doses of dapagliflozin. Urinary

volume is increased as a result of osmotic diuresis associated with glucose excretion in the urine.

4.4.3 Pharmacokinetics

Dapagliflozin

The following is from Dr. Pucino's dapagliflozin review dated December 22, 2013 under the 30-MSU for dapagliflozin (NDA 202293):

"Following oral administration, the bioavailability of dapagliflozin is approximately 78%, reaching maximum plasma concentrations (C_{max}) within approximately two hours (T_{max}) under fasting state. The T_{max} may be delayed approximately one hour when dapagliflozin is administered with a high-fat meal. Dapagliflozin is approximately 91% protein-bound, which is not altered by renal or hepatic impairment. It is inactivated by UDP-glucuronosyltransferase 1A9 (UGT1A9), an enzyme present in the liver and kidney, to an inactive glucuronidated metabolite (dapagliflozin 3-O-glucuronide) and has an elimination half-life of approximately 12 hours. Approximately 75% of a dose is recovered in the urine following oral administration.

Compared to healthy subjects, exposure to dapagliflozin in patients with moderate and severe hepatic impairment was 36% and 67% higher, respectively. No dose adjustment is recommended for patients with hepatic impairment (mild to severe) in the proposed product labeling. There is also no dose adjustment based on renal function. However, the efficacy of dapagliflozin is dependent on the filtered load of glucose, which in turn is dependent on GFR. The Applicant proposes that dapagliflozin should not be taken by patients with moderate renal impairment (defined estimated glomerular filtration [eGFR] rate <60 mL/min/1.73 m² or creatinine clearance [CrCl₂] <60 mL/min).

The drug-drug interaction studies conducted during the clinical program demonstrated that dapagliflozin has limited potential to either affect the metabolism of other drugs or have its metabolism meaningfully affected by coadministration with other drugs."

Metformin

The absolute bioavailability of metformin is about 50-60%. It is minimally bound to plasma proteins. Metformin is excreted unchanged in the urine, with tubular secretion as the major route of elimination. The half-life after oral administration is about 6 hours in the plasma.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Twelve phase 3 studies were submitted in support of the efficacy, safety and tolerability of dapagliflozin + metformin XR FDC tablets. These studies include evaluation of a dapagliflozin/metformin XR initial combination in drug-naïve patients, as well as studies of dapagliflozin in combination with metformin XR or IR in patients on other antihyperglycemic background therapies such as insulin or DPP-IV inhibitors. These trials are described in Table 4.

Table 4: Phase 3 Clinical Trials Supporting the Dapagliflozin/Metformin Fixed-Dose Combination Product

Study No. Metformin Formulation	Study Type/Population	Primary Efficacy Study Duration Extension Period	No. Patients Treated DAPA+MET	No. Patients Treated with Comparator
Studies of Dapagliflozin/Metformin XR Initial Combination				
MB102034 Initial combination with metformin versus control and monotherapy XR	Phase 3, randomized, parallel-group, double-blind, active-controlled; PM dosing Treatment-naive patients with HbA1c $\geq 7.5\%$ – $\leq 12.0\%$ 3 groups: <ul style="list-style-type: none"> dapagliflozin 10 mg + metformin XR up to 2000 mg dapagliflozin 10 mg metformin XR up to 2000 mg Background therapy: None	Superiority: change in HbA1c at 24 weeks versus metformin alone and versus dapagliflozin alone 24 weeks (completed)	211 (DAPA 10 mg + MET)	219 (DAPA 10 mg) 208 (MET alone)
MB102021 Initial combination with metformin versus control and monotherapy XR	Phase 3, randomized, parallel-group, double-blind, active-controlled; PM dosing Treatment-naive patients with HbA1c $\geq 7.5\%$ – $\leq 12.0\%$ 3 groups: <ul style="list-style-type: none"> dapagliflozin 5 mg + metformin XR up to 2000 mg dapagliflozin 5 mg metformin XR up to 2000 mg Background therapy: None	Superiority: change in HbA1c at 24 weeks versus metformin alone and versus dapagliflozin alone 24 weeks (completed)	194 (DAPA 5 mg + MET)	203 (DAPA 5 mg) 201 (MET)
Studies of Dapagliflozin Add-on to Metformin				
MB102014 Add-on to metformin versus placebo XR or IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients on metformin ≥ 1500 mg/day with HbA1c $\geq 7.0\%$ – $\leq 10.0\%$ 4 groups: <ul style="list-style-type: none"> dapagliflozin 2.5, 5, or 10 mg placebo Background therapy: metformin ≥ 1500 mg/day	Superiority: change in HbA1c at 24 weeks versus placebo 24 weeks plus 78 weeks (completed)	137 (DAPA 5 mg + MET) 135 (DAPA 10 mg + MET) 137 (DAPA 2.5 mg + MET)	137 (placebo + MET)

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Dapagliflozin/Metformin XR FDC

Study No. Metformin Formulation	Study Type/Population	Primary Efficacy Study Duration Extension Period	No. Patients Treated DAPA+MET	No. Patients Treated with Comparator
D1690C00012 Add-on to metformin versus placebo IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients on metformin ≥ 1500 mg/day with HbA1c with $\geq 6.5\% - \leq 8.5\%$ 2 groups: <ul style="list-style-type: none"> dapagliflozin 10 mg placebo Background therapy: metformin >1500 mg	Superiority: change in total body weight at 24 weeks versus placebo 24 weeks plus 26 weeks plus 52 weeks (completed)	91 (DAPA 10 mg + MET)	91 (placebo + MET)
D1690C00004 Add-on to metformin versus active comparator IR	Phase 3, randomized, parallel-group, double-blind, active-controlled Patients on metformin >1500 mg/day with HbA1c $\geq 6.5\% - \leq 10.0\%$ 2 groups: <ul style="list-style-type: none"> dapagliflozin titrated dose of 2.5, 5, or 10 mg glipizide titrated dose of 5, 10, or 20 mg Background therapy: metformin >1500 mg	Noninferiority: change in HbA1c at 52 weeks vs. glipizide 52 weeks plus 52 weeks (completed) plus 104 weeks (ongoing at time of data cut)	406 (DAPA titrated to 2.5 mg, 5 mg, 10 mg + MET)	408 (glipizide titrated to 5 mg, 10 mg, 20 mg + MET)

Studies of Dapagliflozin for which Some of the Patients were on Metformin Background Therapy

D1690C00006 Add-on to insulin \pm OADs (incl. MET) versus placebo IR or XR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients with HbA1c with $\geq 7.5\% - \leq 10.5\%$ 4 groups: <ul style="list-style-type: none"> dapagliflozin 2.5, 5, or 10 mg placebo Background therapy: insulin (least 30 IU of injectable insulin per day) \pm OADs, including metformin	Superiority: change in HbA1c at 24 weeks versus placebo 24 weeks plus 24 weeks plus 56 weeks (completed)	Add-on to metformin subgroup 84 (DAPA 10 mg + insulin + MET) 79 (DAPA 5mg + insulin + met)	Add-on to metformin subgroup 80 (placebo + insulin + MET)
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Kaveeta P. Vasisht MD, PharmD
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Dapagliflozin/Metformin XR FDC

Study No. Metformin Formulation	Study Type/Population	Primary Efficacy Study Duration Extension Period	No. Patients Treated DAPA+MET	No. Patients Treated with Comparator
D1690C00010 Add-on to sitagliptin ± metformin versus placebo IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients with HbA1c with $\geq 7.0\%$ – $\leq 10.0\%$ 2 groups: <ul style="list-style-type: none"> dapagliflozin 10 mg placebo Background therapy: sitagliptin 100 mg ± MET (≥ 1500 mg/day)	Superiority: change in HbA1c at 24 weeks versus placebo 24 weeks plus 24 weeks (completed)	Add-on to metformin subgroup 114 (DAPA 10 mg + sitagliptin + MET)	Add-on to metformin subgroup 114 (placebo + sitagliptin + MET)
D1690C00018 Add-on to usual care XR or IR	Phase 3, randomized, double-blind, age-stratified, placebo-controlled Men ≥ 45 years of age and women ≥ 50 years of age diagnosed with T2DM, cardiovascular disease, and hypertension with HbA1c $\geq 7.2\%$ - $\leq 10.5\%$ <ul style="list-style-type: none"> dapagliflozin 10 mg placebo Background therapy: usual care, including metformin (52 % of patients received also insulin)	Superiority: change in HbA1c at 24 weeks versus placebo 24 plus 28 weeks plus 52 weeks (completed)	Add-on to metformin subgroup 165 (DAPA 10 mg + MET)	Add-on to metformin subgroup 159 (placebo + MET)
D1690C00019 Add-on to usual care XR or IR	Phase 3, randomized, double-blind, age-stratified, placebo-controlled Men ≥ 45 years of age and women ≥ 50 years of age diagnosed with T2DM and cardiovascular disease with HbA1c $\geq 7.2\%$ - $\leq 10.5\%$ <ul style="list-style-type: none"> dapagliflozin 10 mg placebo Background therapy: usual care, including metformin (61 % of patients received also insulin)	Superiority: change in HbA1c at 24 weeks versus placebo 24 plus 28 weeks plus 52 weeks (completed)	Add-on to metformin subgroup 183 (DAPA 10 mg + MET)	Add-on to metformin subgroup 195 (placebo + MET)

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Study No. Metformin Formulation	Study Type/Population	Primary Efficacy Study Duration Extension Period	No. Patients Treated DAPA+MET	No. Patients Treated with Comparator
MB102073 Add-on to usual T2DM care; Add- on to antihypertensive XR or IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients with T2DM and inadequately controlled hypertension despite pre-existing stable antihypertensive treatment with an ACEI or ARB, as well as inadequate glycemic control (HbA1c \geq 7.0% and \leq 10.5%) despite pre-existing stable treatment with oral antidiabetics (OADs) or insulin (alone or in combination) at baseline. <ul style="list-style-type: none"> dapagliflozin 10 mg placebo. 	Superiority: change in seated SBP & HbA1c at week 12 versus placebo (coprimary endpoints)	Add-on to metformin subgroup 276 (DAPA 10 mg + MET)	Add-on to metformin subgroup 282 (placebo + MET)
MB102077 Add-on to usual T2DM care; Add-on to Antihypertensive XR or IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Patients with T2DM and inadequately controlled hypertension despite pre-existing stable antihypertensive treatment with an ACEI or ARB + additional antihypertensive drug, as well as inadequate glycemic control (HbA1c \geq 7.0% and \leq 10.5%) despite preexisting stable treatment with oral antidiabetics (OADs) or insulin (alone or in combination) at baseline. <ul style="list-style-type: none"> dapagliflozin 10 mg placebo 	Superiority: change in seated SBP & HbA1c at week 12 versus placebo (coprimary endpoints) 12 weeks (completed)	<u>Overall Population</u> 224 (DAPA 10 mg + OAD) <u>Add-on to metformin subgroup</u> 203 (DAPA 10 mg + MET)	<u>Overall Population</u> 224 (placebo + OAD) <u>Add-on to metformin subgroup</u> 206 (placebo + MET)

Dapagliflozin Administered in the evening (PM) as Monotherapy

MB102013 Monotherapy versus placebo IR	Phase 3, randomized, parallel-group, double-blind, placebo-controlled Drug-naive patients with baseline HbA1c \geq 7.0% - \leq 10.0% 7 groups <ul style="list-style-type: none"> dapagliflozin 2.5, 5 or 10 mg, QAM dapagliflozin 2.5, 5 or 10 mg, QPM placebo 	Superiority: change in HbA1c at 24 weeks versus placebo 24 plus 102 weeks (completed)	76 ST (DAPA 10 mg PM alone) 65 LT (DAPA 10 mg + MET matching placebo)	75 ST (placebo alone) 62 LT (placebo + MET)
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Clinical Review
Kaveeta P. Vasisht MD, PharmD
NDA 205649
Dapagliflozin/Metformin XR FDC

Source: Modified from Integrated Summary of Safety (ISS): Table 1, Page 13-16. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CSR = clinical study report; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin; IR = immediate release; IU = international unit; LT = long-term; MET = metformin; OAD = oral antidiabetic drug; QAM = once-daily morning dosing; QPM = once-daily evening dosing; SBP = systolic blood pressure; ST = short-term; T2DM = type 2 diabetes mellitus; XR = extended release, No.= number of.

5.2 Review Strategy

Five biopharmaceutics studies were submitted in support of the dapagliflozin/metformin FDC and were evaluated by Dr. Sury Sistanarayana.

There were no new phase 3 studies submitted in support of the dapagliflozin/metformin FDC NDA. All of the clinical data supporting the efficacy and safety of dapagliflozin when used with metformin were previously submitted to the dapagliflozin NDA (202293) up through the 30-month update (30MU). Of note, the same data cut-off dates for the studies supporting the DAPA/MET XR FDC NDA were used in the 30MU for dapagliflozin.

Two of the 12 phase 3 studies (MB102021 and MB102034) compared dapagliflozin + metformin to the individual components and are directly related to the dapagliflozin/metformin XR fixed-dose Combination (FDC). Dr. Wei Liu and Dr. John Norton conducted separate biostatistical analyses to confirm the primary and major secondary endpoints for these studies.

The applicant submitted twelve phase 3 studies in support of the safety and tolerability of the dapagliflozin/metformin FDC. The primary focus of this safety review is on the placebo-controlled short term (ST) and long-term (LT) pooled data of eight studies. The active comparator pool of nine studies was reviewed for significant discrepancies from the placebo-controlled pool. See Section 7.1.3 for details of pooling of data for the safety analysis. In addition, the 4-Month Safety Update (4-MSU) submitted by the applicant was reviewed for updated safety information.

5.3 Discussion of Individual Studies/Clinical Trials

As previously stated, all of the studies submitted in support of the dapagliflozin /metformin FDC NDA were previously reviewed. Refer to clinical reviews by Dr. Somya Dunn (dated September 2, 2011 and November 21, 2011) and Dr. Frank Pucino (dated December 22, 2013) and statistical reviews by Dr. Wei Liu (dated December 13 2013) and Dr. John Norton (dated September 9, 2011 and November 21, 2011) for detailed discussions related to the overall design of these studies.

Key inclusion and exclusion criteria are described below for the DAPA/MET program.

Key Inclusion Criteria:

Patients between 18 and 79 years of age with diagnosed T2DM, and a body mass index (BMI) ≤ 45 kg/m². The range of HbA1c inclusion values collectively across studies ranged from $>6.5\%$ to $\leq 12\%$.

Key Exclusion Criteria:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3X upper limit of normal (ULN)
- Serum total bilirubin (TBL) >2 mg/dL (>1.5X ULN in MB102073 and MB102077)
- Creatinine kinase >3X ULN
- Serum creatinine ≥ 1.5 mg/dL for men; serum creatinine ≥ 1.4 mg/dL for women and/or creatinine clearance <60 mL/min. In study D1690C00006, patients with estimated creatinine clearance <50 mL/min (calculated by Cockcroft-Gault formula)
- Urine albumin:creatinine ratio >1800 mg/g
- History of poorly controlled diabetes such as polyuria and polydipsia with >10% weight loss 3 months prior to enrollment and or ketoacidosis
- History of unstable or rapidly progressing renal disease
- Severe uncontrolled hypertension (systolic blood pressure [SBP] ≥ 180 mmHg and/or diastolic blood pressure [DBP] ≥ 110 mmHg)
 - D1690C00018 and D1690C00019, BP exclusion criteria were divided between measurements at enrollment (Visit 1) of SBP ≥ 165 mmHg and/or DBP ≥ 100 mmHg; and at randomization (Visit 4) of SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg
- Major cardiac adverse events within 6 months of enrollment (within 2 months of enrollment in D1690C00018 and D1690C00019)
- Active or unstable renal or hepatic disease
- Congestive heart failure (CHF) New York Heart Association (NYHA) Class III and IV (NYHA Class IV only in D1690C00018 and D1690C00019)

Discontinuation criteria relevant to renal function:

- Patients with serum creatinine ≥ 1.50 mg/dL but <2.00 mg/dL (men) or ≥ 1.40 mg/dL but <2.00 mg/dL (women) OR patients (men or women) with an increase from baseline in serum creatinine of >0.50 mg/dL, had metformin withheld and a confirmatory, repeat serum creatinine drawn within 1 week.
- Patients with serum creatinine ≥ 2.0 mg/dL (men and women) had both study medication and metformin withheld and a confirmatory repeat serum creatinine drawn within 1 week. If the repeat serum creatinine was ≥ 1.50 mg/dL (men) or ≥ 1.40 mg/dL (women), the patient was immediately discontinued

6 Review of Efficacy

Efficacy Summary

The efficacy of dapagliflozin/metformin XR fixed-dose Combination is primarily supported by two phase 3 studies (MB102034 and MB102021). These studies compared the change from baseline in hemoglobin (HbA1c), achieved with dapagliflozin

(5mg and 10 mg) + metformin XR compared with the individual components. In both studies the combination of dapagliflozin and metformin XR resulted in a significant reduction in HbA1c and fasting plasma glucose (FPG) from baseline, and was found to be statistically superior to the individual components for both endpoints. In addition, both studies demonstrated a significant reduction in body weight from baseline and compared to metformin monotherapy.

6.1 Indication

As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

6.1.1 Methods

Since all the phase 3 studies were previously submitted and reviewed under the dapagliflozin NDA (202293), this review briefly summarizes the efficacy of the phase 3 trials the applicant is proposing to label to support the efficacy of the combination product. These trials are briefly described in Table 5.

Table 5: Efficacy Studies Supporting Dapagliflozin in Combination with Metformin

Study	Brief Description	Study Drug Dose	Background Tx (Rescue)	Comparator Dose	Weeks
MB102021	Drug-naïve monotherapy	DAPA 5 mg + MET XR	None	DAPA 5 mg, MET XR	24
MB102034	Drug-naïve monotherapy	DAPA 10 mg + MET XR	None	DAPA 10 mg, MET XR	24
D1690C0000 4	Add-on to Metformin versus Active comparator	DAPA 2.5, 5 mg, 10 mg + MET IR	Metformin >1500 mg	Glipizide 5 mg, 10 mg, 20 mg + MET	52
D1690C0001 0	Add-on to Sitagliptin ± Metformin versus Placebo	DAPA 10 mg + Sitagliptin + MET	Sitagliptin 100 mg ± MET (≥1500 mg/day)	Placebo + Sitagliptin + MET	24
D1690C0000 6	Subgroup : Add-on to Insulin + MET versus Placebo	DAPA 10 mg + Insulin + MET DAPA 5 mg + Insulin + MET	Background therapy: Insulin (at least 30 IU of injectable Insulin per day) + Metformin	Placebo + Insulin + MET	24
MB102014	Subgroup: Add-on to Metformin versus Placebo	DAPA 2.5 mg + MET DAPA 5 mg + Met DAPA 10 mg + MET	Metformin ≥ 1500 mg/day	Placebo + MET	24

Reviewer Generated. Source: Integrated Summary of Safety: Table 1, Page 13-16

Abbreviations: DAPA = dapagliflozin; IU = international units; MET = metformin; XR = extended release

6.1.2 Demographics

Refer to prior clinical reviews by Dr. Somya Dunn (dated September 2, 2011 and November 21, 2011) and Dr. Frank Pucino (dated December 22, 2013) and prior statistical review by Dr. John Norton and Dr. Wei Liu for specific details pertaining to these trials.

6.1.3 Subject Disposition

Refer to prior clinical reviews by Dr. Somya Dunn (dated September 2, 2011 and November 21, 2011) and Dr. Frank Pucino (dated December 22, 2013) and prior statistical review by Dr. John Norton (dated September 9, 2011 and November 21, 2011) and Dr. Wei Liu (dated December 13 2013), for specific details pertaining to these trials.

6.1.4 Analysis of Primary Endpoint(s)

Two of the phase 3 studies compared dapagliflozin + metformin to the individual components and are directly related to the dapagliflozin/metformin XR fixed-dose Combination (FDC).

Initial Combination Studies with Metformin XR

Study MB102034

This study was a randomized, double-blind, active-controlled, parallel-group study designed to compare the change from baseline in glycosylated hemoglobin (HbA1c), achieved with dapagliflozin 10 mg + metformin XR compared with dapagliflozin 10 mg + placebo, and metformin XR + placebo, after 24 weeks of therapy.

The study population included drug-naïve men and women with type 2 diabetes, age ≥ 18 to ≤ 77 years old, who had inadequate glycemic control, defined as HbA1c $\geq 7.5\%$ and $\leq 12.0\%$. The primary analyses were based on similar analysis of covariance (ANOVA) models using the last observation carried forward (LOCF) method for missing observations. The primary efficacy endpoint was change in HbA1c at week 24. As noted in Dr. Norton's statistical review under the dapagliflozin NDA (202293), in order for the study to be deemed positive, the combination of dapagliflozin and metformin had to be statistically superior to each individual component.

As described in Table 6, the combination of dapagliflozin 10 mg + metformin XR up to 2000 mg resulted in statistically and clinically significant mean reductions in HbA1c as compared to both the dapagliflozin 10 mg monotherapy group and the metformin XR monotherapy group.

For the secondary endpoint of fasting plasma glucose (FPG), the combination of dapagliflozin + metformin XR resulted in statistically significant mean reductions in FPG as compared to both the dapagliflozin 10 mg monotherapy group and the metformin XR monotherapy group. A higher proportion of patients achieved a therapeutic glycemic response defined as HbA1c <7% in the dapagliflozin + metformin treatment group. The differences in body weight reductions between the dapagliflozin + metformin treatment group compared with the metformin treatment group were statistically significant in favor of dapagliflozin + metformin when compared to metformin alone at week 24. As noted in Dr. Norton's statistical review, the combination of dapagliflozin + metformin XR was found to be statistically superior to the individual components for HbA1c and FPG and body weight (compared to metformin).

Table 6: Efficacy Results of Dapagliflozin 10 mg + Metformin XR

Study MB102034	Treatment Arm		
	Dapagliflozin 10 mg + Metformin XR N=211	Dapagliflozin 10 mg N=219	Metformin XR N=208
HbA1c (%)			
Baseline (mean)	9.1	9.0	9.0
Change from baseline (adjusted mean*)	-2.0	-1.5	-1.4
Difference from dapagliflozin (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3) p < 0.0001		
Difference from metformin XR (adjusted mean) (95% CI)	-0.5 (-0.8, -0.3) p < 0.0001	0.0 (-0.2, 0.2) p < 0.05	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6 p < 0.05	31.7	35.2
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean)	-60.4	-46.4	-34.8
Difference from dapagliflozin (adjusted mean) (95% CI)	-13.9 (-20.9, -7.0) p < 0.0001		
Difference from metformin XR (adjusted mean) (95% CI)	-25.5 (-32.6, -18.5) p < 0.0001	-11.6 (-18.6, -4.6) p < 0.05	
Body Weight (kg)			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted mean)	-3.3	-2.7	-1.4
Difference from metformin XR (adjusted mean) (95% CI)	-2.0 (-2.6, -1.3) p < 0.0001	-1.4 (-2.0, -0.7) p < 0.0001	

Source: CSR MB102034 Table 7.1. * All adjusted means in the table = least squares mean adjusted for baseline values. Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; XR = extended release

Study MB102021

This study was a randomized, double-blind, active-controlled, parallel-group study designed to compare the change from baseline in hemoglobin (HbA1c), achieved with dapagliflozin 5 mg + metformin XR compared with dapagliflozin 5 mg + placebo, and compared with metformin XR + placebo after 24 weeks of therapy.

The study population included drug-naïve men and women with type 2 diabetes, age ≥18 to ≤77 years, who had inadequate glycemic control, defined as HbA1c ≥7.5% and ≤12.0%. The primary analyses were based on similar ANOVA models using the last

observation carried forward (LOCF) method for missing observations. The primary efficacy endpoint was the comparison of the change from baseline in hemoglobin A1C (HbA1c) achieved with dapagliflozin 5 mg plus metformin extended release (XR) versus dapagliflozin 5 mg plus placebo, and versus metformin XR plus placebo after 24 weeks of treatment. As noted in Dr. Liu’s review, in order for the study to be deemed positive, the combination of dapagliflozin and metformin had to be statistically superior to each individual component for the change in HbA1c from baseline.

As described in

Table 7, the combination of dapagliflozin 5 mg + metformin XR up to 2000 mg resulted in statistically and clinically significant mean reductions in HbA1c as compared to both the dapagliflozin 5 mg and the metformin XR monotherapy groups. For the secondary endpoint of fasting plasma glucose (FPG), the combination of dapagliflozin + metformin XR resulted in statistically significant mean reductions in FPG as compared to both the dapagliflozin 5 mg monotherapy group and the metformin XR monotherapy group. A higher proportion of patients achieved a therapeutic glycemic response defined as HbA1c <7% in the dapagliflozin + metformin treatment group. The differences in body weight reductions were statistically significant in favor of dapagliflozin + metformin when compared to metformin alone at week 24. As noted in Dr. Liu’s statistical review, the combination of dapagliflozin + metformin XR was found to be statistically superior to the individual components for the endpoints of HbA1c, FPG and body weight (compared to metformin).

Table 7: Efficacy Results of Dapagliflozin 5 mg + Metformin XR

Study MB102021	Treatment Arm		
	Dapagliflozin 5 mg + Metformin XR N=194	Dapagliflozin 5 mg N=203	Metformin XR N=201
Efficacy Parameter			
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean*)	-2.1	-1.2	-1.4
Difference from dapagliflozin (adjusted mean) (95% CI)	-0.9 (-1.1, -0.6) p <0.0001		
Difference from metformin XR (adjusted mean) (95% CI)	-0.7 (-0.9, -0.5) p <0.0001		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4 p<0.05	22.5	34.6
FPG (mg/dL)			
Baseline (mean)	193.4	190.8	196.7
Change from baseline (adjusted mean)	-61.0	-42.0	-33.6

Study MB102021	Treatment Arm		
Difference from dapagliflozin (adjusted mean) (95% CI)	-19.1 (-26.7, -11.4) p <0.0001		
Difference from metformin XR (adjusted mean) (95% CI)	-27.5 (-35.1, -19.8) p <0.0001		
Body Weight (kg)			
Baseline (mean)	84.2	86.2	85.8
Change from baseline (adjusted mean)	-2.7	-2.6	-1.3
Difference from metformin XR (adjusted mean) (95% CI)	-1.4 (-2.0, -0.7) p <0.0001		

Source: CSR MB102021 Table 7.1, * All adjusted means in the table = Least squares mean adjusted for baseline values.

Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; XR = extended release

Reviewer Comment: In both study MB102034 and MB102021, the combination of dapagliflozin + metformin XR demonstrated statistically significant and clinically meaningful reductions in HbA1c by 24 weeks. As noted in Dr. Wei Liu’s review “The combination of DAPA + MET is superior to each component in the two studies based on the primary endpoint HbA1c change from baseline at Week 24”. In addition, secondary endpoints of FPG and therapeutic glycemic response defined as HbA1c <7% were statistically significant and favorable for the combination compared to the individual components. These studies are appropriate for inclusion in the product label.

Add-on to Metformin

Study MB102014

This study was a randomized, double-blind, parallel-group study designed to compare the change from baseline in HbA1c achieved with dapagliflozin plus metformin versus placebo plus metformin after 24 weeks of treatment. Dapagliflozin was added on (5 mg or 10 mg) for patients who had been receiving stable metformin (XR or IR) therapy for at least 8 weeks prior to enrollment, at doses ≥ 1500 mg per day.

The study population included men and women with type 2 diabetes, age 18 to ≤ 77 years old, with inadequate glycemic control, defined as HbA1c $\geq 7.0\%$ and $\leq 10\%$. The primary efficacy endpoint was change in HbA1c from baseline at week 24.

As depicted in Table 8, addition of either dose of dapagliflozin (5 or 10 mg) to metformin treatment resulted in significant reductions in both HbA1c and FPG compared to placebo. In addition a greater number of patients in the DAPA group met therapeutic glycemic response of HbA1c <7% when adjusted for baseline HbA1c value. In addition

dapagliflozin + metformin treatment demonstrated a larger reduction in body weight when compared to placebo.

Table 8: Efficacy Results of Dapagliflozin (5 or 10 mg) Added on to Metformin

Study MB102014	Treatment Arm		
Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=135	Dapagliflozin 5 mg + Metformin N=137	Placebo + Metformin N=137
HbA1c (%)			
Baseline (mean)	7.9	8.2	8.1
Change from baseline (adjusted mean*)	-0.8	-0.7	-0.3
Difference from placebo (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3) p<0.0001	-0.4 (-0.6, -0.2) p<0.0001	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6% p<0.05	37.5% p<0.05	25.9%
FPG (mg/dL)			
Baseline (mean)	156.0	169.2	165.6
Change from baseline at Week 24 (adjusted mean)	-23.5	-21.5	-6.0
Difference from placebo (adjusted mean) (95% CI)	-17.5 (-25.0, -10.0) p<0.0001	-15.5 (-22.9, -8.1) p<0.0001	
Body Weight (kg)			
Baseline (mean)	86.3	84.7	87.7
Change from baseline (adjusted mean)	-2.9	-3.0	-0.9
Difference from placebo (adjusted mean) (95% CI)	-2.0 (-2.6, -1.3) p<0.0001	-2.2 (-2.8, -1.5) p<0.0001	

Source: CSR MB102014, Table 7.1. Primary Clinical Review by Dr. Somya Dunn dated September, 2011 and Primary Statistical Review by Dr. John Norton dated September 2011. * All adjusted means in the table = Least squares mean adjusted for baseline values.

Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; XR = extended release

Exploratory assessment of the change from baseline in seated systolic blood pressure in patients with baseline seated systolic blood pressure >140 mmHg revealed dose-related decreases in seated SBP in the DAPA + MET 10 mg (-4.3 mmHg) and DAPA + MET 5 mg (-5.1 mmHg) arms at 24 weeks.

Review Comment: The addition of dapagliflozin to metformin therapy was effective in lowering HbA1c and FPG in patients with T2DM who had inadequate glycemic control on metformin alone. This study supports the combination of dapagliflozin and metformin, and is appropriate for labeling.

Active Comparator Study (Add-on to Metformin)

Study D1690C00004

This study was a randomized, double-blind, parallel-group study designed to examine if the absolute change from baseline in HbA1c with dapagliflozin (5 mg or 10 mg) plus metformin was noninferior (noninferiority margin of 0.35%) to glipizide plus metformin in patients with T2DM, who had inadequate glycemic control on metformin ≥ 1500 mg/day, after 52 weeks oral administration of double-blind treatment.

The study population included men and women with type 2 diabetes, age ≥ 18 years, with inadequate glycemic control, defined as HbA1c $\geq 6.5\%$ and $\leq 10\%$.

The noninferiority of the primary variable was tested first (one-sided 0.025 significance level) followed by the key secondary variable of body weight. The primary efficacy variable was analyzed with an analysis of covariance model (ANCOVA)

Treatment with both dapagliflozin and glipizide resulted in a mean reduction of 0.52% in HbA1c compared to baseline at week 52. Dapagliflozin was noninferior to glipizide for change in HbA1c at week 52. In addition, a statistically significant mean reduction in body weight from baseline to week 52 compared to glipizide was observed in the dapagliflozin treatment group. Although reductions in FPG values were noted in both treatment arms, the difference between treatment groups was not statistically significant.

Table 9: Efficacy Results of Active Comparator Study (Glipizide)

Study D1690C00004	Treatment Arm	
	Dapagliflozin + Metformin N=400	Glipizide + Metformin N=401
Efficacy Parameter		
HbA1c (%)		
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean*)	-0.5	-0.5
Difference from glipizide + metformin (adjusted mean) (95% CI)	0 (-0.1,0.1) NI	
Percent of patients achieving HbA1c <7% adjusted from baseline	27.4	32
*** FPG (mg/dL) ***		
Baseline (mean)	162.3	164.3
Change from baseline at Week 24 (adjusted mean)	-22.4	-18.8

Study D1690C00004	Treatment Arm	
	Dapagliflozin + Metformin N=400	Glipizide + Metformin N=401
Difference from glipizide + metformin (adjusted mean) (95% CI)	-3.6 (-8.0, 0.9) p = 0.11	
Body Weight (kg)		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean)	-3.22	1.44
Difference from glipizide + metformin (adjusted mean) (95% CI)	-4.65 (-5.14,-4.17) p<0.001	

Source: CSR D1690C00004, Table 19. * All adjusted means in the table = Least squares mean adjusted for baseline values.
 *** Not key secondary endpoints
 Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; XR = extended release

Clinical Reviewer Comment: Treatment with dapagliflozin in combination with metformin was noninferior to glipizide + metformin at the primary endpoint.

Efficacy Results from Subpopulations

In the following studies, only a subpopulation of the overall study population represented patients receiving dapagliflozin and metformin:

- D1690C00006: patients were receiving insulin with or without other oral antidiabetic agents (OADs) as background medication. Patients receiving insulin and metformin only were included in the Dapagliflozin plus Metformin Pool.
- D1690C00010: patients were receiving sitagliptin with or without metformin as background medication. From this study, the strata of patients receiving sitagliptin and metformin as background medication were included in the Dapagliflozin plus Metformin Pool.

Add-on combination with a DDP-IV inhibitor in combination with metformin

Study D1690C00010

This study was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effect of dapagliflozin 10 mg daily compared to placebo in combination with sitagliptin or sitagliptin plus metformin. The primary study objective was to compare the change from baseline in HbA1c at 24 weeks between dapagliflozin and placebo.

The study population included men and women ≥ 18 years of age, diagnosed with T2DM who were drug-naïve, or who were treated with sitagliptin 100 mg daily monotherapy, or a combination of sitagliptin 100 mg daily with metformin ≥ 1500 mg/day, or metformin ≥ 1500 mg/day monotherapy. Patients had inadequate glycemic control, defined as HbA1c $\geq 7.2\%$ and $\leq 10.0\%$ (sitagliptin monotherapy) or $\geq 7.7\%$ and $\leq 10.5\%$ (sitagliptin with metformin, metformin monotherapy or drug-naïve).

The study subpopulation received dapagliflozin 10 mg daily (qd) plus open-label sitagliptin 100 mg qd and open-label metformin ≥ 1500 mg/day, or placebo plus open-label sitagliptin 100 mg qd and open-label metformin ≥ 1500 mg/day during the 24-week short-term treatment period.

The difference in the mean decrease of HbA1c between treatment groups was statistically significant in favor of dapagliflozin + metformin + sitagliptin. There was also a placebo-corrected mean decrease in total body weight from baseline at week 24 (-1.87 kg) in patients receiving dapagliflozin. The difference in the mean decrease of total body weight between treatment groups was statistically significant.

Table 10: Efficacy Results of Subpopulation of Patients Receiving Dapagliflozin in Combination with Sitagliptin and Metformin

Study D1690C00010	Treatment Arm	
	Dapagliflozin 10 mg + Sitagliptin + Metformin N=113	Placebo + Sitagliptin + Metformin N=113
Efficacy Parameter		
HbA1c (%)		
Baseline (mean)	7.80	7.87
Change from baseline (adjusted mean*)	-0.43	-0.02
Difference from placebo (adjusted mean) (95% CI)	-0.40 (-0.58, -0.23) p <0.001	
FPG (mg/dL)		
Baseline (mean)	165.9	164.7
Change from baseline at Week 24 (adjusted mean)	-26.2	3.0
Difference from placebo (adjusted mean) (95% CI)	-29.2 (-38.0, -20.4) p <0.001	
Body Weight (kg)		
Baseline (mean)	93.95	94.17

Study D1690C00010	Treatment Arm	
	Dapagliflozin 10 mg + Sitagliptin + Metformin N=113	Placebo + Sitagliptin + Metformin N=113
Efficacy Parameter		
Change from baseline (adjusted mean)	-2.35	-0.47
Difference from placebo (adjusted mean) (95% CI)	-1.87 (-2.61, -1.13) p <0.001	
2-hour PPG (mg/dL)**		
Baseline (mean)	230.2	221.0
Change from baseline (adjusted mean)	-48.9	-7.2
Difference from placebo (adjusted mean) (95% CI)	-41.6 (-55.4, -27.8)	
Patients with HbA1c decrease ≥0.7% (adjusted %)	28.0	16.0

Source: NDA 205649 Clinical Overview Table 5. ** 2-hour PPG level as a response to a 75 gram oral glucose tolerance test (OGTT). * All adjusted means in the table = Least squares mean adjusted for baseline values.
Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; PPG = postprandial glucose

Add-on combination therapy with insulin

Study D1690C00006

This study was a randomized, parallel-group, double-blind, placebo-controlled study with a 24-week short-term treatment period, followed by two extension periods (24 weeks and 56 weeks, respectively), designed to evaluate the efficacy and safety of dapagliflozin 2.5 mg, 5 mg and 10 mg as add-on therapy to insulin.

The study population included adult patients ages 18 to 80 years with T2DM with inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) who were on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day. Patients in the study could also be treated with a maximum of two oral antidiabetic drugs (OADs).

The sponsor conducted a separate ad hoc analysis of patients treated with metformin and insulin alone. Results of that analysis are depicted in Table 11, and demonstrated a statistically significant reduction in HbA1c, FPG and body weight when compared to the placebo arm.

Table 11: Efficacy Results of Subpopulation of Patients Receiving Dapagliflozin in Combination with Insulin and Metformin

Study D1690C00006	Treatment Arm	
Efficacy Parameter	Dapagliflozin 10 mg + Insulin + Metformin N=83	Placebo + Insulin + Metformin N=78
HbA1c (%)		
Baseline (mean)	8.5	8.43
Change from baseline (adjusted mean [†])	-0.93	-0.31
Difference from placebo (adjusted mean [†]) (95% CI)	-0.61 (-0.83, -0.40) p<.0001	
FPG (mg/dL)		
Baseline (mean)	173.8	166.3
Change from baseline at Week 24 (adjusted mean [†])	-25.7	11.
Difference from placebo (adjusted mean [†]) (95% CI)	-37.1 (-50.4.-23.8) p p<0.0001	
Body Weight (kg)		
Baseline (mean)	95.7	98.7
Change from baseline (adjusted mean [†])	-1.77	-0.06
Difference from placebo (adjusted mean [†]) (95% CI)	-1.71 (-2.47, -1.13) p<0.001	

Source: NDA 205649 Clinical Overview Table 6. * All adjusted means in the table = least squares mean adjusted for baseline values. Abbreviations: FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin

Review Comment: Interpretation of results from the ad hoc subpopulation efficacy analyses from study D1690C00006 and D1690C00010 precludes a robust assessment of the risk:benefit profile of dapagliflozin + metformin in combination with a DDP-IV inhibitor or insulin. In addition, conclusions are limited in both studies by the small sample sizes.

(b) (4)

6.1.5 Analysis of Secondary Endpoints

See Section 6.1.4 for discussion of relevant secondary endpoints.

6.1.6 Other Endpoints

New data were not submitted with this NDA.

6.1.7 Subpopulations

New data were not submitted with this NDA.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

New data were not submitted with this NDA.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

New data were not submitted with this NDA.

6.1.10 Additional Efficacy Issues/Analyses

Not conducted.

7 Review of Safety

Safety Summary

This section reviews the safety information pertaining to the dapagliflozin and metformin combination product NDA. The primary focus of this safety review relies on data from the eight placebo-controlled studies of dapagliflozin in combination with metformin for the short term (ST) period of 24 weeks.

Serious adverse events (SAEs) with fatal and nonfatal outcomes were relatively balanced between dapagliflozin + metformin and placebo + metformin. The incidence of hypoglycemia in the pool of eight ST placebo-controlled studies was higher in patients who were also receiving insulin. Genital mycotic infections and urinary tract infections were more common in patients receiving dapagliflozin in combination with metformin compared to placebo + metformin. Volume depletion events were more common among dapagliflozin-treated patients compared to placebo, and a higher proportion of events was observed for patients older than 65 years, patients with renal impairment and patients taking loop diuretics. An increased frequency of AEs of polyuria was observed in patients treated with dapagliflozin and metformin which is consistent with

the diuretic effect of dapagliflozin. Events of renal impairment or failure were experienced by a higher proportion of patients treated with DAPA 10 mg + MET than DAPA 5 mg + MET or placebo + MET. Patients over 65 years of age had a greater incidence of renal impairment compared to placebo. In addition, patients in the DAPA 10 mg + MET pool experienced a small decline in eGFR at week 24.

Overall, review of this application did not identify new or unexpected safety signals with combined use of dapagliflozin and metformin compared to the individual components. The safety and tolerability of coadministration of dapagliflozin and metformin are expected to be similar to that of the individual components.

7.1 Methods

The safety evaluation of dapagliflozin in combination with metformin focused on deaths, nonfatal events, common adverse events and events of special interest. Additionally, select clinical reports, narratives and analysis datasets were reviewed to cross-reference data submitted with the NDA.

The safety and tolerability of dapagliflozin both as monotherapy and in combination with metformin were previously evaluated by Dr. Somya Dunn (dated September 2, 2011 and November 21, 2011, and Dr. Frank Pucino (dated December 22, 2013) for the following submissions:

- Original dapagliflozin new drug application (NDA 202293)
- The 4-month safety update (4-MSU) submitted April 28, 2011 (October 15, 2010 data cut)
- Major amendment data submitted October 28, 2011 (July 15, 2011 data cut)
- 30-month update (30MU) submitted to the agency on July 11, 2013 (November 15, 2012 data cut)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The overall data cut-off date for the dapagliflozin/metformin XR FDC Summary of Clinical Safety (SCS) was November 15, 2012.

A tabular description of the studies utilized in the safety and efficacy review of dapagliflozin in combination with metformin is presented in Table 4 of Section 5.

FOUR MONTH SAFETY UPDATE (4-MSU)

The data cut-off date for the four month safety update (4-MSU) was August 19, 2013 for ongoing studies. The 4-MSU provided new safety data for serious adverse events (SAEs), cancer cases (including breast cancer and bladder cancer), and liver cases (i.e., hepatic disorder events and elevated liver tests). Listings of the nine studies submitted in the 4-MSU are delineated in Table 12 and Table 13.

Table 12: List of Unblinded and/or Completed Studies Four Month Safety Update (4-MSU)

Study No./Description	Subject Population	N Treated with Dapagliflozin/ Total	Treatment Groups / Background Therapy / Randomization	Rescue Treatment	Treatment Duration and Study Status ^a
MB102055: Phase 3, randomized, double-blind, placebo-controlled study of dapa 5 mg, dapa 10 mg, or placebo, all in combination with open-label metformin	Adult Asian subjects with T2DM who have inadequate control (HbA1c ≥ 7.5% and ≤ 10.5% at enrollment) on stable metformin monotherapy	299 / 444 subjects	Dapa 5 mg QD, Dapa 10 mg QD or Placebo QD Background therapy: metformin ≥ 1500 mg/day Randomization: 1:1:1	Open-label pioglitazone	24 weeks (unblinded) ¹
D1690C00004: Phase 3, randomized, parallel-group, double-blind, active-controlled study of dapa compared with SU (glipizide), both in combination with metformin	Adult subjects with T2DM who have inadequate control (HbA1c > 6.5% and ≤ 10.0%) on metformin ≥ 1500 mg/day	406 / 814 subjects	Dapa titrated dose of 2.5, 5, or 10 mg or glipizide titrated dose of 5, 10, or 20 mg Background therapy: metformin ≥ 1500 mg/day Randomization: 1:1	Open-label DPP-4 I (first-choice rescue therapy) or open-label insulin (second-choice rescue therapy) during the 104-week extension	52 weeks (completed) ² plus 52 weeks (completed) ³ plus 104 weeks (completed) ⁴
D1691C00007: Phase 1, open-label, randomized, 4-period, 4-treatment, 4-way crossover bioequivalence study of dapa/met FDC tablet (5 mg/850 mg) relative to dapa 5 mg tablet and metformin 850 mg tablet (Glucophage®, marketed by Sanofi-Aventis) administered in the fasted or fed states	Healthy male and female subjects aged 18 to 55 years with a body mass index between 18.5 and 30.0 kg/m ² (inclusive)	40 / 40 subjects (all treatment arms included dapagliflozin)	Single oral doses of: Treatment A: 5 mg dapa and 850 mg met tablets administered together in the fasted state. Treatment B: dapa/met (5 mg/850 mg) IR FDC tablet in the fasted state. Treatment C: 5 mg dapa and 850 mg met tablets administered together in the fed state. Treatment D: dapa/met (5 mg/850 mg) IR FDC tablet in the fed state.	None	4 treatment periods of 5 days each (Day -1 until Day 4 [72 hours after a single oral dose of Treatment A, B, C, or D]), with a wash out of at least 7 days but less than 14 days between doses (completed) ⁵
Study No./Description	Subject Population	N Treated with Dapagliflozin/ Total	Treatment Groups / Background Therapy / Randomization	Rescue Treatment	Treatment Duration and Study Status ^a
D1693C00005: Phase 3, randomized, double-blind placebo-controlled study of dapagliflozin or placebo, both in combination with metformin + SU	Adult subjects with T2DM and inadequate glycemic control (HbA1c ≥ 7.0% and ≤ 10.5% at randomization) on metformin + SU.	109 / 218 subjects	Dapa 10 mg QD Placebo QD Background therapy: metformin ≥ 1500 mg/day + SU at maximum tolerated dose (at least 50% of maximum dose) Randomization: 1:1	Open-label DPP-4 I (first line therapy) or open-label insulin (second line therapy).	24 weeks (completed) ⁶ plus 28-week extension (unblinded)

^a Completed = final CSR exists; Unblinded = final database lock occurred but final CSR is not yet available. Abbreviations: CSR = clinical study report; Dapa = dapagliflozin; DPP-4 I = dipeptidyl-peptidase-4 inhibitor; FDC = fixed dose combination; IR = immediate release; OAD = oral antidiabetic drug; QD = once daily; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Sources for Ns: Table 5.2A; D1690C00004 208-week CSR, Table 8⁴; D1691C00007 CSR, Section 6.1⁵; D1693C00005 24-week CSR, Table 9⁶.

Source: Four month safety update Table 1, Page 10-11.

Table 13: Five Ongoing Phase 1 and Blinded Phase 2/3 studies (Four-Month Safety Update)

Study Description	Subject Population	N Planned to be Treated with Dapagliflozin/ Total	Treatment Groups/ Background Therapy / Randomization	Rescue Treatment	Treatment Duration and Study Status with Protocol Reference
MB102091: Phase 1, randomized, open-label, parallel-group, single-dose, pediatric PK/PD study	Pediatric subjects aged 10 to 17 years with T2DM, treated with metformin and/or insulin and/or diet and exercise with HbA1c > 6.0% and < 10.0%	24/ 24 (planned to be randomized)	Single oral dose of: dapagliflozin 2.5 mg QD dapagliflozin 5 mg QD, or dapagliflozin 10 mg QD Background therapy: none, or metformin and/or insulin. Randomization: 1:1:1	None	One day (single dose) (ongoing) ⁷
MB102129: Phase 3 double-blind, placebo-controlled study of dapagliflozin compared with placebo, both as add-on to saxagliptin + metformin	Adult subjects with T2DM and inadequate glycemic control on stable metformin monotherapy (HbA1c ≥ 8.0% and ≤ 11.5% at screening; Stratum A) or metformin + DPP-4 I (HbA1c ≥ 7.5% and ≤ 10.5% at screening; Stratum B)	140/ 280 (planned to be randomized)	Dapagliflozin 10 mg QD Placebo QD Background therapy: open-label saxagliptin 5 mg + metformin IR ≥ 1500 mg/day Randomization: 1:1	Insulin or any other antidiabetic agents (except GLP-1 analogs, other DPP-4 I and/or SGLT2 inhibitors or metformin)	24 week double-blind treatment period (ongoing) and 28-week site and subject blind treatment period (ongoing) ⁸
CV181168: Phase 3 double-blind, placebo-controlled study of saxagliptin compared with placebo, both as add-on to dapagliflozin + metformin	Adult subjects with T2DM and inadequate glycemic control (HbA1c ≥ 8.0% and ≤ 11.5% at screening) on metformin ≥ 1500 mg/day	140/ 280 (planned to be randomized)	Saxagliptin 5 mg QD Placebo QD Background therapy: open-label dapagliflozin 10 mg + metformin IR ≥ 1500 mg/day Randomization: 1:1	Insulin or any other antidiabetic agents (except GLP-1 analogs, other DPP-4 I or SGLT2 inhibitors or metformin)	24 week double-blind treatment period (ongoing) and 28-week site and subject blind treatment period (ongoing) ⁹
CV181169: Phase 3 double-blind, randomized, active-controlled study of dapagliflozin + saxagliptin, saxagliptin, or dapagliflozin, all as add-on to metformin XR	Adult subjects with T2DM and inadequate glycemic control (HbA1c ≥ 8.0% and ≤ 12.0% at screening) on metformin ≥ 1500 mg/day	344/ 516 (planned to be randomized)	Dapagliflozin 10 mg QD + saxagliptin 5 mg QD Dapagliflozin 10 mg QD Saxagliptin 5 mg Background therapy: open-label metformin XR ≥ 1500 mg/day Randomization: 1:1:1	Insulin or any other antidiabetic agents (except GLP-1 analogs, other DPP-4 I or SGLT2 inhibitors or metformin)	24 weeks (ongoing) ¹⁰
D1693C00001: Phase 3, randomized, double-blind, placebo-controlled study of dapagliflozin 10 mg on the incidence of CV death, MI, or ischemic stroke	Subjects ≥ 40 years of age with T2DM and high risk for a CV event (either established CV disease and/or multiple risk factors)	8575/ 17,150 (planned to be randomized)	Dapagliflozin 10 mg QD Placebo QD Background therapy: current antidiabetes medication (pioglitazone, rosiglitazone, other SGLT2 inhibitors not permitted)	Adjustments or changes to background antidiabetes medications allowed per Investigators' discretion	Up to 6 years (ongoing) ¹¹

Abbreviations: CV = cardiovascular; Dapa = dapagliflozin; DPP-4 I = dipeptidyl-peptidase-4 inhibitor; FDC = fixed dose combination; IR = immediate release; MI = myocardial infarction; QD = once daily; SGLT2 = sodium-glucose linked transporter; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; XR = extended release.

Source: sources for the N planned to be randomized can be found in the protocols referenced within the table (see last column)

Source 4-MSU Table 3, Page 12-13.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were classified by System Organ Class (SOC) and Preferred Terms (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) version 15.1, which was used for the pooled analyses for the Dapagliflozin + Metformin (DAPA+MET) Pool and Dapagliflozin + Metformin Placebo-Controlled Pool as well as for analyses of the DAPA All Phase 2b/3 Pool.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety and tolerability of dapagliflozin in combination with metformin XR are supported by 12 phase 3 studies and two main pooling strategies (Table 4, Section 5).

1. Dapagliflozin + Metformin Placebo-Controlled Pool (DAPA + MET PB Pool)
 - Eight placebo-controlled studies: MB102014, MB102021, MB102034, D1690C00006, D1690C00010, D1690C00012, D1690C00018, and D1690C00019
2. Dapagliflozin + Metformin Pool (DAPA + MET Pool)
 - Nine studies
 - Eight placebo-controlled studies: MB102014, MB102021, MB102034, D1690C00006, D1690C00010, D1690C00012, D1690C00018, and D1690C00019
 - One active-comparator study (study D1690C00004)

The primary safety analysis was based on the short term (ST) double-blind period, which was 24 weeks for the eight placebo-controlled studies and 52 weeks for the one active-comparator study (D1690C00004). Seven of the nine studies contributed long-term (LT) data: MB102014, D1690C00004, D1690C00006, D1690C00010, D1690C00012, D1690C00018, and D1690C00019. Analyses for the DAPA + MET Pool and DAPA + MET Placebo-Controlled Pool were conducted on both ST and ST+LT data.

A separate pool entitled the DAPA + MET Alone Pool was also used for summaries of hypoglycemia. This pool was comprised of patients in the DAPA + MET Pool who had not used rescue medication and/or background antihyperglycemic drugs other than metformin.

The following studies were not included in the DAPA + MET Pools described above:

- Study MB102013 was not pooled by the sponsor because it was a monotherapy study, in which open-label metformin was used as rescue medication and blinded

metformin was only administered to patients in the placebo arm during the LT period.

- Two studies in patients with T2DM and hypertension were not pooled (studies MB102073 and MB102077).

All of the studies in the DAPA + MET and DAPA + MET Placebo-Controlled Pools are included in the DAPA All Phase 2b and 3 Pool. These data were not the primary focus of this review and were previously reviewed for the dapagliflozin NDA.

The primary focus of this safety review is based on the placebo-controlled pool for the ST period. Long-term data from the placebo-controlled pool were evaluated for concordance with the primary placebo-controlled ST pool. The DAPA All Phase 2b and 3 Pool was utilized by the applicant to look at rarer events (malignancies, hepatic safety, cardiovascular safety, and pyelonephritis).

7.2 Adequacy of Safety Assessments

Safety assessments in the dapagliflozin clinical studies were based on medical review of AEs, laboratory tests, vital sign measurements, electrocardiograms (ECGs), and physical examinations.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall mean duration of exposure was comparable among all treatment arms.

Dapagliflozin + Metformin Pool Placebo-Controlled Pool (ST and ST+LT)

In the placebo-controlled pool higher cumulative exposures were noted in the placebo and DAPA 10 mg pools compared to DAPA 5 mg pool (Table 14). The lower cumulative exposure in the DAPA 5 mg + MET arm was due to the fact that this pool includes patients from two studies.

Dapagliflozin + Metformin Pool (ST and ST+LT)

As detailed in Table 14, in the DAPA + MET pool a higher cumulative exposure was noted in patients receiving DAPA 10 mg. This was due to the inclusion of the active comparator study (D1690C00004), which had a longer treatment period of 52 weeks, and only included the 10 mg dapagliflozin dose + metformin and active comparator + metformin.

These treatment arms provided more patients to the overall pool, thereby increasing the mean duration (days) of exposure and cumulative (person-years) exposure.

Table 14: Exposure for Dapagliflozin/Metformin Combination Pools

Population	Placebo+ MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)	DAPA + MET TOTAL (5 & 10 mg)	
DAPA + MET Placebo-Controlled Pool (ST)					
	N = 1185	N = 410	N = 983	N = 1393	
Mean Duration of Exposure (days)	158.4	159.6	158.3	158.7	
Cumulative Exposure (p-y)	514.0	179.2	425.9	605.1	
DAPA + MET Placebo-Controlled Pool (ST+LT)					
	N = 776	N = 216	N = 772	N = 988	
Mean Duration of Exposure (days)	459.1	571.7	479.4	499.6	
Cumulative Exposure (p-y)	975.4	338.1	1013.3	1351.3	
DAPA + MET Pool (ST)					
Population	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)	DAPA + MET TOTAL (5 & 10 mg)	Comp.+ MET
	N = 1185	N = 410	N = 1389	N = 1799	N = 408
Mean Duration of Exposure (days)	158.4	159.6	205.6	195.1	314.0
Cumulative Exposure (p-y)	514.0	179.2	781.7	960.8	350.8
DAPA + MET Pool (ST+LT)					
	N = 776	N = 216	N = 1178	N = 1394	N = 408
Mean Duration of Exposure (days)	459.1	571.7	618.0	610.8	829.8
Cumulative Exposure (p-y)	975.4	338.1	1993.2	2331.2	926.9

Percentages reported are based on the total number of patients in each treatment group. The extent of exposure to study medication during the ST (or ST+LT) period is defined as the difference between the last and the first dose of study medication of the ST period (or ST+LT period) plus 1 day. Cumulative exposure is calculated as the sum of the exposure to study medication of all patients (in years) in a treatment group. DAPA-treated patients from D1690C00004 are included in DAPA 10 mg + MET. Patients in DAPA 5 mg who titrated to 10 mg in D1690C00006 are included in DAPA 5 mg + MET. DAPA + MET TOTAL include DAPA 5 mg and 10 mg only.

Abbreviations: Comp = comparator; DAPA = dapagliflozin; LT = long-term; MET = metformin; p-y = patient-years; ST = short-term
Source ISS; Table 7, Page 31

FOUR MONTH SAFETY UPDATE

Unblinded and/or completed studies:

- MB102055: mean duration of exposure to placebo + metformin, dapagliflozin 5 mg + metformin, and dapagliflozin 10 mg + metformin was 157.7, 160.3, and 163.3 days, respectively
- D1690C00004: mean duration of exposure was 882.2 days for dapagliflozin + metformin and 830.8 days for glipizide + metformin with a cumulative exposure of 980.7 and 928.0 patient years, respectively

- D1691C00007: Of the 40 volunteers enrolled in the study, 34 completed the study and received all 4 planned treatments
- D1693C00005: mean duration of exposure was 332.3 days for placebo + metformin + SU and 337.3 days for dapagliflozin 10 mg + metformin + SU with a cumulative exposure of 99.2 and 100.6 patient years, respectively

Extent of exposure was not available for ongoing/blinded studies.

7.2.1.1 Demographics of Target Populations

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

Baseline demographic and baseline diabetes characteristics are presented for the ST and ST+LT DAPA + MET placebo-controlled pool in **Table 15**.

The mean age range was similar across treatment arms within the ST and ST+LT pools ranging from 54.1 to 59.7 years. Most patients (68% to 86.8%) were under 65 years of age.

In both the ST and ST+LT pools there was a higher number of women (compared to men in the placebo and DAPA 10 mg pools).

Most patients were white (>84%) and had an overweight BMI >25 (>92%). However, overall mean HbA1c values at baseline were comparable. Most patients had an eGFR value >60 mL/min, and mean systolic and diastolic blood pressure ranged from (129-133.8 mmHg and 78.8–80.9 mmHg).

There were a few notable differences observed between the DAPA 5 mg + MET group and the DAPA 10 mg + MET group for both the ST and ST+LT pools. In the DAPA 5 mg + MET, there was a lower proportion of patients ≥65 years of age for the ST (14.2% versus 25.2%, respectively) and ST+LT pools (17.1% versus 29.7%, respectively). In the ST DAPA 5 mg + MET pool there was a higher number of women compared to the DAPA 10 mg + MET group (54.4 versus 43.7%). In contrast in the ST+LT pool there were more men in the DAPA 10 mg + MET group compared to the DAPA 5 mg group (57.9 versus 42%). Patients in the DAPA 5 mg + MET arm had slightly higher HbA1c values compared to the DAPA 10 mg + MET arm for the ST (8.78 versus 8.2%) and ST+LT (8.37 versus 7.96%). These patients also had a higher fasting plasma glucose (184.4 versus 166.8mg/dL and 175.9 versus 160.6 mg/dL). However, patients in the DAPA 5 mg + MET pool had a mean shorter duration of diabetes (5.3 versus 8.8 years in the ST pool) and (8.6 versus 10.6 years in the ST+LT).

The applicant states that 348 patients in the DAPA 10 mg + MET group came from studies D1690C00018, and D1690C00019, which enrolled patients at high risk for CV

events, whereas no patients in the DAPA 5 mg + MET group came from these 2 studies.

Reviewer Comment: Overall baseline characteristics were balanced with respect to age and mean baseline HbA1c values. However, across treatment groups the majority of patients were white and a small number of patients were older than 75 years of age. Therefore, assessments of safety and efficacy are limited in non-white and elderly patients (≥75 years of age).

Table 15: Baseline Patient and Diabetes Characteristics

Patient Characteristics	DAPA + MET Placebo-Controlled Pool (ST)			DAPA + MET Placebo-Controlled Pool (ST+LT)		
	Placebo + MET N=1185	DAPA 5mg + MET N=410	DAPA 10 mg + MET N=983	Placebo + MET N=776	DAPA 5 mg + MET N=216	DAPA 10 mg + MET N=772
Age (years)						
Mean ± SD	57.2 ± 9.93	54.1 ± 9.64	57.7 ± 9.94	59.7 ± 8.83	56.2 ± 9.46	59.5 ± 9.09
Range	21-82	25-77	20-82	29-82	25-77	29-82
<65 (%)	893 (75.4)	356 (86.8)	733 (74.6)	528 (68.0)	179 (82.9)	543 (70.3)
65 to <75 (%)	271 (22.9)	49 (12.0)	221 (22.5)	230 (29.6)	32 (14.8)	200 (25.9)
≥75 (%)	21 (1.8)	5 (1.2)	29 (3.0)	18 (2.3)	5 (2.3)	28 (3.8)
Gender (%)						
Men	651 (54.9)	187 (45.6)	553 (56.3)	459 (59.1)	109 (50.5)	447 (57.9)
Women	534 (45.1)	223 (54.4)	223 (43.7)	317 (40.9)	107 (49.5)	325 (42.1)
Race (%)						
White	1048 (88.4)	346 (84.4)	884 (89.9)	724 (93.3)	193 (89.4)	710 (92.0)
Black	29 (2.4)	16 (3.9)	32 (3.3)	15 (1.9)	8 (3.7)	21 (2.7)
Asian	79 (6.7)	37 (9.0)	39 (4.0)	13 (1.7)	5 (2.3)	15 (1.9)
Other	29 (2.4)	11 (2.7)	28 (2.8)	24 (3.1)	10 (4.6)	26 (3.4)
Geographic Region (%)						
North America	364 (30.7)	136 (33.2)	278 (28.3)	200 (25.8)	67 (31.0)	182 (23.6)
Latin America	221 (18.6)	132 (32.2)	186 (18.9)	152 (19.6)	84 (38.9)	158 (20.5)
Europe	529 (44.6)	111 (27.1)	473 (48.1)	409 (52.7)	65 (30.1)	409 (53.0)
Asia/Pacific	71 (6.0)	31 (7.6)	46 (4.7)	15 (1.9)	0	23 (3.0)

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Patient Characteristics	DAPA + MET Placebo-Controlled Pool (ST)			DAPA + MET Placebo-Controlled Pool (ST+LT)		
	Placebo + MET N=1185	DAPA 5mg + MET N=410	DAPA 10 mg + MET N=983	Placebo + MET N=776	DAPA 5 mg + MET N=216	DAPA 10 mg + MET N=772
BMI (kg/m ²) n (%)						
< 25	91 (7.7)	36 (8.8)	53 (5.4)	39 (5.0)	15 (6.9)	33 (4.3)
≥ 25	1094 (92.3)	374 (91.2)	930 (94.6)	737 (95.0)	201 (93.1)	793 (95.7)
≥ 27	1000 (84.4)	325 (84.4)	840 (85.5)	679 (87.5)	182 (84.3)	672 (87.0)
≥ 30	743 (62.7)	252 (62.7)	647 (65.8)	514 (66.2)	142 (65.7)	524 (67.9)
Systolic BP (mmHg) Mean ± SD	131.3 ± 14.78	129.0 ± 15.33	132.1 ± 15.25	132.4 ± 14.70	131.6 ± 16.10	133.3 ± 14.94
Range	87-199	88-182	88-187	93-183	92-182	88-179
Diastolic BP (mmHg) Mean ± SD	79.4 ± 8.94	80.3 ± 8.58	79.3 ± 8.98	78.8 ± 9.24	80.9 ± 8.55	79.2 ± 9.16
Range	46-109	53-101	55-104	46-109	53-99	55-104
Duration of T2DM (y) Mean ± SD	7.16 ± 7.826	5.30 ± 6.209	8.80 ± 8.292	10.0 ± 8.000	8.66 ± 6.634	10.61 ± 8.322
Range	0.0-44.2	0.0-42.6	0.0-48.2	0.2-44.2	0.2-42.6	0.3-48.2
HbA1c (%) Mean ± SD	8.36 ± 1.167	8.78 ± 1.221	8.20 ± 1.058	7.97 ± 0.840	8.37 ± 0.952	7.96 ± 0.850
Range	5.6-13.3	6.5-12.9	5.3-11.9	5.6-10.9	6.5-10.5	5.3-10.5
< 8.0%	524 (44.2)	116 (28.3)	482 (49.0)	422 (54.4)	83 (38.4)	436 (56.6)
≥ 8.0 < 9.0%	353 (29.8)	128 (31.2)	278 (28.3)	251 (32.3)	66 (30.6)	221 (28.6)
≥ 9.0%	308 (26.0)	166 (40.5)	223 (22.7)	130 (13.3)	67 (31.0)	115 (14.9)
FPG (mg/dL) Mean ± SD	173.10 ± 51.15	184.44 ± 55.270	166.81 ± 48.123	162.22 ± 43.916	175.96 ± 53.008	160.59 ± 43.053
Range	43-436	32-358	50-460	43-382	32-339	50-460

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Patient Characteristics	DAPA + MET Placebo-Controlled Pool (ST)			DAPA + MET Placebo-Controlled Pool (ST+LT)		
	Placebo + MET N=1185	DAPA 5mg + MET N=410	DAPA 10 mg + MET N=983	Placebo + MET N=776	DAPA 5 mg + MET N=216	DAPA 10 mg + MET N=772
GFR (mL/min/1.73 m ²) n (%)						
< 30	0	0	1 (0.1)	0	0	1 (0.1)
≥ 30 < 45	8 (0.7)	4 (1.0)	10 (1.0)	7 (0.9)	4 (1.9)	10 (1.3)
≥ 45 < 60	104 (8.8)	37 (9.0)	83 (8.4)	83 (10.7)	25 (11.6)	72 (9.3)
≥ 60 < 90	657 (55.4)	221 (53.9)	542 (55.1)	434 (55.9)	124 (57.4)	431 (55.8)
≥ 90	416 (35.1)	148 (36.1)	347 (35.3)	252 (32.5)	63 (29.2)	258 (33.4)

Source: Appendix 3000-3003 and Appendix 4000-4003 of ISS

This table includes all treated patients. Percentages reported are based on the total number of patients in each treatment group. Does not include 2.5 mg treatment groups from Studies MB102014 and D1690C00006. Patients in DAPA 5 mg group who were titrated to 10 mg in D1690C00006 are included in DAPA 5 mg + MET.

Abbreviations: BMI = body mass index; BP = blood pressure; Comp = comparator; DAPA = dapagliflozin; FPG = fasting plasma glucose; GFR = glomerular filtration rate; HbA1c = glycosylated hemoglobin; ISS = Integrated Summary of Safety; LT = long-term; MET = metformin; T2DM = Type 2 Diabetes Mellitus; SD = standard deviation; ST = short-term

7.2.2 Explorations for Dose Response

Adverse events relationships to dose are discussed throughout the safety section.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. Mukesh Summan's review dated .

7.2.4 Routine Clinical Testing

As noted in Dr. Pucino's review (dated December 22, 2013), of the dapagliflozin program, safety assessments included collection of adverse events, clinical laboratory tests, vital signs, body weight and electrocardiograms (ECGs). Routine clinical laboratory assessments studies included blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase); hematology (including complete blood count [CBC], differential, and absolute neutrophil count); urinalysis; creatinine kinase; and urine pregnancy testing (performed in women of childbearing potential).

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the clinical pharmacology review by Dr. Sury Sistanarayana for additional metabolic clearance and interaction data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

These events included hepatic events, dyslipidemia, hypoglycemia, genital and urinary tract infections, renal impairment/failure, polyuria, volume depletion, and fractures.

7.3 Major Safety Results

7.3.1 DEATHS

At the time of the original NDA submission overall death rates were comparable between patients treated with dapagliflozin 10 mg + metformin and placebo + metformin (0.6% and 0.8%, respectively). There were no deaths in the dapagliflozin 5 mg + metformin pool. The most common death events in the dapagliflozin group occurred in the "General Disorders" and "Infections and Infestations" System Organ Classes (0.2%, 2 events each). Most deaths in the dapagliflozin group were due to single events; except two patients expired from events of sudden death and one patient each had an event of multiorgan failure and septic shock. Overall there did not appear to be a safety signal for fatal events.

Dapagliflozin + Metformin Pool (On and Post Therapy)

At the time of the NDA submission a total of twenty-one deaths occurred in the DAPA + MET Pool. Death events were balanced between the DAPA 10 mg + MET (0.6%, 7 events) and placebo + MET (0.8%, 6 events) treatment arms. No deaths occurred in the DAPA 5 mg + MET group. A higher incidence of deaths occurred in the comparator + MET arm (1.2%, 5 events).

Fatalities were attributed to the following events and are described in Table 16:

- DAPA 5 mg + MET: None
- DAPA 10 mg + MET (seven patients): sudden death (two patients), meningitis, septic shock, esophageal varices hemorrhage, renal failure, and infarction
 - One patient experienced death 30 days post treatment due to multi-organ failure.
- Placebo + MET (six patients): myocardial infarction (two patients) death, bronchial carcinoma, malignant lung neoplasm, and metastatic squamous cell carcinoma
- Comparator + MET (five patients): abdominal pain, sudden death, acute myocardial infarction, myocardial infarction, and road traffic accident.

Table 16: On-Therapy Fatal Serious Adverse Events by Treatment Group

Subject ID Age/Gender/Race Treatment Group	Treatment Treatment Period	Study Day	System Organ Class/ Preferred Term/ Relationship
Dapa 5 mg +Met			
None			
Dapa 10 mg+Met			
D1690C00004-5402-16 (50/F/C) Dapa 10 mg+Met	After Study Treatment Follow-Up	(b) (6)	General Disorders And Administration Site Conditions/ Multi-Organ Failure***/ Unrelated
D1690C00012-304-6 (72/M/C) Dapa 10 mg+Met	After Study Treatment Follow-Up		Gastrointestinal Disorders / Oesophageal Varices Haemorrhage/ Unrelated
D1690C00018-201-12 (77/F/C) Dapa 10 mg+Met	Dapa 10 mg + Met ST		General Disorders and Administration Site Conditions Sudden Death/ Unrelated
D1690C00004-2710-20 (57/M/C) Dapa 10 mg+Met	*Dapa 10 mg + Met 2000 mg + Vil 50 mg LT Treat 2		Renal and Urinary Disorders/ Renal Failure/ Unrelated
D1690C00004-4918-1 (63/M/C) Dapa 10 mg+Met	*Dapa 10 mg LT Treat 2		Infections and Infestations / Septic Shock/ Unrelated
D1690C00019-5717-17 (68/F/C) Dapa 10 mg+Met	Dapa 10mg + Ins + Met LT Treat 1		Infections and Infestations/ Meningitis / Unrelated
D1690C00018-1007-1 (70/M/C) Dapa 10 mg+Met	*Dapa 10 mg + Ins + Met LT Treat 1		Vascular Disorders/ Infarction / Unrelated
D1690C00018-211-4 (58/M/C) Dapa 10 mg+Met	Met Follow-Up		General Disorders and Administration Site Conditions/ Sudden Death / Unrelated
Placebo+Met			
D1690C00010-2006-1 (65/F/C) Placebo+Met	Placebo + Sit 100 mg + Met 2000 mg ST		Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)/Metastatic Squamous Cell Carcinoma**/ Unrelated
D1690C00018-7007-2 (82/F/C) Placebo+Met	Ins Follow-Up		Respiratory, Thoracic and Mediastinal Disorders/ Acute Pulmonary Oedema***/ Unrelated
D1690C00019-403-4 (60/M/C) Placebo+Met	Placebo + Ins + Met ST		Cardiac Disorders / Myocardial Infarction / Myocardial Infarction / Unrelated

Subject ID Age/Gender/Race Treatment Group	Treatment Treatment Period	Study Day	System Organ Class/ Preferred Term/ Relationship
MB102034-105-816 (68/F/C) Placebo+Met	Ended treatment Post treatment	(b) (6)	Cardiac Disorders / Myocardial Infarction / Unrelated
D1690C00018-7895-5 (79/M/C) Placebo+Met	*Placebo + Met + SU LT Treat 2		Cardiac Disorders / Myocardial Infarction / Unrelated
D1690C00019-3309-9 (54/F/C) Placebo+Met	Placebo + Met LT Treat 1		General Disorders and Administration Site Conditions / Death / Unrelated
D1690C00019-7858-4 (63/F/C) Placebo+Met	*Ins + Met Follow-Up		Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) / Bronchial Carcinoma / Unrelated
MB102014-53-446 (67/M/C) Placebo+Met	Ended treatment Post treatment		Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps) / Lung Neoplasm Malignant / Unrelated
Comparator+met			
D1690C00004-3406-2 (64/F/C) Comparator+Met	Glip 20 mg + Met 2550 mg ST		Gastrointestinal Disorders / Abdominal Pain / Unrelated
D1690C00004-5404-7 (72/M/C) Comparator+Met	Glip 20 mg + Met 2000 mg ST		General Disorders and Administration Site Conditions / Sudden Death/ Unrelated
D1690C00004-2704-1 (35/F/A) Comparator+Met	Met 2500 mg Follow-Up		Injury, Poisoning and Procedural Complications / Road Traffic Accident / Unrelated
D1690C00004-5406-21 (70/M/C) Comparator+Met	*Glip 20 mg + Met 1500mg + Ins 18 IU LT Treat 2		Cardiac Disorders / Myocardial Infarction / Unrelated
D1690C00004-5413-13 (71/F/C) Comparator+Met	Glip 20 mg + Met 2000 mg ST		Cardiac Disorders / Acute Myocardial Infarction / Unrelated

Source: ISS Table 18, Page 56-57.

Brief summaries of death events in the dapagliflozin 10 mg + metformin treatment arm are delineated below. All data for the dapagliflozin and metformin FDC product were previously presented to the dapagliflozin NDA.

Subject D1690C00018-211-4: A 58 year-old male former smoker with a history of coronary artery disease, previous myocardial infarction, and congestive heart failure experienced **sudden death** while sleeping on study day (b) (6). His last dose of dapagliflozin was on study day 210.

Reviewer Comment: The paucity of data regarding the event of sudden death limits determination of causality. However, the patient had a notable cardiac history which also confounds determination of study drug causality.

Subject D1690C00018-201-12: A 77 year-old woman with a history coronary artery disease and previous myocardial infarction suffered **sudden death** on study day (b) (6)

Reviewer Comment: Sudden death on study day (b) (6) is unlikely related to study drug. In addition, the case is confounded by the patient's underlying cardiac history.

Subject D1690C00004-5402-16: A 50 year-old woman with a history of hypothyroidism and obesity experienced a urinary tract infection around study day 86-138. On study day 302 the patient experienced symptoms of cough, dyspnea and fever, with neurological deterioration. Chest X-ray revealed opacities of the lungs with infiltration of the right base. Urine cultures were positive for gram-positive cocci, and the patient also had positive tracheal and blood cultures. Study medication was stopped due to pneumonia on day 302. The patient expired on study day (b) (6) due to **multi-organ failure**.

Review Comment: The applicant refers to this case as post-treatment. However, the initial presentation of symptoms of pneumonia began while the patient was receiving dapagliflozin in combination with metformin. Although there is a lack of information to determine relatedness to study medication, a relationship to study drug cannot be excluded.

Subject D1690C00004-2710-20: A 57 year-old man, with a medical history of hypertension, hyperlipidemia, diverticulosis and positive smoking and alcohol use (two drinks per day) was admitted in kidney failure around study day (b) (6). Weeks prior to the admission the patient reportedly suffered severe emotional distress and the narrative states he "drank excessively during the festive season". The patient died of kidney failure (b) (6) days post admission. The patient received dapagliflozin 10 mg + metformin 2000 mg as study treatment and vildagliptin 50 mg as rescue therapy at the time the renal failure occurred. The probable cause of death was described as **renal failure**.

Reviewer Comment: Dapagliflozin use has been associated with the development of renal impairment. However interpretation of study drug causality in this case is limited by reported "excessive" alcohol consumption, which can also compromise kidney function.

Subject D1690C00004-4918-1: A 63 year-old white man with a history of hypertension, post-thrombotic syndrome, atrial fibrillation, mesenteric infarct and peripheral arterial occlusive disease developed skin irritation on both feet and was hospitalized on study day (b) (6) for treatment of diabetic foot syndrome. The patient received antibiotics and subsequently developed diarrhea and was found to have colitis. He underwent a subtotal colectomy with ileostomy. The patient developed **septic shock** (details not provided) on study day (b) (6) and expired (b) (6) days later.

Reviewer Comment: Determination of the cause of death is difficult to make as there are numerous factors that may have contributed to the development of septic shock in this patient; diabetic foot infection, colitis and complications of cholecystectomy are all additional possible etiologies.

D1690C00018-1007-1: A 70 year-old white man with an extensive cardiac history (stable angina, coronary artery disease, previous myocardial infarction) and smoking history experienced two weeks of chest pain and was hospitalized on study day (b) (6). Cause of death was determined to be a **myocardial infarction**.

Reviewer Comment: Determination of a relationship to study drug is confounded by the underlying cardiac history.

D1690C00012-304-6: A 72 year-old man with a history of smoking, chronic obstructive pulmonary disease, hypertension, and coronary artery disease, history of focal colonic malignant polyps (additional details not provided), and history of tachyarrhythmia on chronic anticoagulation was admitted for pneumonia on study day (b) (6). The patient developed atrial fibrillation and an upper gastrointestinal bleed resulting in death. The certificate of death states that the direct cause of death was “hemorrhagic shock as a consequence of **esophagus varix rupture**, as a consequence of liver fibrosis, as a consequence of non-insulin dependent diabetes mellitus”.

Reviewer Comment: While the presentation of pneumonia may have precipitated an arrhythmia event, determination of death causality in this case is confounded by the underlying history of tachyarrhythmia and anticoagulation use. The overall lack of relevant information makes determination of causality difficult.

A 68 year-old white woman with a history of renal stone, hypertension and dyslipidemia was found unconscious on study day (b) (6). The patient expired and zoonose disease was confirmed with a positive leptospirosis test indicating leptospirosis **meningitis**

Reviewer Comment: The bacteria that cause leptospirosis are spread through the urine of infected animals, which may contaminate water or soil. This event is likely not related to study drug.

FOUR MONTH SAFETY UPDATE (4-MSU) - DEATHS

The following are new death events not reported in the dapagliflozin NDA.

There was one death due to pulmonary embolism in the open-label treatment period of study CV181168, in the dapagliflozin 10 mg + metformin IR arm. This case is described below. There was one death in the placebo arm in the complete studies and one death in the placebo arm of the ongoing studies.

Subject CV181168-65-255: A 66 year-old Caucasian woman with hypertension, diabetic retinopathy, diabetic nephropathy, and dyslipidemia, was in the open-label phase of the study and had received dapagliflozin 10 mg daily. On study day (b) (6) the patient failed to show up to her appointment and her relatives indicated that patient died suddenly. The investigator reported a serious adverse event of **pulmonary embolism** (recorded as verbatim term ‘thromboembolia of the pulmonary artery’).

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Dapagliflozin + Metformin Placebo-Controlled Pool (ST)

Overall nonfatal SAEs were balanced between patients receiving metformin in combination with dapagliflozin 10 mg (4.1%), dapagliflozin 5 mg (3.4%), with a slightly higher incidence in the placebo (5.1%) pool. Table 17 depicts SAEs by SOC and PT that occurred in at least one dapagliflozin + metformin-treated patient, and which also had a greater incidence compared to placebo + metformin.

The highest incidence of on-therapy SAEs occurred in the “Cardiac Disorders” and “Infections and Infestations” SOCs. Events (by Preferred Term) that occurred in ≥3 patients in any DAPA + MET group with a higher incidence than in the placebo arm were: angina pectoris, cholecystitis (two events of cholecystitis and one event of acute cholecystitis), pneumonia and pulmonary tuberculosis. Of note, in most cases the overall numbers were small.

Table 17: Nonfatal Serious Adverse Events in the Dapagliflozin + Metformin Placebo-Controlled Pool with at Least One Event in the Dapagliflozin Arm, and with a Higher Incidence for Dapagliflozin than for Placebo (Short-Term)

MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=1185 n (%)	DAPA 5 mg + MET N=410 n (%)	DAPA 10 mg + MET N=983 n (%)
		60 (5.1)	14 (3.4)	47 (4.8)
CARDIAC DISORDERS		13 (1.10%)	1 (0.24%)	9 (0.92%)
	ANGINA UNSTABLE	3 (0.25%)	0 (0.00%)	3 (0.31%)
	ANGINA PECTORIS	0 (0.00%)	1 (0.24%)	2 (0.20%)
	MYOCARDIAL INFARCTION	0 (0.00%)	0 (0.00%)	2 (0.20%)
	VENTRICULAR TACHYCARDIA	0 (0.00%)	0 (0.00%)	1 (0.10%)
INFECTIONS AND INFESTATIONS		9 (0.76%)	5 (1.22%)	6 (0.61%)
	PNEUMONIA	0 (0.00%)	1 (0.24%)	4 (0.41%)

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MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=1185 n (%)	DAPA 5 mg + MET N=410 n (%)	DAPA 10 mg + MET N=983 n (%)
	PULMONARY TUBERCULOSIS	1 (0.08%)	3 (0.73%)	0 (0.00%)
	ERYSIPELAS	0 (0.00%)	1 (0.24%)	0 (0.00%)
	HERPES ZOSTER	0 (0.00%)	1 (0.24%)	0 (0.00%)
	OSTEOMYELITIS	0 (0.00%)	0 (0.00%)	1 (0.10%)
	RESPIRATORY TRACT INFECTION	0 (0.00%)	0 (0.00%)	1 (0.10%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		4 (0.34%)	1 (0.24%)	6 (0.61%)
	INTERVERTEBRAL DISC PROTRUSION	0 (0.00%)	1 (0.24%)	1 (0.10%)
	ARTHRALGIA	0 (0.00%)	0 (0.00%)	1 (0.10%)
	OSTEITIS	0 (0.00%)	0 (0.00%)	1 (0.10%)
	ROTATOR CUFF SYNDROME	0 (0.00%)	0 (0.00%)	2 (0.20%)
	SPINAL OSTEOARTHRITIS	0 (0.00%)	0 (0.00%)	1 (0.10%)
GASTROINTESTINAL DISORDERS		3 (0.25%)	2 (0.49%)	5 (0.51%)
	INGUINAL HERNIA, OBSTRUCTIVE	0 (0.00%)	1 (0.24%)	0 (0.00%)
	OESOPHAGITIS	0 (0.00%)	1 (0.24%)	0 (0.00%)
	ABDOMINAL PAIN	0 (0.00%)	0 (0.00%)	1 (0.10%)
	ABDOMINAL PAIN UPPER	0 (0.00%)	0 (0.00%)	1 (0.10%)
	GASTRIC ULCER	0 (0.00%)	0 (0.00%)	1 (0.10%)
	HAEMORRHOIDS	0 (0.00%)	0 (0.00%)	1 (0.10%)
	UMBILICAL HERNIA	0 (0.00%)	0 (0.00%)	1 (0.10%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		7 (0.59%)	1 (0.24%)	5 (0.51%)
	GUN SHOT WOUND	0 (0.00%)	1 (0.24%)	0 (0.00%)
	ANKLE FRACTURE	1 (0.08%)	0 (0.00%)	1 (0.10%)
	EPICONDYLITIS	0 (0.00%)	0 (0.00%)	1 (0.10%)
	EXCORIATION	0 (0.00%)	0 (0.00%)	1 (0.10%)
	FACIAL BONES FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.10%)
	HIP FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.10%)
	URETHRAL INJURY	0 (0.00%)	0 (0.00%)	1 (0.10%)
NERVOUS SYSTEM DISORDERS		6 (0.51%)		4 (0.41%)
	CAROTID ARTERY STENOSIS	0 (0.00%)		1 (0.10%)
	SYNCOPE	0 (0.00%)		1 (0.10%)
VASCULAR DISORDERS		7 (0.59%)		4 (0.41%)
	HYPERTENSION	1 (0.08%)		1 (0.10%)
	HYPERTENSIVE CRISIS	1 (0.08%)		1 (0.10%)
	ARTERIOSCLEROSIS	0 (0.00%)		1 (0.10%)
	THROMBOPHLEBITIS SUPERFICIAL	0 (0.00%)		1 (0.10%)

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MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=1185 n (%)	DAPA 5 mg + MET N=410 n (%)	DAPA 10 mg + MET N=983 n (%)
HEPATOBIILIARY DISORDERS			1 (0.24%)	3 (0.31%)
	CHOLECYSTITIS		1 (0.24%)	1 (0.10%)
	CHOLECYSTITIS ACUTE		0 (0.00%)	1 (0.10%)
	CHOLELITHIASIS		0 (0.00%)	1 (0.10%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		7 (0.59%)		3 (0.31%)
	MENINGIOMA	0 (0.00%)		1 (0.10%)
	PANCREATIC CARCINOMA	0 (0.00%)		1 (0.10%)
	RENAL NEOPLASM	0 (0.00%)		1 (0.10%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		2 (0.17%)	2 (0.49%)	2 (0.20%)
	DEVICE DISLOCATION	0 (0.00%)	1 (0.24%)	0 (0.00%)
	THROMBOSIS IN DEVICE	0 (0.00%)	1 (0.24%)	0 (0.00%)
	CHEST PAIN	1 (0.08%)	0 (0.00%)	1 (0.10%)
	MEDICAL DEVICE PAIN	0 (0.00%)	0 (0.00%)	1 (0.10%)
EAR AND LABYRINTH DISORDERS		1 (0.08%)		1 (0.10%)
	VERTIGO	0 (0.00%)		1 (0.10%)
IMMUNE SYSTEM DISORDERS		0	0	1 (0.10%)
	DRUG HYPERSENSITIVITY	0	0	1 (0.10%)
INVESTIGATIONS				
	BLOOD PARATHYROID HORMONE DECREASED	0	0	1 (0.10%)
METABOLISM AND NUTRITION		0	1 (0.20%)	1 (0.10%)
	HYPOGLYCEMIA	0	1 (0.20%)	1 (0.10%)
RENAL AND URINARY DISORDERS		0	0	1 (0.10%)
	BLADDER DIVERTICULUM	0	0	1 (0.10%)
RESPIRATORY, THORACIC AND MEDISTINAL		1 (0.10%)	1 (0.20%)	1 (0.10%)
	DYSYPNEA		1 (0.20%)	

Source: Reviewer-generated

Abbreviations: DAPA = dapagliflozin; INCL = including; MedDRA = Medical Dictionary for Regulatory Activities; MET= metformin; PT = Preferred Term; SOC = System Organ Class

Dapagliflozin + Metformin Placebo-Controlled Pool (ST+LT)

In the placebo-controlled ST+LT pool nonfatal SAEs were comparable in incidence between patients treated with metformin plus placebo (16%) and dapagliflozin 10 mg

(15%), and each of these groups had a slightly higher incidence than patients treated with dapagliflozin 5 mg + MET (10.6%). See Table 18.

On-therapy SAEs (by Preferred Term) that occurred in ≥ 3 patients in the DAPA + MET pool, with a higher incidence for dapagliflozin compared to placebo were events of pneumonia and breast cancer.

Table 18. Nonfatal Serious Adverse Events in the Dapagliflozin + Metformin Placebo-Controlled Pool with at Least One Event in the Dapagliflozin Arm and with a Higher Incidence for Dapagliflozin than for Placebo (Short-Term + Long-Term)

MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=776 n (%)	DAPA 5 mg + MET N=216 n (%)	DAPA 10 mg + MET N=772 n (%)
CARDIAC DISORDERS		40 (5.15%)	4 (1.85%)	24 (3.11%)
	ATRIAL FLUTTER	1 (0.13%)	1 (0.46%)	1 (0.13%)
	BRADYCARDIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	SUPRAVENTRICULAR TACHYCARDIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	VENTRICULAR TACHYCARDIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	ARTERIOSCLEROSIS CORONARY ARTERY	0 (0.00%)	1 (0.46%)	0 (0.00%)
	CARDIAC FAILURE	2 (0.26%)	1 (0.46%)	0 (0.00%)
INFECTIONS AND INFESTATIONS		17 (2.19%)	2 (0.93%)	19 (2.46%)
	PNEUMONIA	5 (0.64%)	0 (0.00%)	8 (1.04%)
	SEPSIS	0 (0.00%)	0 (0.00%)	2 (0.26%)
	ARTHRITIS INFECTIVE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	BRONCHITIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	CELLULITIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	OSTEOMYELITIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	BACTERAEMIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	ARTHRITIS BACTERIAL	0 (0.00%)	0 (0.00%)	1 (0.13%)
	RESPIRATORY TRACT INFECTION	0 (0.00%)	0 (0.00%)	1 (0.13%)
	ABSCESS LIMB	1 (0.13%)	0 (0.00%)	1 (0.13%)
	STAPHYLOCOCCAL INFECTION	0 (0.00%)	0 (0.00%)	1 (0.13%)
	ERYSIPELAS	0 (0.00%)	1 (0.46%)	0 (0.00%)
	VIRAL INFECTION	1 (0.13%)	1 (0.46%)	0 (0.00%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		15 (1.93%)	2 (0.93%)	17 (2.20%)
	BREAST CANCER	2 (0.26%)	0 (0.00%)	5 (0.65%)
	PROSTATE CANCER	1 (0.13%)	0 (0.00%)	2 (0.26%)

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MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=776 n (%)	DAPA 5 mg + MET N=216 n (%)	DAPA 10 mg + MET N=772 n (%)
	MENINGIOMA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	MENINGIOMA BENIGN	0 (0.00%)	0 (0.00%)	1 (0.13%)
	MALIGNANT MELANOMA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	LUNG NEOPLASM MALIGNANT	0 (0.00%)	0 (0.00%)	1 (0.13%)
	RECTOSIGMOID CANCER	0 (0.00%)	0 (0.00%)	1 (0.13%)
	RENAL NEOPLASM	0 (0.00%)	0 (0.00%)	1 (0.13%)
	SQUAMOUS CELL CARCINOMA OF SKIN	0 (0.00%)	0 (0.00%)	1 (0.13%)
	VULVAL CANCER	0 (0.00%)	0 (0.00%)	1 (0.13%)
	BLADDER TRANSITIONAL CELL CARCINOMA	0 (0.00%)	1 (0.46%)	0 (0.00%)
NERVOUS SYSTEM DISORDERS		18 (2.32%)	1 (0.46%)	12 (1.55%)
NERVOUS SYSTEM DISORDERS				
	SYNCOPE	3 (0.39%)	1 (0.46%)	2 (0.26%)
	CAROTID ARTERY STENOSIS	1 (0.13%)	0 (0.00%)	2 (0.26%)
	TRANSIENT GLOBAL AMNESIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	CERVICAL CORD COMPRESSION	0 (0.00%)	0 (0.00%)	1 (0.13%)
GASTROINTESTINAL DISORDERS		6 (0.77%)	3 (1.39%)	10 (1.30%)
	ABDOMINAL PAIN	1 (0.13%)	1 (0.46%)	2 (0.26%)
	ABDOMINAL PAIN UPPER	0 (0.00%)	0 (0.00%)	1 (0.13%)
	DUODENAL ULCER	0 (0.00%)	0 (0.00%)	1 (0.13%)
	GASTRIC ULCER	0 (0.00%)	0 (0.00%)	1 (0.13%)
	GASTROINTESTINAL HAEMORRHAGE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	HAEMORRHOIDS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	HERNIAL EVENTRATION	0 (0.00%)	0 (0.00%)	1 (0.13%)
	PANCREATOLITHIASIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	UMBILICAL HERNIA	0 (0.00%)	0 (0.00%)	1 (0.13%)
	INGUINAL HERNIA, OBSTRUCTIVE	0 (0.00%)	1 (0.46%)	0 (0.00%)
	DIABETIC GASTROPARESIS	0 (0.00%)	1 (0.46%)	0 (0.00%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		8 (1.03%)	1 (0.46%)	9 (1.17%)
	ABDOMINAL INJURY	0 (0.00%)	0 (0.00%)	1 (0.13%)
	CHEST INJURY	0 (0.00%)	0 (0.00%)	1 (0.13%)
	EPICONDYLITIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	EXCORIATION	0 (0.00%)	0 (0.00%)	1 (0.13%)
	FEMUR FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	HIP FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	HUMERUS FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	LOWER LIMB FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.13%)

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MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=776 n (%)	DAPA 5 mg + MET N=216 n (%)	DAPA 10 mg + MET N=772 n (%)
	OPEN FRACTURE	0 (0.00%)	0 (0.00%)	1 (0.13%)
	URETHRAL INJURY	0 (0.00%)	0 (0.00%)	1 (0.13%)
	LIGAMENT RUPTURE	0 (0.00%)	1 (0.46%)	0 (0.00%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		8 (1.03%)	2 (0.93%)	6 (0.78%)
	MEDICAL DEVICE PAIN	0 (0.00%)	0 (0.00%)	1 (0.13%)
	DRUG WITHDRAWAL SYNDROME	0 (0.00%)	0 (0.00%)	1 (0.13%)
	THROMBOSIS IN DEVICE	0 (0.00%)	1 (0.46%)	0 (0.00%)
	DEVICE DISLOCATION	0 (0.00%)	1 (0.46%)	0 (0.00%)
HEPATOBIILIARY DISORDERS		1 (0.13%)	1 (0.46%)	5 (0.65%)
HEPATOBIILIARY DISORDERS	CHOLECYSTITIS ACUTE	0 (0.00%)	0 (0.00%)	2 (0.26%)
	CHOLELITHIASIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	HEPATITIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
	CHOLECYSTITIS	0 (0.00%)	1 (0.46%)	1 (0.13%)
RENAL AND URINARY DISORDERS		1 (0.13%)	3 (1.39%)	4 (0.52%)
	CALCULUS URETERIC	0 (0.00%)	1 (0.46%)	2 (0.26%)
	CYSTITIS HAEMORRHAGIC	0 (0.00%)	0 (0.00%)	1 (0.13%)
	BLADDER DIVERTICULUM	0 (0.00%)	0 (0.00%)	1 (0.13%)
	URINARY INCONTINENCE	0 (0.00%)	1 (0.46%)	0 (0.00%)
	RENAL FAILURE ACUTE	1 (0.13%)	1 (0.46%)	0 (0.00%)
METABOLISM AND NUTRITION DISORDERS		1 (0.13%)	1 (0.46%)	3 (0.39%)
	HYPOGLYCAEMIA	0 (0.00%)	1 (0.46%)	2 (0.26%)
	DIABETIC KETOACIDOSIS	0 (0.00%)	0 (0.00%)	1 (0.13%)
EAR AND LABYRINTH DISORDERS		2 (0.26%)		2 (0.26%)
	VERTIGO	1 (0.13%)		2 (0.26%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		3 (0.39%)		2 (0.26%)
	BREAST MASS	0 (0.00%)		1 (0.13%)
	BREAST CALCIFICATIONS	0 (0.00%)		1 (0.13%)

MedDRA SOC or Equivalent	MedDRA PT or Equivalent	Placebo + MET N=776 n (%)	DAPA 5 mg + MET N=216 n (%)	DAPA 10 mg + MET N=772 n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		6 (0.77%)	1 (0.46%)	2 (0.26%)
	DYSPNOEA	0 (0.00%)	1 (0.46%)	0 (0.00%)
IMMUNE SYSTEM DISORDERS				1 (0.13%)
	DRUG HYPERSENSITIVITY			1 (0.13%)
INVESTIGATIONS				
	BLOOD PARATHYROID HORMONE DECREASED	0		1 (0.13%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		3 (0.39%)		1 (0.13%)
	PRURITUS	0 (0.00%)		1 (0.13%)

Source: Reviewer-generated

Abbreviations: DAPA = dapagliflozin; INCL = including; MedDRA = Medical Dictionary for Regulatory Activities; MET= metformin; PT = Preferred Term; SOC = System Organ Class

Cases coded as events of Pneumonia:

In the ST placebo-controlled pool the greatest imbalance in nonfatal SAEs not in favor of dapagliflozin when compared to placebo occurred in pneumonia events (DAPA + MET 10 mg [four patients, 0.41%] and DAPA + MET 5 mg [one patient] versus zero in the Placebo + MET pool). However, in the ST+LT placebo-controlled pool there were more pneumonia events in the placebo arm compared to the ST pool. The overall magnitude in the dapagliflozin 10 mg + MET pool was 1% (eight patients) compared to 0.6% (five patients) in placebo + MET group.

In addition, in the non-placebo-controlled ST+LT pool an additional two patients receiving DAPA10 mg + metformin had an event coded as pneumonia. As depicted in Table 19, there was a slightly higher incidence of pneumonia events in the dapagliflozin treatment arm at the 10 mg dose. Pneumonia events that occurred in any DAPA + MET pool are detailed in Table 20.

Table 19: Serious Pneumonia Events

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)	Comparator (Glipizide) + MET
DAPA + MET Placebo-Controlled Pool (ST)				
N	1185	410	983	
Pneumonia	0	1 (0.2)	4 (0.4)	
DAPA + MET Placebo-Controlled Pool (ST+LT)				
N	776	216	772	
Pneumonia	5 (0.6)	0	8 (1.0)	
DAPA + MET Pool (ST)				
	1185	410	1389	408
Pneumonia	0	1 (0.2)	5 (0.4)	1 (0.2)
DAPA + MET Pool (ST+LT)				
N	776	216	1178	408
Pneumonia	5 (0.6)	0	10 (0.8)	1 (0.2)

Source: Reviewer-generated

Abbreviation: DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term

Table 20: Description of Pneumonia Events in the Dapagliflozin Treatment Arm

Subject ID Age/ Sex Ethnicity	Past Medical History Risk Factors	HPI and Clinical Presentation	Radiographic Data	Study Day	Maximum Intensity/ Withdrawn / Action Taken	Comments
D1690C00018-1004-3 60/Woman White	GERD Sleep Apnea Former smoker	Shortness of breath	Chest x-ray (CXR) – Right lower lobe and left middle lobe pneumonia with effusion	(b) (6)	Severe/Yes/Drug Discontinued	Hospitalized and treated with antibiotics and steroids and right decortication of empyema with resolution of the event.
D1690C00010-4007-3 70/Man White	GERD Former smoker x 45 years (quit 1999) ETOH 1 drink daily	Described as hyperthermia			Severe/No/None	Hospitalized and treated with antibiotics with resolution of the event. <i>Reviewer Comment: Limited information in narrative</i>
D1690C00012-106-8 36/Man White	smoker x13 year (quit 2004)	3 days of cough and chest pain and fever	CXR- bilateral infiltrates suggestive of pneumonia		Moderate/No/None	Hospitalized and treated with antibiotics with resolution of the event.
D1690C00012-304-6 72/Man White	Former smoker x 40 years (quit 1989) COPD	Weakness, fever	CXR- left infiltrate		Severe/No/None	Hospitalized. Patient developed sudden uncontrolled bleeding resulting in hemorrhagic shock and death <i>Reviewer Comment: History of duodenal ulcer, colonic polyps and focal carcinoma of unknown etiology.</i>

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Subject ID Age/ Sex Ethnicity	Past Medical History Risk Factors	HPI and Clinical Presentation	Radiographic Data	Study Day	Maximum Intensity/ Withdrawn / Action Taken	Comments
D1690C00012-108-11 46/Man White	Smoker x 20 years (quit 2006)	Severe cough with yellow sputum, chills, headache, fatigue	X-ray - additional information not provided	(b) (6)	Moderate/No/None	Hospitalized and treated with antibiotics with resolution of the event
D1690C00006-1209-20 66/Man White	2 ETOH drinks/ day	Hospitalized for a motor vehicle accident on study day 139	CXR- possible pneumonia Respiratory culture – Staphylococcus aureus		Severe/??/? ?= information not provided.	Hospitalized for accident and received antibiotics for pneumonia <i>Reviewer Comment: Hospital course complicated by TIA and DVT. It is unclear if the patient developed nosocomial pneumonia.</i>
D1690C00019-403-32 71/Man White	Smoker x 40 years (quit 2002)	Cough	Spiral CT- Neg. for pulmonary embolism Blood draw – “Infection markers elevated” Reviewer Comment: It is unclear which “infection markers” were elevated.		Moderate/No/Drug interrupted	Hospitalized and treated with antibiotics with resolution of event.
D1690C00018-8403-1 61/Woman Asian	History of stroke	Cough, fever, yellow sputum			Severe/No/Drug interrupted	Hospitalized and treated with antibiotics with resolution of the event.
D1690C00004-5402-16 50/Woman White	No smoking or alcohol	Cough, dyspnea, fever	CXR- right base opacity with infiltration Urine and tracheal cultures= + positive cocci, blood culture positive.		Severe/No/Stopped	Patient died due to multi-organ failure

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Subject ID Age/ Sex Ethnicity	Past Medical History Risk Factors	HPI and Clinical Presentation	Radiographic Data	Study Day	Maximum Intensity/ Withdrawn / Action Taken	Comments
D1690C00004- 5419-10 63/Man White	No smoking or alcohol	Vomiting, cough	CAT scan of the chest showed alveolar infiltrates in both lungs. Lab: 11400 white blood cells	(b) (6)	Severe/No/ None	Hospitalized and treated with antibiotics with resolution of the event. Hospitalization complicated with left ventricular impaired functioning requiring coronary angioplasty and drug eluting stent placement.

Source: Reviewer-generated.

Abbreviations: CAT = computerized axial tomography; CT = computerized tomography; CXR = Chest X-ray; COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; ETOH = ethanol; GERD = gastroesophageal reflux disease; HPI = history of present illness; ID = identification; TIA = transient ischemic attack

Reviewer Comment: *The majority of pneumonia events occurred in men and many patients had a previous smoking history. The onset of pneumonia events did not suggest a temporal association to study drug. The majority of cases responded to antimicrobial treatment. One patient with a history of gastroesophageal reflux disease (GERD), smoking and sleep apnea had an underlying empyema. Many of the narratives lacked sufficient information to make an assessment of study drug causality. In addition, the overall small number of total cases and underlying risk factors present in many patients with events (smoking history, chronic obstructive pulmonary disease [COPD], GERD) limit any meaningful conclusions.*

Cases coded as events of Angina Pectoris:

In the ST placebo-controlled pool three patients experienced events of angina pectoris compared to none in placebo. Narrative review of cases classified as “angina pectoris” demonstrated an onset date ranging from 4 days to 113 days. All patients had underlying cardiac disease. One event was due to cardiac stent thrombosis and another event was due to coronary artery disease.

Cases coded as events of Pulmonary Tuberculosis:

In the ST placebo-controlled pool there were three cases of pulmonary tuberculosis (0.7%) in the dapagliflozin + metformin pool compared to one case (0.08%) in the placebo+metformin pool. All three events occurred in Asian women, ages 42-46 years, between study days 20-108. Of note, one patient had a history of pulmonary tuberculosis (TB) that was incompletely treated, and a second patient had a history of upper respiratory tract infections (additional details were not provided). There were no pulmonary TB events in the ST+LT treatment pools.

Reviewer Comment: *The small number of patients and the underlying pulmonary medical history in two of the three patients limit any meaningful assessments of relatedness to study drug.*

Cases coded as events of Cholecystitis:

In the ST pool there were three cases of cholecystitis in the dapagliflozin arm (one case [0.24%] in DAPA 5 mg and 2 cases [0.2%] in the DAPA 10 mg pool), and none in placebo. Events occurred in two men and one woman, ages 52-73 years with a symptom onset ranging from study days 14-160. However, determination of causality was confounded as one patient was an active current smoker with a prior history of gallstones, another patient had a history of dyslipidemia and smoking history, and the third patient was found to have chronic cholecystitis on study day 40.

In the ST+LT placebo-controlled pool one additional patient, a 56 year-old man with a history of cholecystolithiasis, who received DAPA 10 mg + MET had an event termed as cholecystitis on study day 178.

Reviewer Comment: The small number of patients with events and the underlying medical histories do not support a safety signal.

Cases coded as events of Breast Cancer:

In the ST+LT placebo-controlled pool there were five events coded as breast cancer in the dapagliflozin 10 mg + MET arm versus two events in placebo-treated patients. In addition, there was one event of breast mass. Breast Cancer events are discussed further in section 7.6.1, Malignant or Unspecified Tumors (including Breast Cancer).

Additional Events of Interest (drug hypersensitivity and hepatitis)

One patient experienced **drug hypersensitivity** on study day 12 after Duracef (cephadroxil) administration.

A case coded as **hepatitis** was previously reviewed and is briefly described below from Dr. Pucino's clinical review (dated December 22, 2013).

D1690C00018-201-8 - 70 year-old white man, treated with dapagliflozin 10 mg and metformin, experienced hepatitis on study day (b) (6). The patient was hospitalized with diffuse abdominal pain, nausea, and vomiting. The patient was discontinued from study medication on study day 289 due to the SAE. On study day 289, ALT was 3.1X the upper limit of the reference range (ULRR), AST was 7.7X ULRR, alkaline phosphatase (ALP) was 1.5X ULRR and TBL was 1.4X ULRR. The ALT and AST peaked on study day 290 (10.3X ULRR and 18X ULRR, respectively), when TBL was 3.6X ULRR. Computerized tomography (CT) of the abdomen on study Day 360 showed "a discrete thickening of the gallbladder wall with uptake of the intravenous contrast agent, which could correspond to an inflammatory process." The blinded hepatic adjudication indicated that relationship to study therapy was unlikely.

Reviewer Comment: Dr. Senior's hepatology consultation dated November 11, 2013, noted that this patient tolerated dapagliflozin for approximately 36 weeks without liver test abnormalities before developing both symptoms and laboratory abnormalities. He noted that biliary tract disease was clinically suspected in this patient, but this was not very well-proven.

Dr. Senior recommended that patients should be warned of concerns regarding potential liver safety issues with dapagliflozin use. He also noted that there is no good justification for requiring any periodic monitoring (e.g., monthly ALT testing). Rather, he suggested that patients should be informed to report any

early symptoms of possible liver injury or dysfunction (e.g., anorexia, fatigue, nausea, dark urine, vomiting, yellowish sclera, right upper, epigastric or other abdominal discomfort) to their healthcare providers immediately. Further, with the presence of symptoms, therapy should be temporarily interrupted while prompt investigation is undertaken to assess for possible liver injury due to dapagliflozin therapy.

7.3.3 Dropouts and/or Discontinuations

For the DAPA/MET placebo-controlled pools (ST and ST+LT), discontinuations from study due to AEs were higher in the dapagliflozin treatment arms compared to placebo. Adverse events reported in at least three dapagliflozin-treated patients (and at a rate higher than placebo) involved events of changes in renal function, and genital or urinary tract infections.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST)

A slightly higher proportion of patients discontinued study treatment in the DAPA 10 mg + MET group (4.0%) compared to the DAPA 5 mg + MET (2.0%) and placebo + MET (3.3%). The most commonly reported AEs leading to discontinuation in the DAPA 10 mg + MET group were renal impairment (seven patients [0.7%]), blood creatinine increased (two patients [0.2%]), creatinine renal clearance decreased (two patients [0.2%]), and urinary tract infections (two patients [0.2%]). The most commonly reported AEs leading to discontinuation (i.e., reported in more than one patient) in the DAPA 5 mg + MET treatment group were: pulmonary tuberculosis and pruritus (in two patients (0.5%).

Dapagliflozin + Metformin Placebo-Controlled Pool (ST+LT)

Similar to the ST placebo-controlled pool, in the ST+LT placebo-controlled group there was a slightly higher proportion of patients who discontinued study treatment in the DAPA 10 mg + MET treatment group (8.9%, 69/772) compared with the DAPA 5 mg + MET (5.6%, 12/216) and placebo + MET (7.6%, 59/776). Similar to the ST pool in the DAPA 10 mg + MET arm the most common events leading to discontinuation were for renal impairment and decreased renal creatinine clearance (1% each).

7.3.4 Significant Adverse Events

Significant adverse events are discussed under nonfatal serious adverse events in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

HYPOGLYCEMIA

Patients taking dapagliflozin (5 or 10 mg) in combination with metformin had a higher incidence of hypoglycemia when compared to patients taking placebo + metformin. Events of hypoglycemia were minor events (see definitions of minor and major events below). Review of individual study hypoglycemia events in the placebo-controlled studies revealed the highest proportion of overall events occurring in the add-on to insulin study. Patients who received dapagliflozin plus insulin had a higher rate of hypoglycemic events than patients who received dapagliflozin plus placebo.

Data from the dapagliflozin+ metformin alone pool represented patients without rescue or background antihyperglycemics other than metformin. Overall hypoglycemic events were much lower and comparable between arms.

Patients were provided with glucometers and diaries to monitor plasma glucose values and were instructed to report promptly any plasma glucose values and/or signs and symptoms suggestive of hypoglycemia.

Supplemental case report forms (CRFs) were used to collect detailed information. Investigators were instructed to report hypoglycemia events in the special CRF pages if they fulfilled any of the following protocol-specified criteria. A subgroup of the DAPA + MET Pool, called the DAPA + MET Alone Pool was also used for summaries of hypoglycemia. This pool was comprised of patients in the DAPA + MET Pool who had not used rescue medication and/or background antihyperglycemic drugs other than metformin.

- A major hypoglycemic episode was defined as a symptomatic episode requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL, and prompt recovery after glucose or glucagon administration.
- A minor episode was defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

As depicted in Table 21, for both the ST and ST+LT placebo-controlled groups, patients receiving dapagliflozin (5 mg or 10 mg) in combination with metformin experienced a higher incidence of hypoglycemia events compared to patients receiving placebo and metformin. In the ST group the incidence of hypoglycemic events was slightly higher in

the DAPA 10 mg + MET arm (12.3%) compared to the DAPA 5 mg + MET arm (10.5%). There were no major hypoglycemic events.

Table 21: Hypoglycemia Incidence, Placebo-Controlled Short-Term Pool

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
	N = 1185	N = 410	N = 983
All events	89 (7.5)	43 (10.5)	121 (12.3)
Major events	0	0	0
Minor events	77 (6.5)	34 (8.3)	107 (10.9)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
	N = 776	N = 216	N = 772
All events	101 (13.0)	45 (20.8)	146 (18.9)
Major events	0	0	0
Minor events	94 (12.1)	37 (17.1)	137 (17.7)

Source: Adapted from ISS Table 21, Page 62

Abbreviations: DAPA = dapagliflozin; ISS = Integrated Summary of Safety; LT = long-term; MET = metformin; ST = short-term

Hypoglycemia events per study in the dapagliflozin + metformin placebo-controlled pool (ST)

Table 22 depicts the incidence of major and minor hypoglycemia per study in the ST placebo-controlled pool. The highest incidence of hypoglycemic events was in the add-on to insulin study. There was an imbalance not in favor of dapagliflozin at both the 10 mg and 5 mg dose when compared to placebo, with higher incidence in the 10 mg arm.

Table 22: Incidence of Major and Minor Hypoglycemia (Excluding data after Rescue) in Dapagliflozin + Metformin Placebo-Controlled Studies (Short-Term Pool)

	Placebo + MET	DAPA + MET 5 mg	DAPA + MET 10 mg
D1690C00006 (add-on to insulin)	N=80	N=79	N=84
Major [n (%)]	0	0	0
Minor [n (%)]	27 (33.8)	30 (38.0)	37 (44.0)
D1690C00010 (add-on to sitagliptin)	N=114	-	N=114
Major [n (%)]	0	-	0
Minor [n (%)]	0	-	1 (0.9)

	Placebo + MET	DAPA + MET 5 mg	DAPA + MET 10 mg
D1690C00012 (add-on to metformin)	N=91	-	N=91
Major [n (%)]	0	-	0
Minor [n (%)]	2 (2.2)	-	2 (2.2)
D1690C00018 (high CV risk add-on to usual care)	N=159	-	N=165
Major [n (%)]	0	-	0
Minor [n (%)]	19 (11.9)	-	24 (14.5)
D1690C00019 (high CV risk add-on to usual care)	N=195	-	N=183
Major [n (%)]	0	-	0
Minor [n (%)]	28 (14.4)	-	41 (22.4)
MB102014 (add-on to metformin)	N=137	N=137	N=135
Major [n (%)]	0	0	0
Minor [n (%)]	0	2 (1.5)	1 (0.7)
MB102021 (initial combination with metformin)	N=201	N=194	-
Major [n (%)]	0	0	-
Minor [n (%)]	0	2 (1.0)	-
MB102034 (initial combination with metformin)	N=208	-	N=211
Major [n (%)]	0	-	0
Minor [n (%)]	1 (0.5)	-	1 (0.5)

Source: Appendix 3.2 and Appendix 3.10 IR SDN

Abbreviations: CV = cardiovascular; DAPA = dapagliflozin; MET = metformin

Dapagliflozin + Metformin Alone Placebo-Controlled Pool (ST)

The DAPA + MET Alone Pool was a subgroup, in which patients treated with rescue medications and/or background antihyperglycemic drugs other than metformin were excluded. Compared with the DAPA + MET placebo-controlled pools, overall incidences of hypoglycemia were lower. There were no major events. Patients treated with dapagliflozin in combination with metformin had a slightly higher incidence of hypoglycemia when compared to placebo and metformin.

Table 23: Incidence of Major and Minor Hypoglycemia (Excluding Data after Rescue) in Dapagliflozin +Metformin Alone Placebo-Controlled Studies (Short-Term Pool)

	Placebo + MET	DAPA + MET 5 mg	DAPA + MET 10 mg
Dapa + MET Alone Placebo-Controlled ST Pool	N=755	N=331	N=540
Major [n (%)]	0	0	0
Minor [n (%)]	4 (0.5)	4 (1.2)	4 (0.7)
Individual Studies			
D1690C00012 (add-on to metformin)	N=91	-	N=91
Major [n (%)]	0	-	0
Minor [n (%)]	2 (2.2)	-	2 (2.2)
D1690C00018 (high CV risk add-on to usual care)	N=62	-	N=60
Major [n (%)]	0	-	0
Minor [n (%)]	1 (1.6)	-	0
D1690C00019 (high CV risk add-on to usual care)	N=56	-	N=43
Major [n (%)]	0	-	0
Minor [n (%)]	0	-	0
MB102014 (add-on to metformin)	N=137	N=137	N=135
Major [n (%)]	0	0	0
Minor [n (%)]	0	2 (1.5)	1 (0.7)
MB102021 (initial combination with metformin)	N=201	N=194	-
Major [n (%)]	0	0	-
Minor [n (%)]	0	2 (1.0)	-
MB102034 (initial combination with metformin)	N=208	-	N=211
Major [n (%)]	0	-	0
Minor [n (%)]	1 (0.5)	-	1 (0.5)

Source: Appendix 3.2 and Appendix 3.10

Abbreviations: CV = cardiovascular; DAPA = dapagliflozin; MET = metformin; ST = short-term

Two patients receiving DAPA 10 mg + MET in combination with insulin experienced an SAE of hypoglycemia. One patient discontinued treatment due to the serious event (blood glucose [BG] 35 mg/dL). The other patient did not have a BG recorded, but did require third party intervention.

Reviewer Comment: The greatest incidence of hypoglycemia events occurred in combination with insulin in all treatment groups with a higher proportion of

events in patients receiving dapagliflozin (5 and 10 mg) in combination with insulin.

Genital Infection and Urinary Tract Infection (UTI) Events (Including Pyelonephritis)

Due to dapagliflozin's mechanism of causing glucosuria, genital and urinary tract infections (including pyelonephritis) were considered events of special interest.

Investigators were requested to question patients proactively about signs and symptoms of genital infections and urinary tract infections (UTIs) at each visit, and to confirm the diagnosis by a physical examination, culture of the secretion, or positive response to the typical treatment. Investigators were requested to report additional data on supplemental CRFs. A prespecified list of Preferred Terms (PTs) was used to identify events specific to genital infection and UTIs (refer to Appendix C of the Integrated Summary of Safety [ISS]).

GENITAL INFECTIONS

Patients treated with dapagliflozin in combination with metformin had a higher incidence of genital infections at both the 5 and 10 mg dose compared to placebo. Infections occurred more frequently in women compared to men and were primarily driven by events of vulvomyotic infections and balanitis, respectively. While there were no serious events, a high number of patients discontinued treatment in the DAPA 10 mg groups. The majority of infections resolved with antimicrobial management and did not require additional treatment.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

Treatment with dapagliflozin in combination with metformin for the DAPA 10 mg and the DAPA 5 mg treatment pools was associated with an increased risk for genital infections compared to placebo + MET for both the ST (6.1%, 7.1% versus 0.7%, respectively) and ST+LT (8.3%,10.6% versus 1%, respectively) periods.

As depicted in Table 24, genital infections were more common in women than in men with events of vulvovaginal mycotic infections and balanitis being the most common events for women and men, respectively (Table 25).

The majority of patients with a genital infection experienced one event (DAPA 10 mg + MET [86.7%], DAPA 5 mg + MET [76%] and 100% for placebo + MET). Most patients in the DAPA 10 mg + MET, DAPA 5 mg + MET and placebo pool received treatment (82.6%, 93.8% and 87.5%, respectively). Approximately 4.3% of patients in the DAPA 10mg + MET pool and 6.3% in the DAPA 5 mg + MET pool required additional treatment compared to none in the placebo group.

There were no serious genital mycotic infection events. Only one patient in the DAPA 5 mg + MET pool had a severe event. A small number of patients discontinued treatment (three patients [0.3%]) in the DAPA 10 mg + MET group. There were no discontinuations in the placebo group. In the ST+LT pool, there was one additional patient discontinued in the DAPA 5 mg + MET group.

Table 24: Events of Genital Mycotic Infections

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
Genital infection	8 (0.7)	29 (7.1)	60 (6.1)
Females	8 (1.5)	21 (9.4)	40 (9.3)
Males	0	8 (4.3)	20 (3.6)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
Genital infection	8 (1.0)	23 (10.6)	64 (8.3)
Females	8 (2.5)	18 (16.8)	39 (12.0)
Males	0	5 (4.6)	25 (5.6)

Source: Adapted from ISS Table 22, Page 64 and response to Request for Information dated April 30, 2014 Appendix 2.1 and 2.2 SDN 14/16
Abbreviations: DAPA = dapagliflozin; ISS = Integrated Summary of Safety; MET = metformin

Table 25: Genital Mycotic Infection Events by Gender (ST Placebo-Controlled Pool)

SEX	MedDRA Preferred Term	Placebo + MET	DAPA 5 mg + MET	DAPA 10 mg + MET
WOMEN		N=534	N=223	N=430
	TOTAL GENITAL MYCOTIC INFECTIONS	8 (1.50%)	21 (9.42%)	40 (9.30%)
	VULVOVAGINAL MYCOTIC INFECTION	4 (0.75%)	6 (2.69%)	16 (3.72%)
	VAGINAL INFECTION	0 (0.00%)	5 (2.24%)	7 (1.63%)
	GENITAL INFECTION	1 (0.19%)	0 (0.00%)	6 (1.40%)
	VULVOVAGINITIS	0 (0.00%)	2 (0.90%)	5 (1.16%)
	GENITAL INFECTION FUNGAL	0 (0.00%)	3 (1.35%)	3 (0.70%)
	VULVOVAGINAL CANDIDIASIS	0 (0.00%)	4 (1.79%)	2 (0.47%)
	VULVAL ABSCESS	1 (0.19%)	0 (0.00%)	1 (0.23%)
	GENITAL CANDIDIASIS	0 (0.00%)	1 (0.45%)	0 (0.00%)
	VAGINITIS BACTERIAL	2 (0.37%)	0 (0.00%)	0 (0.00%)

SEX	MedDRA Preferred Term	DAPA 5 mg + MET	DAPA 10 mg + MET
MEN*		187	553
	TOTAL GENITAL MYCOTIC INFECTIONS	8 (4.28%)	20 (3.62%)
	BALANITIS	3 (1.60%)	11 (1.99%)
	GENITAL INFECTION FUNGAL	1 (0.53%)	3 (0.54%)
	BALANITIS CANDIDA	1 (0.53%)	2 (0.36%)
	GENITAL CANDIDIASIS	1 (0.53%)	2 (0.36%)
	GENITAL INFECTION	1 (0.53%)	1 (0.18%)
	POSTHITIS	0 (0.00%)	1 (0.18%)
	BALANOPOSTHITIS	1 (0.53%)	0 (0.00%)

Source: Reviewer-generated from placebo-controlled datasets

* There were no genital mycotic infection events for males in the placebo + metformin pool

Abbreviations: DAPA = dapagliflozin; MedDRA = Medical Dictionary for Regulatory Activities; MET = metformin

URINARY TRACT INFECTIONS

Patients treated with dapagliflozin in combination with metformin had a higher incidence of urinary tract infections at both the 5 and 10 mg dose compared to placebo. Infections occurred more frequently in women compared to men. The majority of infections resolved with antimicrobial management and did not require additional treatment.

In cases of suspected events of UTI, investigators were asked to perform urine cultures followed by a second culture within 7 days of resolution.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

Treatment with dapagliflozin in combination with metformin for both the DAPA 10 mg and the DAPA 5 mg pools was associated with an increased risk for urinary tract infections compared to placebo + MET for both the ST (5.5%, 6.1% versus 3.6%, respectively) and ST+LT periods (9.8%, 10.6% versus 5.9%, respectively).

As depicted in Table 26 infection events were more common in women than in men with events of urinary tract infection and cystitis being the most common events reported for both women and men (Table 27).

There were no SAEs of UTI in the DAPA + MET groups during active treatment. There was one serious event of UTI in a patient assigned to DAPA 10 mg + MET reported at a follow-up visit over 30 days after last dose of the study drug. There were three SAEs in patients assigned to placebo + MET. As depicted in Table 26, UTIs were more common in women than in men, with events of urinary tract infections and cystitis being the most common Preferred Terms in women, and urinary tract infections and pyelonephritis the most common events in men (Table 27).

In the ST pool, the majority of patients with a urinary tract infection experienced one event (DAPA 10 mg + MET (83.3%), DAPA 5 mg + MET (80%), and 88.4% for placebo + MET. Very few patients experienced severe events across treatment groups (two in the DAPA 5 mg + MET arm and one in placebo + MET pool). Most patients in both the DAPA 10 mg + MET, DAPA 5 mg + MET and placebo pool received treatment (80.3%, 71% and 91.7%, respectively). A higher proportion of patients receiving placebo + MET (18.8%) required additional treatment due to an inadequate response to the initial treatment compared to patients receiving DAPA 10 mg + MET (7.6%). There were no patients in the DAPA 5 mg + MET treatment arm who required additional treatment.

A small number of patients discontinued treatment (two patients in the DAPA 10 mg + MET group, one patient in the DAPA 5 mg + MET group, and two patients in the placebo group).

Table 26: Urinary Tract Infection Events (Short-Term and Short-Term + Long-Term Placebo-Controlled Pool)

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
UTI	43 (3.6)	25 (6.1)	54 (5.5)
UTI in Women	N=534	N=223	N=430
	32 (6)	23 (10.3)	42 (9.8)
UTI in Men	651	187	553
	11 (1.7)	2 (1.1)	12 (2.2)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
	776	216	772
UTI	46 (5.9)	23 (10.6)	76 (9.8)
Women	317	107	325
	30 (9.5)	18 (16.8)	54 (16.6)
Men	N=459	N=105	N=447
	16 (3.5)	5 (4.6)	22 (4.9)

Source: Adapted from ISS Table 22, Page 64 and response to request for Information dated April 30, 2014 Appendix 2.3 and 2.4 SDN 14/16

Abbreviations: DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term; UTI = urinary tract infection

Table 27: Urinary Tract Infection Events by Gender

DAPA + MET Placebo-Controlled Pool (ST)				
GENDER	MedDRA Preferred Term	Placebo + MET	DAPA 5 mg + MET	DAPA 10 mg + MET
WOMEN		534	223	430
	TOTAL URINARY TRACT INFECTIONS	32 (6)	23 (10.3)	42 (9.8)
	URINARY TRACT INFECTION	27 (5.10%)	21 (9.41%)	34 (7.9%)

DAPA + MET Placebo-Controlled Pool (ST)				
GENDER	MedDRA Preferred Term	Placebo + MET	DAPA 5 mg + MET	DAPA 10 mg + MET
	CYSTITIS	5 (0.93%)	2 (0.89%)	8 (1.86%)
MEN		651	187	553
	TOTAL URINARY TRACT INFECTIONS	11 (1.7)	2 (1.1)	12 (2.2)
	URINARY TRACT INFECTION	6 (0.92%)	2 (1.06%)	9 (1.62%)
	CYSTITIS	2 (0.31%)	0 (0.00%)	2 (0.36%)
	URETHRITIS	1 (0.15%)	0 (0.00%)	1 (0.18%)
	PROSTATITIS	2 (0.30%)	0 (0.00%)	0 (0.00%)
	PYELONEPHRITIS	1 (0.15%)	1 (0.53%)	0 (0.00%)

Source: Reviewer-generated

Abbreviations: DAPA = dapagliflozin; MedDRA = Medical Dictionary for Regulatory Activities; MET = metformin; ST = short-term

PYELONEPHRITIS

The applicant did not provide additional information due to the low overall incidence of events.

FRACTURES

In the ST pool the occurrence of fractures was low and balanced between dapagliflozin + metformin and placebo + metformin treatment pools. There was a slightly higher incidence of fractures in the DAPA + MET 5 mg pool in the ST+LT pool compared to the other treatment arms. However overall numbers were small and a specific pattern was not identified.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

A prespecified list of PTs was used to identify events of fracture (See Appendix C of the ISS).

As depicted in Table 28 the incidence of fractures was similar among all treatment arms in the ST pool. In the ST+LT pool the proportions of patients with fractures were slightly higher with DAPA 5 mg + MET (3.7%) relative to DAPA 10 mg + MET (1.8%) or placebo + MET (1.9%).

Table 28: Fracture Incidence Dapagliflozin/Metformin Placebo-Controlled Pool

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of fracture	8 (0.7)	3 (0.7)	6 (0.6)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of fracture	15 (1.9)	8 (3.7)	14 (1.8)

Source: Modified from ISS Table 32, Page 90

Abbreviations: DAPA = dapagliflozin; ISS = Integrated Summary of Safety; LT = long-term; MET = metformin; ST = short-term

Narrative review of fracture events in the 5 mg cohort did not suggest an additional safety concern as fracture types were distributed and not predominantly at one anatomic location and many were after a traumatic event.

Wrist fracture, hand fracture, and bone fissure were the most commonly reported PTs in the DAPA 5 mg + MET group, each reported in two patients. Ankle fracture and foot fracture were the most commonly reported PTs in the DAPA 10 mg + MET group.

Reviewer Comment: The overall low incidence and small numbers of fracture events limit any conclusions. However, fractures were identified as an event of interest in the dapagliflozin clinical program and should also be monitored for the dapagliflozin/metformin combination product.

VOLUME DEPLETION

Volume depletion events were more common among dapagliflozin-treated patients compared to placebo. In addition, a higher proportion of events was observed for patients older than 65 years, patients with renal impairment, and patients who used loop diuretics. However, events were few for all treatment arms, making it difficult to assess adequately for at-risk patient populations or dose-response relationships.

Dapagliflozin + Metformin (ST and ST+LT)

A prespecified list of PTs was used to identify events of volume depletion, which encompassed events of hypotension, dehydration and hypovolemia. Refer to Appendix C, in the ISS for the list of terms.

In the ST DAPA + MET placebo-controlled pool, a higher proportion of patients treated with DAPA 5 mg + MET (1.0%) and DAPA 10 mg + MET (1.2%) had events of volume

depletion compared with placebo + MET (0.4%). The most common Preferred Terms were for hypotension in the DAPA 10 mg arm (0.9%), and hypotension and orthostatic hypotension for the 5 mg group (0.5%, respectively). In the placebo group the most common adverse events were due to orthostatic hypotension and syncope (0.2%, two patients each).

Similar to the ST pool, in the ST+LT DAPA + MET placebo-controlled pool, a higher proportion of patients treated with DAPA 5 mg + MET (2.8%) or DAPA 10 mg + MET (2.3%) had events of volume depletion compared with placebo + MET (1.3%). The most common events in the DAPA group were related to hypotension. Syncope was the most common event in the placebo + MET group.

Table 29: Volume Depletion Events, Dapagliflozin/Metformin Placebo-Controlled Pool

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	N = 1185	N = 410	N = 983
AE of volume depletion	5 (0.4)	4 (1.0)	12 (1.2)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	N = 776	N = 216	N = 772
AE of volume depletion	10 (1.3)	6 (2.8)	18 (2.3)

Source: Modified from ISS Table 26, Page 75

Abbreviations: AE = adverse event; DAPA = dapagliflozin; ISS = Integrated Summary of Safety; LT = long-term; MET = metformin; ST = short-term

There was one volume depletion SAE in the DAPA 5 mg + MET pool, and two SAEs in the DAPA 10 mg + MET (study drug was interrupted in one event), and four volume depletion SAEs in patients receiving placebo + MET. In addition, one patient experienced two hypotensive events while on DAPA 10 mg + MET, and had the study drug discontinued.

Volume depletion events in subgroups

Volume depletion events were further analyzed by the following subgroups: age category subgroup (<65 years, ≥65 years), baseline eGFR category (≥30 and <60 mL/min/1.73m², ≥60 mL/min/1.73m²), and loop diuretic use (yes, no). Results of subgroup analyses are detailed in Table 30.

As observed in the original DAPA program and described in Table 29, volume depletion events were more frequently observed in the subgroups of patients ≥65 years of age (versus <65 years of age), patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), or patients taking loop diuretics (versus not taking loop diuretics).

**Table 30: Adverse Events of Volume Depletion in Subgroups
Dapagliflozin/Metformin Placebo-Controlled Pool (Short-Term)**

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
	N = 1185	N = 410	N = 983
Age	5 (0.4)	4 (1.0)	12 (1.2)
Patients < 65 years of age	N = 893	N = 356	N = 733
	5 (0.6)	3 (0.8)	6 (0.8)
Patients ≥ 65 years of age	N = 292	N = 54	N = 250
	0	1 (1.9)	6 (2.4)
Patients using loop diuretic	N = 90	N = 11	N = 93
	1 (1.1)	0	3 (3.2)
Patients not using loop diuretic	N = 1095	N = 399	N = 890
	4 (0.4)	4 (1.0)	9 (1.0)
Patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73m ²	N = 112	N = 41	N = 93
	1 (0.9)	0	1 (1.1)
Patients with baseline eGFR ≥ 60 mL/min/1.73m ²	N = 1073	N = 369	N = 889
	4 (0.4)	4 (1.1)	11 (1.2)

Source: Adapted from Table 2 in IR SDN14 (16): Appendix 3011, and Appendix 4009

Abbreviations: DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; IR = information request; MET = metformin; ST = short-term

POLYURIA

An increased incidence of polyuria was observed in patients treated with dapagliflozin, consistent with the diuretic effect of SGLT2 inhibition.

The definitions of polyuria events are based on the dapagliflozin list of prespecified PTs (pollakiuria, polyuria, and urine output increased); see Appendix C.

Dapagliflozin + Metformin Placebo-Controlled Pool ST and ST+LT)

A slightly increased frequency of AEs of polyuria was observed in patients treated with DAPA 5 mg + MET or DAPA 10 mg + MET compared with patients treated with placebo + MET. This is consistent with the diuretic effect of dapagliflozin. None of the events were serious and two patients receiving dapagliflozin in combination with metformin discontinued due to polyuria.

Table 31: Polyuria Events

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of polyuria	16 (1.4)	10 (2.4)	26 (2.6)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of polyuria	14 (1.8)	9 (4.2)	26 (3.4)

Source: Modified from ISS Table 33

Abbreviations: AE = adverse event; DAPA = dapagliflozin; LT = long-term; MET = metformin. ST = short-term

RENAL EVENTS

Events of renal impairment or failure were experienced by a higher proportion of patients treated with DAPA 10 mg + MET than DAPA 5 mg + MET or placebo + MET. Patients over 65 years of age had a greater incidence of renal impairment when taking dapagliflozin in combination with metformin compared to placebo and metformin. Patients in the DAPA 10 mg + MET pool experienced a small decline in eGFR at week 24.

The definitions of renal impairment or failure are based on the dapagliflozin list of prespecified PTs described in Appendix C of the ISS.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

As described in Table 32, renal adverse events occurred more often in both the ST and ST+LT pool for DAPA 10 mg + MET treatment arms (2.5 and 5.4%, respectively), compared to placebo + MET (3.9 and 1.4%, respectively).

Table 32: Adverse Events of Renal Impairment or Failure

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of renal impairment or failure	16 (1.4)	8 (2.0)	25 (2.5)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of renal impairment or failure	30 (3.9)	6 (2.8)	42 (5.4)

Source: Modified from ISS Table 29 (including data after rescue)

Abbreviations: AE = adverse event; DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term

Overall in the DAPA + MET program (including the active comparator trial), there were three SAEs in the dapagliflozin group compared to one in the placebo arm. In the ST pool a slightly higher percentage of patients withdrew due to an event in the DAPA 10 mg + MET pool (1.3%, 13/983) compared to the DAPA 5mg + MET (2/410), or placebo + MET (0.8%, 9/1185).

Renal impairment events in age subgroup ≥ 65 years

The sponsor conducted subgroup analyses of renal events in patients ≥65 years of age, and patients less than 65 years of age. Patients receiving DAPA 10 mg + MET had the highest incidence of events for both the ST and ST+LT pools (6.8 and 12.2% respectively), compared to DAPA 5 mg + MET (5.4 and 3.7, respectively) and placebo + MET (6.9 and 2.7, respectively). This difference was primarily due to more events in the DAPA 10 mg pool of “decreased creatinine renal clearance” and “renal impairment” (2%, 5/250) each). For patients less than 65 years of age in the ST pool, events of “blood creatinine increased” were the most common renal AEs for all treatment arms (0.4% for DAPA 10mg+ MET and 0.6%, for DAPA 5mg+MET and Placebo +MET)

Table 33: Adverse Events of Renal Impairment or Failure by Age

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of renal impairment or failure	16 (1.4)	8 (2.0)	25 (2.5)
Patients <65 years of age	893	356	733
	8 (0.9)	6 (1.7)	8 (1.1)
Patients ≥65 years of age	292	54	250
	8 (2.7)	2 (3.7)	17 (6.8)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of renal impairment or failure	30 (3.9)	6 (2.8)	42 (5.4)
Patients <65 years of age	528	179	543
	13 (2.5)	4 (2.2)	14 (2.6)
Patients ≥65 years of age	248	37	229
	17 (6.9)	2 (5.4)	28 (12.2)

Source: Adapted from Table 1 in IR SDN14 (16): Page 5

Abbreviations: AE = adverse event; DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term

Subgroup analysis by eGFR

Consistent with metformin's contraindication, patients with a history of unstable or rapidly progressing renal disease or creatinine ≥ 1.5 mg/dL (men) or ≥ 1.4 mg/dL (women) or abnormal creatinine clearance were not enrolled.

In the DAPA + MET Pool (ST and ST+LT), the majority of patients across treatment groups had mild impairment or normal renal function. In the ST pool subgroup analyses of patients with eGFR >60 mL/min revealed a similar incidence of adverse events between DAPA 10 mg + MET, DAPA 5 mg + MET and placebo + MET (1.2, 1.1, and 0.7%, respectively).

Laboratory assessments related to renal function

Serum Creatinine:

Marked abnormalities (MAs) for serum creatinine were defined as:

- Creatinine $\geq 1.5 \times$ baseline
- Creatinine ≥ 2.5 mg/dL

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

In the ST pool MAs of creatinine $\geq 1.5X$ pre-treatment levels were reported in a similar number of patients receiving DAPA 10 mg + MET (2.5%), DAPA 5 mg + MET (1.7%) and Placebo + MET (1.9%). This pattern was also observed in the ST+LT pool (3.4, 2.8 and 3.6%, respectively). There were no MAs of creatinine ≥ 2.5 mg/dL in patients treated with dapagliflozin + metformin.

Changes in Serum Creatinine over Time

In the ST pool the maximum increase in serum creatinine from baseline for the DAPA 10 mg + MET and DAPA 5 mg + MET pools occurred at week 1 (0.039, 0.019 mg/dL, respectively). The mean change from baseline at week 24 in serum creatinine was 0.014 mg/dL for the DAPA 10 mg + MET pool, -0.009 for the DAPA 5 mg + MET pool and 0.002 mg/dL for the Placebo + MET group.

Changes in eGFR (estimated glomerular filtration rate) over time

In the ST pool, at week 24, the mean change from baseline in eGFR was -1.320 mL/min/1.73m² for the DAPA 10 mg + MET group, 1.620 mL/min/1.73m² for the DAPA 5 mg + MET, and 0.083 mL/min/1.73m² for the placebo + MET group. The maximum change for the DAPA 10 mg and 5 mg groups occurred at week 1 (-3.75 \pm 0.5, -2.139 \pm 0.5). In the DAPA 5 mg + MET arm patients experienced a recovery by week 24.

Reviewer Comment: The applicant recommends that the dapagliflozin/metformin FDC not be initiated in patients with an eGFR of <60 mL/min/1.73 m². Patients

over 65 years of age appear to be at a higher risk for renal impairment events. In addition, in current labeling, metformin use is not recommended in moderate-to-severe renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min). Due to the increase in serum creatinine and decrease in eGFR with dapagliflozin + metformin compared to placebo + metformin, the combination product will be contraindicated in patients with moderate-to-severe renal impairment and prescribers will be advised to monitor eGFR. Therefore, renal function should be evaluated prior to initiation of the FDC product, and monitored periodically, with discontinuation of therapy for eGFR < 60 mL/min/1.73 m².

LACTIC ACIDOSIS

There were no AEs or SAEs with terms indicative of lactic acidosis reported in any treatment arm in any of the DAPA + MET pools.

HEPATIC SAFETY

In the dapagliflozin/metformin FDC pools overall adverse hepatic events were balanced between groups. There were small imbalances in laboratory abnormalities not in favor of the combination with three events of biochemical Hy's law in the DAPA 10 mg + MET arm. Pertinent cases were reviewed by Dr. John Senior (review dated November 11, 2013), Dr. Leonard Seeff (dated November 21, 2011) and Dr. Frank Pucino (review dated December 22, 2013). Previous review of serious hepatic events and laboratory abnormalities did not suggest a causal association with dapagliflozin.

Hepatic adverse events in the dapagliflozin clinical development program were identified using a list of standardized MedDRA queries (SMQs) (Appendix C in the ISS). Analyses of hepatic adverse events were performed for the DAPA + MET Pool (ST and ST+LT) and include the following: AEs and SAEs of hepatic disorder by PT and treatment group, and listing of AEs of hepatic disorder. In addition, analyses of adjudicated hepatic events were performed on the DAPA All phase 2b and 3 Pool plus data from blinded and open-label studies.

All patients with liver abnormalities meeting at least one of the following criteria were reviewed by a blinded Hepatic Adjudication Committee to assess any causal relationship to study drug:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $> 3\times$ upper limit of normal (ULN) and TBL $> 1.5\times$ ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT $> 5\times$ ULN
- Hepatic disorders AEs/SAEs in patients who prematurely discontinued study treatment due to any AE/SAE

- Hepatic disorders AEs/SAEs in any patients who died

Supplemental CRFs were required to collect detailed data on hepatic clinical events and hepatic tests, for both the initial findings and protocol-required follow up.

A complete review of hepatic events for dapagliflozin was provided/reviewed in the dapagliflozin NDA 202293. The data cut for the data reviewed in dapagliflozin is the same as that used for the DAPA/MET XR FDC NDA.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

As depicted in Table 34, overall AEs were balanced between patients treated with dapagliflozin + metformin and placebo + metformin. In both the ST and ST+LT pools a slightly higher overall incidence of hepatic disorder AEs were observed in the placebo group. The most frequent hepatic AEs across treatment arms in the ST pool were for increased alanine aminotransferase values (0.5% for each treatment group).

Table 34: Incidence of Hepatic Adverse Events

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of hepatic disorder	21 (1.8)	7 (1.7)	10 (1.0)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of hepatic disorder	21 (2.7)	5 (2.3)	17 (2.2)

Source: Modified from IR Response June 4, 2104 Appendix 1.1 and 1.2

Abbreviations: AE = adverse event; DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term

Serious Hepatic Adverse Events

There were four serious hepatic adverse events in the DAPA + MET treatment group and one in placebo. All cases narratives for patients with SAEs were previously reviewed in consultation with the agency's Office of Surveillance and Epidemiology (OSE) hepatology group, and are detailed in previous reviews by Dr. John Senior (dated November 11, 2013), and Dr. Leonard Seeff (dated November 21, 2011). Review of case narratives for serious hepatic adverse events did not suggest a clear causal association to dapagliflozin.

Elevations in Liver Enzymes

In the ST DAPA + MET placebo-controlled pool, the proportion of patients with elevated liver laboratory tests was the same for the DAPA 10mg and placebo groups (3.2% each). There was a slightly higher incidence of hepatic enzyme abnormalities in the DAPA 5 mg + MET pool (4.4%). As detailed in a Table 35 a similar pattern was observed for the ST+LT placebo-controlled pool.

In all treatment groups, the most frequently reported elevated liver function tests were AST or ALT elevations >3X ULN. In the DAPA 10 mg + MET pool 0.3% (three patients) had AST or ALT >3X ULN, and met biochemical criteria for Hy's law. One patient in the DAPA 10 mg + MET pool met criteria for ALT >20X ULN.

All cases meeting biochemical Hy's law as well as transaminase elevations >10X ULN were previously reviewed under the dapagliflozin clinical program up to the 30MU. Cases of marked elevations of both serum transaminases and total bilirubin had alternate diagnoses and were assessed as less likely to be related to dapagliflozin than to another etiology. As noted in Dr. Pucino's review (dated December 22, 2013), the long-term follow-up of one possible case of drug-induced liver injury (DILI) was supportive of a diagnosis of autoimmune hepatitis, although an association with dapagliflozin cannot be entirely excluded for this case.

Table 35: Marked Liver Laboratory Test Abnormalities, Dapagliflozin + Metformin Placebo-Controlled Pool

Liver Laboratory Abnormality	Placebo + MET	Placebo + MET	DAPA 5 mg + MET	DAPA 5 mg + MET	DAPA 10 mg + MET	DAPA 10 mg + MET
	ST	ST+LT	ST	ST+LT	ST	ST+LT
Patients with Elevated Liver Laboratory Test(s) s (%)	38/1180 (3.2)	36/772 (4.7)	18/408 (4.4)	12/214 (5.6)	31/975 (3.2)	33/765 (4.3)
AST						
>3X ULRR	5/1179 (0.4)	8/771 (1.0)	4/408 (1.0)	6/214 (2.8)	6/975 (0.6)	8/765 (1.0)
>5X ULRR	1/1179(0.1)	1/771 (0.1)	0	0	1/975 (0.1)	4/765 (0.5)
>10X ULRR	0	0	0	0	0	2/765 (0.3)
>20X ULRR	0	0	0	0	0	
ALT						
>3X ULRR	14/1180 (1.2)	10/772(1.3)	6/408 (1.5)	4/214 (1.9)	05/975 (1.0)	15/765 (2.0)
>5X ULRR	3/1180 (0.3)	4/772 (0.5)	1/408 (0.2)	1/214 (0.5)	1/975 (0.1)	5/765 (0.7)
>10X ULRR	1/1180 (0.1)	0	0	0	0	2/765 (0.3)
>20X ULRR	0	0	0	0	0	1/765(0.1)
Total Bilirubin >2X ULRR						
>2X ULRR	1/1179 (0.1)	1/772 (0.1)	2/408 (0.5)	0	2/974 (0.2)	3/764 (0.4)
Biochemical Hy's Law AST >3X ULRR or ALT >3X ULRR and TBL >2X ULRR*	0	1/772 (0.1)	0	0	1/974 (0.1)	2/764 (0.3)

Source: ISS Appendix 3019 and 4017

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; Biochemical Hy's Law = AST or ALT >3X ULRR and TBL >2X ULRR; DAPA = dapagliflozin; LT = long-term; MET = metformin; ST = short-term; TBL = total bilirubin

FOUR MONTH SAFETY UPDATE (4-MSU)

In the nine studies included in this 4-MSU, 20 AEs of hepatic disorder were reported in 14 patients.

Unblinded/Completed Studies

All events were nonserious, of mild or moderate intensity, and did not lead to discontinuation of study treatment.

Ongoing Phase 1 Studies and Blinded Phase 2/3 Studies

One SAE of cholelithiasis was reported on study Day 21 (Day 1 of the blinded short-term treatment period). This SAE resulted in interruption of blinded study drug, but did not lead to study discontinuation.

There were no cases meeting ALT >3X ULRR and TBL >2X ULRR

POSTMARKETING

The sponsor conducted a postmarketing interval search of the company safety database from October 5, 2012 to October 4, -2013 of a standardized MedDRA query (SMQ), for hepatic disorders. The search identified a single case described below.

A 74 year-old man received dapagliflozin 10 mg and was found to have cholangiocarcinoma two months after starting dapagliflozin treatment.

Reviewer Comment: The temporal relationship between the event of cholangiocarcinoma and dapagliflozin initiation (approximately 2 months) does not suggest a causal association with study drug.

Overall, a hepatic safety signal was not obvious in the dapagliflozin/metformin combination. However, the sponsor's proposed postmarketing enhanced pharmacovigilance program is appropriate to elucidate further any potential hepatic toxicity related to the use of dapagliflozin, and may be applicable to the FDC product.

CARDIOVASCULAR SAFETY

Cardiovascular safety data specific to dapagliflozin in combination with metformin were not provided with the NDA submission. For the DAPA All phase 2b and 3 pool the primary analysis of the composite primary endpoint (cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina) resulted in an estimated hazard ratio of 0.787 (95% CI: 0.579, 1.070). The hazard ratio for the MACE composite endpoint (cardiovascular death, myocardial infarction and stroke) was 0.772 (95% CI: 0.543, 1.097). The upper bound of the 95% CI for the MACE endpoint was less than 1.8, consistent with recommendations for ruling out excess cardiovascular risk for initial approval in the FDA 'Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes' (issued December 2008). See Dr. Frank Pucino's clinical review dated December 22, 2013, and Dr. Andraca-Carrera's statistical review dated December 16, 2013 for details of the cardiovascular safety of dapagliflozin.

Malignant or Unspecified Tumors (including Breast Cancer)

See Section 7.6.1

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Dapagliflozin + Metformin Placebo-Controlled Pool (ST)

Common adverse events occurring in the ST placebo-controlled pool with an incidence >2% in descending order (by the 5mg dose) are depicted in Table 36.

Table 36: Common Adverse Events with an Incidence >2% in any Dapagliflozin-Treated Patient (Dapagliflozin + Metformin Placebo-Controlled Pool- Short-Term)

MedDRA PT or Equivalent	DAPA 10 mg + MET	DAPA 5 mg +MET	Placebo + MET
N	983	410	1185
NASOPHARYNGITIS	51 (5.19%)	26 (6.34%)	70 (5.91%)
DIARRHOEA	41 (4.17%)	24 (5.85%)	66 (5.57%)
URINARY TRACT INFECTION	43 (4.37%)	23 (5.61%)	33 (2.78%)
HEADACHE	32 (3.26%)	22 (5.37%)	33 (2.78%)
UPPER RESPIRATORY TRACT INFECTION	21 (2.14%)	17 (4.15%)	49 (4.14%)
INFLUENZA	26 (2.64%)	17 (4.15%)	28 (2.36%)
NAUSEA	26 (2.64%)	16 (3.90%)	24 (2.03%)
BACK PAIN	25 (2.54%)	14 (3.41%)	38 (3.21%)
COUGH	14 (1.42%)	13 (3.17%)	23 (1.94%)
DIZZINESS	18 (1.83%)	13 (3.17%)	26 (2.19%)
CONSTIPATION	19 (1.93%)	12 (2.93%)	19 (1.60%)
DYSLIPIDAEMIA	15 (1.53%)	11 (2.68%)	16 (1.35%)
PHARYNGITIS	15 (1.53%)	11 (2.68%)	13 (1.10%)
HYPERTENSION	27 (2.75%)	11 (2.68%)	46 (3.88%)
DYSURIA	16 (1.63%)	9 (2.20%)	13 (1.10%)

Reviewer-generated

Abbreviations: DAPA = dapagliflozin; MedDRA = Medical Dictionary for Regulatory Activities; MET = metformin; PT = Preferred Term

Reviewer Comment: In the proposed product labeling the sponsor has added the incidence of pooled terms for genital mycotic infections, urinary tract infections, and polyuria to the common adverse event table. This is in alignment with the dapagliflozin label and is acceptable.

7.4.2 Laboratory Findings

Laboratory abnormalities were evaluated based on marked abnormality values (MA). The predefined criteria for MAs are presented under each respective section.

Change from baseline during the treatment period is summarized by treatment group for the following laboratory parameters: lipids (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol [TC], triglycerides [TG]), hematocrit, and phosphorus.

HEMATOCRIT AND HEMOGLOBIN

There were small mean increases in hematocrit associated with dapagliflozin in combination with metformin compared to placebo and metformin treatment. These observed hematocrit increases are likely related to diuretic effect of dapagliflozin resulting in mild intravascular volume contraction. The clinical relevance of these mild changes has not been elucidated.

Marked laboratory abnormalities (MAs) were defined as:

- Hematocrit (>55%) and hemoglobin (>18 g/dL)

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

Small numbers of patients had MAs reported of elevated hematocrit (>55%) or hemoglobin (>18 g/dL). Elevations were more frequently reported in the ST and ST+LT pools for the DAPA 10 mg + MET group (0.9% and 1.1%, respectively) and DAPA 5 mg + MET group (1.2 and 0.7%) compared to the placebo + MET group (0.2% and 0.2%, respectively).

There were small increases in mean hematocrit values beginning at week 1 for both the DAPA 10 and 5 mg groups (0.6 ± 0.08 and 0.43 ± 0.08) and continuing up to week 16 for the DAPA 10 mg group (2.12 ± 0.09 , and) and week 20 for the DAPA 5 mg group (1.9 ± 0.13). The mean change from baseline in hematocrit at week 24 was 2.1% in the DAPA 10 mg + MET group, 1.5% in the DAPA 5 mg + MET arm, and -0.52% for the placebo + MET group.

Data from the ST+LT placebo-controlled pool supported the ST safety findings.

PHOSPHOROUS

Marked laboratory abnormalities (MAs) were defined as:

- Hypophosphatemia: ≤ 1.8 mg/dL if age 17-65 years or ≤ 2.1 mg/dL if ≥ 66 years
Hyperphosphatemia: ≥ 5.6 mg/dL if age 17-65 years or ≥ 5.1 mg/dL if age ≥ 66 years

No MA of increased or decreased phosphorus was reported as an AE.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

In the ST DAPA + MET placebo-controlled pool, the proportion of patients with high serum phosphorus was slightly higher in the DAPA 10 mg + MET group (2.1%), and DAPA 5 mg + MET (1.2%) compared to placebo + MET (0.9%). The mean change from baseline in serum phosphorus at week 24 was 0.12 mg/dL for the DAPA 10 mg + MET group, and 0.00 mg/dL for the placebo + MET group. Mean serum phosphorus levels increased by week 1 and persisted but did not increase in magnitude through weeks 24 and 102.

There was a comparable incidence of hypophosphatemia between DAPA 10 mg + MET (0.1%) and placebo + MET (0.2%).

Results from the ST+LT DAPA + MET placebo-controlled pool supported findings of the ST pool.

LIPIDS

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

In the ST placebo-controlled pool, a mean increase in HDL-C was noticed in all arms and was slightly higher in the dapagliflozin + metformin pools. Increases in LDL-C and total cholesterol were observed with the DAPA 10 mg + MET arm, and not in the DAPA 5 mg or placebo + MET pools. However, in the ST+LT pool increases in LDL-C and TC were observed for both DAPA 10 mg + MET and DAPA 5 mg + MET with a greater increase in the DAPA 5 mg + MET treatment pool.

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

In the ST DAPA + MET Pool, greater increases from baseline were observed at week 24 for the DAPA 10 mg + MET group compared with DAPA 5 mg + MET and placebo + MET for HDL-C (6.3%, 6.1%, 4.3%, respectively) and for total cholesterol (3.3%, 0.2, -0.4%, respectively). Changes from baseline at week 24 for LDL-C increased with DAPA 10 mg + MET (3.7%) and decreased with DAPA 5mg and placebo + MET (-2.7 and -2.9%, respectively).

In the ST+LT DAPA + MET placebo-controlled pool, a slightly larger increase from baseline was noted at week 102 for the DAPA 10 mg + MET and DAPA 5 mg + MET treatment arms compared to placebo + MET in HDL-C (7.4%, 11.4 versus 3.5%, respectively), LDL-C (5.3, 8, and 0.6%, respectively), and TC (3.0, 4.1, and 0.6%, respectively).

Reviewer Comment: Patients taking DAPA 10 mg + MET experienced elevations in LDL-C, HDL and total cholesterol when compared to placebo + MET. The long-term clinical consequences of these changes are unknown.

SODIUM AND POTASSIUM

Review of changes in sodium and potassium did not suggest an additional safety signal.

7.4.3 Vital Signs

Dapagliflozin + Metformin Placebo-Controlled Pool (ST and ST+LT)

In the DAPA + MET placebo-controlled ST pool, the mean changes in seated systolic blood pressure (SBP) from baseline at week 24 were -3.6 mmHg, -3.9 mmHg, and -1.0 mmHg for the DAPA+MET 10 mg, 5mg and placebo groups, respectively. The mean changes in seated diastolic blood pressure (DBP) from baseline at week 24 were -1.9, -2.4 and -0.5 mmHg, respectively.

A subgroup analysis in patients with baseline seated SBP >140 mmHg demonstrated a greater reduction in SBP in the DAPA/MET 10 mg and 5mg groups compared to placebo (-12.1, -13.7, versus -9.3). Orthostatic hypotension (fall in SBP of >20 mmHg or DBP of >10 mmHg [supine to standing]) was similar across treatment groups. There was no significant change in heart rate in either subgroup across treatment groups.

In the two dedicated BP studies (MB102073 and MB102077), orthostatic hypotension was reported in 3.2% and 1.7% of patients in the dapagliflozin 10 mg and placebo treatment arms, respectively. See Table 4 for a description of each study, and Dr. Pucino's review (dated December 22, 2013), for additional details.

Reviewer Comment: Mean decreases from baseline in SBP and DBP were consistent with changes associated with SGLT2 inhibitors.

7.4.4 Electrocardiograms (ECGs)

ECG data were not provided with this submission.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies submitted to the NDA.

7.4.6 Immunogenicity

Immunogenicity data were not provided with this submission.

7.5 Other Safety Explorations

No other safety explorations were performed.

7.5.1 Dose Dependency for Adverse Events

Dose related adverse events are presented throughout this review.

7.5.2 Time Dependency for Adverse Events

Discussion of adverse events related to ST and ST+LT periods are presented throughout this review when appropriate.

7.5.3 Drug-Demographic Interactions

Discussed throughout the review.

7.5.4 Drug-Disease Interactions

Discussed throughout the review.

7.5.5 Drug-Drug Interactions

A two-way pharmacokinetic (PK) drug interaction study between dapagliflozin and metformin was performed in healthy volunteers and submitted with the original dapagliflozin NDA. There was no effect of either metformin on the PK of dapagliflozin or dapagliflozin on the PK of metformin.

Refer to the original NDA or product labeling for information related to the potential for drug interactions with dapagliflozin or metformin.

7.6 Additional Safety Evaluations

Morning Versus Evening Dose

The proposed time of dosing submitted with the initial DAPA/MET XR FDC NDA was to be taken once daily (b) (4) . (b) (4)

A once-daily evening meal dosing regimen of dapagliflozin was investigated in 3 studies (MB102021, MB102034, and MB102013). Safety data from MB102021 and MB102034 were included in the DAPA + MET and DAPA + MET placebo-controlled pools. In these

two studies, both dapagliflozin and metformin were administered with the evening meal (DAPA 5 mg + MET XR in MB102021 and DAPA 10 mg + MET XR in MB102034).

In study MB102013, patients were randomized to either dapagliflozin 5 mg or 10 mg given in the morning (QAM) or dapagliflozin 5 mg or 10 mg given in the evening (QPM). The primary study period was 24 weeks followed by a 78 week extension period.

Summaries of AEs of special interest pertaining to evening dosing for the 24- and 102-week treatment periods are presented in Table 37. Overall AEs were highest in the dapagliflozin 10 mg QAM dosing group. In the ST period patients in the both QPM dapagliflozin dosing arms had a higher incidence of nocturia and dizziness compared to the QAM groups. Similarly, in the ST+LT period there was a slightly higher incidence of volume depletion, nocturia and dizziness in the dapagliflozin QPM treatment arms. However, the overall numbers of events are too small to make any meaningful conclusions.

Table 37: Summary of 24-Week (Short-Term) and 102-Week (Short-Term + Long-Term) Safety in MB102013 - Including Data After Rescue - Treated Patients

n (%) Patients with event	Placebo N = 75	DAPA 5 mg QAM	DAPA 10 mg QAM	DAPA 5 mg QPM	DAPA 10 mg QPM
24-week (ST Treatment Period)					
AE	45 (60.0)	37 (57.8)	48 (68.6)	44 (64.7)	45 (59.2)
Hypoglycemia	2 (2.7)	0	2 (2.9)	0	1 (1.3)
Fracture*	0	0	0	0	0
Volume Depletion*	1 (1.3)	0	1 (1.4)	0	0
Nocturia**	0	0	0	2 (2.9)	3 (3.9)
Falls**	0	1 (1.6)	1 (1.4)	0	0
Dizziness**	1 (1.3)	1 (1.6)	2 (2.9)	2 (2.9)	2 (2.6)
102-week (ST+LT Treatment Period)					
AE	58 (77.3)	43 (67.2)	56 (80.0)	50 (73.5)	54 (71.1)
Hypoglycemia	4 (5.3)	0	3 (4.3)	0	2 (2.6)
Fracture*	1 (1.3)	0	1 (1.4)	0	0
Volume Depletion*	1 (1.3)	0	1 (1.4)	0	2 (2.6)
Nocturia**	0	0	0	2 (2.9)	3 (3.9)
Falls**	0	1 (1.6)	1 (1.4)	1 (1.5)	0
Dizziness**	2 (2.7)	1 (1.6)	2 (2.9)	4 (5.9)	3 (3.9)
Orthostatic hypotension***	9 (12.0)	4 (6.5)	9 (12.9)	7 (10.8)	8 (11.0)

Copied from Source Type C Meeting Briefing Package, SDN 9/10, March 5, 2014, Table 3, Page 13.

*A prespecified list of PTs was used to identify events of Fracture and Volume depletion in the study database.

**Assessment based on single PT only (Nocturia, Fall, Dizziness).

*** Patients with orthostatic hypotension during the ST+LT double-blind treatment period defined as decrease from supine to standing of >20 mmHg in systolic blood pressure or >10 mmHg in diastolic blood pressure during vital signs assessment. Includes nonserious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 4 days. Includes serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days.

Abbreviations: AE = adverse event; DAPA = dapagliflozin; LT = long-term; QAM = once-daily dosing with the morning meal; PT = Preferred Term; QPM =

once-daily dosing with the evening meal; ST = short-term.

Reviewer Comment: In a teleconference with the sponsor on April 7, 2014, the agency discussed the concern for potential AEs related to volume depletion with the proposed QPM dosing instructions. The sponsor subsequently changed the dosing instructions to QAM to align with the approved dapagliflozin label.

7.6.1 Human Carcinogenicity

Malignant or Unspecified Tumors (including Breast Cancer)

Data for adverse events of malignant and unspecified tumors were presented for the DAPA all phase 2b and 3 pool. These data were previously submitted to the dapagliflozin NDA 30MU. The applicant did not conduct a specific analysis for the dapagliflozin/metformin FDC due to the overall small number of events. For details regarding malignant and unspecified tumors in the dapagliflozin clinical program refer to Dr. Pucino's review (dated December 22, 2013) under NDA 202293, section 7.3.4.2.

In the previous dapagliflozin submission an imbalance not in favor of dapagliflozin was noted for events of **bladder cancer** and **breast cancer**.

BREAST CANCER

In the ST+LT DAPA +MET placebo-controlled pool there were five nonfatal serious adverse events of breast cancer in the DAPA 10 mg + MET arm versus two in placebo. In the ST+LT non placebo-controlled pool one additional case of breast cancer occurred in the dapagliflozin 10 mg + MET treatment pool.

Breast cancer was an adverse event of interest identified in the dapagliflozin clinical program. In the DAPA All phase 2b and 3 Pool, breast cancer was reported in 12 of 2693 dapagliflozin-treated women [0.45%] and 3 of 1439 control-treated women [0.21%]. An excerpt from Dr. Pucino's clinical review (dated December 22, 2013), describing the incidence rate ratio (IRR) for breast cancer is below.

As noted during the previous review cycle, there remains a numeric imbalance of breast cancer cases (i.e., 0.45% and 0.21% for dapagliflozin and comparator arms, respectively) which favors the comparator arm (IRR 2.472; 95% CI, 0.636 to 14.095). Due to a decline in the incidence rate ratio (IRR) since the 2011 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting (i.e., the IRR was 4.41; 95% CI 0.57 to 200.86), the lack of screening mammography prior to study entry in a population at risk for breast cancer, and a diagnosis within the first year of exposure to dapagliflozin for the majority of patients, Dr. Genevieve Schechter, the consultant from the Division of Oncology Products (DOP), acknowledged that this imbalance in cancer events may be a spurious finding.

BLADDER CANCER

Additional data regarding cases of bladder cancer were not submitted to the dapagliflozin/metformin FDC NDA. All bladder cancer cases were previously submitted and reviewed under the dapagliflozin NDA. In the dapagliflozin clinical program a numeric imbalance in cases of bladder cancer, not favoring dapagliflozin (i.e., 10

cases/6045 [0.17%] dapagliflozin-treated patients and 1/3512 [0.03%] in the control arm) was observed. The incidence rate ratio in the dapagliflozin total group versus control was 6.111 (95% CI: 0.827, 272.02).

4-MSU

At the time of 4-MSU data cut-off there were no new events of bladder or breast cancer that were not previously reported under the dapagliflozin NDA. One case of metastatic squamous cell carcinoma occurred on study day 1 in a blinded treatment arm.

POSTMARKETING

The sponsor conducted a postmarketing interval search of the company safety database from October 5, 2012 to October 4, 2013 for a standardized MedDRA query (SMQ), with tumor origin in the urinary bladder. The search identified a single case which is described below.

“This 67 year-old male patient experienced hematuria and a likely bladder tumor, presumed by cystoscopy (large clot obscured visualization), approximately four months after initiation of treatment with dapagliflozin 10 mg daily. Treatment with dapagliflozin was stopped, but no improvement was reported two weeks later. Final diagnosis after further workup was reported later as transitional cell cancer of the bladder. Based on the risk factors in this polymedicated patient, age, gender and tobacco use, and the very short time to onset of the event of bladder tumor with significant hematuria of four months, causal relationship was assessed as definitively not related to dapagliflozin.”

Reviewer Comment: The narrative lacks relevant data regarding risk factors for bladder cancer. The diagnosis after only four months of exposure makes initiation of bladder cancer related to dapagliflozin unlikely. However a relationship to study drug for tumor promotion cannot be excluded. Breast and bladder cancer are adverse events of special interest that will continue to be followed in the large cardiovascular outcomes trial for dapagliflozin.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in patients treated with dapagliflozin in combination with metformin. Studies in lactating animals have not been conducted with the combined components of dapagliflozin/metformin XR FDC. It is not known whether dapagliflozin/metformin XR FDC is excreted in human milk. In studies performed with the individual components, both dapagliflozin and metformin were excreted in the milk of lactating rats.

Based on animal data, dapagliflozin may cause fetal harm during the second and third trimesters of pregnancy. The sponsor is recommending that dapagliflozin/metformin XR FDC not be used in the second and third trimesters of pregnancy or by nursing women.

Metformin is Pregnancy Category B, since there are no adequate and well-controlled studies of pregnant women with metformin.

Pregnancy category recommendation for the FDC is pending as of the time of this review.

Reviewer comment: The sponsor's recommendation to not use the FDC product in the second and third trimesters of pregnancy, or while nursing, seems reasonable. However, final pregnancy category is usually determined by the Pharmacology/Toxicology review team.

7.6.3 Pediatrics and Assessment of Effects on Growth

The PK and pharmacodynamics (PD) of dapagliflozin are currently being assessed in pediatric patients ages 10 to 17 years with T2DM in Study MB102091, and the safety and efficacy of dapagliflozin in combination with metformin will be assessed in the planned Study MB102138.

The sponsor states that the dapagliflozin pediatric studies (MB102091 and MB102138) will adequately characterize the safety, efficacy, and tolerability of dapagliflozin as add-on to metformin therapy in T2DM pediatric patients who are 10 to 17 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Data are not currently available with regard to overdose of the dapagliflozin/metformin XR FDC. In Dr. Pucino's dapagliflozin review (dated December 22, 2013), he notes that dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the maximum recommended human dose [MRHD]). In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for two weeks in healthy subjects and patients with T2DM, the incidence of hypoglycemia was slightly higher than placebo and did not appear to be dose-related. However, dapagliflozin doses greater than 10 mg daily have been associated with increased AEs without additional efficacy.

8 Postmarket Experience

Dapagliflozin/metformin FDC product has not been approved.

9 Appendices

None

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

Labeling negotiations and signatory review for this NDA are still pending at the time of this review, and therefore a detailed outline of all recommended revisions will not be included in this review. Labeling recommendations are delineated throughout this review.

1. **Section 6 Adverse Reactions:** This section should be updated to reflect safety data representing the dapagliflozin and metformin placebo-controlled pool. Excluding Table 1, the applicant has presented data (b) (4)

2. **Section 14 Clinical Studies**

(
b
)
(
4
)

9.3 Advisory Committee Meeting

An advisory committee meeting was not convened for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAVEETA P VASISHT
07/10/2014

KAREN M MAHONEY
07/11/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			<ul style="list-style-type: none"> • 1 Phase 3 dapagliflozin monotherapy study supporting the safety and tolerability of once daily dosing with the evening meal (QPM), the proposed dosing regimen of dapagliflozin/metformin in XR FDC tablets: Study MB102013 • 11 Phase 3 studies supporting the safety and tolerability of dapagliflozin in combination with metformin <ul style="list-style-type: none"> ◦ 9 studies in patients with T2DM (Dapagliflozin + Metformin Pool) <ul style="list-style-type: none"> ◻ 8 placebo-controlled studies (Dapagliflozin + Metformin Placebo controlled Pool): Studies MB102014, MB102021, MB102034, D1690C00006, D1690C00010, D1690C00012, D1690C00018, and D1690C00019 ◻ 1 active-comparator study: Study D1690C00004 • 2 studies in patients with T2DM and hypertension: Studies MB102073 and MB102077
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	not previous Agency agreements regarding primary/secondary endpoints.				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		About 30% of randomized subjects are from US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	Addressed in the original dapagliflozin NDA 202253
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			Adverse events coded using MedDRA coding system version 15.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Narratives for SAEs and discontinuations provided in individual CSRs previously under dapagliflozin NDA 202293
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		x		

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		About 30% of randomized subjects are from US
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			Defer also to statistical reviewer regarding efficacy data - safety data appears to be complete
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			Defer also to statistical reviewer
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Ali Mohamadi
Reviewing Medical Officer/Clinical Team Leader

December 9, 2013
Date

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI MOHAMADI
12/19/2013