FDA BRIEFING DOCUMENT

NDA 202293

DAPAGLIFLOZIN ORAL TABLETS, 5 AND 10 MG

SPONSOR: BRISTOL-MYERS SQUIBB

ADVISORY COMMITTEE MEETING
DECEMBER 12, 2013

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 202293 (dapagliflozin) to this Advisory Committee in order to gain the Committee's insights and opinions on selected matters, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Division Director's Memo:

In the original dapagliflozin review cycle, the preplanned primary cardiovascular (CV) safety analysis for dapagliflozin was a meta-analysis of 14 completed and ongoing Phase 2b/3 trials not primarily designed to assess CV-risk. The analysis utilized a four component composite endpoint of time to first cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina ("MACE+"). In the original analysis a trend favoring dapagliflozin over comparator was noted [i.e., hazard ratio for MACE+: 0.67 (95% CI, 0.38-1.18) based on 78 primary events].

Safety signals for clinically serious events (i.e., bladder and breast malignancy and liver toxicity) were identified in the data submitted with the original application. To further assess these putative risks and consider them in light of potential CV-benefits suggested by dapagliflozin's observed effects on HbA1c, blood pressure and weight the applicant was asked to update analyses of cancer risk, liver toxicity and CV-risk using all data available in November 2011.

An updated analysis of CV-risk, based on cumulative data from the original 14 trials (with additional extension phase data) and from 5 additional Phase 3 trials, was received. This updated analysis included 145 "MACE+" events. The hazard ratio was again noted to be leaning in favor of dapagliflozin, though the magnitude of the CV-risk reduction observed was attenuated compared to the first analysis [hazard ratio for "MACE+": 0.82 (0.58, 1.15)].

Two of the five new trials (Trials 18 and 19) contributed the largest sample size and the longest exposure duration in the updated analysis. These two trials evaluated the effect of dapagliflozin in participants specifically recruited because they had documented CV disease at baseline and contributed more than 40% of the events in this updated analysis. In the pool of patients participating in Trials 18 and 19 the point estimate (95% CI) for the hazard ratios of "MACE+" and MACE were 1.07 (0.64, 1.77) and 1.27 (0.69, 2.31) respectively and were discordant with the trend noted in the overall analysis.

As a result of these updated analyses the Agency could not conclude with any level of confidence that the purported CV-benefit associated with dapagliflozin use outweighed the observed imbalance in specific malignancies or potential liver toxicity risks.

At the advisory committee meeting updates to the identified malignancy and liver toxicity signals will be provided. In addition, CV analyses reflecting current data will be presented. Based on presentations at the advisory committee meeting and materials in the briefing documents, you will be asked to weigh in on the several key topics.

Draft Points to Consider

1) CV-Risk

Based on the information provided in the briefing package and presentations at the advisory committee meeting, please address the following with regards to the cardiovascular-risk assessment for dapagliflozin.

1. Comment on which data (i.e., overall population, enriched population) best inform the cardiovascular risk associated with dapagliflozin use and discuss the weight you place on the evidence provided by the subgroup of patients specifically recruited on the basis of established CVD in trials 18 and 19.
2. Discuss whether you believe the updated CV-risk data derived from trials 18 and 19 are consistent with the overall findings reported for the pool of 21 clinical trials.
3. Discuss the clinical importance you place on the observed changes in blood pressure, weight, glycemic control and lipid parameters in informing overall cardiovascular risk of dapagliflozin.
4. Discuss additional concerns, if any, you may have with regards to dapagliflozin and CV risk.
5. In accordance with FDA's Guidance for Industry titled "Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes", has the Applicant provided sufficient evidence that dapagliflozin, relative to comparators, has an acceptable CV risk profile.

2) Malignancy

Based on the information provided in the briefing package and presentations at the advisory committee meeting, discuss your level of concern with regards to the observed association between dapagliflozin use and occurrence of cancer identified in the application. Specifically, comment on whether you believe use of dapagliflozin is associated with an increased risk of bladder cancer and explain your rationale.

3) Liver Toxicity

Based on the information provided in the briefing package and the presentations at the advisory committee meeting, discuss your level of concern with regards to dapagliflozin use and drug-induced liver injury. Specifically, comment on whether you believe use of dapagliflozin is associated with an increased risk of drug-induced liver injury and explain your rationale.

4) Overall Benefit Risk

Based on the information included in the briefing materials and presentations at the advisory committee meeting, do the benefits of dapagliflozin use outweigh identified risks and support marketing of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?

CLINICAL BRIEFING MATERIAL

NDA 202293: DAPAGLIFLOZIN (FARXIGA)
APPLICANT: BRISTOL-MYERS SQUIBB

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING

DECEMBER 12, 2013

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TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

SECTION 1. INTRODUCTION

1.1. Background

This document provides the clinical briefing material for New Drug Application (NDA) 202293, FARXIGA (dapagliflozin), submitted on July 11, 2013. Dapagliflozin is an orally active, selective sodium glucose co-transporter 2 (SGLT2) inhibitor. By inhibiting SGLT2, dapagliflozin reduces renal glucose reabsorption, leading to increased urinary excretion of excess glucose and reduction in plasma glucose concentrations. Dapagliflozin is a new molecular entity (NME) but not a first-in-class drug (i.e., canagliflozin, another SGLT2 inhibitor, was approved on March 29, 2013). The Applicant, Bristol-Myers Squibb, is requesting approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

This Application is being reviewed for a second cycle under a six-month review clock. During the first NDA review cycle, a Complete Response Letter (CRL) was issued on January 17, 2012, due to a benefit-risk assessment of modest efficacy and concerns regarding a possible increase in cancer risk (i.e., bladder cancer), hepatotoxicity, and cardiovascular (CV) safety. The clinical review for this briefing document will focus primarily on the updated safety information provided in the 30-Month Update (30-MU) pertaining primarily to bladder cancers and hepatic safety, as well as the additional information and data included in the Application for evaluation of the overall risk-benefit assessment of this product.

1.2. Regulatory History

New Drug Application 202293 (dapagliflozin) was originally submitted on December 28, 2010. The key milestone meetings and regulatory actions for this product are outlined in Table 1. During the first review cycle, potential safety concerns were identified, which the Agency felt were not balanced by the modest efficacy observed in the clinical program. Specifically, there was a numeric imbalance in favor of the comparator for bladder cancer (i.e., nine events in dapagliflozin-treated patients vs. one in the comparator arm), incidence rate ratio [IRR], 5.38; 95% confidence interval [CI], 0.84 to 122.2), and a case of drug-induced liver injury (DILI) deemed "probable". Further, the analysis of the stratified hazard ratio (HR) for major adverse CV events (MACE) from a pool of two large Phase 3 clinical trials (D1690C00018 and D1690C00019) enriched with individuals at high CV risk resulted in a point estimate greater than one with a 95% upper bound greater than 1.8 (HR, 1.26; 95% CI, 0.69 to 2.31). These two studies contributed approximately 40% of the total CV events for the larger pool of 19 Phase 2b/3 clinical trials; the larger pool included these two studies and 17 other studies; the latter 17 studies

were a lower CV-risk pool. The results for the two higher CV risk trials alone were discordant with those reported in the overall meta-analysis of the 19 studies (HR, 0.861; 95% CI, 0.534 to 1.388). On January 17, 2012, a CRL was issued by the Agency. Relevant excerpts from this letter included the following:

> "While we cannot conclude that dapagliflozin is associated with an excess CV risk based on an analysis of only these two trials [Studies D1690C00018 and D1690C00019], the findings from these two large, adequate and well-designed trials in a relevant patient population cannot be ignored. More importantly, we cannot include any suggested CV benefit observed in the original meta-analysis in a risk-benefit consideration in regard to cancer and liver safety signals.

> Furthermore, while the glucose-lowering effect of dapagliflozin is the result of a novel mechanism of action that does not rely on insulin secretion or insulin sensitivity, the achieved HbA1c reductions are modest and attenuated or absent in patients as renal function decreases. An antidiabetic therapy that is ineffective in patients with moderate to severe renal impairment is a major limitation as many patients with T2DM have or will develop renal impairment.

> Overall, the observed clinical benefits of dapagliflozin in your current clinical development program may be achieved with other available antidiabetic therapies. In the absence of a unique benefit of dapagliflozin over these other therapies, an unmet need that may be filled by dapagliflozin could not be identified to offset potential risks of bladder cancer and hepatic toxicity."

The Applicant stated that they would be committed to conducting a large CV outcomes trial and a large pharmacoepidemiology study to quantify definitively the CV risk profile of the drug and assess cancer and hepatotoxicity risks.

Table 1: Key Meetings and Regulatory Actions

Date	Meeting/ Submission Type	Comments
09/01/2007	End-of-Phase 2	• Inclusion of dapagliflozin doses <2.5 mg and patients with renal impairment in the Phase 3 clinical program recommended by the Agency
12/28/2010	Original NDA submitted	• NDA filed: 03/04/2011 • PDUFA date: 10/28/2011
07/19/2011	Endocrinology and Metabolic Advisory Committee (EMDAC) Meeting	• The EMDAC voted not to support approval of dapagliflozin based on the current data • More data are needed regarding the risks of bladder cancers and liver injury
10-20-2011	Major Amendment submitted	• Requested by the Agency • Trigger PDUFA date shift • Additional data from studies D1690C00018 and D1690C00019, and updated analyses for CV safety, malignancy, and hepatic safety to be submitted

Date	Meeting/ Submission Type	Comments
01/17/2012	CRL issued	• CV safety data from studies D1690C00018 and D1690C00019 were discordant with the CV safety data submitted in the initial NDA • An unmet need that could not be identified to offset the potential risks of bladder cancer and hepatic toxicity • Path Forward — Applicant should submit additional clinical trial data (at least for 52-week completers from studies D1690C00018 and D1690C00019) — Analyses should include updated information on bladder cancer events, hepatic safety, and the CV meta-analysis
07/11/2013	NDA resubmission	• PDUFA date: 01/11/2014

Source: Modified from the Applicant's Reviewer's Guide Document (page 16-22 of 51; labeled as Appendix 1).
Abbreviations: AC, Advisory Committee; CRL, Complete Response Letter; CV, cardiovascular; NDA, New Drug Application; and PDUFA, Prescription Drug User Fee Act.

On July 11, 2013, the Applicant submitted the following additional data in their resubmission:

- A 30-month update (30-MU), which includes updated nonclinical and clinical safety data/information
- A response to the CRL, which summarizes the updated clinical and nonclinical data/information relating to the deficiencies identified in the CRL
- Clinical Study Reports for studies included in the pooled safety analyses
- Updated CV Meta-Analysis
- Updated Hepatic Adjudication Report
- Datasets (Study Data Tabulation Model [SDTM] for raw data, and Analysis Data Model [ADaM] for derived analysis datasets)
- Nonclinical reports for thirteen nonclinical studies
- Updated proposed draft labeling
- Response to the Agency regarding additional CRL comments related to Product Quality

This briefing document will focus primarily on the updated safety information pertaining to bladder cancers and hepatic safety, as well as the additional information and data relating to other safety concerns associated with dapagliflozin and the SGLT2 inhibitor drug class (e.g., cancer risks, hepatic disorders, genital infections, renal impairment or failure, volume depletion, polyuria, fractures and hypoglycemia). Please refer to Dr. Eugenio Andraca-Carrera's safety statistics briefing document for further information regarding cardiovascular outcomes, and to Dr. Wei Liu's efficacy statistics briefing document for further information regarding efficacy.

1.3.   Product Description

Dapagliflozin is a selective and reversible inhibitor of SGLT2, the major transporter responsible for the renal glucose reabsorption. The SGLT2 is selectively expressed in the kidney. Dapagliflozin causes renal elimination of glucose (i.e., glycuresis).

Dapagliflozin reaches maximum plasma concentrations (Cmax) within approximately two hours (Tmax) under fasting state; Tmax 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. Dapagliflozin is inactivated by 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 12.5 hours. Please refer to Appendix 1. Clinical Pharmacology Summary, for further details on pharmacokinetic characteristics of dapagliflozin.

The proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed dose of dapagliflozin is 5 mg or 10 mg taken once daily at any time of the day regardless of meals.

There is no proposed dose adjustment based on renal function. However, 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 m^2 or creatinine clearance [CrCl;] <60 mL/min). The efficacy of dapagliflozin is dependent on the filtered load of glucose, which in turn is dependent on GFR. Because dapagliflozin causes an increase in urinary volume excretion, the proposed dose for patients at risk for volume depletion due to coexisting conditions is 5 mg once daily.

1.4.   Description of Clinical Development Program

The dapagliflozin clinical development program consisted of 37 Phase 1 studies (26 from the original NDA submission and eleven new studies in the 30-MU) and 26 Phase 2b and Phase 3 (referred to as Phase 2b/3 from this point forward) clinical trials (fifteen from the original submission, plus six new core studies and five supportive studies in the 30-MU). A description of the Phase 2b/3 clinical development program is presented in Table 2. These trials included diverse populations of patients with T2DM. There were drug-naïve patients at an early stage of disease and patients taking oral antidiabetic agents and/or insulin at later stages of the disease. The effects of dapagliflozin were also evaluated in patients with moderate renal insufficiency, established cardiovascular disease, and hypertension. Integrated safety datasets from 21 of the 26 studies were included in the 30-MU. Review of these 21 trials comprises the main safety review for this NDA.

Table 2. Phase 2b/3 Clinical Trials in the Dapagliflozin Clinical Development Program

Study Number	Study Phase / Description	Patient Population	Duration	Dapa (mg) / Background Therapy	Number of Patients per Arm (dose—N)
Core Studies Included in the Summary of Clinical Safety					
MB102008 (30-MU)*	Phase 2b / Monotherapy vs. placebo vs. metformin XR 750/1500 mg	Drug naïve Baseline HbA1c ≥7 to ≤10%	12 weeks	Dapa 2.5, 5, 10, 20, 50	Dapa 2.5 mg-59, 5 mg-58, 10 mg-47, 20 mg-59, 50 mg-56 / placebo-54 / metformin-56
MB102009 (30-MU)*	Phase 2b / Add-on to insulin vs. placebo	On insulin sensitizer + insulin Baseline HbA1c ≥7.5 to ≤10%	12 weeks	Dapa 10, 20 / 50% on original insulin dose + metformin or TZD	Dapa 10 mg-24, 20 mg-24 / placebo-23
MB102064 D1692C00005 (30-MU)*	Phase 2b / Monotherapy vs. placebo	Drug naïve Japanese patients Baseline HbA1c ≥7 to ≤10%	12 weeks	Dapa 1, 2.5, 5, 10	Dapa 1 mg-59, 2.5 mg-56, 5 mg-58, 10 mg-53 / placebo-54
MB102045 (30-MU)*	Phase 2b / Add-on to metformin ± insulin secretagogue vs. placebo	On metformin ± insulin secretagogue (SU, DPP4, or glinide) Baseline HbA1c ≥7 to ≤10%	12 weeks	Dapa 5 / metformin ± insulin secretagogue	Dapa 5 mg-23 / placebo-21
MB102013 (30-MU)*	Phase 3 / Monotherapy vs. placebo	Drug naïve Baseline HbA1c ≥7.5 to ≤10% or >10 to ≤12%	24 weeks + 78 week extension	Dapa 2.5, 5, 10	Dapa 2.5 mg-65, 5 mg-64, 10 mg-70 / placebo-75
MB102032 (30-MU)*	Phase 3 / Monotherapy vs. placebo	Drug naïve Baseline HbA1c ≥7.5 to ≤10%	24 weeks	Dapa 1, 2.5, 5	Dapa 1 mg-72, 2.5 mg-74, 5 mg-68 / placebo-68
MB102014 (30-MU)*	Phase 3 / Add-on to metformin IR vs. placebo	On metformin ≥1500 mg Baseline HbA1c ≥7 to ≤10%	24 weeks + 78 week extension	Dapa 2.5, 5, 10 / metformin ≥1500 mg	Dapa 2.5 mg-137, 5 mg-137, 10 mg-135 / placebo-137
MB102021 (30-MU)*	Phase 3 / Dapa + metformin XR vs. metformin XR vs. Dapa monotherapy	Drug naïve Baseline HbA1c ≥7.5 to ≤12%	24 weeks	Dapa 5 mg / metformin up to 2000 mg	Dapa + metformin-194 / Dapa 5 mg-203 / metformin-201
MB102034 (30-MU)*	Phase 3 / Dapa + metformin XR vs. metformin XR vs. Dapa monotherapy	Drug naïve Baseline HbA1c ≥7.5 to ≤12%	24 weeks	Dapa 10 mg / metformin up to 2000 mg	Dapa + metformin-211 / Dapa 10 mg-219 / metformin-208
MB102030 (30-MU)*	Phase 3 / Add-on to TZD vs. placebo	Inadequate glycemic control on background AD	24 weeks + 24 week extension	Dapa 5, 10 / pioglitazone ≥30 mg	Dapa 5 mg-141, 10 mg-140 / placebo-139
MB102028 D1690C00005 (30-MU)*	Phase 3 / Add-on to SU vs. placebo	On SU Baseline HbA1c ≥7 to ≤10%	24 weeks + 24 week extension	Dapa 2.5, 5, 10 / glimepiride 4 mg	Dapa 2.5 mg-154, 5 mg-142, 10 mg-151 / placebo-145
MB102029 (30-MU)*	Phase 2b and 3 / Monotherapy vs. placebo	Moderate renal impairment On any AD combination except metformin Baseline HbA1c ≥7 to ≤11%	24 weeks + 28 week extension + 52 week extension	Dapa 5, 10 / any AD combination except metformin	Dapa 5 mg-83, 10 mg-85 / placebo-84
MB102022 D1690C00004 (30-MU)*	Phase 3 / Add-on to metformin IR vs. glipizide	On metformin ≥1500 mg Baseline HbA1c ≥6.5 to ≤10%	52 weeks + 52 week extension + 104 week extension	Dapa 2.5, 5, 10 / metformin ≥1500 mg vs. glipizide 10 or 20 mg	Dapa 2.5 to 10 mg-400 glipizide-401
MB102033 D1690C00006 (30-MU)*	Phase 3 / Add-on to insulin vs. placebo	On insulin ≥30 units ± maximum 2 OAD Baseline HbA1c ≥7.5 to ≤10.5%	24 weeks + 24 week extension + 56 weeks extension	Dapa 2.5, 5, 10 / insulin ≥30 units ± maximum 2 OAD	Dapa 2.5 mg-202, 5 mg-211, 10 mg-194 / placebo-193
MB102047 D1690C00012 (30-MU)*	Phase 3 / Add-on to metformin vs. placebo	On metformin ≥1500 mg BMI ≥ 25 kg/m2 Baseline HbA1c ≥6.5 to ≤8.5%	24 weeks 78 week extension	Dapa 10 / metformin ≥1500 mg/day	Dapa 10 mg-91 / placebo-91
Additional Core Studies Completed Since the Original Summary of Clinical Safety					

Study Number	Study Phase / Description	Patient Population	Duration	Dapa (mg) / Background Therapy	Number of Patients per Arm (dose—N)
MB102061 D1690C00010 (30-MU)*	Phase 3 / Add-on to DPP4 inhibitor ± metformin vs. placebo	Inadequate glycemic control on background AD Baseline HbA1c ≥7 to ≤10%	24 weeks + 24 week extension	Dapa 10 / sitagliptin 100mg/day and/or metformin ≥ 1500 mg/day	Dapa 10 mg-223 / placebo-224
MB102067 D1690C00018 (30-MU)*	Phase 3 / Add-on to usual care vs. placebo	CVD + HTN On OAD and/or insulin Baseline HbA1c ≥7 to ≤10%	24 weeks + 28 week extension + 52 week extension	Dapa 10 / OAD and/or insulin	Dapa 10 mg-455 / placebo-459
MB102080 D1690C00019 (30-MU)*	Phase 3 / Add-on to usual care vs. placebo	CVD On OAD and/or insulin Baseline HbA1c ≥7 to ≤10%	24 weeks + 28 week extension + 52 week extension	Dapa 10 / OAD and/or insulin	Dapa 10 mg-480 / placebo-482
MB102035 (30-MU)*	Phase 2b / Effect on GFR as add-on to metformin ± SU	On metformin ± SU HTN Baseline HbA1c ≥6.6 to ≤9.5%	12 weeks	Dapa 10 vs. HCTZ / metformin ± SU	Dapa 10 mg-24 / placebo-51
MB102073	Phase 3 / Dedicated BP study	HTN On OAD and/or insulin Baseline HbA1c ≥7 to ≤10.5%	12 weeks	Dapa 10 / OAD and/or insulin	Dapa 10 mg-302 / placebo-311
MB102077	Phase 3 / Dedicated BP study	HTN On OAD and/or insulin Baseline HbA1c ≥7 to ≤10.5%	12 weeks	Dapa 10 / OAD and/or insulin	Dapa 10 mg-225 / placebo-224
Completed Supportive Phase 2/3 Studies: Other Indications					
MB102072 (30-MU)*	Phase 2b / Add-on to insulin vs. placebo	T1DM Baseline HbA1c ≥7 to ≤10%	14 days	Dapa 1, 2.5 / insulin	Dapa 1 mg-13, 2.5 mg-15, 5 mg-14, 10 mg-15 / placebo-13
New Regional Studies					
MB102106 D1692C00006	Phase 3 / Japan monotherapy vs. placebo	Japanese drug naïve Baseline HbA1c ≥6.5 to ≤10% or on AD with Baseline HbA1c ≤8%	24 weeks	Dapa 5, 10	Dapa 5 mg-86, 10 mg-88 / placebo-87
D1692C00012	Phase 3 / Japan monotherapy or OADs	Japanese with or without OADs Baseline HbA1c ≥6.5 to ≤10%	52 weeks	Dapa 5 titrated to 10 / none or selected OADs	Dapa 5-10 mg-728
MB102054 (30-MU)*	Phase 3 / Multinational Asia (primarily China) Monotherapy	Asian drug naïve Baseline HbA1c ≥7.5 to ≤10.5%	24 weeks	Dapa 5, 10	Dapa 5 mg-128, 10 mg-133 / placebo-132
Studies to Support Dapagliflozin/Metformin IR and XR FDC					
D1691C00003	Phase 3 / BID Dosing Study	Baseline HbA1c ≥6.5 to ≤10%	24 weeks	2.5 BID, 5 BID, 10 QD / metformin IR BID (≥ 1500 mg/day)	Dapa 2.5 mg-100, 5 mg-100, 10 mg-99 / placebo-101
TOTAL NUMBER OF PHASE 2B AND 3 STUDIES: 26 (15 from SCS/4MSU and 10 from 30-MU)					

Source: Modified from the Applicant's 30-Month Update, Part 1 (page 10 of 200, labeled as Table 1); 30-Month Update, Part 2 (List of Appendices, pages 29-41 of 18920, labeled as Table 1), and the FDA Briefing Document, July 19, 2011 (page 3 of 149; labeled as Table 1).
Abbreviations: 4MSU, Four-Month Safety Update; 30-MU, 30-Month Update; AD, antidiabetic medication; BID, twice daily; BP, blood pressure; CVD, cardiovascular disease; Dapa, dapagliflozin; DPP4, dipeptidyl peptidase-4 inhibitors; HbA1c, hemoglobin A1c; HCTZ, hydrochlorothiazide; HTN, hypertension; IR, immediate-release; OAD, oral antidiabetic medication; QD, daily; SCS, Summary of Clinical Safety; SU, sulfonylurea; T1DM, type 1 diabetes mellitus; TZD, thiazolidinedione; and XR, extended-release.
* Studies for which integrated safety datasets were provided for the 30-Month Updates.

1.5. Analysis Datasets for Safety Evaluation

The Applicant's pooling strategy for the evaluation of safety in their integrated safety datasets included the following two major study pools (Table 3):

1) <u>All Phase 2b/3 Pool</u>, consisting of 21 clinical trials (including both the short- and long-term extension phases of these studies)
2) <u>Placebo-Controlled Pool</u>, consisting of Phase 2b/3 placebo-controlled clinical trials with both short-term (ST; N=13) and short- plus long-term (ST+LT; N=9 of the 13 clinical trials included in the ST pool) treatment periods.

The All Phase 2b/3 Pool was intended to evaluate less common adverse events (AEs), while the Placebo-Controlled Pool is intended to evaluate safety and tolerability of dapagliflozin relative to placebo.

In correspondence prior to the resubmission of this NDA (December 3 and 13, 2012), the Applicant proposed to include only the 10 mg dapagliflozin dose cohort in the Placebo-Controlled Pool for the 30-MU. The rationale provided was as follows:

> "Almost all of the new data to be included in the placebo-controlled pools in the NDA resubmission is (sic) for patients on dapa 10 mg or placebo. Of the 5 studies providing new data in the placebo-controlled pool in the 30-month safety update, no studies provide additional data for the ST and only 1 study, D1690C00006, provides additional data for the LT from patients on dapa 2.5mg/5mg since the 4-month safety update (15Oct2010). In this study there are 65 and 64 patients for dapa 2.5mg/5mg arms respectively still ongoing at time of the 4MSU data cut, with a maximum additional exposure of 3 months per patient. There is one additional SAE for each arm and no discontinuation due to AE/death. In summary, there is (sic) no new data on dapa 2.5 mg and 5 mg in the ST placebo-controlled pool since the initial NDA. There will be very limited new data on dapa 2.5 mg and 5 mg in the ST+LT placebo-controlled pool: Less than 4 patient-year additional exposure on top of 867 to 977 patient-year exposures from 4MSU for dapa 2.5mg and 5mg arms, comparing with additional ~ 1160 patient-year exposure on top of 921 to 1107 patient-year exposures from 4MSU for placebo and dapa 10 mg arms. Therefore, we consider the safety assessment across dapa doses (2.5 mg, 5 mg, 10 mg, and dapa total) is more appropriately viewed in the initial NDA and the 4-month safety update vs. including them in the 30 month safety update where almost all of the new information is on the dapa 10 mg dose and placebo."

This proposal was acceptable to the Agency. However, to adequately characterize the safety of dapagliflozin in relation to dose, this review also includes selected data for the 2.5 mg and 5 mg dose cohorts previously presented in the Summary of Clinical Safety (SCS) and Four-Month Safety Update (4MSU) for the placebo-controlled pools. Additional safety data from the All Phase 2b/3 Pool by dose cohorts and the Major Amendment are also presented when applicable.

Table 3: Pooling Strategy of the Applicant for Clinical Evaluation of Safety

All Phase 2b and 3 Pool	Placebo-Controlled Pool	
(N=21)	Short-term (N = 13)	Short-term + Long-term (N = 9)
MB102008 (monotherapy)	MB102008	*
MB102009 (add-on to insulin)	MB102009	*
MB102013 (monotherapy)	MB102013	MB102013
MB102014 (add-on to metformin)	MB102014	MB102014
MB102021 (initial combination with metformin)	*	*
MB102029 (moderate renal impairment)	*	*
MB102030 (add-on to TZD)	MB102030	MB102030
MB102032 (low dose monotherapy)	*	*
MB102034 (initial combination with metformin)	MB102034	*
MB102035 (effect on glomerular filtration rate [GFR])	*	*
MB102045 (insulin sensitivity)	*	*
MB102054 (multinational Asia; primarily China, monotherapy)	*	*
D1690C00004 (add-on to metformin)	*	*
D1690C00005 (add-on to SU)	D1690C00005	D1690C00005
D1692C00005 (monotherapy)	D1692C00005	*
D1690C00006 (add-on to insulin)	D1690C00006	D1690C00006
D1692C00006 (Japan monotherapy)	*	*
D1690C00010 (add-on to sitagliptin)	D1690C00010	D1690C00010
D1690C00012 (add-on to metformin)	D1690C00012	D1690C00012
D1690C00018 (high CV risk add-on to usual care)	D1690C00018	D1690C00018
D1690C00019 (high CV risk add-on to usual care)	D1690C00019	D1690C00019

Source: Reproduced from the Applicant's 30-MU, Part 1 (page 14 of 200, labeled as Table 5).

1.6. Exposure to Dapagliflozin

The data cutoff for resubmission of this NDA was November 15, 2012. A total of 9339 patients (5936 received dapagliflozin and 3403 control) were included in the integrated safety datasets for the 21 Phase 2b/3 study pool submitted with the 30-MU.

Exposure by dose is presented in Table 4 below. The cumulative exposure to dapagliflozin was 6247 patient-years. The original NDA submission and 4MSU (submitted during the last review cycle) included 4009 and 4354 patient-years of exposure to dapagliflozin, respectively. The NDA resubmission provides over 40% additional patient-years of exposure to dapagliflozin since the 4MSU. The Applicant notes that there are limited new data for the 2.5 mg and 5 mg dose cohorts, which contribute less than 4 patient-years of exposure to dapagliflozin since the 4MSU. Therefore, only the 10 mg dose cohort is presented for the summary tables of placebo-controlled study pools throughout the 30-MU.

Table 4: Extent of Exposure to Study Medications (All Phase 2b/3 Pool)

	Dapa 2.5 N=1220	Dapa 5 mg N=2048	Dapa 10 mg N=3417	Dapa Total N=5936	All Control N=3403
Cumulative Exposure (p-y)	979.1	1372.5	3864.7	6247.2	3637.6
Duration (days)					
1-90	544 (44.6)	589 (28.8)	368 (10.8)	876 (14.8)	499 (14.7)
90-180	115 (9.4)	686 (33.5)	739 (21.6)	1543 (26.0)	783 (23.0)
181-270	15 (1.2)	33 (1.6)	106 (3.10	152 (2.6)	130 (3.8)
271-360	180 (14.8	437 (21.3)	584 (17.1)	1049 (17.7)	565 (16.6
361-450	17 (1.4)	20 (1.0)	604 (17.7)	491 (8.3)	459 (13.5)
451-540	10 (0.8)	11 (0.5)	54 (1.6)	100 (1.7)	89 (2.6)
541-630	22(1.8)	19 (0.9)	40 (1.2)	92 (1.5)	56 (1.6)
631-720	165 (13.5)	168 (8.2)	294 (8.6)	619 (10.4)	226 (6.6)
721-810	147 (12.0)	74 (3.6)	451 (13.2)	814 (13.7)	413 (12.1)
811-900	0	0	9 (0.3)	5 (0.1)	4 (0.1)
901-1080	1 (0.1)	2 (0.1)	11 (0.3)	14 (0.2)	13 (0.4)
1081-1260	0	0	9 (0.3)	16 (0.3)	17 (0.5)
>1260	4 (0.3)	9 (0.4	148 (4.3)	165 (2.8)	149 (4.4)
Summary Statistics (days)					
Mean	293.1	244.8	413.1	384.4	390.4
Median	168.5	169.0	344.0	336.0	337.0
Range	5-1471	1-1436	1-1520	1-1556	1-1478

Source: Modified from the Applicant's 30-Month Update, Part 3 (page 15829 of 18333, labeled as Appendix 304).
Abbreviations: Dapa, dapagliflozin; Max, maximum; Min, minimum; and p-y, patient-years.

1.7. Demographics

The three study pools used in safety assessments were: the Placebo-Controlled Pool (ST) pool (i.e., includes all PBO controlled trials with data up to primary efficacy endpoint), the Placebo-Controlled Pool (ST+LT) [i.e., includes only placebo controlled trials with planned long-term safety extension with data up to trial completion (efficacy portion + extension phase)] and the All Phase 2b/3 pool (i.e., includes all Phase 2b/3 trials with data up to trial completion).

Patient demographics and baseline characteristics for the three study pools are presented in Table 5. Generally the treatment arms for each study pool were balanced for relevant baseline disease parameters and demographic characteristics. The total number of treated patients in the All Phase 2b/3 study pool was 9339, of which 2739 (27.8%) were North American (29.3%). Across the three study pools, the majority of patients were Caucasian males, age <65 years, with a body mass index >30 kg/m^2, a mean HbA1c of approximately 8.1%, and a mean duration of T2DM of >7 years. As noted during the first review cycle, black or African American patients still represented <4% of the patient population for the entire clinical program included in the 30-MU.

Table 5: Demographics and Baseline Characteristics of the Study Pools

Patient Characteristics	Placebo-Controlled Pool (ST)		Placebo-Controlled Pool (ST+LT)		All Phase 2b/3 Pool (ST+LT)	
	Dapa 10 mg (N=2360)	Placebo (N=2295)	Dapa 10 mg (N=2026)	Placebo (N=1956)	Dapa Total (N=5936)	All Control (N=3403)
Age (y), Mean ± SD	58.4 ± 10.0	58.9 ± 10.0	59.3 ± 9.7	59.8 ± 9.6	56.9 ± 10.4	58.1 ± 10.3
(Range)	(20-84)	(21-86)	(22-84)	(22-86)	(18-92)	(20-86)
<65 (%)	1695 (71.8)	1584 (69.0)	1406 (69.4)	1301 (66.5)	4512 (76.0)	2424 (71.2)
65 to <75 (%)	567 (24.0)	630 (27.5)	523 (25.8)	578 (29.6)	1217 (20.5)	859 (25.2)
≥75 (%)	98 (4.2)	81 (3.5)	97 (4.8)	77 (3.9)	207 (3.5)	120 (3.5)
Gender (%)						
Male	1357 (57.5)	1343 (58.5)	1174 (57.9)	1157 (59.2)	3243 (54.6)	1964 (57.7)
Female	1003 (42.5)	952 (41.5)	852 (42.1)	799 (40.8)	2693 (45.4)	1439 (42.3)
Race (%)						
White	1976 (83.7)	1930 (84.1)	1739 (85.8)	1695 (86.7)	4505 (75.9)	2644 (77.7)
Black	81 (3.4)	73 (3.2)	66 (3.3)	61 (3.1)	208 (3.5)	125 (3.7)
Asian	209 (8.9)	206 (9.0)	131 (6.5)	120 (6.1)	1050 (17.7)	513 (15.1)
Other	94 (4.0)	86 (3.7)	90 (4.4)	80 (4.1)	173 (2.9)	121 (3.6)
Geographic Region (%)						
North America	769 (32.6)	705 (30.7)	617 (30.5)	548 (28.0)	1787 (30.1)	952 (28.0)
Latin America	423 (17.9)	407 (17.7)	380 (18.8)	368 (18.8)	1103 (18.6)	609 (17.9)
Europe	952 (40.3)	976 (42.5)	888 (43.8)	910 (46.5)	2046 (34.5)	1367 (40.2)
Asia/Pacific	216 (9.2)	207 (9.0)	141 (7.0)	130 (6.6)	565 (9.5)	256 (7.5)
Japan	—	—	—	—	174 (2.9)	87 (2.6)
Not Reported	—	—	—	—	261 (4.4)	132 (3.9)
Body Mass Index (kg/m^2), (%)	32.2 ± 5.7	32.1 ± 5.8	32.4 ± 5.6	32.3 ± 5.8	31.6 ± 5.8	31.3 ± 5.7
Mean ± SD (Range)	(16.6-66.6)	(17.5-62.4)	(18.5-66.6)	(18.8-62.4)	(15.9-62.4)	(14.9-66.6)
<25	173 (7.3)	209 (9.1)	123 (6.1)	156 (8.0)	722 (12.2)	405 (11.9)
25 to <30	709 (30.0)	676 (29.5)	604 (29.8)	563 (28.8)	1846 (31.1)	1049 (30.8)
≥30	1478 (62.6)	1410 (61.4)	1299 (64.1)	1237 (63.2)	3368 (56.7)	1949 (57.3)
Blood Pressure (mmHg)						
SBP, Mean ± SD	131.7 ± 15.3	131.6 ± 14.9	132.1 ± 15.2	131.9 ± 14.9	130.4 ± 15.7	131.1 ± 14.9
(Range)	(87-195)	(82-199)	(87-195)	(82-181)	(85-195)	(82-199)
DPB, Mean ± SD	78.5 ± 9.1	78.6 ± 9.0	78.3 ± 9.2	78.4 ± 9.1	78.8 ± 9.1	78.8 ± 8.9
(Range)	(41-108)	(46-113)	(41-108)	(46-113)	(41-120)	(46-113)
Duration of T2DM (y),	8.9 ± 8.0	8.8 ± 8.0	9.8 ± 8.1	9.8 ± 7.9	7.0 ±7.5	7.6 ± 7.7
Mean ± SD (Range)	(0.0-54.4)	(0.0-48.0)	(0.0-54.4)	(0.0-48.0)	(0.0-54.4)	(0.0-48.0)
HbA1c (%), Mean ± SD	8.2 ± 0.9	8.2 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	8.2 ± 1.0	8.1 ± 1.0
(Range)	(5.3-12.2)	(5.6-13.3)	(5.3-12.2)	(5.6-10.9)	(5.3-13.0)	(5.6-13.3)
Fasting Plasma Glucose (mg/dL),	164.8 ± 46.6	165.4 ± 45.3	162.8 ± 45.1	163.3 ± 43.7	167.2 ± 48.8	165.3 ± 46.5
Mean ± SD (Range)	(38.0-498.0)	(43.0, 382.0)	(38.0, 498.0)	(43.0, 382.0)	(32.0-498.0)	(43.0-436.0)
GFR (mL/min/1.73 m2)	82.7 ± 20.3	82.2 ± 20.2	81.0 ± 19.1	80.7 ± 19.2	83.6 ± 21.1	83.9 ± 21.3
Mean ± SD (Range)	(19.0-201.6)	(12.0-236.5)	(19.0-177.0)	(12.0-190.0)	(12.0-236.5)	(13.0-222.7)
<30	1	1	1	1	9 (0.2)	6 (0.2)
≥30 and <60	265 (11.2)	268 (11.7)	251 (12.4)	249 (12.7)	668 (11.3)	387 (11.4)
≥60 and <90	1303 (55.2)	1281 (55.8)	1140 (56.3)	1113 (56.9)	3113 (52.4)	1793 (52.7)
<90	791 (33.5)	744 (32.4)	634 (31.3)	592 (30.3)	2146 (36.2)	1216 (35.7)

Source: Modified from the Applicant's 30-Month Update, Part 2 (pages 175-185 of 18920, labeled as Appendices 100-103; pages 11372-11382 of 18920, labeled as Appendices 200-203) and Part 3 (pages 15859-15867 of 18333, labeled as Appendices 300-302 and pages 15873-15874 of 18333, labeled Appendix 303.

Abbreviations: —, data not reported; Dapa, dapagliflozin; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; LT, long-term; SD, standard deviation; SBP, systolic blood pressure; y, years; ST, short-term; ST+LT, short-term plus long-term; T2DM, type 2 diabetes mellitus; and y, years.

SECTION 2. EFFICACY

For a detailed summary of the new and previous efficacy data submitted to this Application, please refer to the Statistical Review by Dr. Wei Liu. Most of the efficacy data for this resubmission were previously evaluated during the first review cycle. The Applicant's rationale for their Phase 3 dose selection, which was also evaluated during the first review cycle, is presented in Appendix 1. Clinical Pharmacology Summary. Recently completed clinical trials which the Sponsor intends to include in the proposed product labeling for this NDA resubmission include the following studies conducted in patients with T2DM: MB102067 (D1690C00018; patients with established cardiovascular disease [CVD] and hypertension [HTN]), MB102080 (D1690C00019; patients with established CVD), MB102061 (D1690C00010; add-on to dipeptidyl peptidase-4 [DPP4] inhibitor), MB102073 (dedicated BP study), and MB102077 (dedicated blood pressure [BP] study). This section will primarily discuss the top-line efficacy findings (i.e., reductions in HbA1c, weight and BP) that the Applicant intends to include in product labeling.

In their clinical development program, the Applicant evaluated the use of dapagliflozin as both monotherapy and in combination with other antidiabetic agents (e.g., metformin, glimepiride, pioglitazone, sitagliptin, and/or insulin) for patients with T2DM. The study populations enrolled in their Phase 2b/3 clinical program were diverse, and included patients with T2DM and established cardiovascular disease, hypertension, and mild to moderate renal impairment. The proposed product labeling for this NDA refers to 16 of the 21 double-blind, controlled clinical trials classified by the Applicant as "Core Studies." In these 16 efficacy studies, 9412 adult patients with T2DM were treated for 12 (two studies), 24 (13 studies) or 52 (one study) weeks, of which 5952 patients received dapagliflozin. Additionally, 11 of these studies also included 24 to 80 week long-term extension phases. These studies are briefly described in Table 2 above, and efficacy results for thirteen of the studies are presented in Table 6 and Table 7. For most of these trials, the Applicant used the Last Observation Carried Forward (LOCF) strategy as the primary method for imputation of missing data for these analyses.

For the proposed doses of 5 mg and 10 mg, the placebo/comparator-adjusted mean reductions in HbA1c in the monotherapy and add-on trials were modest (ranging from 0% to -0.9%), but consistently statistically significant, except when compared to active comparators for noninferiority. Reductions in fasting and 2-hour postprandial glucose concentrations, weight, and blood pressure, as well as the proportion of patients achieving HbA1c concentrations <7%, were usually supportive of the primary efficacy findings. Additionally dapagliflozin treatment arms were also associated with some reduction in weight (i.e., mean comparator-adjusted changes from baseline of -0.7 to -4.7 kg) and BP (i.e., mean placebo-adjusted changes from baseline in SBP of -0.9 to -4.3 mmHg). The dapagliflozin dose evaluated for 14 of the 16 studies was 10 mg once daily. Although the 2.5 mg and 5 mg doses were also evaluated in several clinical trials, the Applicant stated that the 2.5 mg dose was not consistently effective for glycemic control. Further, for five studies which included both 5 mg and 10 mg dapagliflozin treatment arms, the primary efficacy results were numerically better with the 10 mg dose, while safety of the 5 mg dose was considered comparable. The efficacy results for 5 mg and 10

mg doses specifically in patients with moderate renal impairment are discussed in Appendix 1. Clinical Pharmacology Summary.

Table 6: Phase 2b/3 Core Studies Included in Proposed Product Labeling

HbA1c (%)	Dapa (mg) N	Dapa (mg) N	Comparator N
24-Week (LOCF*) Placebo-Controlled Study of Monotherapy			
STUDY: MB102013	**Dapa 10 mg N=70**	**Dapa 5 mg N=64**	**Placebo N=75**
HbA1c (%)			
Baseline (mean)	8.0	7.8	7.8
Change from baseline (adjusted mean)	−0.9	−0.8	−0.2
Difference from placebo (adjusted mean) (95% CI)	−0.7 (−1.0, −0.4)	−0.5 (−0.8, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	50.8%	44.2%	31.6%
Body Weight (kg)			
Baseline (mean)	94.1	87.2	88.8
Change from baseline (adjusted mean)	−3.2	−2.8	−2.2
Difference from placebo (adjusted mean) (95% CI)	−1.0 (−2.2, 0.3)	−0.7 (−1.9, 0.6)	
24-Week (LOCF) Active-Controlled Study of Combination Therapy with Metformin XR			
STUDY: MB102034	**Dapa 10 mg + Metformin XR N=211**	**Dapa 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)		
Difference from metformin XR (adjusted mean) (95% CI)	−0.5 (−0.8, −0.3)	0.0 (−0.2, 0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%	31.7%	35.2%
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)	−1.4 (−2.0, −0.7)	

HbA1c (%)	Dapa (mg) N	Dapa (mg) N	Comparator N
24-Week (LOCF) Active-Controlled Study of Combination Therapy with Metformin XR			
STUDY: MB102021	**Dapa 5 mg + Metformin XR N=194**	**Dapa 5 mg N=203**	**Metformin XR N=201**
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)		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4%	22.5%	34.6%
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)		
24-Week (LOCF) Placebo-Controlled Study as Add-On Combination with Metformin IR			
STUDY: MB102014	**Dapa 10 mg + Metformin IR N=135**	**Dapa 5 mg + Metformin IR N=137**	**Placebo + Metformin IR 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)	−0.4 (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%	37.5%	25.9%
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)	−2.2 (−2.8, −1.5)	
52-Week (LOCF) in an Active-Controlled Study Compared to Glipizide as Add-On to Metformin IR			
STUDY: MB102022 / D1690C00004	**Dapa (2.5 to 10 mg) + Metformin IR N=400[†]**		**Glipizide + Metformin IR N=401[†]**
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 (−0.1, 0.1)		

HbA1c (%)	Dapa (mg) N	Dapa (mg) N	Comparator N
Body Weight (kg)			
Baseline (mean)	88.4		87.6
Change from baseline (adjusted mean)	−3.2		1.4
Difference from glipizide + metformin (adjusted mean) (95% CI)	−4.7 (−5.1, −4.2)		
24-Week (LOCF) Placebo-Controlled Study in Combination with Glimepiride			
STUDY: MB102028 / D1690C00005 **Intent-to-Treat Population**	**Dapa 10 mg** **N=151**	**Dapa 5 mg** **N=142**	**Placebo** **N=145**
HbA1c (%)			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	−0.8	−0.6	−0.1
Difference from placebo + glimepiride (adjusted mean) (95% CI)	−0.7 (−0.9, −0.5)	−0.5 (−0.7, −0.3)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7%	30.3%	13.0%
Body Weight (kg)			
Baseline (mean)	80.6	81.0	80.9
Change from baseline (adjusted mean)	−2.3	−1.6	−0.7
Difference from placebo + glimepiride (adjusted mean) (95% CI)	−1.5 (−2.2, −0.9)	−0.8 (−1.5, −0.2)	
24-Week (LOCF) Placebo-Controlled Study in Combination with Pioglitazone			
STUDY: MB102030 **Intent-to-Treat Population**	**Dapa 10 mg** **N=140**	**Dapa 5 mg** **N=141**	**Placebo** **N=139**
HbA1c (%)			
Baseline (mean)	8.4	8.4	8.3
Change from baseline (adjusted mean)	−1.0	−0.8	−0.4
Difference from placebo (adjusted mean) (95% CI)	−0.6 (−0.8, −0.3)	−0.4 (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	38.8%	32.5%	22.4%
Body Weight (kg)			
Baseline (mean)	84.8	87.8	86.4
Change from baseline (adjusted mean)	−0.1	0.1	1.6
Difference from placebo (adjusted mean) (95% CI)	−1.8 (−2.6, −1.0)	−1.6 (−2.3, −0.8)	
24-Week (LOCF) Placebo-Controlled Study in Combination with Sitagliptin ± Metformin			
STUDY: MB102061 / D1690C00010 **Intent-to-Treat Population**	**Dapa 10 mg** **N=223**	**–**	**Placebo** **N=224**
HbA1c (%)			
Baseline (mean)	7.90	–	7.97

18

HbA1c (%)	Dapa (mg) N	Dapa (mg) N	Comparator N
Change from baseline (adjusted mean)	−0.45	–	0.04
Difference from placebo (adjusted mean) (95% CI)	−0.48 (−0.62, −0.34)	–	
Body Weight (kg)			
Baseline (mean)	91.02	–	89.23
Change from baseline (adjusted mean)	−2.14	–	−0.26
Difference from placebo (adjusted mean) (95% CI)	−1.89 (−2.37, −1.40)	–	
Seated systolic blood pressure at Week 8 in patients with baseline seated systolic blood pressure ≥130 mmHg (mmHg)			
Baseline (mean)	140.5 (N=111)	–	139.3 (N=101)
Change from baseline (adjusted mean)	−6.0	–	−5.1
Difference from placebo (adjusted mean) (95% CI)	−0.86 (−3.8, 2.0)	–	
24-Week (LOCF) Placebo-Controlled Study in Combination with Insulin ± Up to 2 Oral Antidiabetic Therapies			
STUDY: MB102033 / D1690C00006 **Intent-to-Treat Population**	**Dapa 10 mg** **N=194**	**Dapa 5 mg** **N=211**	**Placebo** **N=193**
HbA1c (%)			
Baseline (mean)	8.6	8.6	8.5
Change from baseline (adjusted mean)	−0.9	−0.8	−0.3
Difference from placebo (adjusted mean) (95% CI)	−0.6 (−0.7, −0.5)	−0.5 (−0.7, −0.4)	
Body Weight (kg)			
Baseline (mean)	94.6	93.2	94.2
Change from baseline (adjusted mean)	−1.7	−1.0	0.0
Difference from placebo (adjusted mean) (95% CI)	−1.7 (−2.2, −1.2)	−1.0 (−1.5, −0.5)	

Source: Modified from Proposed Dapagliflozin Product Labeling (pages 27-44 of 88).
Abbreviations: CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; IR, immediate-release; LOCF, last observation carried forward; N, sample size; and XR, extended-release.

Table 7: Phase 2b/3 Studies in Special Populations

HbA1c (%)	Study 1		Study 2	
	Dapa 10 mg + Usual Treatment	Placebo + Usual Treatment	Dapa 10 mg + Usual Treatment	Placebo + Usual Treatment
12-Week Placebo-Controlled Studies in Patients with T2DM and Hypertension				
Studies	**MB102073**		**MB102077**	
Sample Size	**302**	**311**	**225**	**224**
HbA1c (%)				
Baseline (mean)	8.1	8.0	8.1	8.0
Change from baseline (adjusted mean)	−0.6	−0.1	−0.6	0.0
Difference from placebo (adjusted mean) (95% CI)	−0.5 (−0.6, −0.3)		−0.6 (−0.8, −0.5)	
Seated Systolic Blood Pressure (mmHg)				
Baseline (mean)	149.8	149.5	151.0	151.3
Change from baseline (adjusted mean)	−10.4	−7.3	−11.9	−7.6
Difference from placebo (adjusted mean) (95% CI)	−3.1 (−4.9, −1.2)		−4.3 (−6.5, −2.0)	
Week 24 (LOCF) Placebo-Controlled Studies in Patients with T2DM and Cardiovascular Disease				
Studies	**MB102067 / D1690C00018**		**MB102080 / D1690C00019**	
Sample Size	**455**	**459**	**480**	**482**
HbA1c (%)				
Baseline (mean)	8.2	8.1	8.0	8.1
Change from baseline (adjusted mean)	−0.4	0.1	−0.3	0.1
Difference from placebo (adjusted mean) (95% CI)	−0.5 (−0.6, −0.4)		−0.4 (−0.5, −0.3)	
Body Weight (kg)				
Baseline (mean)	92.6	93.6	94.5	93.2
Change from baseline (adjusted mean)	−2.6	−0.3	−2.5	−0.6
Difference from placebo (adjusted mean) (95% CI)	−2.3 (−2.6, −1.9)		−1.9 (−2.3, −1.5)	
Seated Systolic Blood Pressure (mmHg)				
Change from baseline at Week 24 (adjusted mean)	−3.0	−1.0	−2.7	0.3
Difference from placebo (adjusted mean) (95% CI)	−2.0 (−3.6, −0.3)		−3.0 (−4.6, −1.5)	

Source: Modified from Proposed Dapagliflozin Product Labeling (pages 27-44 of 88).
Abbreviations: CI, confidence interval; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; IR, immediate-release; LOCF, last observation carried forward; N, sample size; T2DM, type 2 diabetes mellitus; and XR, extended-release.

SECTION 3. MAJOR SAFETY ISSUES

The primary focus of this safety review is to summarize the updated safety information pertaining to bladder cancer risk and hepatotoxicity, which were major issues of interest in the previous review cycle. Additionally, the updated data and information regarding cardiovascular safety, and other AEs of interest associated with dapagliflozin and the SGLT2 inhibitor pharmacologic class will be briefly reviewed in relation to the overall risk-benefit assessment of dapagliflozin.

3.1. Bladder Cancer

In the previous review cycle for dapagliflozin, bladder cancer was an issue of concern.

Across all trials of dapagliflozin submitted to date, including all information submitted for the current review cycle, there were 10 cases of bladder cancer among 6045 patients treated with dapagliflozin (0.17 %), and 1/3512 (0.03 %) among patients treated with comparator. This represents 0.148 cases per 100 patient-years (p-y) of exposure for dapagliflozin, and 0.025 cases per 100 p-y for comparator.

During the first review cycle for this NDA, an imbalance in bladder cancer cases was noted in the All Phase 2b/3 Pool and reported with the 4MSU. The safety population at that time consisted of 4310 patients with 4354 p-y of exposure treated with at least one dose of dapagliflozin 2.5 mg or higher. A total of 1962 patients with 1899 p-y of exposure were treated with placebo/comparator. Seven (0.2%) cases of bladder cancer in dapagliflozin-treated patients were identified versus none among those patients in the control arm. Three additional cases were reported about one month later via dapagliflozin Investigational New Drug Safety Reports. Two of these cases were in dapagliflozin-treated patients, and one was in a placebo-treated patient. In total, there were nine cases of bladder cancer out of approximately 5501 patients exposed (0.16%) to dapagliflozin compared to a single patient in the control arm (1/3184, 0.03%). The IRR for bladder cancer was 5.38 (95% CI, 0.84 to 122.1). In the January 17 2012, CRL, it was noted that although the "accompanying 95% confidence interval (CI) of 0.84-122.2 includes the possibility of a chance finding due to the lack of precision, the magnitude of the risk estimate (i.e., exceeding 5) is cause for concern." Further, baseline characteristics of patients in the Phase 2b/3 controlled clinical trials were balanced for risk factors that might contribute to the development of bladder cancer. Review of the case narratives at that time did not note evidence of detection bias (i.e., resulting from more frequent monitoring of dapagliflozin treatment arms due to higher rates of urogenital AEs), although detection bias could not be ruled out.

The 30-MU now includes 9339 patients (i.e., 5936 treated with dapagliflozin vs. 3403 in the control arms), providing 43% additional patient-year exposure to dapagliflozin. In the Applicant's Response to CRL (June 24, 2013), they note that their nonclinical studies have not shown evidence of tumor initiation or promotion, nor of enhancement of tumor

growth/progression associated with dapagliflozin based on in vitro and in vivo genotoxicity studies, 2-year rodent carcinogenicity studies and a 1-year dog toxicology study. The Applicant also reported the following nonclinical data to provide support that dapagliflozin does not promote bladder tumor growth:

1. In vitro stimulation of tumor cell proliferation was not observed in six human bladder transitional cell carcinomas (TCC) cell lines treated with dapagliflozin or its 3-O-glucuronide metabolite at concentrations ≥100 x human Cmax at the maximum recommended human dose [MRHD]).
2. Dapagliflozin administration at doses up to 75x MRHD exposures to male and female nude mice bearing human TCC tumors did not significantly enhance the size of the human TCC tumors implanted in these mice.
3. Dapagliflozin did not cause transcriptional changes characteristic of tumor promoters in a ZDF rat model.
4. Five human TCC cell lines were exposed to increasing concentrations of glucose. Increases in glucose concentrations did not lead to an increase the rate of tumor cell growth (high concentrations were cytostatic).

As discussed in the nonclinical section of the FDA briefing document, each of these experimental approaches had deficiencies in terms of limitations or relevancy, particularly the pivotal xenograft bladder tumor transplant model. Results of these studies confirm but do not substantially extend what the FDA already concluded: that dapagliflozin by itself does not act as a carcinogen. Any putative human bladder risk from dapagliflozin would likely be related to tumor promotion secondary to changes in the microenvironment of the bladder *in vivo*.

Since the integrated database lock for the 30-MU, one additional case of bladder cancer was reported in in a 53 year-old female receiving dapagliflozin 10 mg daily for less than 3.8 months. This patient had hematuria at baseline and a 40 pack-year smoking history. The Applicant notes that six of the ten cases occurred within the first year of exposure to dapagliflozin, and that the incidence rate remained stable over the first two years of drug exposure, and then fell with an additional 428 p-y of exposure. The Applicant proposes the following post-marketing plan:

1. Continued clinical and statistical surveillance throughout the conduct of the Applicant's ongoing CV outcomes trial (i.e., Dapagliflozin Effect on Cardiovascular Events [DECLARE; TIMI-58; Study D1693C00001]), with pre-defined evaluations performed by an independent Data Monitoring Committee. All events of bladder cancer will be independently adjudicated.
2. Expansion of an ongoing pharmacoepidemiology study (being conducted in the European Union) to the United States should dapagliflozin be approved.
3. Enhanced pharmacovigilance in countries where dapagliflozin is already approved.

On August 22, 2013, Dr. Y. Max Ning of the Division of Oncology Products (DOP) / Office of Hematology and Oncology Products (OHOP) was consulted regarding the

observed imbalance in the incidence of bladder cancers and likelihood that dapagliflozin may have contributed to this imbalance. The following excerpts are copied from this consultation:

Observed imbalance in incidence of bladder cancers in the pooled Phase 2b/3 controlled clinical trials:

"Based on the verified data, the pooled 30-month updated safety analysis was from 21 randomized, controlled Phase 2b and 3 clinical trials of dapagliflozin. These trials enrolled approximately 10,000 patients in total and had an overall median treatment time of approximately one year. The pooled analysis revealed no overall imbalance in the diagnosis of malignancies between treatment arms during the trials. However, 9 cases (0.15%) of bladder cancer were diagnosed in 5936 patients on dapagliflozin compared to 1 case (0.03%) diagnosed in 3403 patients on control, suggestive of a considerable, cumulative imbalance in the diagnosis of bladder cancer during the trials. The incidence rate ratio associated with dapagliflozin versus control treatment was 5.2 for the tumor. Table 8 summarizes key information about bladder cancer cases diagnosed in the pooled analysis."

Table 8: Index Bladder Cancer Cases in Phase 2b/3 Clinical Program

Study ID (Country)	Dapa Dose (mg)	Age	Diagnosis Time in Trial (Day)	Tumor Type/Stage*/Grade	Tobacco Use	Prior Pioglitazone Use	Baseline Hematuria **
DAPAGLIFLOZIN TREATMENT ARMS							
1.1.1 D1692C00005-1-11 (Japan)	2.5	75	43	Papillary/T2/G2	50 pack-years	No	Positive, Occult
1.1.2 D1690C00006-1004-6 (Austria)	5	63	358	TCC/Ta/G2	100 pack-years	No	Negative
1.1.3 MB102014-34-524 (Canada)	5	60	512	TCC/Ta/Low	25 pack-years	No	Positive: Occult (w/ureteric calculus)
1.1.4 MB102030-90-880 (Argentina)	5	67	144	TCC/T2/Mod	No	Yes	Positive: Trace
1.1.5 D1690C00004-4916-2 (Germany)	10	76	727	TCC/T1/G3	20 pack-years	No	Negative
1.1.6 D1690C00006-1501-6 (Hungary)	10	67	399	TCC/NA/G2	No	No	Positive: Occult
1.1.7 D1690C00006-2206-14 (United States)	10	66	581	TCC/NA/Low	53 pack-years	No	Negative
1.1.8 D1690C00018-7831-5 (United States)	10	48	74	TCC/Noninvasive/Low	34 pack-years	No	Negative**
1.1.9 D1690C00018-7401-9 (China)	10	55	169	TCC/Noninvasive/NA	No	No	Positive: Trace

23

CONTROL ARMS							
1.1.10 D1690C00019-1016-7 (Canada)	—	66	136	Papillary/ Microinvasive/High	50 pack-years	No	Positive: Occult
BLADDER CANCER CASES OCCURRING AFTER THE NOVEMBER 2012 INTEGRATED DATABASE LOCK							
D1693C00005-6706-14 (Slovakia)	10	53	114	TCC/G1	40 pack-years	No	Positive: Trace

Source: Modified from the October 3, 2013, DOP/OHOP Memorandum of Consultation.
Abbreviations: NA, not available; and TCC, transitional cell carcinoma.
*   Localized disease per the report
**   Note that baseline hematuria was found in 8.5% of patients assigned to receive dapagliflozin and 8.1% assigned to receive control. Patient D1690C00018-7831-5 had a history of hematuria, but events within six months of randomization could not be confirmed.

"This difference in the cumulative incidence rate of bladder cancer during the clinical trials may be suggestive of an increased risk for bladder cancer diagnosis with dapagliflozin treatment. Close examination of the reported bladder cancer cases showed that all were diagnosed in men from 8 different countries. Approximately 60% of them used tobacco or had a history of using tobacco. Five of the 9 patients on dapagliflozin had their bladder cancer diagnosed between 1-2 years of treatment compared to none of patients not taking dapagliflozin during the same time period. The other 4 cases of bladder cancer in patients on dapagliflozin were detected within 6 months of study entry, compared to 1 case in patients on control.

In the current NDA resubmission, there was one additional bladder cancer reported to the dapagliflozin arm of Study D1693C00005. This study was not included in the above pooled analysis due to uncompleted dataset lock at the time of analysis. This case (D1693C00005-6706-14) was a 53 year-old female who had TCC without muscle infiltration diagnosed 114 days after study treatment initiation. She used tobacco actively (40 pack-years) but had no prior treatment with pioglitazone. Inclusion of this case along with the study in the pooled analysis resulted in a bladder cancer incidence rate of 0.17% (10/6045) for dapagliflozin-treated patients compared to a rate of 0.03% (1/3512) for patients not receiving dapagliflozin. The incidence rate ratio in the dapagliflozin-treated versus control-treated patients increased to 6.1.

According to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) statistics, the overall age-adjusted bladder cancer incidence rate during 2006-2010 was 20.7 per 100,000 men and women per year in United States. This rate corresponds to an annual incidence rate of 0.02%. The median age at diagnosis was 73 years. Given that the current pooled safety analysis was based on 21 trials conducted internationally, the SEER data may serve as a reference with regard to the expected background incidence of bladder cancer. Note that this 0.02% background incidence rate of bladder cancer appears to be closer to the incidence rate of 0.03% observed in patients not taking dapagliflozin in the pooled analysis. Taken together, the current available evidence appears to suggest an increased risk of bladder cancer diagnosis in patients taking dapagliflozin. Although determination of the attribution to dapagliflozin or of the causality could be difficult due to confounding factors, it is important to recognize that this increased bladder cancer risk was detected from the pooled analysis of 21 randomized, controlled trials that enrolled approximately 10,000 patients. In addition, the baseline hematuria rate (~8%) was balanced between the dapagliflozin and control arms, making the imbalance in bladder cancer diagnosis less likely to be secondary to potential detection bias. To the oncology consultant's best understanding, this risk should not be disregarded because of the small number of patients diagnosed with bladder cancer in the trials, but rather should be further studied, carefully monitored, and possibly labeled as a Precaution or Warning for its safe use if approved."

Likelihood of the study medication contributing to the observed imbalance:

> "The non-clinical evidence provided by the Applicant shows that dapagliflozin did not act as a carcinogenic agent in 2-year carcinogenicity studies or as a tumor growth enhancer in animal models bearing human transitional cell carcinoma (TCC). Please note that these animal models did not have TCC implanted in the bladder. The clinical relevance of findings from the studies remains unknown. The current clinical data do not address whether dapagliflozin may promote or enhance TCC growth in long-term treatment. Given the observed increased risk of bladder cancer diagnosis in this large pooled analysis, the possibility that dapagliflozin or its metabolites may contribute to the increased incidence or diagnosis of bladder TCC could not be ruled out."

The Pharmacology/Toxicology review team also felt that the xenograft model fails to mimic the pharmacodynamic (PD) processes of most interest to the issue of bladder tumor promotion in this case (i.e., secondary changes in urine flow and composition caused by dapagliflozin). They felt that a study in a rodent bladder tumor promotion model using 4-hydroxybutyl(butyl)nitrosamine as the initiator would be the most relevant and preferred toxicology study.

Case summaries of all bladder cancer events are presented in Appendix 2. Bladder Cancer Narratives (reproduced from the Applicant's Individual Patient Narratives: Events of Bladder Neoplasms, pages 1-19 of 19).

Postmarketing Reports and Medical Literature

Additionally, on August 22, 2013, Dr. Christine Chamberlain of the Division of Pharmacovigilance (DPV) I/Office of Surveillance and Epidemiology (OSE) was consulted to evaluate postmarketing reports in the FDA Adverse Events Reporting System (FAERS) database and medical literature for an association between dapagliflozin and cancer (especially bladder and breast cancer) and severe liver adverse events. Postmarketing reports for canagliflozin, a first-in-class SGLT2 inhibitor, were also reviewed to evaluate the potential for a possible class effect. Since dapagliflozin is currently approved outside of the United States (i.e., Europe, Australia and Mexico), Vigibase, the World Health Organization global individual case safety report database system, was also searched. A total of 113 FAERS reports were retrieved for canagliflozin and dapagliflozin using a comprehensive search. Dr. Chamberlain identified five cases of bladder cancer (four reported as urothelial carcinoma, and one described as a nested variant of urothelial carcinoma, a rare, aggressive neoplasm) associated with the use of canagliflozin, and none with dapagliflozin. Based on the diagnosis dates, these events are considered incident cases that are in addition to those reported in the NDA review of canagliflozin prior to approval. Four of the five cases involved patients with a current or past history of smoking, a known risk factor for bladder cancer. Further, it was acknowledged that bladder cancer is a relatively common cancer in the mature adult population, and therefore inference on causality from spontaneous reports is severely limited. Relevant medical literature was not identified for either SGLT2 inhibitor product. Dr. Chamberlain concluded that given the limitations of spontaneous reporting for common cancers, it is difficult to draw inference of causality from the identified bladder cancer cases.

3.2.   Malignant or Unspecified Tumors (including Breast Cancer)

Across the entire dapagliflozin clinical development program, there did not appear to be an imbalance in the overall incidence of malignancies between dapagliflozin and control/comparator treatment arms. The stratified IRR versus control is 1.030 (95% CI, 0.711 to 1.506). At the time of the Major Amendment, the IRR was reported as 1.047 (95% CI, 0.702 to 1.579). Although there were no statistically significant differences between dapagliflozin and control arms for specific tumor types, there was a numeric imbalance in favor of the comparator arms for bladder (discussed above) and breast cancers. Compared to controls, the IRRs for the following tumor types were higher for dapagliflozin-treated patients:

Dapagliflozin vs. All Control (no statistical correction for multiple comparisons)
- Bladder: 0.15% vs. 0.03%; IRR 5.17 (95% CI, 0.68 to 233.55)
- Breast: 0.45% vs. 0.21%; IRR 2.47 (95% CI, 0.64 to 14.10)
- Musculoskeletal/Soft Tissue: 0.02% vs. 0%
- Pancreatic: 0.10% vs. 0.06%; IRR 1.84 (95% CI, 0.31 to 19.46)
- Prostate: 0.34% vs. 0.31%; IRR 1.6 (95% CI, 0.53 to 5.35)

Breast Cancers

Across all trials of dapagliflozin submitted to date, including all information submitted for the current review cycle, there were 12 cases of breast cancer among 2693 female patients treated with dapagliflozin (0.45%), and 3/1439 (0.21%) among patients treated with comparator. This represents 0.40 cases per 100 p-y of exposure for dapagliflozin, and 0.19 cases per 100 p-y for comparator. One additional case of breast cancer was reported in a dapagliflozin-treated patient participating in an open-label study without a control arm (i.e., Study D1692C00012).

On August 22, 2013, Dr. Genevieve Schechter, from DOP/OHOP, was consulted regarding the observed imbalance in the incidence of breast cancers in favor of the control arm. The following information summarizes this consultation review and the updated information provided by the Applicant in the 30-MU.

Since the Major Amendment, two additional cases of breast cancer were diagnosed in dapagliflozin-treated patients. In total, there are 15 events of breast cancer in the dapagliflozin development program; 12 (0.45% of 2693 females) and three (0.21% of 1429 females) were reported in patients receiving dapagliflozin and comparator, respectively. Of the 15 cases, 13 were diagnosed within one year of exposure to study medication, and these patients were typically overweight/obese, Caucasian females over age 50, with a current or past history of smoking. Study days of diagnoses for the 10 breast cancer cases occurring in patients receiving dapagliflozin ranged from six to 334 days. None of the patients were receiving estrogen replacement prior to randomization; although the narrative for patient MB102013-33-261 reported prior combined estrogen/progesterone replacement therapy for 15 years. Summary tables of breast cancer cases by patient (Table 9) and by study across the pool of 2b/3 clinical trials (Table 10)

are provided below. Two of the 10 dapagliflozin-treated patients reported at the time of the July 15, 2011 database cut-off date were diagnosed with invasive ductal breast cancer on study days six and sixteen, and therefore temporal associations with dapagliflozin were unlikely. Two patients were diagnosed by mammography, although only three patients appear to have had routine screening. The tumors for seven of the ten cases in patients who received dapagliflozin were estrogen receptor positive, and progesterone receptor positivity also was reported in five.

The Applicant's reported rates by exposure are 0.40 per 100 p-y and 0.19 per 100 p-y in the dapagliflozin and control treatment arms, respectively. The IRR reported in the 30-MU is 2.472 (95% CI, 0.636 to 14.095), which was previously 1.903 (95% CI, 0.461 to 11.230) at the time of the Major Amendment.

As of 2008, the incidence of invasive breast cancer worldwide in the female population was reported as 42.3 new cases/100,000 (0.04%).[1] Additionally, based on data collected in the Surveillance Epidemiology and End Results (SEER) database from the years 2000 to 2009, the incidences of breast cancer in non-Hispanic white and black females, Asian women and Hispanic women were reported as 0.21-0.24%, 0.21-0.22%, 0.16-0.18% and 0.15%, respectively.[2] Further, a recent meta-analysis report suggests that the incidence (HR= 1.23; 95% CI, 1.12 to 1.34) and mortality (HR=1.38; 95% CI, 1.2 to 1.58) of breast cancer may be higher among diabetic women compared to non-diabetic women.[3]

In her review, Dr. Schechter noted that median age of the pooled safety population for the dapagliflozin program is 58 years for patients receiving dapagliflozin and 59 years for the control arm. Since approximately 89% of new breast cancer cases are diagnosed after age 40 and the incidence increases with age,[1] she felt that the finding of breast cancer cases in the study population is not unexpected but does not explain why an imbalance between treatment arms was observed. The following summary and conclusion are reproduced from Dr. Schechter's consultation:

> "Ten cases of breast cancer occurred on the dapagliflozin arm. Two cases are eliminated due to detection of breast cancer on Day 6 and Day 16 of study so that the incidence is about 0.13%. Three cases of breast cancer were reported on the comparator arm for an incidence 0.08%. The incidence of breast cancer observed on the pooled data from the randomized clinical trials conducted to study dapagliflozin is consistent with the incidence observed in the SEER database (0.15-0.23%). While an increased incidence of breast cancer is observed on the dapagliflozin relative to the comparator arm, the decline in the incidence risk ratio over time, the lack of screening mammography prior to study entry coupled with the occurrence of the breast cancers within the first year of dapagliflozin therapy, the median time from diagnosis of diabetes of seven years, the history of prior exposure to other oral hypoglycemic agents, and the hormone receptor positivity of the breast cancers suggests that the increased incidence of breast cancer is a spurious finding. Furthermore, there is not enough information in the narratives provided to assess risk factors for breast cancer in each individual patient who was diagnosed with breast cancer. The data with regard to breast cancer risk in association with this drug are inconclusive and insufficient to recommend inclusion in the label. If concerns about a breast cancer risk remain, an Applicant-sponsored registry to collect information on breast cancer cases with dapagliflozin use over a prolonged period of time may provide enough additional information to determine if there is increased risk of breast cancer with dapagliflozin use."

Table 9: Malignant Breast Cancer Events

Patient ID Age/Sex/Race/Smoking Status/BMI/Estrogen Use Prior to Randomization	Treatment	Tumor Type	Grade	TNM[a]	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Weight Change (kg)	Study Day of Diagnosis
D1690C00006-1403-2 63/F/White/Never/40/No	Dapa 2.5 mg + Ins	Invasive ductal carcinoma	2	T1c, N0, M0	Highly Positive, IRS 12	Highly Positive, IRS 12	2+	0	6
MB102-021-59-482 53/F/White/Former/23/No	Dapa 5 mg	Intraductal carcinoma	3	M0	—[c]	—[c]	—[c]	-12	39
D1690C00004-4405-20 60/F/White/Former/29/No	Dapa 10 mg + Met[b]	Ductal carcinoma	1	T1,N0	Positive, 8/8	Positive, 8/8	Negative	0	193
D1690C00006-1005-18 61/F/White/Former/32/No	Dapa 10 mg + Ins	Invasive lobular, carcinoma	2	T2, N3a, M0	Strongly Positive	Mildly Positive	Negative	-1.5	204
D1690C000018-7894-1 59/F/White/Never/39/No	Dapa 10 mg + Met	Invasive, ductal carcinoma	2	T2, N3, MX	Positive[e]	Positive[e]	Negative[e]	-1.9	204
D1690C00012-202-4 64/F/White/Current/29/No	Dapa 10 mg + Met	Invasive, ductal carcinoma	2-3	T1c, N1a, M0	Positive 40%-50%	Positive 85-90%	Negative	-1.5	211
MB102014-50-151 64/F/White/Former/31/No	Dapa 10 mg + Met	Infiltrating adenocarcinoma	3	T2, N2a, MX	Negative	Negative	Negative	-10.0	285
D1690C00006-1803-7 58/F/White/Never/24/No	Dapa 2.5 mg + Ins	Unknown	2	T2, N0, M0	Moderately Positive (25%-50%)	Negative	Weakly Positive	1.0	292
MB102013-33-261 74/F/White/Former/32/No	Dapa 2.5 mg	Invasive ductal carcinoma	2	T1b, N0	Strongly Positive	Strongly Positive	Negative	-3.8	321
D1690C00005-4012-46 69/F/Asian/Never/25/No	Dapa 10 mg + Glip	NA[d]	NA[d]	NA[d]	NA[d]	NA[d]	NA[d]	-2.3	334
D1690C00010-2009-3 73/F/White/Never/28/No	Comparator	Invasive, lobular carcinoma	2	T3, N3a	Positive > 80% (IRS 12)	Positive > 80% (IRS 12)	Negative	-4.7	57
D1690C00018-7841-5 60/Asian/White/Former/40/No	Comparator	Infiltrating ductal breast cancer	1-2	T1c, N0, M0	Positive, 100%	Positive, 70%	Negative	-2.5	113

28

Patient ID Age/Sex/Race/Smoking Status/BMI/Estrogen Use Prior to Randomization	Treatment	Tumor Type	Grade	TNM[a]	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Weight Change (kg)	Study Day of Diagnosis
D1690C00019-7833-2 60/F/White/Former/49/No	Comparator	Ductal carcinoma in situ[f]	1	T1, N0, M0	Positive (>10%)	Positive (>10%)	NA	-3.1	347
NEW EVENTS AFTER 15-JULY-2011 DATABASE CUT-OFF									
D1690C00019-3315-11 75/F/White/Former/33/No	Dapa 10 mg	Invasive ductal carcinoma	1	T2, N0	Positive	Positive	Positive	-0.2	687
D1690C00019-7841-9 70/F/White/Never/43/No	Dapa 10 mg	Invasive ductal carcinoma	3	NA	Negative	Negative	Negative	NA	722

Source: Modified from the Applicant's 30-Month Update, Part 3. (pages 16946-16947/18333, labeled as Appendix 350).

Abbreviations: Dapa, dapagliflozin; F, Female; Glip, glipizide; HER2/neu, human epidermal growth factor receptor 2; Ins, insulin; Met, metformin; IRS, insulin receptor substrate; and NA, not applicable.

Note: D1692C00012 is an open-label, long-term regional study, and data from this study are not included in any of the 30-MU integrated safety analysis pools

a TNM Classification of Malignant Tumors.

b Patient started at 2.5 mg and titrated up to 5 mg and then 10 mg.

c Tests not performed.

d Patient withdrew consent

e Needle biopsy diagnosis.

f Needle biopsy diagnosis. Lumpectomy: no further malignancy found; patient started tamoxifen.

g One additional patient had an event of breast cancer after 15-July-2011. Patient D1692C00012-7-6, a 63 year old Japanese female, treated with dapagliflozin 5mg was diagnosed on Study Day 149 with non-invasive ductal carcinoma (T1s, N0, M0 - estrogen receptor positive, progesterone receptor positive, HER2/neu negative). This patient and data from Study D1692C00012 (open-label, long-term regional study) were not included in any of the 30-MU integrated safety analysis pools since this was not a controlled study and all patients were treated with dapagliflozin. Individual data tables and listings for study D1692C00012 are included in 30-MU Section 7.2.

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Table 10: Summary of Cases of Malignancies in the All Phase 2b/3 Pool

Study ID	Number of Treated Patients	Number of Patients by Arm		Median Age (years) (range)*		Treatment Duration† (days) Median (range)*		Number of Malignancies (All Types) in the Study‡		Number of Breast Cancers‡		Number of Bladder Cancers‡	
	(N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)
MB102008	389	279	110 P or M	55.0-57.5	52-53	85/ 79.4-84.1	84-85/ 74.9-80.1	1	0	0	0	0	0
MB102009**	71	48	23 P+I	57.5-59	59	85/ 80.1-82.8	84/ 70.7	0	0	0	0	0	0
MB102013**	485	410	75 P	51-56	53	700-713/ 536.4-595.8	707/ 515.9	8	2	1	0	0	0
MB102014	546	409	137 P+M	53-56	54	708-712/ 574.4-599.3	701/ 541.1	7	3	1	0	1	0
MB102021	598	397	201 M	51-53	52	168/ 153.2-159.3	168/ 154.6	2	0	1	0	0	0
MB102022*** D1690C00004	814	406	408 G+M	59	60	750.5/ 881.5	716.5/ 829.8	13	10	1	0	1	0
MB102028 D1690C00005	596	450	146 P+G	59-60	61	337/ 309-315.8	337/ 310	7	0	1	0	0	0
MB102029	252	168	84 P	66-68	67	720-721/ 528.5-558.0	700/ 479.3	2	2	0	0	0	0
MB102030	420	281	139 P+Pio	53-54.5	54	336-337/ 300.6-311.4	336/ 291.4	3	0	0	0	1	0
MB102032**	210	142	68 P	50.5-54.0	53.5	169/ 159.6-161.8	169/ 168.8	0	0	0	0	0	0
MB102033 D1690C00006	807	610	197 P+I	59-60	59	725-727/ 553.1-596.6	721/ 516.5	18	8	3	0	3	0
MB102034	638	430	208 M	51	54	168/ 154.2-155.4	168/ 155.9	0	2	0	0	0	0
MB102035	75	24	51 H or P	53.5	56-62	85.5/ 85	85-85.5/ 85-88.4	0	0	0	0	0	0
MB102045	44	23	21 P+B	59	54	87/ 87.9	85/ 83.4	0	0	0	0	0	0
MB102047 D1690C00012	182	91	91 P+M	62	61	714/ 612.1	714/ 642.1	2	2	1	0	0	0

30

Study ID	Number of Treated Patients	Number of Patients by Arm		Median Age (years) (range)*		Treatment Duration† (days) Median (range)*		Number of Malignancies (All Types) in the Study‡		Number of Breast Cancers‡		Number of Bladder Cancers‡	
	(N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)
MB102054	393	261	132 P	52-53	49.5	169/ 156.1-156.7	169/ 157.4	1	0	0	0	0	0
MB102061 D1690C00010	451	225	226 P+S	55	55	337/ 314.8	337/ 305.8	2	6	0	1	0	0
MB102064** D1692C00005	220	166	54 P	57-59	60	85/ 83.3-84.9	85/ 81.8	1	0	0	0	1	0
MB102067 D1690C00018	922	460	462 P	63	63	364/ 401.4	365/ 401.2	13	5	1	1	2	0
MB102080 D1690C00019	965	482	483 P	64	64	365/ 435.5	364/ 427	9	11	2	1	0	1
MB102106	261	174	87 P	58-61	62	168/ 157.3-161.5	168/ 158.8	0	0	0	0	0	0
Total	9339	5936	3403	58 (18-92)	59 (20-86)	336/384.4	337/390.4	89 / IRR = 1.030 (95% CI, 0.711, 1.506) ‖	51	12/2693 Females / IRR = 2.472 (95% CI, 0.636, 14.095) ¶	3/1439 Females	9 / IRR = 5.168 (95% CI, 0.677, 233.55) §	1
ADDITIONAL STUDIES (NOT INCLUDED IN THE ALL PHASE 2B AND 3 POOL)													
D1692C00012 (Uncontrolled)	728	728	NA	59	NA	364/ 333.9	NA	7	NA	1	NA	0	NA
D1693C00005	216	108	108	60.5	62.0	168/ 161.9	168/ 159.3	1	1	0	0	1 §	0

Source: Modified from the Applicant's September 17, 2013 Response to the Agency's Information Request dated September 12, 2013.

Abbreviations: 30-MU, 30-Month Update; B, background antidiabetic medication; Dapa, dapagliflozin; G, glipizide; H, hydrochlorothiazide; ID, identification; I, insulin; IRR, incidence rate ratio dapagliflozin v. control; M, metformin; P, placebo; Pio, pioglitazone; pts, patients; and S, sitagliptin.

*   Median or range of medians across treatment arms.

†   Extent of Exposure to Study Medication - Double-blind Period.

‡   Total number of patients in the study with at least one event.

**   Cohort1 in study MB102009, group 2 in study MB102013, dapa 1mg groups in study MB102032 and MB102064 are not included in All Phase 2b/3 Pool. None of these patients have events.

*** This study was ongoing at the time of the 30-MU. There were no additional malignancies in this Study from the time of the data cut for the 30-MU (15-Nov-2012) until the study completion.

‖   Applicant's 30-MU, Part 3 (page 16741 of 18333, labeled as Appendix 322).

¶   Applicant's 30-MU, Part 3 (page 16743 of 18333, labeled as Appendix 322).

§   30-month-update-appsa. Appendix 322, page 16745/18333. Note: updated bladder cancers based on all ongoing blinded and open-label studies since the 30-MU integrated safety database lock includes one additional dapagliflozin-treated patient, D1693C00005-6706-14: 10/6045 v. 1/3512; **IRR = 6.111 (95% CI, 0.827, 272.02)**.

3.3.   Hepatic Safety

Dr. John Senior of the Drug-Induced Liver Disease (DILI) Team/OSE is conducting a review of the hepatic safety of dapagliflozin, and his consultation report is pending as of November 11, 2013. During the first review cycle, no imbalances in patients experiencing marked transaminase elevations were observed between dapagliflozin and control treatment arms. However, hepatic safety of dapagliflozin was questioned following a single case of biochemical Hy's Law (Patient D16900004-4402-6), defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of reference range (ULRR) with serum total bilirubin (TBL) >2x ULRR. The updated case summary from the Hepatic Adjudication Report is provided below. Following a thorough review by Agency hepatologists for alternative etiologies, this event was classified as "probable" DILI associated with dapagliflozin. In the CRL, the Applicant was informed that they would need to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. These additional data were to include updated review of hepatic safety, including cases that meet the definition of Hy's law, with narratives of each case and incidence of transaminase elevations at 3x, 5x, 10x, and 20x ULRR in treatment arms. The Agency stated that it "did not find the single case of severe hepatotoxicity in the NDA database, which was complicated by features of autoimmune hepatitis, as concerning as it would be in the setting of a strong signal of transaminitis among dapagliflozin patients (Hy's Law)." In their Response to CRL, the Applicant provided additional information related to the potential case of DILI, now suggesting that autoimmune hepatitis may be the probable etiology. They noted that initially dechallenge of dapagliflozin with addition of immunosuppression (i.e., corticosteroids and azathioprine) resulted in resolution of abnormal liver laboratory tests. However, following withdrawal of dapagliflozin, elevations in ALT concentrations were observed on two separate occasions while the patient continued to receive azathioprine. Consultation by the Applicant with two expert hepatologists resulted in reclassification of the event as probable autoimmune hepatitis, although possible drug-associated autoimmune hepatitis could not be ruled out. The complete narrative for this case is included in Appendix 3. Serious Liver Event Narratives.

Marked Elevations in Liver Enzymes

Transaminase levels were routinely monitored during the dapagliflozin clinical development program. Similar to the findings reported for the Major Amendment, there did not appear to be any obvious imbalances in transaminase elevations of 3x, 5x, 10x and 20x ULRR or biochemical Hy's Law cases across the All Phase 2b/3 safety database, nor were there major shifts in proportions of patients experiencing these events since the previous review (Table 11). Additionally, narratives for the dapagliflozin-treated patients meeting biochemical Hy's Law criteria and for cases of dapagliflozin-treated patients with marked elevations in transaminase concentrations (i.e., >10x the upper laboratory

reference limit) were reproduced from the Hepatic Adjudication Report and are included below in Appendix 3. Serious Liver Event Narratives.

A dose-response relationship was not noted, but this was difficult to assess definitively because the number of patients exposed to the 2.5 and 5 mg doses was relatively small compared to the number of patients exposed to 10 mg.

Table 11: Marked Liver Laboratory Test Abnormalities - All Phase 2b/3 Pool

LFT Abnormality	30-MU Dapa Total N=5936 X/N# (percent)	30-MU All Control N=3403 X/N# (percent)	Major Amendment Dapa Total N=5466 X/N# (percent)	Major Amendment All Control N=3161 X/N# (percent)
Patients with Elevated LFTs	255/5895 (4.3)	152/3380 (4.5)	242/5501 (4.4)	133/3161 (4.2)
AST				
>3X ULRR	45/5895 (0.8)	35/3379 (1.0)	40/5466 (0.7)	30/3160 (0.9)
>5X ULRR	15/5895 (0.3)	13/3379 (0.4)	12/5466 (0.2)	11/3160 (0.3)
>10X ULRR	8/5895 (0.1)	3/3379 (0.1)	5/5466 (0.1)	3/3160 (0.1)
>20X ULRR	4/5895 (0.1)	0/3379 (0)	4/5466 (0.1)	0/3160 (0)
ALT				
>3X ULRR	78/5895 (1.3)	54/3380 (1.6)	72/5466 (1.3)	47/3161 (1.5)
>5X ULRR	23/5895 (0.4)	17/3380 (0.5)	18/5466 (0.3)	13/3161 (0.4)
>10X ULRR	7/5895 (0.1)	5/3380 (0.1)	4/5466 (0.1)	4/3161 (0.1)
>20X ULRR	3/5895 (0.1)	2/3380 (0.1)	2/5466 (<0.1)	1/3161 (<0.1)
Total Bilirubin > 2X ULRR >2X ULRR	22/5894 (0.4)	11/3379 (0.3)	20/5465 (0.4)	4/3160 (0.1)
Biochemical Hy's Law AST >3X ULRR or ALT >3X ULRR and TBL >2X ULRR*	7/5894 (0.1)	4/3379 (0.1)	5/5465 (0.1)	3/3160 (0.1)
ALP >3X ULRR	8/5894 (0.1)	6/3380 (0.2)	—	—

Source: Modified from the Applicant's 30-Month Update, Part 2 (pages 16952-3 of 18920, labeled as Appendix 337) and NDA Major Amendment Clinical Review (page 20 of 42, labeled Table 15).
Abbreviations: —, data not reported; 30-MU, 30-Month Update; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of treated patients; N#, number of patients with at least one non-missing post-baseline value; TBL, total bilirubin; ULRR, upper limit of reference range; and X, number of patients with a value meeting the criterion.
* Total bilirubin elevation on or within 14 days after AST or ALT elevation.

Additionally, dapagliflozin-treated patients and controls were relatively balanced for liver AEs (1.6% v. 1.9%, respectively), and discontinuations due to adverse hepatic disorder events (0.2% vs. 0.1%, respectively); again, a dose-response was not observed.

The Applicant had an adjudication plan in place for assessment of possible liver-related abnormalities. This involved an independent Hepatic Adjudication Committee (HAC), composed of three expert hepatologists, blinded to treatment assignments. The HAC reviewed patients' cases in the dapagliflozin program to determine the likelihood that drug-induced liver injury (DILI) was the cause of liver-related abnormalities. The HAC created and maintained the HAC Charter, and completed adjudication forms on which it summarized its assessment of liver-related cases. Each hepatologist submitted an opinion regarding the probability of DILI associated with study medication. This was followed by a consensus agreement on each case. The potential cases adjudicated were from the Applicant's Phase 2 and 3 clinical trials (27 studies; N=7303 dapagliflozin-treated patients and N=4039 controls). For many of these trials, the events were adjudicated retrospectively. Criteria for referral to the HAC included at least one of the following four events:

1. AST and/or ALT >3X ULRR and total bilirubin (TBL) > 1.5X ULRR (within 14 days of the AST and/or ALT elevation)
2. AST and/or ALT >5X ULRR
3. Liver-related serious or non-serious standardized Medical Dictionary for Regulatory Affairs (MedDRA) queries (SMQ) adverse event (serious adverse event [SAE] or AE, respectively) in patients who prematurely discontinued study treatment due to any SAE/AE
4. Liver-related SMQ SAE or AE in any patients who died

Causality for DILI events was assessed using a five-point numeric/descriptive likelihood causality scale, with causal relationship described as definite, highly likely, probably, possible and unlikely (Table 12).

Table 12: Hepatic Adjudication Causality Scale

Causal Relationship	Likelihood	Description
Definite	>95%	The evidence for the study drug causing the injury is beyond a reasonable doubt
Highly Likely	75%- 95%	The evidence for the study drug causing the injury is clear and convincing but not definite
Probably	50%- 74%	The preponderance of the evidence supports the link between the study drug and the liver injury
Possible	25%- 49%	The evidence for the study drug causing the injury is equivocal but present
Unlikely	<2%	There is clear evidence that an etiological factor other than the study drug caused the injury

Source: Modified from the Applicant's Hepatic Adjudication Report (page 11 of 367, labeled as Table 2).

During the dapagliflozin clinical development program, 81 cases (from 80 patients) met one or more criteria for inclusion in the liver adjudication process across the 27 completed studies. Seven cases were excluded due to prespecified analysis criteria (i.e., the case occurred more than 30 days after last dose of drug or the patient was treated with 1 mg dapagliflozin, as described in the Statistical Analysis Plan). In total, 74 patients

(i.e., 45 [0.6%] receiving dapagliflozin 2.5-50 mg vs. 26 [0.6%] controls) met liver adjudication analysis criteria. Three additional patients who met adjudication criteria were treated with dapagliflozin (5 mg titrated to 10 mg) in an open-label, single active treatment arm study. None of the 74 cases were assessed as "definitely" or "highly likely" associated with the blinded study medication. Three cases from the placebo treatment arms were assessed by the HAC as "probably" related to study medication. Seventeen events (10 [0.1%] dapagliflozin-treated patients vs. six [0.1%] controls), and one event (0.1%) in a dapagliflozin-treated patient from the open-label study were assessed as "possibly" related to study medication.

Of the 20 cases adjudicated for which the causal relationship was classified as "possible" or "probably," four (three in dapagliflozin-treated patients and one in the placebo arm) are new events submitted since the Major Amendment. The following case summaries of the three additional adjudicated events for patients receiving dapagliflozin were reproduced from the Hepatic Adjudication Report (pages 17-18 of 367):

> **"Patient D1691C00003-3306-11**, a 64-year-old white female treated with dapagliflozin 5 mg, experienced herpes zoster rash under the right costal arch (Study Day -6 through Study Day 9) before the liver test elevation was reported (Study Day 29). According to investigator´s opinion the occurring herpes zoster infection may be in the background of the temporary elevation of the SGPT (ALT) level. The patient was treated with high dose of oral acyclovir (Herpesin 4 g/day from Study Day -6 through Study Day 9; according to drug Summary Product Characteristics (SPC) transient elevation of liver tests may occur). Five days later the ALT value decreased below 3xULRR and the liver tests normalized on Study Day 57. Study drug was not interrupted. The investigator considered marked laboratory abnormalities (MAs) of AST ≥ 5X ULRR and ALT ≥ 1.5X baseline (Study Day 29) possibly related to study drug."

> **"Patient D1692C00012-8-8**, a 51-year-old Japanese female treated with dapagliflozin 5 mg titrated to 10 mg (open-label), had a rise in transaminase levels (ALT and AST) on Study Day 141. The investigator considered the events to be of mild (Grade 1) intensity and not related to study drug. The patient discontinued due to the event."

> **"Patient MB102077-321-71182**, a 60-year-old white female treated with dapagliflozin 5 mg, had an abnormal ALT result > 5X ULRR on Study Day 58 (293 IU/L; normal range: 10 to 36 IU/L). The patient was a nonsmoker. At the time of enrollment, the patient was reported to consume alcohol at the rate of ≤ 2 drinks per day on average. Per patient's medical progress note on March 21, 2012, the investigator stated that the patient admitted to an excessive alcohol binge. No hepatobiliary symptoms were reported. The investigator assessed the event to be mild (Grade 1) in severity and not related to study medication. No treatment was required for the event and no action was taken with the study medication. On Study Day 63, the event of elevated hepatic enzymes (ALT) was reported as resolved. On Study Day 86, the patient's ALT level (23 IU/L) returned to normal range."

Additionally, 14 adjudicated events (10 in patients receiving dapagliflozin 2.5-10 mg and four in patients treated with placebo) met the combined definition for biochemical Hy's Law (i.e., AST/ALT >3x ULRR and TBL >2x ULRR) in the Phase 2/3 clinical trials. The HAC classified two events as possibly related and 12 were assessed as either unlikely or excluded. Four of the 14 events (three patients receiving dapagliflozin and one placebo) are new since the Major Amendment. The following case summaries for the three dapagliflozin-treated patients were reproduced from the Hepatic Adjudication Report (pages 24-25 of 367):

"**Patient D1690C00018-201-8**, a 70-year-old white male, treated with dapagliflozin 10 mg and metformin, experienced hepatitis on Study Day 289. The patient was hospitalized with diffuse abdominal pain predominantly in the epigastric and right hypochondrial region, nausea, and vomiting. The SAE of hepatitis was assessed as serious intensity and related to the study medication. The patient was discontinued from study medication on Study Day 289 due to the SAE. On Study Day 289, ALT was 3.1X 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 3.6 x ULRR. The TBL peaked on Study Day 291 with 4.3X ULRR, while ALT and AST then started to decrease and were 5.9X ULRR and 5.3X ULRR, respectively. An abdominal ultrasound on Study Day 290 showed no signs of obstruction or dilation, and a repeat ultrasound on Study Day 293 revealed steatosis and fatty infiltration of the pancreas. The AE resolved after 9 days. Further follow-up indicated that the patient also had liver enzyme elevations reported as AEs on Study Days 314 (AST, ALP, and TBL elevation) and 326 (ALT, ALP, and AST elevation). Liver enzymes were still elevated on Study Day 342 and associated with abdominal symptoms. However, laboratory values had normalized at Study Day 349. 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."

"**Patient D1690C00018-203-4**, a 72-year-old white male, treated with dapagliflozin 10 mg + metformin + insulin, had MAs of ALT and ALT > 10X ULRR and TBL > 2X ULRR on Study Day 549. The patient had a history of gallstones and an abdominal ultrasound performed on Study Day 550 showed multiple mobile gallbladder lithiasis. He received treatment with scopolamine but was not hospitalized and the liver enzyme elevations declined. On Study Day 623 he underwent a cholecystectomy and the AE was reported as resolved. No action was taken regarding the study medication and the patient completed the study. Blinded assessment by the HAC was that the event was unlikely related to study drug."

"**Patient MB102077-88-70996**, a 57-year-old Asian male treated with dapagliflozin 10 mg, took his last dose of study treatment on Study Day 86. On Study Day 87, the patient had elevated AST of 248 U/L (> 5X ULRR). On Study Day 90, the patient had elevated ALT of 4316 U/L (>10X ULRR) and AST of 2269 U/L (> 10X ULRR). On Study Day 108, hepatitis E IgM antibody screen showed a high positive result, resulting in a diagnosis of Grade II Hepatitis E being made from Study Day 87. The event of hepatitis E resolved on Study Day 130. Blinded assessment by the HAC was that the event was excluded from having a relationship to study drug."

Follow-up information for the case deemed "probable" DILI (Patient D1690C00004-4402-6), who was discussed in the previous review cycle, is provided with the 30-MU. The following updated case summary was reproduced from the Hepatic Adjudication Report (pages 25-26 of 367):

"**Patient D1690C00004-4402-6**, a 79-year-old Asian male living in the United Kingdom, who was treated with dapagliflozin 2.5 mg plus 2000 mg metformin, had elevations in ALT and AST starting on Day 85 of treatment (Figure 1). Maximal elevations of the liver tests were recorded on Study Day 200 (ALT: 1858 U/L [ULRR 50U/L], TBL: 4.2 mg/dL [ULRR 1.5 mg/dL]). The patient was discontinued from study medication on Study Day 191. By that time, the patient was asymptomatic. Liver ultrasound "did not show conclusive findings". Liver biopsy results were reported as severe hepatitis (acute-on-chronic) with questionable cause. The three main possibilities considered in the differential diagnosis were viral agents, drugs, and autoimmune hepatitis. Viral hepatitis tests were negative. The patient had also somewhat elevated ferritin levels, and tested as heterozygous for a genetic mutation for hemochromatosis. Liver tests improved slightly after discontinuation of the study drug, although they were still severely elevated indicating together with the liver biopsy results an ongoing hepatitis. The patient had

elevated IgG, IgA, and IgM on Study Day 357. The patient started oral prednisolone on Study Day 349, and achieved substantial improvement in liver tests (ALT: 166 U/L [Study Day 363]) with regression to baseline levels. On Study Day 382, azathioprine was added and prednisolone was down-titrated. Prednisolone was discontinued on Study Day 475. On Study Day 521 the patient's ALT was 50 U/L and TBL was normal (0.5 mg/dL). Additional follow-up information was received on this patient since the Major Amendment (described in Appendix 3). The immunosuppression treatment with azathioprine had been continued for approximately three and a half years up to the last follow up received, and the patient is clinically considered to have autoimmune hepatitis. Despite continuous immunosuppression there were two separate episodes of significantly elevated liver laboratory tests. On Study Day 704, the patient had an increase in ALT (563 U/L). Values peaked on Study Day 714 (ALT [569 U/L]; TBL [1.5 mg/dL]), and ALT decreased to 105 U/L (Study Day 749) and later normalized. A repeat liver ultrasound on Study Day 783 did not show any lesions. The ALT values worsened again starting on Study Day 992 (801 days after discontinuation of dapagliflozin) (ALT: 111 U/L and TBL: 0.3 mg/dL), and ALT values peaked on Study Day 1132 (ALT: 180 U/L and TBL: 0.5 mg/dL). On Study Day 1215, ALT was 40 U/L and TBL was 0.7 mg/dL. On Study Day 1321, ALT was 17 U/L and TBL was 0.4 mg/dL. Bristol-Myers Squibb and AstraZeneca obtained consultation on this case again with two expert hepatologists (Drs. Maddrey and Watkins). In their opinion, this patient has a clinical picture consistent with a diagnosis of autoimmune hepatitis and not drug-induced autoimmune hepatitis. While drug-induced autoimmune hepatitis cannot be completely excluded, the temporal relationship between onset of the disease and treatment with dapagliflozin in addition to the ongoing autoimmune process that recurred despite discontinuation of dapagliflozin years earlier makes this diagnosis unlikely. Drug-induced autoimmune hepatitis gradually subsides after drug withdrawal. In light of the lack of any other signal either from preclinical program or from large clinical safety data, it was felt to be unlikely that this case constitutes a safety signal for liver injury."
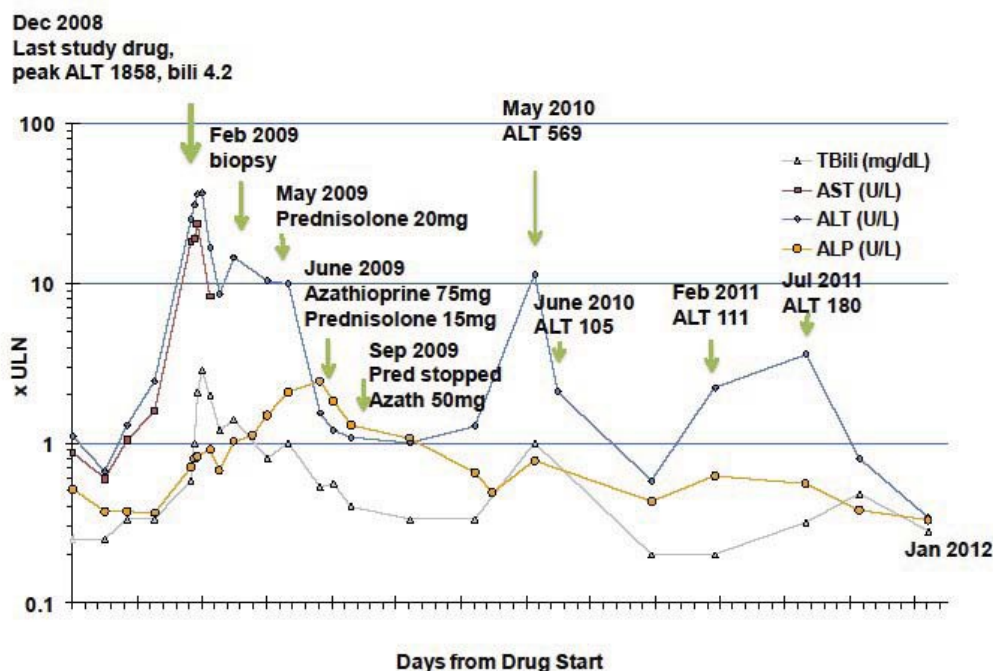
Source: Reproduced from the Applicant's Hepatic Adjudication Report (page 26 of 367, labeled as Figure 1).

A listing of all new or updated case information on adjudicated liver-related events submitted since the last Hepatic Adjudication Report (i.e., Addendum 02; October 25, 2011), is presented in Table 13.

Table 13: New / Updated Adjudicated Cases since the October 25, 2011 Hepatic Adjudication Report

Patient ID(Age/Gender/Race	Treatment Group	Criteria Meeting Adjudication	Final Adjudicated Causality Assessment
D1690C00010-1012-14 (63/F/White)	Placebo	AST and/or ALT > 3X ULN and TBL > 1.5X ULN	Unlikely
D1690C00012-211-12 [a] (73/F/White)	Dapagliflozin 10 mg	Liver-related SAE/AE in patient who discontinued	Excluded
D1690C00018-201-8 (70/M/White)	Dapagliflozin 10 mg	AST and/or ALT >5X ULN Liver-related SAE/AE in patient who discontinued	Unlikely (UPDATED)
D1690C00018-203-4 (70/M/White)	Dapagliflozin 10 mg	AST and/or ALT > 3X ULN and TBL > 1.5X ULN AST and/or ALT > 5X ULN	Unlikely
D1690C00018-212-12 (56/M/White)	Placebo	AST and/or ALT >5X ULN	Unlikely
D1690C00018-1005-3 [b] (59/M/Asian)	Placebo	AST and/or ALT > 5X ULN	Excluded (UPDATED)
D1690C00018-2608-6 (58/M/White)	Dapagliflozin 10 mg	AST and/or ALT >5X ULN	Unlikely
D1690C00018-6109-11 [c] (60/M/White)	Dapagliflozin 10 mg	Liver-related SAE/AE in patient who discontinued	Unlikely (Excluded from summary)
D1690C00019-904-8 (65/M/White)	Placebo	AST and/or ALT >5X ULN	Unlikely
D1690C00019-918-16 (60/M/White)	Dapagliflozin 10 mg	Liver-related SAE/AE in patient who discontinued	Unlikely
D1690C00019-5708-10 (62/M/White)	Dapagliflozin 10 mg	AST and/or ALT >5X ULN	Unlikely
D1691C00003-3306-11 (64/F/White)	Dapagliflozin 5 mg	AST and/or ALT >5X ULN	Possible (UPDATED)
D1692C00006-4307-6 (59/M/Asian)	Dapagliflozin 5 mg	Liver-related SAE/AE in patient who discontinued	Unlikely
D1692C00012-8-8 * (51/F/Asian)	Dapagliflozin 5-10 mg	Liver-related SAE/AE in patient who discontinued	Possible
D1692C00012-33-11 * (61/M/Asian)	Dapagliflozin 5-10 mg	AST and/or ALT > 3X ULN and TBL > 1.5X ULN	Unlikely
D1692C00012-34-30 * (48/M/Asian)	Dapagliflozin 5-10 mg	Liver-related SAE/AE in patient who discontinued	Unlikely
MB102054-24-498 (63/M/Asian)	Placebo	AST and/or ALT > 3X ULN and TBL > 1.5X ULN AST and/or ALT >5X ULN	Unlikely (UPDATED)
MB102073-275-968 [b] (41/F/White)	Dapagliflozin 10 mg	AST and/or ALT >5X ULN	Excluded
MB102073-446-2701 (63/F/White)	Placebo	Liver-related SAE/AE in patient who discontinued	Probable
MB102077-66-70996 [d] (57/M/Asian)	Dapagliflozin 10 mg	AST and/or ALT > 3X ULN and TBL > 1.5X ULN AST and/or ALT >5X ULN	Excluded
MB102077-88-70220 (47/F/White)	Dapagliflozin 10 mg	AST and/or ALT >5X ULN	Unlikely (UPDATED)
MB102077-321-71182 (60/F/White)	Dapagliflozin 5 mg	AST and/or ALT >5X ULN	Possible

Source: Modified from the Applicant's June 19, 2013 Hepatic Adjudication Report (pages 12-16 of 3567, labeled as Table 3).

[a] Patient D1690C00012-211-12 diagnosed with cholangiogenic carcinoma with possible lesion present by MR day -21 prior to study.

[b] Patient D1690C00018-1005-3 was "inconsistently included in the tables and text and the narrative" and was omitted.

[c] Patients D1690C00018-6109-11 and MB102073-275-968 had liver function test abnormalities that occurred >30 days after discontinuation of blinded study drug (a prespecified analysis criteria) and were excluded from the overall summary of adjudicated liver cases.

[d] Patient MB102077-66-70996 was diagnosed with Grade II Hepatitis E that the HAC excluded from a relationship with study drug.

[*] Note: Patients D1692C00012-8-8, D1692C00012-33-11, and D1692C00012-34-30 were enrolled in open-label study with a single active treatment arm (5 mg dapagliflozin titrated to 10 mg dapagliflozin) without any comparator (D1692C00012).

The Applicant states that hepatotoxicity has been identified as a potential risk in their Risk Management Plan (RMP). Therefore, similar to their proposal for assessment of bladder cancer risk, the Applicant proposes that a "comprehensive and scientifically rigorous" evaluation be conducted postmarketing through the following approach:

1. Continued surveillance throughout the conduct of their ongoing CV outcome trial (i.e., Dapagliflozin Effect on Cardiovascular Events [DECLARE; TIMI-58; Study D1693C00001])
2. A dedicated pharmacoepidemiology study

Postmarketing Reports and Medical Literature

In response to the August 22, 2013 consultation request, Dr. Christine Chamberlain from the FDA Division of Pharmacovigilance I (DPV I) in the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports in the FDA Adverse Event Reporting System (FAERS) and Vigibase databases, and searched the medical literature for cases of severe liver injury associated with dapagliflozin or canagliflozin. Two serious liver adverse events were identified in the FAERS database, both from blinded dapagliflozin clinical trials; there were none with canagliflozin. The two cases of liver events were serious in that one case resulted in hospitalization and the other resulted in death. At the time these reports were submitted, both studies remained blinded. However, based on review of the Hepatic Adjudication Report, the liver adverse event case resulting in the death of a 67-year-old white female patient (D1690C00004-4916-16) had been reviewed by the blinded HAC, who assessed that a causal relationship to study medication was unlikely. Subsequently, it was determined that the patient had been randomized to the placebo treatment arm. The second case involved an 83-year-old white male (MB102029-4-276) receiving concomitant medications with known hepatotoxic potential (i.e., niacin, pravastatin, and levofloxacin). On study Day 173, the patient presented with liver enzyme abnormalities (ALT and AST >5X ULRR), and was asymptomatic at that time. Due to these abnormal laboratory findings, the study medication, pravastatin and niacin were all discontinued on Day 175. This patient had two additional events (i.e., TBL >2X ULRR on Day 197, and AST/ALT >3X ULRR and TBL >1.5X ULRR on Day 707) after discontinuation of blinded study medication and during a complex series of medical events (e.g., stricture with subsequent stent placement

of the common hepatic duct, urosepsis, heart failure, and myocardial infarction). The HAC excluded the patient from the overall summary of adjudicated liver cases. Subsequently, it was determined that the patient had been randomized to the dapagliflozin 10 mg treatment arm.

No new adverse events or issues related to liver/hepatic adverse events were noted in the medical literature.

3.4. Cardiovascular Safety

CV-Risk Assessment:

During the first review cycle, the Applicant submitted a meta-analysis of a pool of fourteen Phase 2b and Phase 3 clinical trials to support CV safety of dapagliflozin. The prespecified primary endpoint for this analysis was a composite of time-to-first event of CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina, with all events adjudicated by an independent endpoints committee, blinded to treatment assignments. The HR point estimate of this analysis was 0.67 (98% CI: 0.38-1.18) in favor of dapagliflozin over comparators (i.e., placebo and active controls). It was felt that these results were reassuring and might justify acceptance of potential safety concerns (i.e., bladder cancer and liver safety) identified during the first review cycle. To support these findings, the Agency requested an updated meta-analysis that included five additional trials (i.e., a total of 19 clinical trials), including Studies D1690C00018 and D1690C00019, two trials which were enriched with individuals at high risk for CV events. The meta-analysis of 19 trials included the same primary composite endpoint, as well as a secondary analysis of major cardiovascular events (MACE) with the composite endpoint of CV death, nonfatal MI, and nonfatal stroke. The HR point estimates for both the primary composite endpoint (i.e., HR 0.82; 95% CI, 0.59 to 1.14) and MACE endpoint (i.e., HR 0.79; 95% CI, 0.54 to 1.17) were higher in the updated meta-analysis, but remained less than 1.0, with an upper bound of the 95% CI excluding both 1.8 and 1.3 (consistent with recommendations in the FDA '*Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*', issued December 2008).

As noted, the updated meta-analysis also encompassed Studies D1690C00018 and D1690C00019. These 24-week, placebo-controlled clinical trials had identical study designs, and each had an 80-week extension period. The entry criteria for enrollment included established CVD and inadequate glycemic control (i.e., HbA1c $\geq 7.0\%$ and $\leq 10.0\%$), despite the use of stable doses of oral antidiabetic medications or insulin. However, for Study D1690C00018, all patients were also required to have a diagnosis of hypertension prior to enrollment. Cardiovascular disease was defined as the following: a history of MI, congestive heart failure, hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular accident, carotid artery disease, carotid endarterectomy or stenting,

peripheral vascular disease, peripheral vascular surgery, or amputation. Eligible patients were randomized to dapagliflozin 10 mg or placebo treatment arms, stratified by age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1 year or <1 year prior to enrollment).

Although the mean treatment durations at the time of the updated meta-analysis (provided during the first review cycle) were only approximately six months, these two trials contributed 60 CV events, which comprised approximately 40% of all events included in the updated meta-analysis. Since both trials had similar study designs and enrolled clinically relevant patient populations (i.e., at high risk for CV events), separate CV analyses were performed in which data from only these two trials were considered. The HR point estimates for the primary composite endpoint (i.e., HR 1.07; 95% CI, 0.64 to 1.77) and MACE endpoint (i.e., HR 1.26; 95% CI, 0.69 to 2.31) from the pool of these two trials were discordant with the overall results from the updated meta-analysis. At that time, the Agency felt that the findings from these two large, adequate, and well-controlled clinical trials in a relevant patient population could not be ignored, and that the Agency could not accept any implied CV benefit observed in the original meta-analysis in a risk-benefit assessment in regard to the cancer and liver safety signals.

As a path forward, the Agency recommended that the Applicant submit additional follow-up data from the updated safety analyses of the NDA database, including at least 52 weeks of data from Studies D1690C00018 and D1690C00019. In this resubmission, the Applicant has included Clinical Study Reports for studies included in the pooled safety analyses, in addition to an updated CV Meta-Analysis of 21 Phase 2b and 3 studies. The remainder of this section will summarize some of these data. For more detailed discussion of CV safety, refer to the review by Dr. Eugenio Andraca-Carrera included in this briefing document.

For Studies D1690C00018 and D1690C00019, 1887 patients were randomized to dapagliflozin 10 mg (i.e., 942 patients) or placebo (i.e., 945 patients) treatment arms. The majority of patients had a diagnosis of hypertension for more than 10 years, and many had a history of coronary heart disease (75%), stroke (22%), congestive heart failure (15%), or the use of loop diuretics (19%). In their analyses, the Applicant reports a placebo-adjusted change from baseline to week 24 in HbA1c of -0.5% (-0.6, -0.3) and -0.6 (-0.8, -0.5) for Studies D1690C00018 and D1690C00019, respectively, when dapagliflozin 10 mg was added to pre-existing antidiabetic therapy. Placebo-adjusted reductions in body weight (i.e., -2.3 kg; 95% CI, -2.6 to -1.9, and -1.9 kg; 95% CI, -2.3 to -1.5, respectively) and systolic blood pressure (i.e., -2.0 mmHg; 95% CI, -3.6 to -0.3 and -3; 95% CI, -4.6 to -1.5, respectively) were also observed.

In the updated CV events meta-analysis, the Applicant evaluated the 21 Phase 2b and 3 clinical trials submitted for the 30-MU (Table 14), which included 6594 p-y exposure to dapagliflozin (5936 patients randomized) and 3831 p-y to comparator (3403 patients randomized). The number of patients with confirmed adjudicated events was 178 for the primary CV composite endpoint, and 135 for the composite MACE endpoint. The HR point estimate reported for the primary composite endpoint was 0.81 (95% CI, 0.59 to

1.09) and for the MACE endpoint was 0.78 (95% CI, 0.55 to 1.11). For a subpopulation of patients with a history of CVD (i.e., 1856 patients randomized to dapagliflozin and 1358 to comparator), the HR point estimates for the primary and MACE composite endpoints were 0.81 (95% CI, 0.56 to 1.16) and 0.80 (95% CI, 0.53 to 1.22), respectively. The Applicant also performed a pooled analysis of Studies D1690C00018 and D1690C00019. The HR point estimates for the primary and MACE composite endpoints were 0.98 (95% CI, 0.64 to 1.49) and 1.11 (95% CI, 0.67 to 1.83), respectively. Similar to findings from the previous meta-analysis, divergence in Kaplan-Meier curves, in favor of dapagliflozin, is observed for the primary CV composite endpoint after approximately eight months. However, it should be noted that ten primary events (CV death, myocardial infarction, stroke, and hospitalization for unstable angina) were reported within 30 days of treatment exposure, of which eight of the ten had been randomized to dapagliflozin treatment arms. Treatment allocation to dapagliflozin and control study arms was approximately two to one, respectively. The major cardiovascular events in the eight dapagliflozin-treated patients included CV death (n=1), hospitalization for unstable angina (n=2), myocardial infarction (n=2), and stroke (n=3). The majority of these early events occurred in patients with established peripheral and/or cardiovascular disease, of whom four were enrolled in Studies D1690C00018 and D1690C00019.

Table 14: Updated Meta-Analysis Results of Composite Primary and MACE Endpoints

Study Endpoints	Number of CV Events (Dapa/Comparator)	HR (95% CI)
All Phase 2b/3 Study Pool (N=5936 dapagliflozin vs. N=3403 comparator)		
Primary Composite Endpoint	178 (97/81)	0.81 (95% CI, 0.59 to 1.09)
MACE	135 (73/62)	0.78 (95% CI, 0.55 to 1.11)
Patients with a History of CV Disease from the All Phase 2b/3 Study Pool (N=1856 dapagliflozin vs. N=1358 comparator)		
Primary Composite Endpoint	128 (67/61)	0.81 (95% CI, 0.56 to 1.16)
MACE	95 (50/45)	0.80 (95% CI, 0.53 to 1.22)
Pool of Studies D1690C00018 and D1690C00019 (N=942 dapagliflozin vs. N=945 comparator)		
Primary Composite Endpoint	87 (43/44)	0.98 (95% CI, 0.64 to 1.49)
MACE	61 (32/29)	1.11 (95% CI, 0.67 to 1.83)

Source: Modified from the Applicant's 30-Month Update, Part 1 (pages 84 of 200, labeled as Table 30) and the Statistical Review Section of the Background Document.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; HR, hazard ratio; MACE, major cardiovascular events; N, sample size.
Primary composite endpoint = cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. MACE = cardiovascular death, myocardial infarction or stroke

Blood Pressure Changes

In this NDA resubmission, the Applicant also includes data from two 12-week, placebo-controlled dedicated blood pressure studies (i.e., MB102073 and MB102077). Across both studies, 1062 patients were enrolled (527 patients randomized to dapagliflozin 10 mg and 535 to placebo). Patient entry criteria included inadequately controlled type 2 diabetes (i.e., HbA1c ≥7.0% and ≤10.5%), despite stable therapy with oral antidiabetic medications or insulin, and hypertension, despite stable doses of an angiotensin-converting enzyme (ACE) inhibitor (ACE) or angiotensin receptor blocker (ARB) alone (Study MB102073) or in combination with an additional antihypertensive medication (Study MB102077). At Week 12, the placebo-adjusted mean changes from baseline in seated systolic blood pressure were -3.1 (95% CI, -1.2 to -4.9) mmHg and -4.3 (95% CI, -2.0 to -6.5) mmHg in Studies MB102073 and MB102073, respectively. The placebo-adjusted mean changes from baseline to Week 12 in 24-hour ambulatory systolic blood pressure were -2.9 (95% CI, -0.9 to -4.9) mmHg and -4.5 (95% CI, -1.8 to -7.1) mmHg, respectively. Placebo-adjusted mean changes from baseline to Week 12 in seated diastolic blood pressure were not statistically significant for either study, and a statistical difference in 24-hour mean ambulatory diastolic blood pressure was observed only in Study MB102077 (i.e., placebo-adjusted mean change from baseline of -2.0; 95% CI, 0.3 to -3.7) mmHg.

Lipid Parameter Changes

In the placebo-controlled short-term study pool (baseline to Week 24), adverse events of dyslipidemia were reported in 2.6% (i.e., 62/2360) of patients randomized to dapagliflozin 10 mg compared to 1.9% (43/2295) for controls. For the short-term plus long-term study pool (baseline to Week 102), events of dyslipidemia were reported in 4.3% (87/2026) and 3.3% (65/1956) of dapagliflozin- and placebo-treated patients, respectively. Dapagliflozin was associated with mean placebo-subtracted increases in both low density lipoprotein cholesterol (LDL) (4-5%) and high density lipoprotein cholesterol (HDL) (approximately 4% increase). Mean changes in lipid parameters are presented in Table 15.

**Table 15: Mean Changes from Baseline to End-of-Study in Lipid Parameters
(ST and ST+LT Study Pools)**

Lipid Parameter	Placebo-Controlled Pool (ST) (Baseline to Week 24)		Placebo-Controlled Pool (ST+LT) (Baseline to Week 102)	
	Dapa 10 mg (N=2360)	Placebo (N=2295)	Dapa 10 mg (N=2026)	Placebo (N=1956)
TC (mg/dL)				
Baseline (mean ± SD)	181.9 ± 46.6	180.6 ± 45.79	179.4 ± 44.9	177.3 ± 44.3
EOS (mean ± SD)	186.2 ± 47.1	180.5 ± 46.1	183.2 ± 46.2	174.3 ± 41.8
Percent Change (mean ± SE)	2.5 ± 0.4	0.0 ± 0.4	2.1 ± 0.9	-1.5 ± 0.9
LDL-C (mg/dL)				
Baseline (mean ± SD)	101.2 ± 38.6	100.7 ± 38.0	99.9 ±38.4	98.0 ± 35.3
EOS (mean ± SD)	104.0 ± 39.2	99.8 ± 38.1	102.4 ± 40.1	95.7 ± 33.7
Percent Change (mean ± SE)	2.9 ± 0.7	-1.0 ± 0.7	2.9 ± 1.4	-2.2 ± 1.5
HDL-C (mg/dL)				
Baseline (mean ± SD)	45.0 ± 12.1	45.3 ± 11.0	44.9 ± 11.8	46.5 ± 11.2
EOS (mean ± SD)	47.7 ± 12.4	46.6 ± 11.5	47.9 ± 12.7	47.7 ± 12.0
Percent Change (mean ± SE)	6.0 ± 0.4	2.7 ± 0.4	6.6 ± 0.7	2.1 ± 0.8
Triglycerides (mg/dL)				
Baseline (mean ± SD)	187.1 ± 160.1	177.2 ± 111.2	179.9 ± 126.5	168.5 ± 119.8
EOS (mean ± SD)	180.4 ± 145.3	178.6 ± 137.7	176.1 ± 108.4	168.3 ± 149.6
Percent Change (mean ± SE)	-2.7 ± 0.9	-0.7 ± 0.9	-1.8 ± 1.8	-1.8 ± 1.8

Source: Modified from the Applicant's 30-Month Update, Parts 2 and 3 (pages 11298-11309 of 18920, labeled as Appendices 169-170 and pages 15802-15813 of 18333, labeled as Appendices 275-276).
Abbreviations: Dapa, dapagliflozin; EOS, end-of-study; N, sample size; SD, standard deviation; SE, standard error; ST, short-term study pool; ST+LT, and short-term plus long-term study pool.

SECTION 4. ADVERSE EVENTS OF INTEREST

4.1. Deaths, Serious Adverse Events, and Adverse Events Leading to Withdrawal

Summary tables of adverse events (AEs) for the entire All Phase 2b/3 and Placebo-Controlled (ST and ST+LT) study pools are presented in Table 16 and
Table 17. Across all study pools, the proportions of deaths and of patients experiencing at least one SAE were similar between dapagliflozin and control treatment arms. Compared to placebo, the proportions of AEs (total and those leading to discontinuation from study) were similar, but higher in the dapagliflozin treatment arms. Besides the expected increase in the number of events reported following additional treatment exposure for the 30-MU, no obvious shifts in the pattern of events were observed since the first review cycle.

Deaths

In the All Phase 2b/3 Pool, there were 37 (0.6%) deaths with dapagliflozin and 24 (0.7%) in the control arm (Table 16). Many of the deaths reported after the 4MSU database lock were associated with the Cardiac Disorders System Organ Class (SOC), and, with the exception of a single case, were in patients receiving the 10 mg dose for the deaths reported in the patients receiving dapagliflozin (Table 18). It should be noted that most of these deaths occurred in the Applicant's two large long-term clinical trials (i.e., 26 of 30 deaths came from Studies D1690C000018 and D1690C000019), and that these trials only enrolled patients with established CV disease. Further, only the 10 mg dapagliflozin dose was evaluated in these studies. Because events are limited, it is difficult to ascertain a dose-relationship for deaths. At the time of the database lock for the original NDA submission, the proportion of deaths reported by dose in the ST and ST+LT studies were:

- *Placebo-Controlled Pool (ST):* 0.12% (1/814), 0.18% (2/1145), and 0.25% (3/1193) in dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 0.07% (1/1393) in the placebo arm.

- *Placebo-Controlled Pool (ST+LT):* 0.80% (5/625), 0.52% (4/767), and 0.39% (3/768) in dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 0.14% (1/694) in the placebo arm.

The Applicant also received nine reports of death (8 for patients receiving dapagliflozin) after the follow-up visit and closure of clinical data collection for respective studies. The eight deaths for patients receiving dapagliflozin were attributed to: acute myocardial infarction (n=1); hepatic neoplasm (n=1); lung cancer metastatic/lung neoplasm malignant (n=2); mixed hepatocellular cholangiogenic (sic) carcinoma (n=1); and pancreatic carcinoma/pancreatic carcinoma metastatic (n=3).

Serious Adverse Events

In the All Phase 2b/3 Pool, SAEs were reported for 602 (10.1%) and 408 (12%) of patients assigned to the dapagliflozin and control treatment arms, respectively (Table 16). For the placebo-controlled pools (
Table 17), the proportions of patients experiencing an SAE were also similar between treatment arms for both the ST (5.1% vs. 5.4%) and the ST+LT (13.7% vs. 14.6%) studies. The frequency of events by SOC that occurred more commonly in dapagliflozin-treated patients is presented in Table 19.

Withdrawals Due to Adverse Events

For the Placebo-Controlled Pools (ST and ST+LT), discontinuations from study due to AEs were higher in the dapagliflozin treatment arms compared to placebo (
Table 17). Adverse events leading to withdrawal that were reported in at least three dapagliflozin-treated patients, and at a rate higher than placebo, involved changes in renal function, and genital or urinary tract infections.

Table 16: Frequency Table of Safety Events for the All Phase 2b/3 Pool

| Event | 30-MU | | 4MSU | |
	Dapa N=5936 (%)	All Comparators N=3403(%)	Dapa N=4310 (%)	All Comparators N=1962 (%)
Deaths	37 (0.6)	24 (0.7)	22 (0.5)	12 (0.6)
At Least One SAE	602 (10.1)	408 (12.0)	363 (8.4)	184 (9.4)
At Least One AE	3594 (60.5)	1979 (58.2)	1398 (62.1)	467 (59.5)

Source: Modified from the Applicant's 4-Month Safety Update (page 71 of 18822, labeled as Table 7; and page 1722 of 18822, labeled as Appendix 17A) and Derived from the ADCV datasets provided in the submission.
Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; AE, adverse event; Dapa, dapagliflozin; SAE, serious adverse event; ST, short-term study pool; ST+LT, and short-term plus long-term study pool.

Table 17: Frequency Table of Safety Events for the Placebo-Controlled Pools (ST and ST+LT)

| Event | Placebo-Controlled Pool (ST) | | | | Placebo-Controlled Pool (ST+LT) | | | |
| | 30-MU | | NDA Database Lock | | 30-MU | | NDA Database Lock | |
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)	Dapa 10 mg N=1193 (%)	Placebo N=1393 (%)	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 10 mg N=768 (%)	Placebo N=694 (%)
Deaths	7 (0.3)	4 (0.2)	3 (0.3)	1 (0.1)	18 (0.9)	12 (0.6)	3 (0.4)	1 (0.1)
SAEs Leading to Discontinuation	16 (0.7)	24 (1.0)	9 (0.8)	11 (0.8)	36 (1.8)	50 (2.6)	10 (1.3)	15 (2.2)
At Least One SAE	120 (5.1)	123 (5.4)	42 (3.5)	46 (3.3)	278 (13.7)	286 (14.6)	66 (8.6)	70 (10.1)
AEs Leading to Discontinuation	102 (4.3)	82 (3.6)	38 (3.2)	35 (2.5)	172 (8.5)	145 (7.4)	36 (4.7)	35 (5.0)
At Least One AE	1416 (60.0)	1279 (55.7)	734 (61.5)	792 (56.9)	1508 (74.4)	1399 (71.5)	564 (73.4)	494 (71.2)
At Least One Hypoglycemic AE	324 (13.7)	284 (12.4)	128 (10.7)	112 (8.0)	435 (21.5)	437 (22.3)	144 (18.8)	136 (19.6)

Source: Modified from the Applicant's 30-MU (pages 31-32 of 200, labeled as Tables 12 and 13).
Abbreviations: AE, adverse event; Dapa, dapagliflozin; N, sample size; SAE, serious adverse event; ST, short-term; and ST+LT, short-term plus long-term.

Table 18: Frequency Table of Causes of Death for the All Phase 2b/3 Pool

MedDRA Preferred Term	30-MU						Original NDA Database Lock	
MedDRA Preferred Term	New Events by Dose (mg) after Database Lock for 4MSU*				Dapa Total N=5936 (%)	Control N=3403 (%)	Dapa Total N=4287 (%)	Control N=1941 (%)
	2.5 N=1220	5 N=1668	10 N=2909	Control N=3403				
MYOCARDIAL INFARCTION	0	0	3	4	6 (0.10)	5 (0.15)	3 (0.07	1 (0.05)
SEPTIC SHOCK	0	0	2	0	3 (0.05)	0	1 (0.02)	0
SUDDEN DEATH	0	0	3	1	3 (0.05)	2 (0.06)	0	1 (0.05)
ACUTE MYOCARDIAL INFARCTION	0	0	0	0	2 (0.03)	4	2 (0.05)	3 (0.16)
CARDIAC FAILURE	0	0	1	0	2 (0.03)	1 (0.03)	1 (0.02)	1 (0.05)
CARDIOGENIC SHOCK	0	0	0	0	2 (0.03)	0	1 (0.02)	0
CARDIO-RESPIRATORY ARREST	0	0	0	0	2 (0.03)	0	2 (0.05)	0
MULTI-ORGAN FAILURE	0	0	1	0	2 (0.03)	0	1 (0.02)	0
PULMONARY EMBOLISM	0	0	0	1	2 (0.03)	1 (0.03)	2 (0.05)	0
RENAL FAILURE	0	0	2	0	2 (0.03)	1 (0.03)	0	1 (0.05)
ANGINA PECTORIS	0	0	0	0	1 (0.02)	0	1 (0.02)	0
CARDIAC ARREST	0	1	0	0	1 (0.02)	0	0	0
CARDIOPULMONARY FAILURE	0	0	0	0	1 (0.02)	0	1 (0.02)	0
CIRCULATORY COLLAPSE	0	0	1	0	1 (0.02)	0	0	0
CONTUSION	0	0	0	0	1 (0.02)	0	1 (0.02)	0
DEATH	0	0	1	1	1 (0.02)	1 (0.03)	0	0
DUODENAL ULCER HEMORRHAGE	0	0	1	0	1 (0.02)	0	0	0
INFARCTION	0	0	1	0	1 (0.02)	0	0	0
MENINGITIS	0	0	1	0	1 (0.02)	0	0	0
ESOPHAGEAL VARICES HEMORRHAGE	0	0	0	0	1 (0.02)	0	1 (0.02)	0
RENAL FAILURE ACUTE	0	0	0	0	1 (0.02)	0	1 (0.02)	0
SEPSIS	0	0	0	0	1 (0.02)	0	0	0
SUDDEN CARDIAC DEATH	0	0	0	0	1 (0.02)	0	1 (0.02)	0
ABDOMINAL PAIN	0	0	0	0	0	1 (0.03)	0	1 (0.05)
ACUTE PULMONARY OEDEMA	0	0	0	1	0	1 (0.03)	0	0
BRONCHIAL CARCINOMA	0	0	0	1	0	1 (0.03)	0	0
CEREBROVASCULAR ACCIDENT	0	0	0	1	0	1 (0.03)	0	0
COLON CANCER	0	0	0	1	0	1 (0.03)	0	0
CRANIOCEREBRAL INJURY	0	0	0	0	0	1 (0.03)	0	1 (0.05)
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0	0	0	1 (0.03)	0	0
INTRAVENTRICULAR HEMORRHAGE	0	0	0	1	0	1 (0.03)	0	0
LUNG NEOPLASM MALIGNANT	0	0	0	0	0	1 (0.03)	0	1 (0.05)
METASTATIC SQUAMOUS CELL CARCINOMA	0	0	0	1	0	1 (0.03)	0	0
ROAD TRAFFIC ACCIDENT	0	0	0	0	0	1 (0.03)	0	1 (0.05)
TOTAL PATIENTS WITH AN EVENT OF DEATH	**0**	**1**	**17**	**13**	**37 (0.6)**	**24 (0.7)**	**18 (0.4)**	**9(0.5)**

Source: Modified from the Applicant's 30-Month Update (pages 39-44 of 200, labeled as Tables 16-18).
Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; and N, sample size.
* Note: Total number is derived from the All Phase 2b/3 Pool, and exposure in the 2.5 mg and 5 mg dose cohorts has been limited since the 4MSU.

Events of Hypoglycemia

In the dapagliflozin clinical development program, the Applicant defined events of hypoglycemia as major for symptomatic episodes 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. Minor hypoglycemic events were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode. In the placebo-controlled short-term and short-term plus long-term study pools, at least one hypoglycemic adverse event was reported in 13.7% vs. 12.4% and 21.5% vs. 22.3% of dapagliflozin- and placebo-treated patients, respectively (
Table 17). The proportions of patients experiencing these events were similar to those observed during the first review cycle. The occurrence of hypoglycemia was infrequently classified as major and often depended on the type of background therapy used in each study, with higher frequencies reported when dapagliflozin was administered as add-on therapy to sulfonylurea or insulin therapy. In Study MB102028 (D1690C00005), in which dapagliflozin was added on to glimepiride for up to 48 weeks, a single episode of major hypoglycemia was reported in a patient treated with dapagliflozin 2.5 mg plus glimepiride. Minor episodes of hypoglycemia occurred in 7.9% and 2.1% of patients treated with dapagliflozin 10 mg plus glimepiride and placebo plus glimepiride, respectively. In Study MB102033 (D1690C00006), a 24-week study in which dapagliflozin or placebo was added on to insulin (with or without two oral antidiabetic agents), there was again a single episode of major hypoglycemia in a patient receiving combination therapy with dapagliflozin 10 mg plus insulin. By week 104, major episodes of hypoglycemia were reported in 1.0% and 0.5% of patients treated with dapagliflozin 10 mg or placebo added on to insulin, respectively, and minor episodes were reported in 53.1% and 41.6% of patients, respectively. Two additional studies (D1690C00018 and D1690C00019) that included patient populations receiving background insulin therapy (alone or with one or more oral antidiabetic treatments) also reported higher rates of minor hypoglycemic events in patients receiving combination therapy with dapagliflozin 10 mg compared to placebo.

Table 19: Serious Adverse Events Occurring More Frequently with Dapagliflozin than With Comparator in the All Phase 2b/3 Pool

Event	30-MU		4MSU				
	Dapa* N=5936 (%)	Control N=3403 (%)	Dapa 2.5 mg N=1220 (%)	Dapa 5 mg N=1454 (%)	Dapa 10 mg N=1497 (%)	Dapa Total N=4310 (%)	Control N=1962 (%)
TOTAL NUMBER (%) PATIENTS WITH SAEs	602 (10.14)	408 (12.00)	139 (11.39)	105 (7.22)	116 (7.75)	363 (8.42)	184 (9.38)
CARDIAC DISORDERS	139 (2.34)	106 (3.11)	30 (2.46)	28 (1.93)	16 (1.07)	74 (1.72)	44 (2.24)
ARTERIOSCLEROSIS CORONARY ARTERY	3 (0.05)	0	1 (0.08)	1 (0.07)	0	2 (0.05)	0
ATRIAL FLUTTER	3 (0.05)	1 (0.03)	0	2 (0.14)	0	2	0
CARDIOMYOPATHY	3 (0.05)	0	0	1 (0.07)	0	0	0
SICK SINUS SYNDROME	3 (0.05)	0	1 (0.08)	1 (0.07)	1 (0.07)	3 (0.07)	0
INFECTIONS AND INFESTATIONS	102 (1.72)	55 (1.62)	21 (1.72)	17 (1.17)	23 (1.54)	61 (1.42)	24 (1.22)
PULMONARY TUBERCULOSIS	5 (0.08)	1 (0.03)	0	5 (0.34)	0	5 (0.26)	1 (0.51)
GANGRENE	3 (0.05)	1 (0.03)	0	2 (0.14)	0	2 (0.05)	0
INFLUENZA	3 (0.05)	0	2 (0.16)	0	0	2 (0.05)	0
SEPSIS	3 (0.05)	0	1 (0.08)	0	2 (0.13)	3 (0.07)	0
SEPTIC SHOCK	3 (0.05)	0 (0.00)	1 (0.08)	1 (0.07)	1 (0.07)	3 (0.07)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	82 (1.38)	45 (1.32)	20 (1.64)	15 (1.03)	17 (1.14)	53 (1.23)	17 (0.87)
BREAST CANCER	12 (0.20)	2 (0.06)	4 (0.33)	1 (0.07)	4 (0.27)	9 (0.21)	0
BLADDER TRANSITIONAL CELL CARCINOMA	5 (0.08)	0	0	1 (0.07)	2 (0.13)	3 (0.07)	0
LUNG NEOPLASM MALIGNANT	5 (0.08)	0	1 (0.08)	1 (0.07)	0	2 (0.05)	1 (0.05)
PANCREATIC CARCINOMA	3 (0.05)	1 (0.03)	1 (0.08)	0	1 (0.07)	2 (0.05)	1 (0.05)
NERVOUS SYSTEM DISORDERS	62 (1.04)	51 (1.50)	21 (1.72)	2 (0.14)	13 (0.87)	36 (0.84)	22 (1.12)
CAROTID ARTERY STENOSIS	5 (0.08)	1 (0.03)	1 (0.08)	1 (0.07)	0	2 (0.05)	0
LOSS OF CONSCIOUSNESS	3 (0.05)	1 (0.03)	2 (0.16)	0	0	2 (0.05)	1 (0.05)
GASTROINTESTINAL DISORDERS	53 (0.89)	33 (1.00)	12 (0.98)	8 (0.55)	9 (0.60)	29 (0.67)	13 (0.66)
ABDOMINAL PAIN UPPER	4 (0.07)	0	1 (0.08)	0	1 (0.07)	2 (0.05)	0
GASTRIC ULCER	4 (0.07)	1 (0.03)	0	0	0	0	1 (0.05)
GASTROINTESTINAL HEMORRHAGE	3 (0.05)	0	0	0	1 (0.07)	1 (0.02)	0
HEMORRHOIDS	3 (0.05)	0	2 (0.16)	0	0	2 (0.05)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	43 (0.72)	26 (0.76)	10 (0.82)	7 (0.48)	9 (0.60)	26 (0.60)	15 (0.76)
ROTATOR CUFF SYNDROME	7 (0.12)	1 (0.03)	0	2 (0.14)	2 (0.13)	4 (0.09)	1 (0.05)
ARTHRALGIA	4 (0.07)	1 (0.03)	1 (0.08)	0	2 (0.13)	3 (0.07)	1 (0.05)

49

Event	30-MU		4MSU				
	Dapa* N=5936 (%)	Control N=3403 (%)	Dapa 2.5 mg N=1220 (%)	Dapa 5 mg N=1454 (%)	Dapa 10 mg N=1497 (%)	Dapa Total N=4310 (%)	Control N=1962 (%)
INTERVERTEBRAL DISC PROTRUSION	4 (0.07)	1 (0.03)	3 (0.25)	1 (0.07)	0	4 (0.09)	1 (0.05)
VASCULAR DISORDERS	**37 (0.62)**	**19 (0.59)**	**5 (0.41)**	**9 (0.62)**	**9 (0.60)**	**23 (0.53)**	**3 (0.15)**
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	10 (0.17)	4 (0.12)	0	2 (0.14)	0	2 (0.05)	0
HYPERTENSION	4 (0.07)	1 (0.03)	1 (0.08)	0	3 (0.20)	4 (0.09)	0
METABOLISM AND NUTRITION DISORDERS	**25 (0.42)**	**14 (0.41)**	**4 (0.27)**	**8 (0.55)**	**4 (0.27)**	**16 (0.37)**	**7 (0.36)**
HYPERGLYCEMIA	4 (0.07)	1 (0.03)	0	2 (0.14)	2 (0.13)	8 (0.19)	4 (0.20)
HEPATOBILIARY DISORDERS	**21 (0.35)**	**13 (0.38)**	**6 (0.49)**	**3 (0.21)**	**1 (0.07)**	**10 (0.23)**	**5 (0.25)**
CHOLELITHIASIS	11 (0.19)	4 (0.12)	4 (0.33)	2 (0.14)	1 (0.07)	8 (0.19)	1 (0.05)
RENAL AND URINARY DISORDERS	**21 (0.35)**	**13 (0.38)**	**3 (0.25)**	**6 (0.41)**	**3 (0.20)**	**12 (0.28)**	**10 (0.51)**
CALCULUS URETERIC	3 (0.05)	1 (0.03)	0	1 (0.07)	0	1 (0.02)	1 (0.05)
RENAL FAILURE	3 (0.05)	0	0	1 (0.07)	0	1 (0.02)	1 (0.05)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**20 (0.34)**	**17 (0.50)**	**5 (0.41)**	**5 (0.34)**	**1 (0.07)**	**11 (0.26)**	**9 (0.46)**
DYSPNEA	3 (0.05)	1 (0.03)	0	3 (0.21)	0	3 (0.07)	1 (0.05)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**12 (0.2)**	**4 (0.1)**	**3 (0.25)**	**2 (0.14)**	**0**	**5 (0.12)**	**1 (0.05)**
ANGIOEDEMA	4 (0.07)	0	2 (0.16)	1 (0.07)	0	3 (0.07)	0

Source: Modified from the Applicant's 30-MU (pages 48-49 of 200, labeled as Table 21) and derived from the 30-MU and 4MSU datasets (Note: Frequencies are reported as MedDRA Preferred Terms).

Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; N, sample size; and SAE, serious adverse events.

*A total of 3417 (approximately 58%) dapagliflozin-treated subjects were randomized to the 10 mg treatment arm.

4.2. Genital Infections

As noted during the first review cycle and anticipated with SGLT2 inhibitors, dapagliflozin was associated with increased risk for genital infections. Consistent with the previous findings from data submitted during the first review cycle, genital infection events were more common in females (8.4% vs. 1.2% in dapagliflozin and control arms, respectively) than in males (3.4% vs. 0.2%, respectively) and typically resolved with treatment. Comparison of events observed during the previous review cycle with this NDA resubmission are presented for the placebo-controlled short-term and short-term plus long-term treatment pools in Table 20 and Table 21, respectively. Events of vulvovaginal mycotic infections and balanitis were the most common genital infections reported for women and men, respectively. Approximately 17% of patients experienced a second infection in the 10 mg dapagliflozin treatment arm, with two having three infections during study. No events of genital infections were classified as severe or serious, but five dapagliflozin-treated patients withdrew from study due to these events (i.e., three with vulvovaginal mycotic infection, and one each with vulvovaginal candidiasis, and balanitis).

New data regarding dose-response were not provided with this NDA resubmission. However, the Applicant previously provided Kaplan-Meier curves of the time to onset of first genital infection event (Figure 1). These curves indicate that patients treated with dapagliflozin were at a greater risk for a first event of genital infection than those treated with placebo as early as one month after initiating study medication. Also, it appears that the curves for the dapagliflozin 5 mg and 10 mg dose groups started to separate from the 2.5 mg dose group at approximately eight weeks.

Table 20. Events of Genital Infections in Placebo-Controlled Studies (Short-Term Pool)

Event	30-MU		Original NDA				
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)	Dapa 2.5 mg N=814 (%)	Dapa 5 mg N=1145 (%)	Dapa 10 mg N=1193 (%)	Dapa Total N=3291 (%)	Placebo N=1393 (%)
TOTAL NUMBER (%) PATIENTS WITH GENITAL INFECTION EVENTS	**130 (5.5)**	**14 (0.6)**	**33 (4.1)**	**65 (5.7)**	**57 (4.8)**	**167 (5.1)**	**12 (0.9)**
FEMALES	84/1003 (8.4)	11/952 (1.2)	23/400 (5.8)	49/581 (8.4)	41/598 (6.9)	122/1648 (7.4)	10/677 (1.5)
MALES	46/1357 (3.4)	3/1343 (0.2)	10/414 (2.4)	16/564 (2.8)	16/595 (2.7)	45/1643 (2.7)	2/716 (0.3)
TOTAL EVENTS	154	15	—	—	—	—	—
RECEIVED ANTIMICROBIAL TREATMENT	125/154 (81.2)	12/15 (80.0)	—	—	—	—	—
RECURRENT INFECTIONS	22/130 (16.9)	1/15 (7.1)	—	—	—	—	—
*PREFERRED TERMS**							
VULVOVAGINAL MYCOTIC INFECTION	34 (1.4)	7 (0.3)	8 (1.0)	13 (1.1)	20 (1.7)	45 (1.4)	5 (0.4)
BALANITIS	29 (1.2)	0	4 (0.5)	7 (0.6)	7 (0.6)	18 (0.5)	1 (0.1)
VAGINAL INFECTION	18 (0.8)	1 (<0.1)	6 (0.7)	14 (1.2)	10 (0.8)	33 (1.0)	1 (0.1)
GENITAL INFECTION FUNGAL	12 (0.5)	2 (0.1)	6 (0.7)	7 (0.6)	6 (0.5)	20 (0.6)	1 (0.1)
GENITAL INFECTION	11 (0.5)	1 (<0.1)	0	2 (0.2)	2 (0.2)	4 (0.1)	0
VULVOVAGINAL CANDIDIASIS	8 (0.3)	1 (<0.1)	3 (0.4)	10 (0.9)	4 (0.3	18 (0.5)	1 (0.1)
BALANITIS CANDIDA	6 (0.3)	0	2 (0.2)	2 (0.2)	2 (0.2)	7 (0.2)	0
VULVOVAGINITIS	5 (0.2)	0	2 (0.2)	4 (0.3)	3 (0.3)	9 (0.3)	0
GENITAL CANDIDIASIS	3 (0.1)	0	0	3 (0.3)	2 (0.2)	5 (0.2)	0
VULVITIS	2 (0.1)	0	2 (0.2)	1 (0.1)	1 (0.1)	4 (0.1)	0
BALANOPOSTHITIS	1 (<0.1)	1 (<0.1)	0	1 (0.1)	0	2 (0.1)	0
GENITAL INFECTION MALE	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
GENITOURINARY TRACT INFECTION	1 (<0.1)	0	0	1 (0.1)	0	1 (<0.1)	0
PENILE ABCESS	1 (<0.1)	0	0	0	0	0	0
PENILE INFECTION	1 (<0.1)	0	0	0	1 (0.1)	2 (0.1)	0
POSTHITIS	1 (<0.1)	0	0	1 (0.1)	0	1 (<0.1)	0
VULVAL ABSCESS	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (0.1)

Source: Modified from the Applicant's 30-Month Update (pages 109-110 of 200, labeled as Tables 38 and 39) and October 25, 2013 Response to FDA Request for Information.

Abbreviations: —, data not reported; 30-MU, 30-Month Update; Dapa, dapagliflozin; and N, sample size.

* The Applicant used a customized MedDRA query for genital infection events using a prespecified list of preferred terms, including: balanitis, balanitis candida, balanoposthitis, balanoposthitis infective, Bartholin's abscess, bartholinitis, cellulitis of male external genital organ, clitoris abscess, erosive balanitis, Escherichia vaginitis, gangrenous balanitis, genital abscess, genital burning sensation, genital candidiasis, genital discharge, genital infection, genital infection bacterial, genital infection female, genital infection fungal, genital infection male, genital rash, genitourinary tract infection, penile abscess, penile infection, posthitis, pruritus genital, urogenital infection bacterial, urogenital infection fungal, vaginal abscess, vaginal cellulitis, vaginal discharge, vaginal infection, vaginal inflammation, vaginitis bacterial, vulval abscess, vulval cellulitis, vulvitis, vulvovaginal candidiasis, vulvovaginal erythema, vulvovaginal mycotic infection, vulvovaginal pruritus, vulvovaginitis, vulvovaginitis streptococcal, and vulvovaginal burning sensation.

Table 21: Events of Genital Infections in Placebo-Controlled Studies (Short-Term plus Long-Term Pool)

Event	30-MU		4MSU				
	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 2.5 mg N=625 (%)	Dapa 5 mg N=767 (%)	Dapa 10 mg N=859 (%)	Dapa Total N=2251 (%)	Placebo N=785 (%)
TOTAL NUMBER (%) PATIENTS WITH GENITAL INFECTION EVENTS	**156 (7.7)** 98/852 (11.5) 58/1174 (4.9)	**19 (1.0)** 15/799 (1.9) 4/1157 (0.3)	**40 (6.4)** 27/313 (8.6) 13/312 (4.2)	**68 (8.9)** 54/388 (13.9) 14/379 (3.7)	**68 (7.9)** 45/447 (10.1) 23/412 (5.6)	**176 (7.8)** 126/1148 (11.0) 50/1103 (4.5)	**10 (1.3)** 10/387 (2.6) 0/398
FEMALES							
MALES							
*PREFERRED TERMS**							
VULVOVAGINAL MYCOTIC INFECTION	38 (1.9)	8 (0.4)	6 (1.0)	16 (2.1)	18 (2.1)	40 (1.8)	6 (0.8)
BALANITIS	36 (1.8)	0	6 (1.0)	6 (0.8)	12 (1.4)	24 (1.1)	0
VAGINAL INFECTION	21 (1.0)	1 (0.1)	6 (1.0)	18 (2.3)	12 (1.4)	36 (1.6)	1 (0.1)
GENITAL INFECTION FUNGAL	15 (0.7)	2 (0.1)	9 (1.4)	7 (0.9)	7 (0.8)	23 (1.0)	0
GENITAL INFECTION	12 (0.6)	1 (0.1)	1 (0.2)	2 (0.3)	2 (0.2)	5 (0.2)	1 (0.1)
VULVOVAGINAL CANDIDIASIS	11 (0.5)	1 (0.1)	5 (0.8)	9 (1.2)	7 (0.8)	21 (0.9)	0
BALANITIS CANDIDA	8 (0.4)	0	3 (0.5)	1 (0.1)	4 (0.5)	8 (0.4)	0
VULVOVAGINITIS	8 (0.4)	1 (0.1)	4 (0.6)	5 (0.7)	4 (0.5)	13 (0.6)	0
GENITAL CANDIDIASIS	7 (0.3)	0	0	2 (0.3)	4 (0.5)	6 (0.3)	0
BALANOPOSTHITIS	4 (0.2)	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.1)	0
GENITOURINARY TRACT INFECTION	3 (0.1)	2 (0.1)	0	1 (0.1)	0	1 (<0.1)	0
VULVAL ABSCESS	3 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (<0.1)	1 (0.1)
VULVITIS	3 (0.1)	0	2 (0.3)	1 (0.1)	2 (0.2)	5 (0.2)	0
PENILE INFECTION	2 (0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
GENITAL INFECTION FEMALE	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
GENITAL INFECTION MALE	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
PENILE ABCESS	1 (<0.1)	0	0	0	0	0	0
POSTHITIS	1 (<0.)1	0	1 (0.2)	1 (0.1)	0	2 (<0.1)	0
VAGINAL ABSCESS	0	1 (0.1)	0	0	0	0	0

Source: Modified from the Applicant's 30-MU (pages 109-110 of 200, labeled as Tables 38 and 40) and October 25, 2013 Response to FDA Request for Information.

Abbreviations: 4MSU, 4 Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; and N, sample size.

* The Applicant used a customized MedDRA query for genital infection events using a prespecified list of preferred terms, including: balanitis, balanitis candida, balanoposthitis, balanoposthitis infective, Bartholin's abscess, bartholinitis, cellulitis of male external genital organ, clitoris abscess, erosive balanitis, Escherichia vaginitis, gangrenous balanitis, genital abscess, genital burning sensation, genital candidiasis, genital discharge, genital infection, genital infection bacterial, genital infection female, genital infection fungal, genital infection male, genital rash, genitourinary tract infection, penile abscess, penile infection, posthitis, pruritus genital, urogenital infection bacterial, urogenital infection fungal, vaginal abscess, vaginal cellulitis, vaginal discharge, vaginal infection, vaginal inflammation, vaginitis bacterial, vulval abscess, vulval cellulitis, vulvitis, vulvovaginal candidiasis, vulvovaginal erythema, vulvovaginal mycotic infection, vulvovaginal pruritus, vulvovaginitis, vulvovaginitis streptococcal, and vulvovaginal burning sensation.

Figure 1: Time to First Event of Genital Infection in the Short-Term plus Long-Term Placebo-Controlled Pool
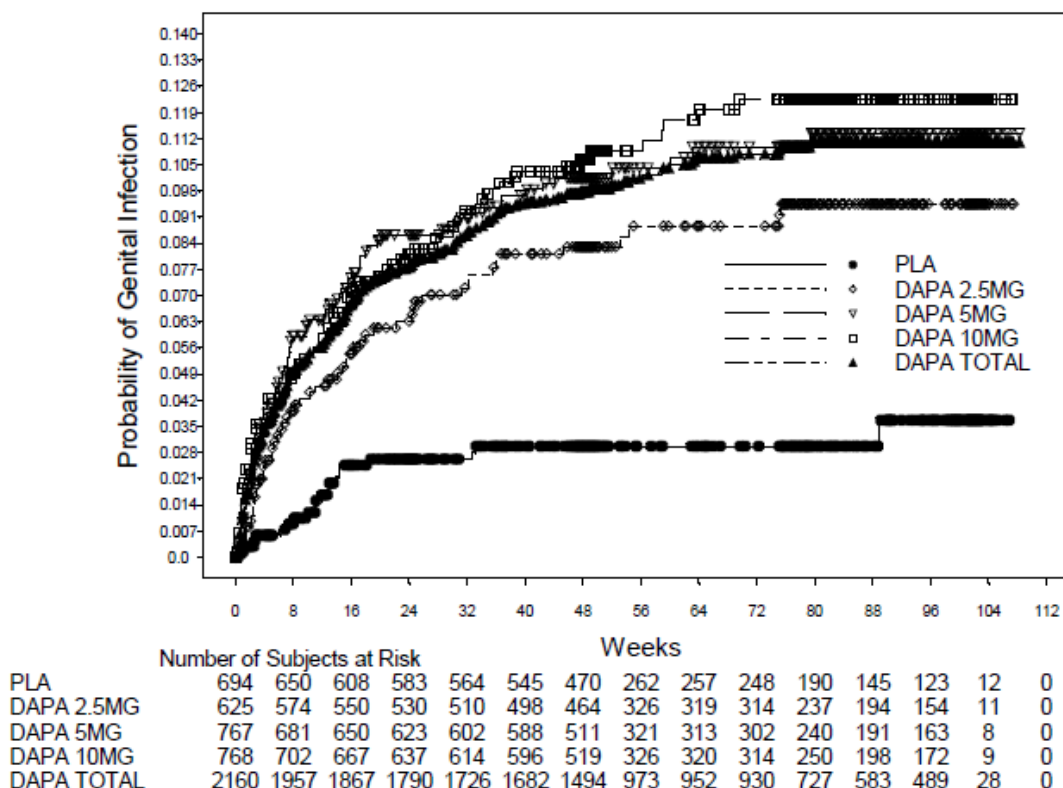
Number of Subjects at Risk															
PLA	694	650	608	583	564	545	470	262	257	248	190	145	123	12	0
DAPA 2.5MG	625	574	550	530	510	498	464	326	319	314	237	194	154	11	0
DAPA 5MG	767	681	650	623	602	588	511	321	313	302	240	191	163	8	0
DAPA 10MG	768	702	667	637	614	596	519	326	320	314	250	198	172	9	0
DAPA TOTAL	2160	1957	1867	1790	1726	1682	1494	973	952	930	727	583	489	28	0

Symbols represent censored observations.
Week is not scheduled visit week but actual days from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.
The results beyond Week 102 should be interpreted with caution as the number of subjects at risk might be limited.

Source : Applicant's Summary of Clinical Safety (pages 183 of 435, labeled as Figure 2).

4.3. Urinary Tract Infection

Similar to the occurrence of genital infection events, dapagliflozin treatment arms were associated with increased risk for urinary tract infections (UTI) compared the placebo treatment arms for both the placebo-controlled short-term (i.e., 4.7% vs. 3.5%, respectively) and short-term plus long-term (8.6% vs. 6.7%, respectively) study pools (Table 22 and Table 23). The proportions of patients experiencing UTI events were also higher for both dapagliflozin and placebo treatment arms in the long-term plus short-term pool than for the short-term pool. Consistent with the previous findings, UTI events were

more common in females than in males and typically resolved with antimicrobial therapy. More than twenty percent of patients with UTI events in both placebo-controlled study pools had possible predisposing risk factors (i.e., history of recurrent UTI, benign prostatic hypertrophy, renal-urinary tract stones and nocturia).

In the placebo-controlled short-term pool five patients (0.2%) receiving dapagliflozin and two randomized to placebo (0.1%) withdrew from study due to UTI events, and events were classified as SAEs for three patients (i.e., two in the placebo arm and one patient receiving dapagliflozin). In the placebo-controlled short-term plus long-term pool, six patients (0.3%) receiving dapagliflozin and two patients (0.1%) receiving placebo withdrew due to UTI events. For eight patients (four receiving dapagliflozin and four placebo) the UTI event was reported as an SAE. Approximately 78% of patients in either treatment arm experienced a single UTI event. Across the All Phase 2b/3 safety population, events of pyelonephritis were uncommon ($\leq 0.2\%$ in dapagliflozin and control treatment groups).

Based on data provided during the first review cycle, there did not appear to be an obvious dose-response relationship between UTI events and dose. Inspection of Kaplan-Meier curves, depicting time-to-first-UTI event data, show separation of the curves for the dapagliflozin 5 mg and 10 mg groups from the dapagliflozin 2.5 mg and placebo groups starting at approximately eight weeks and continuing through Week 104 (Figure 2).

Table 22: Events of Urinary Tract Infections in Placebo-Controlled Studies (Short-Term Pool)

Event	30-MU		Original NDA				
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)	Dapa 2.5 mg N=814 (%)	Dapa 5 mg N=1145 (%)	Dapa 10 mg N=1193 (%)	Dapa Total N=3291 (%)	Placebo N=1393 (%)
TOTAL NUMBER (%) PATIENTS WITH UTI EVENTS	110 (4.7)	81 (3.5)	29 (3.6)	65 (5.7)	51 (4.3)	158 (4.8)	52 (3.7)
FEMALES	85/1003 (8.5)	64/952 (6.7)	23/400 (5.8)	56/581 (9.6)	46/598 (7.7)	137/1648 (8.3)	45/677 (6.6)
MALES	25/1357 (1.8)	17/1343 (1.3)	6/414 (1.4)	9/564 (1.6)	5/595 (0.8)	21/1643 (1.3)	7/716 (1.0)
PREFERRED TERMS*							
URINARY TRACT INFECTION	91 (3.9)	61 (2.7)	25 (3.1)	54 (4.7)	43 (3.6)	131 (4.0)	38 (2.7)
CYSTITIS	16 (0.7)	15 (0.7)	2 (0.2)	7 (0.6)	8 (0.7)	21 (0.6)	11 (0.8)
ESCHERICHIA URINARY TRACT INFECTION	1 (<0.1)	0	0	1 (0.1)	1 (0.1)	2 (0.1)	0
GENITOURINARY TRACT INFECTION	1 (<0.1)	0	0	1 (0.1)	0	1 (<0.1)	0
PYELONEPHRITIS	1 (<0.1)	1 (<0.1)	2 (0.2)	1 (0.1)	0	3 (0.1)	1 (0.1)
TRIGONITIS	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
URETHRITIS	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (0.1)
KIDNEY INFECTION	0	1 (<0.1)	0	0	0	0	0
PROSTATITIS	0	3 (0.1)	1 (0.1)	2 (0.2)	0	3 (0.1)	2 (0.1)

Source: Modified from the Applicant's 30-MU (pages 109-110 of 200, labeled as Tables 38 and 39) and the October 25, 2013 Response to FDA Request for Information.

Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; N, sample size; and UTI, urinary tract infection.

* The Applicant used a customized MedDRA query for urinary tract infection events using a prespecified list of preferred terms, including: bacterial prostatitis, bacterial pyelonephritis, bacteriuria, bladder candidiasis, candiduria, costovertebral angle tenderness, culture urine positive, cystitis, cystitis bacterial, cystitis erosive, cystitis Escherichia, cystitis glandularis, cystitis klebsiella, cystitis pseudomonal, cystitis ulcerative, cystitis-like symptom, dysuria, emphysematous cystitis, emphysematous pyelonephritis, Escherichia urinary tract infection, Escherichia urinary tract infection, fungal cystitis, genitourinary tract infection, kidney infection, leukocyturia, malacoplakia vesicae, nitrite urine present, nitrituria, perinephric abscess, prostatic abscess, prostatitis, prostatovesiculitis, pyelocystitis, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, pyelonephritis fungal, pyelonephritis mycoplasmal, pyonephrosis, pyuria, renal abscess, renal cyst infection, streptococcal urinary tract infection, trigonitis, urachal abscess, urethral abscess, urethral carbuncle, ureter abscess, urethritis, urinary bladder abscess, urinary tract abscess, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, urinary tract infection fungal, urinary tract infection pseudomonal, urinary tract inflammation, urinary tract staphylococcal, urine leukocyte esterase positive, urogenital infection bacterial, urogenital infection fungal, white blood cells urine positive.

Table 23: Events of Urinary Tract Infections (UTI) in Placebo-Controlled Studies (Short-Term plus Long-Term Pool)

Event	30-MU		4MSU				
	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 2.5 mg N=625 (%)	Dapa 5 mg N=767 (%)	Dapa 10 mg N=859 (%)	Dapa Total N=2251 (%)	Placebo N=785 (%)
TOTAL NUMBER (%) PATIENTS WITH UTI EVENTS	174 (8.6)	121 (6.2)	37 (5.9)	64 (8.3)	65 (7.6)	166 (7.4)	49 (6.2)
FEMALES	121/952 (14.2)	86/799 (10.8)	27/313 (8.6)	51/388 (13.1)	52/447 (11.6)	130/1148 (11.3)	40/387 (10.3)
MALES	53/1174 (4.5)	35/1157 (3.0)	10/312 (3.2)	13/379 (3.4)	13/412 (3.2)	36/1103 (3.3)	9/398 (2.3)
PREFERRED TERMS							
URINARY TRACT INFECTION	138 (6.8)	92 (4.7)	30 (4.8)	52 (6.8)	55 (6.4)	137 (6.1)	35 (4.5)
CYSTITIS	21 (1.0)	20 (1.0)	3 (0.5)	9 (1.2)	7 (0.8)	19 (0.8)	12 (1.5)
PROSTATITIS	7 (0.3)	6 (0.3)	2 (0.3)	2 (0.3)	2 (0.2)	6 (0.3)	1 (0.1)
GENITOURINARY TRACT INFECTION	3 (0.1)	2 (0.1)	0	1 (0.1)	0	1 (<0.1)	1 (0.1)
ESCHERICHIA URINARY TRACT INFECTION	2 (0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
PYELONEPHRITIS	1 (<0.1)	2 (0.1)	2 (0.3)	1 (0.1)	0	3 (0.1)	0
PYELONEPHRITIS CHRONIC	1 (<0.1)	0	0	0	0	1 (<0.1)	0
TRIGONITIS	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
URETHRITIS	1 (<0.1)	1 (0.1)	1 (0.2)	0	0	1 (<0.1)	1 (0.1)
URINARY TRACT INFECTION BACTERIAL	1 (<0.1)	0	0	0	0	0	0
KIDNEY INFECTION	0	1 (0.1)	0	0	0	0	0

Source: Modified from the Applicant's 30-Month Update (pages 117-122 of 200, labeled as Tables 43 and 45) and the October 25, 2013 Response to FDA Request for Information.
Abbreviations: 4MSU, 4 Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; N, sample size; and UTI, urinary tract infection.

* The Applicant used a customized MedDRA query for urinary tract infection events using a prespecified list of preferred terms for urinary tract infection events, including: bacterial prostatitis, bacterial pyelonephritis, bacteriuria, bladder candidiasis, candiduria, costovertebral angle tenderness, culture urine positive, cystitis, cystitis bacterial, cystitis erosive, cystitis Escherichia, cystitis glandularis, cystitis klebsiella, cystitis pseudomonal, cystitis ulcerative, cystitis-like symptom, dysuria, emphysematous cystitis, emphysematous pyelonephritis, Escherichia urinary tract infection, Escherichia urinary tract infection, fungal cystitis, genitourinary tract infection, kidney infection, leukocyturia, malacoplakia vesicae, nitrite urine present, nitrituria, perinephric abscess, prostatic abscess, prostatitis, prostatovesiculitis, pyelocystitis, pyelonephritis, pyelonephritis acute, pyelonephritis chronic, pyelonephritis fungal, pyelonephritis mycoplasmal, pyonephrosis, pyuria, renal abscess, renal cyst infection, streptococcal urinary tract infection, trigonitis, urachal abscess, urethral abscess, urethral carbuncle, ureter abscess, urethritis, urinary bladder abscess, urinary tract abscess, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, urinary tract infection fungal, urinary tract infection pseudomonal, urinary tract inflammation, urinary tract staphylococcal, urine leukocyte esterase positive, urogenital infection bacterial, urogenital infection fungal, white blood cells urine positive.

Figure 2. Time to First Urinary Tract Infection Event - Placebo-Controlled Short-Term plus Long-term Pool
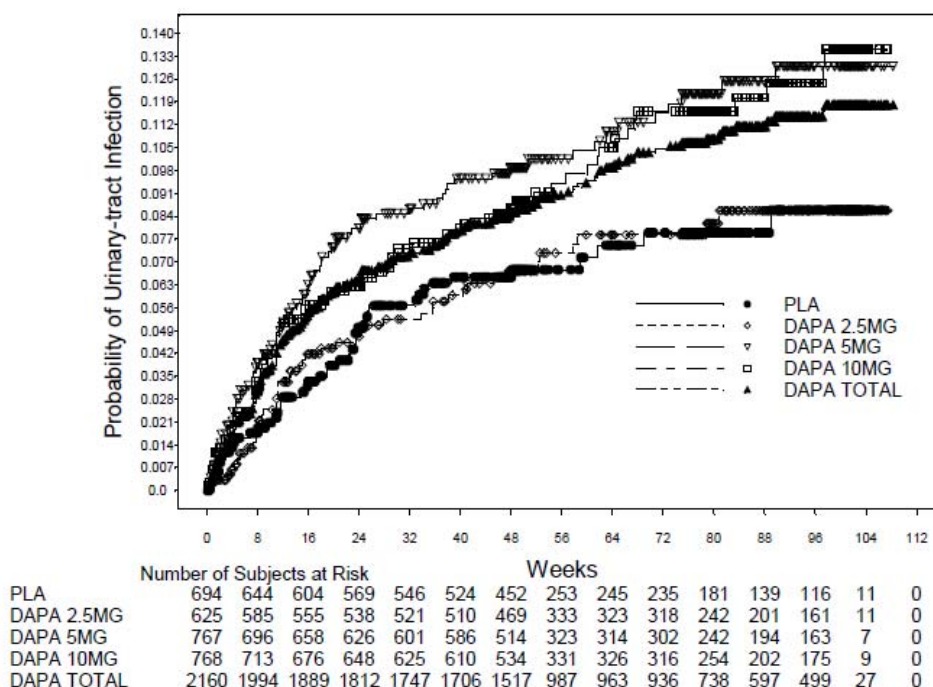
Number of Subjects at Risk														
PLA	694	644	604	569	546	524	452	253	245	235	181	139	116	11	0
DAPA 2.5MG	625	585	555	538	521	510	469	333	323	318	242	201	161	11	0
DAPA 5MG	767	696	658	626	601	586	514	323	314	302	242	194	163	7	0
DAPA 10MG	768	713	676	648	625	610	534	331	326	316	254	202	175	9	0
DAPA TOTAL	2160	1994	1889	1812	1747	1706	1517	987	963	936	738	597	499	27	0

Symbols represent censored observations.
Week is not scheduled visit week but actual days from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.
The results beyond Week 102 should be interpreted with caution as the number of subjects at risk might be limited.

Source Applicant's Summary of Clinical Safety (pages 205 of 435, labeled as Figure 3).

4.4.   Renal Impairment and Volume Depletion Events

__Renal Impairment__

The dapagliflozin clinical development program included 4906 patients with mild renal impairment, defined as an estimated glomerular filtration rate (eGFR) ≥ 60 to <90 mL/min/1.73 m^2, and 1070 patients with a baseline eGFR <60 mL/min/1.73 m^2. Since efficacy is limited with significant renal dysfunction, patients with severe renal impairment, defined as an eGFR <30 mL/min/1.73 m^2 or end stage kidney disease, were

excluded from study participation. The Abbreviated Modification of Diet in Renal Disease Study (MDRD) equation was used throughout the dapagliflozin clinical program to calculate eGFR. For assessing renal safety across the Phase 2b/3 clinical program, the Applicant used a customized MedDRA query for renal impairment/failure events (refer to Table 24 and Table 25). Across the All Phase 2b and 3 Pool (N=9339), there were fourteen SAEs of renal impairment, nine (0.2%) in dapagliflozin-treated patients and five (0.1%) in the all controls arm. Compared to placebo, adverse events of renal impairment/failure were reported more frequently in dapagliflozin treatment arms for both the thirteen-study short-term (3.2% in the dapagliflozin-treated patients vs. 1.8% with placebo) and the nine-study short-term plus long-term (6.7% vs. 4.2%, respectively) placebo-controlled data pools. The numbers and proportions were increased with this NDA resubmission, which the Applicant attributed to inclusion of patients with moderate renal insufficiency.

In a subgroup analyses, patients who were over age 65 or had moderate renal impairment appeared to be at increased risk for renal impairment/failure events, with the highest proportion of events reported in individuals with both of these patient characteristics. The data submitted from the original NDA submission were also reviewed to assess for possible dose-response relationships with renal impairment/failure events, especially in these subpopulations of interest (e.g., >65 years old and/or baseline eGFR <60 mL/min/1.73 m$^{2)}$. Based on review of these data, a dose-response relationship was not apparent.

In the placebo-controlled study pools, the proportions of patients with marked renal function laboratory abnormalities were relatively infrequent for both treatment arms (Table 24 and Table 25).

Additionally, the Applicant evaluated the use of dapagliflozin in a dedicated study (MB102029) that included patients with moderate renal impairment (defined as an eGFR between 30 to <60 mL/min/1.73 m^2). In this clinical trial, dapagliflozin 10 mg daily was associated with a -4.46 mL/min/1.73 m^2 reduction from baseline in mean eGFR compared to. -2.58 mL/min/1.73 m^2 with placebo. Reductions in eGFR occurred by the first week of treatment and persisted throughout the 104-week treatment period. Please see Appendix 1. Clinical Pharmacology Summary for results of longitudinal change in eGFR in two subgroups of moderate renal impairment patients, namely moderate A with eGFR 45-<60 and moderate B with eGFR 30-<45 mL/min/1.73 m^2.

Table 24: Events of Renal Impairment/Failure and Laboratory Abnormalities in Placebo-Controlled Studies (Short-Term Pool)

Event	30-MU		Original NDA				
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)	Dapa 2.5 mg N=814 (%)	Dapa 5 mg N=1145 (%)	Dapa 10 mg N=1193 (%)	Dapa Total N=3291 (%)	Placebo N=1393 (%)
NUMBER (%) OF PATIENTS WITH RENAL IMPAIRMENT/FAILURE EVENTS	76 (3.2)	42 (1.8)	11 (1.4)	15 (1.3)	11 (0.9)	38 (1.2)	12 (0.9)
<65 years old	25/1695 (1.5)	15/1584 (0.9)	5/621 (0.8)	10/929 (1.1)	6/989 (0.6)	22/2660 (0.8)	9/1117 (0.8)
≥65 years old	51/665 (7.7)	27/711 (3.8)	6/193 (3.1)	5/216 (2.3)	5/204 (2.5)	16/631 (2.5)	3/276 (1.1)
eGFR ≥60 mL/min/1.73 m^2	27/2094 (1.3)	17/2025 (0.8)	3/740 (0.4)	8/1038 (0.8)	4/1104 (0.4)	15/3014 (0.5)	6/1286 (0.5)
eGFR 30 to <60 mL/min/1.73 m^2	49/265 (18.5)	25/268 (9.3)	8/74 (10.8)	7/107 (6.5)	7/89 (7.9)	23/277 (8.3)	6/107 (5.6)
<65 years old and eGFR ≥60 mL/min/1.73 m^2	9/1569 (0.6)	6/1462 (0.4)	2/583 (0.3)	6/872 (0.7)	2/940 (0.2)	10/2512 (0.4)	4/1064 (0.4)
≥65 years old and eGFR 30 to <60 mL/min/1.73 m^2	33/139 (23.7)	16/148 (10.8)	5/36 (13.9)	3/50 (6.0)	3/40 (7.5)	11/129 (8.5)	1/54 (1.9)
PREFERRED TERMS*							
CREATININE RENAL CLEARANCE DECREASED	27 (1.1)	16 (0.7)	0	0	1 (0.1)	1 (<0.1)	0
RENAL IMPAIRMENT	20 (0.8)	12 (0.5)	2 (0.2)	2 (0.2)	0	4 (0.1)	1 (0.1)
BLOOD CREATININE INCREASED	15 (0.6)	9 (0.4)	6 (0.7)	6 (0.5)	9 (0.8)	22 (0.7)	7 (0.5)
GLOMERULAR FILTRATION RATE DECREASED	7 (0.3)	3 (0.1)	1 (0.1)	3 (0.3)	1 (0.1)	5 (0.2)	0
RENAL FAILURE	4 (0.2)	2 (0 1)	0	2 (0.2)	0	3 (0.1)	3 (0.2)
RENAL FAILURE ACUTE	3 (0.1)	1 (<0.1)	0	0	0	0	0
CYSTATIN C INCREASED	2 (0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
ACUTE PRERENAL FAILURE	1 (<0.1)	0	0	0	1 (0.1)	0	0
CREATININE RENAL CLEARANCE ABNORMAL	1 (<0.1)	1 (<0.1)	0	0	0	0	0
RENAL FUNCTION TEST ABNORMAL	1 (<0.1)	0	0	1 (0.1)	0	1 (<0.1)	0
URINE FLOW DECREASED	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
URINE OUTPUT DECREASED	0	1 (<0.1)	1 (0.1)	0	0	1 (<0.1)	1 (0.1)
MARKED LABORATORY ABNORMALITIES – RENAL FUNCTION							
BUN >60 mg/dL or Urea >21.4 mmol/L	2 (0.1)	2 (0.1)	0	2 (0.2)	2 (0.2)	4 (0.1)	0
Creatinine ≥1.5X Pre-treatment Creatinine	48 (2.1)	34 (1.5)	11 (1.4)	22 (1.9)	21 (1.8)	56 (1.7)	22 (1.6)
Creatinine ≥2.5 g/dL	2 (0 1)	1 (<0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)

Source: Modified from the Applicant's 30-MU (pages 125-136 of 200, labeled as Tables 46, 47, 49, 50, 51, 52 and 53) and the October 25, 2013 Response to FDA Request for Information.
Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate by MDRD equation; and N, sample size.

* The Applicant used a customized MedDRA query for renal impairment/failure events using a prespecified list of preferred terms, including: acute prerenal failure, anuria, azotemia, blood creatinine, abnormal, blood creatinine abnormal, blood creatinine increased, blood urea nitrogen/creatinine ratio increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, cystatin C abnormal, cystatin C increased, glomerular filtration rate abnormal, glomerular filtration rate decreased, hypertensive nephropathy, insulin renal clearance abnormal, insulin renal clearance decreased, obstructive uropathy, oliguria, pigment nephropathy, postrenal failure, renal cortical necrosis, renal failure, renal failure acute, renal failure chronic, renal function analyses, renal function test abnormal, renal failure and impairment, renal impairment, renal vascular and ischemic conditions, renal vascular and ischemic conditions, nephropathies, and tubular urine flow decreased, and urine output decreased. Note: Patients may be listed more than once for individual preferred terms.

Table 25: Events of Renal Impairment/Failure and Laboratory Abnormalities in Placebo-Controlled Studies (Short-Term plus Long-Term Pool)

Event	30-MU		4MSU				
	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 2.5 mg N=625 (%)	Dapa 5 mg N=767 (%)	Dapa 10 mg N=859 (%)	Dapa Total N=2251 (%)	Placebo N=785 (%)
NUMBER (%) OF PATIENTS WITH RENAL IMPAIRMENT/FAILURE EVENTS	136 (6.7)	82 (4.2)	15 (2.4)	14 (1.8)	16 (1.9)	45 (2.0)	13 (1.7)
<65 years old	49/1406 (3.5)	30/1301 (2.3)	6/472 (1.3)	9/605 (1.5)	10/700 (1.4)	25/1777 (1.4)	9/595 (1.5)
≥65 years old	87/620 (14.0)	52/655 (7.9)	9/153 (5.9)	5/162 (3.1)	6/159 (3.8)	20/474 (4.2)	4/190 (2.1)
eGFR ≥60 mL/min/1.73 m^2	65/1774 (3.7)	42/1705 (2.5)	3/355 (0.8)	7/440 (1.6)	7/467 (1.5)	17/1262 (1.3)	6/442 (1.4)
eGFR 30 to <60 mL/min/1.73 m^2	71/251 (28.3)	40/249 (16.1)	10/72 (13.9)	7/88 (8.0)	9/75 (12.0)	26/235 (11.1)	5/77 (6.5)
<65 years old and eGFR ≥60 mL/min/1.73 m^2	25/1289 (1.9)	17/1191 (1.4)	3/435 (0.7)	5/560 (0.9)	5/660 (0.8)	13/1655 (0.8)	6/559 (1.1)
≥65 years old and eGFR 30 to <60 mL/min/1.73 m^2	47/134 (35.1)	27/141 (19.1)	7/35 (20.0)	3/43 (7.0)	4/35 (11.4)	14/113 (12.4)	2/41 (4.9)
PREFERRED TERMS*							
CREATININE RENAL CLEARANCE DECREASED	46 (2.3)	28 (1.4)	0	0	1 (0.1)	1 (<0.1)	0
RENAL IMPAIRMENT	39 (1.9)	21 (1.1)	2 (0.3)	2 (0.3)	1 (0.1)	5 (0.2)	2 (0.3)
BLOOD CREATININE INCREASED	24 (1.2)	16 (0.8)	8 (1.3)	6 (0.8)	9 (1.0)	23 (1.0)	5 (0.6)
GLOMERULAR FILTRATION RATE DECREASED	11 (0.5)	8 (0.4)	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
RENAL FAILURE	11 (0.5)	7 (0.4)	1 (0.2)	3 (0.4)	2 (0.2)	6 (0.3)	2 (0.3)
RENAL FAILURE ACUTE	4 (0.2)	2 (0.1)	1 (0.1)	1 (0.1)	0	2 (<0.1)	1 (0.1)
CREATININE RENAL CLEARANCE ABNORMAL	3 (0.1)	1 (0.1)	0	0	0	0	0
CYSTATIN C INCREASED	3 (0.1)	0	0	0	0	0	0
URINE FLOW DECREASED	3 (0.1)	0	0	0	3 (0.3)	3 (0.1)	0
GLOMERULAR FILTRATION RATE ABNORMAL	1 (<0.1)	0	0	0	0	0	0
RENAL FAILURE CHRONIC	1 (<0.1)	0	0	0	0	0	0
RENAL FUNCTION TEST ABNORMAL	1 (<0.1)	0	0	1 (0.1)	0	1 (<0.1)	0
URINE OUTPUT DECREASED	1 (<0.1)	1 (0.1)	1 (0.2)	0	1 (0.1)	2 (<0.1)	1 (0.1)
ANURIA	0	1 (0.1)	0	0	0	0	1 (0.1)
MARKED LABORATORY ABNORMALITIES – RENAL FUNCTION							
BUN >60 mg/dL or Urea >21.4 mmol/L	3 (0.1)	4 (0.2)	0	2 (0.3)	2 (0.2)	4 (0.2)	2 (0.3)
Creatinine ≥1.5X Pre-treatment Creatinine	75 (3.8)	61 (3.1)	15 (2.4)	19 (2.5)	17 (2.0)	51 (2.3)	17 (2.2)
Creatinine ≥2.5 g/dL	3 (0.2)	3 (0.2)	0	2 (0.3)	2 (0.2)	4 (0.2)	3 (0.4)

Source: Modified from the Applicant's 30-MU (pages 125-136 of 200, labeled as Tables 46, 47, 49, 50, 51, 52 and 53) and the October 25, 2013 Response to FDA Request for Information.
Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate by MDRD equation; and N, sample size.
* The Applicant used a customized MedDRA query for renal impairment/failure events using a prespecified list of preferred terms, including: acute prerenal failure, anuria, azotemia, blood creatinine, abnormal, blood creatinine abnormal, blood creatinine increased, blood urea nitrogen/creatinine ratio increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, cystatin C abnormal, cystatin C increased, glomerular filtration rate abnormal, glomerular filtration rate decreased, hypertensive nephropathy, insulin renal clearance abnormal, insulin renal clearance decreased, obstructive uropathy, oliguria, pigment nephropathy, postrenal failure, renal cortical necrosis, renal failure, renal failure acute, renal failure chronic, renal function analyses, renal function test abnormal, renal failure and impairment, renal impairment, renal vascular and ischemic conditions, renal vascular and ischemic conditions, nephropathies, and tubular urine flow decreased, and urine output decreased. Note: Patients may be listed more than once for individual preferred terms.

Table 26: Events of Volume Depletion and Polyuria in Placebo-Controlled Studies (Short-Term Pool)

Event	30-MU		Original NDA				
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)	Dapa 2.5 mg N=814 (%)	Dapa 5 mg N=1145 (%)	Dapa 10 mg N=1193 (%)	Dapa Total N=3291 (%)	Placebo N=1393 (%)
NUMBER (%) OF PATIENTS WITH VOLUME DEPLETION EVENTS	27 (1.1)	17 (0.7)	8 (1.0)	7 (0.6)	8 (0.7)	24 (0.7)	5 (0.4)
<65 years old	16/1695 (0.9)	11/1584 (0.7)	3/621 (0.5)	6/929 (0.6)	6/989 (0.6)	16/2660 (0.6)	4/1117 (0.4)
≥65 years old	11/665 (1.7)	6/771(0.8)	5/193 (2.6)	1/216 (0.5)	3/204 (1.5)	8/631 (1.3)	1/276 (0.4)
Not Receiving Loop Diuretics	21/2124 (1.0)	13/2028 (0.6)	5/777 (0.6)	7/1105 (0.6)	6/1162 (0.5)	18/3177 (0.6)	4/1338 (0.3)
Receiving Loop Diuretic	6/236 (2.5)	4/267 (1.5)	3/37 (8.1)	0/40	3/31 (9.7)	6/114 (5.3)	1/55(1.8)
eGFR ≥60 mL/min/1.73 m^2	22/2094 (1.1)	13/2025 (0.6)	6/740 (0.8)	6/1038 (0.6)	8/1104 (0.7)	20/3014 (0.7)	3/1286 (0.2)
eGFR 30 to <60 mL/min/1.73 m^2	5/265 (1.9)	4/268 (1.5)	2/74 (2.7)	1/107 (0.9)	1/89 (1.1)	4/277 (1.4)	2/107 (1.9)
PREFERRED TERMS*							
HYPOTENSION	15 (0.6)	5 (0 2)	6 (0.7)	5 (0.4)	5 (0.4)	16 (0.5)	2 (0.1)
SYNCOPE	6 (0.3)	3 (0.1)	0	0	2 (0.2)	2 (0.1)	1 (0.1)
DEHYDRATION	2 (0.1)	0	0	0	0	0	0
ORTHOSTATIC HYPOTENSION	2 (0.1)	6 (0.3)	1 (0.1)	2 (0.2)	0	4 (0.1)	0
BLOOD PRESSURE DECREASED	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (0.1)
URINE FLOW DECREASED	1 (<0.1)	0	0	0	1 (0.1)	1 (<0.1)	0
CIRCULATORY COLLAPSE	0	1 (<0.1)	0	0	0	0	0
URINE OUTPUT DECREASED	0	1 (<0.1)	1 (0.1)	0	0	1 (<0.1)	1 (0.1)
EVENTS OF POLYURIA**							
NUMBER (%) OF PATIENTS WITH POLYURIA EVENTS	78 (3.3)	27 (1.2)	18 (2.2)	33 (2.9)	45 (3.8)	103 (3.1)	24 (1.7)
POLLAKIURIA	49 (2.1)	16 (0.7)	9 (1.1)	13 (1.1)	26 (2.2)	53 (1.6)	14 (1.0)
POLYURIA	21 (0.9)	5 (0 2)	7 (0.9)	16 (1.4)	14 (1.2)	39 (1.2)	5 (0.4)
URINE OUTPUT INCREASED	11 (0.5)	7 (0.3)	3 (0.4)	5 (0.4)	7 (0.6)	16 (0.5)	6 (0.4)
HEMATOLOGIC CHANGES FROM BASELINE TO END-OF-STUDY							
Hemoglobin (g/dL) Mean ± SD Change from Baseline	0.62 ± 0.82	-0.14 ± 0.74	—	—	—	—	—
Hematocrit (%) Baseline (mean ± SD) Week 24 (mean ± SD) Percent Change (mean ± SE)	42.29 ± 3.99 44.55 ± 4.27 2.30 ± 0.06	42.40 ± 4.00 42.12 ± 4.02 -0.33 ± 0.06	—	—	—	—	—
Number (%) of Patients with Marked Abnormality of Hematocrit (>55%) and/or Hemoglobin (>18 g/dL)	48 (2.0)	13 (0.6)	—	—	—	—	—

Source: Modified from the Applicant's 30-MU (pages 137-147 of 200, labeled as Tables 54, 55, 56, 57, 58, 60 and 61) and the October 25, 2013 Response to FDA Request for Information.

Abbreviations: —, data not reported; 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate by MDRD equation; and N, sample size

The Applicant used a customized MedDRA query for volume depletion events using a prespecified list of preferred terms, including: blood osmolarity increased, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, blood urea nitrogen/creatinine ratio increased, capillary nail refill test abnormal, circulatory collapse, diastolic hypotension, femoral pulse decreased, mean arterial pressure decreased, venous pressure decreased, central venous pressure decreased, circulatory collapse, decreased ventricular preload, dehydration, hypoperfusion, hypotension, hypovolemic shock, left ventricular end-diastolic pressure decreased, orthostatic hypotension, peripheral circulatory failure, pulmonary arterial pressure decreased, pulmonary arterial wedge pressure decreased, pulse volume decreased, radial pulse decreased, shock, syncope, renal ischemia, urine flow decreased, urine output decreased, venous pressure jugular decreased, volume blood decreased. Note: Patients may be listed more than once for individual preferred terms.

**The Applicant used a customized MedDRA query for polyuria events using a prespecified list of preferred terms, pollakiuria, polyuria, urine output increased.

62

Table 27: Events of Events of Volume Depletion and Polyuria in Placebo-Controlled Studies (Short-Term plus Long-Term Pool)

Event	30-MU		4MSU				
	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 2.5 mg N=625 (%)	Dapa 5 mg N=767 (%)	Dapa 10 mg N=859 (%)	Dapa Total N=2251 (%)	Placebo N=785 (%)
NUMBER (%) OF PATIENTS WITH VOLUME DEPLETION EVENTS	38 (1.9)	27 (1.4)	9 (1.4)	8 (1.0)	13 (1.5)	30 (1.3)	6 (0.8)
<65 years old	24/1406 (1.7)	16/1301 (1.2)	4/472 (0.8)	8/605 (1.3)	10/700 (1.4)	22/1777 (1.2)	4/595 (0.7)
≥65 years old	14/620 (2.3)	11/655 (1.7)	5/153 (3.3)	0/162	3/159 (1.9)	8/474 (1.7)	2/190 (1.1)
Not Receiving Loop Diuretics	31/1792 (1.7)	20/1696 (1.2)	7/590 (1.2)	8/731 (1.1)	11/829 (1.3)	26/2150 (1.2)	4/737 (0.5)
Receiving Loop Diuretic	7/234 (3.0)	7/260 (2.7)	3/35 (8.6)	0/36	2/30 (6.7)	5/101 (5.0)	2/48 (4.2)
eGFR ≥60 mL/min/1.73 m^2	30/1774 (1.7)	21/1705 (1.2)	6/553 (1.1)	7/679 (1.0)	10/784 (1.3)	23/2016 (1.1)	3/708 (0.4)
eGFR 30 to <60 mL/min/1.73 m^2	8/251 (3.2)	6/249 (2.4)	3/72 (4.2)	1/88 (1.1)	3/75 (4.0)	7/235 (3.0)	3/77 (3.9)
PREFERRED TERMS*							
HYPOTENSION	18 (0.9)	6 (0.3)	7 (1.1)	4 (0.5)	5 (0.6)	16 (0.7)	1 (0.1)
SYNCOPE	11 (0.5)	10 (0.5)	0	2 (0.3)	4 (0.5)	6 (0.3)	3 (0.4)
ORTHOSTATIC HYPOTENSION	3 (0.1)	7 (0.4)	1 (0.2)	2 (0.3)	0	3 (0.1)	0
URINE FLOW DECREASED	3 (0.1)	0	0	0	3 (0.3)	3 (0.1)	0
BLOOD PRESSURE DECREASED	2 (0.1)	2 (0.1)	0	0	0	0	1 (0.1)
CIRCULATORY COLLAPSE	1 (<0.1)	2 (0.1)	0	0	0	0	0
DEHYDRATION	1 (<0.1)	0	0	0	0	0	0
URINE OUTPUT DECREASED	1 (<0.1)	1 (0.1)	1 (0.2)	0	1 (0.1)	2 (<0.1)	1 (0.1)
EVENTS OF POLYURIA**							
NUMBER (%) OF PATIENTS WITH POLYURIA EVENTS	79 (3.9)	28 (1.4)	17 (2.7)	28 (3.7)	42 (4.9)	87 (3.9)	18 (2.3)
POLLAKIURIA	48 (2.4)	17 (0.9)	9 (1.4)	14 (1.8)	23 (2.7)	46 (2.0)	10 (1.3)
POLYURIA	22 (1.1)	5 (0.3)	8 (1.3)	11 (1.4)	13 (1.5)	32 (1.4)	4 (0.5)
URINE OUTPUT INCREASED	13 (0.6)	7 (0.4)	1 (0.2)	5 (0.7)	9 (1.0)	15 (0.7)	5 (0.6)
HEMATOLOGIC CHANGES FROM BASELINE TO END-OF-STUDY							
Hemoglobin (g/dL) Mean ± SD Change from Baseline	—	—	—	—	—	—	—
Hematocrit (%) Baseline (mean ± SD) Week 102 (mean ± SD) Percent Change (mean ± SE)	42.06 ± 3.97 45.04 ± 4.38 2.68 ± 0.12	42.22 ± 3.96 42.07 ± 4.09 -0.46 ± 0.12	42.39 ± 4.01 43.60 ± 4.18 1.57 ± 0.10	42.31 ± 3.84 44.09 ± 3.92 1.81 ± 0.08	42.51 ± 4.01 44.46 ± 4.10 2.15 ± 0.08	42.40 ± 3.934 44.11 ± 4.068 1.88 ± 0.05	42.54 ± 3.88 42.08 ± 3.86 -0.40 ± 0.07
Number (%) of Patients with Marked Abnormality of Hematocrit (>55%) and/or Hemoglobin (>18 g/dL)	59 (2.9)	16 (0.8)	—	—	—	—	—

Source: Modified from the Applicant's 30-MU (pages 137-143 of 200, labeled as Tables 54, 55, 56, 57, 58 and 60) and the October 25, 2013 Response to FDA Request for Information.

Abbreviations: —, data not reported; 4MSU, 4 Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate by MDRD equation; and N, sample size.

*The Applicant used a customized MedDRA query for volume depletion events using a prespecified list of preferred terms, including: blood osmolarity increased, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, blood urea nitrogen/creatinine ratio increased, capillary nail refill test abnormal, circulatory collapse, diastolic hypotension, femoral pulse decreased, mean arterial pressure decreased, venous pressure decreased, central venous pressure decreased, circulatory collapse, decreased ventricular preload, dehydration, hypoperfusion, hypotension, hypovolemic shock, left ventricular end-diastolic pressure decreased, orthostatic heart rate response increased, orthostatic hypotension, peripheral circulatory failure, pulmonary arterial pressure decreased, pulmonary arterial wedge pressure decreased, pulse volume decreased, radial pulse decreased, shock, syncope, renal ischemia, urine flow decreased, urine output decreased, venous pressure jugular decreased, volume blood decreased. Note: Patients may be listed more than once for individual preferred terms.

**The Applicant used a customized MedDRA query for polyuria events using a prespecified list of preferred terms, pollakiuria, polyuria, urine output increased.

Volume Depletion (hypotension/ hypovolemia/ dehydration)

The Applicant used a customized MedDRA query for volume depletion events (e.g., dehydration, hypotension, hypovolemia) using a prespecified list of preferred terms (refer to Table 26 and Table 27). In the placebo-controlled short-term and short-term plus long-term study pools, volume depletion adverse events were reported in 1.1% vs. 0.7% and 1.9% vs. 1.4% of patients receiving dapagliflozin 10 mg and placebo, respectively. The proportion of patients with events of volume depletion increased in the subpopulations ≥65 years of age, receiving loop diuretics or having moderate renal insufficiency (i.e., eGFR 30 to ≤60 mL/min/1.73 m2). Additionally, SAEs associated with volume depletion were infrequent in both study arms (0.1% and 0.2% in dapagliflozin 10 mg and placebo treatment arms, respectively).

Inspection of the data submitted during the first review cycle did not reveal an apparent dose-response relationship associated with the occurrence of volume depletion events. Based on these data, events related to volume depletion were reported in 0.8% and 0.6% of patients who received dapagliflozin 10 mg and 5 mg, respectively, compared with 0.4% for patients who received placebo in the short-term, placebo-controlled study pool. Of interest, there were no events of volume depletion among 40 patients receiving loop diuretics in the 5 mg dose cohort. However, the number of events occurring in patients >65 years of age, receiving loop diuretics and/or who had a baseline eGFR <60 mL/min/1.73m2 were limited, making any inference regarding dose-response difficult.

Polyuria

Since the mechanism of action of dapagliflozin results in diuresis, adverse events of polyuria were anticipated and occurred more frequently in patients receiving dapagliflozin 10 mg compared to placebo for both the placebo-controlled short-term and short-term plus long-term study pools (Table 26 and Table 27). Hemoglobin and hematocrit changes from baseline were also measured to evaluate the potential for hemoconcentration related to dapagliflozin-induced diuresis, and a possible risk for thromboembolic events. In the placebo-controlled short-term study pool, there were small increases in mean hematocrit concentrations beginning at week 1 (0.55 ±0.05) and continuing up to week 16 (2.32 ± 0.06) in the dapagliflozin-treated patients, when the maximum difference from baseline was observed. The mean change from baseline to week 24 in hemoglobin concentrations was reported as 0.62 ± 0.82 g/dL. The proportions of patients with marked abnormalities in hematocrit and/or hemoglobin were higher in the dapagliflozin-treated patients than in the placebo arms for both the short-term (2% vs. 0.6%, respectively) and short-term plus long-term (2.9% vs. 0.8%, respectively) study pools. During the first review cycle, mean (± SE) hematocrit (1.81 ± 0.08% vs. 2.15 ± 0.08%) and hemoglobin (0.47 ± 0.03 g/dL vs. 0.58 ± 0.03 g/dL) changes from baseline to week 24 were increased with both the 5 and 10 mg dapagliflozin doses, respectively.

4.5. Bone Health

Because dapagliflozin may alter renal tubular transport of several minerals (e.g., calcium, magnesium and phosphorus), cause weight changes and affect metabolism of vitamin D, the Applicant prospectively monitored for changes in biomarkers of bone metabolism and the occurrence of fractures throughout the dapagliflozin clinical program. In their placebo-controlled short-term plus long-term study pool, the proportions of patients with fractures were relatively low, balanced between dapagliflozin (1.1%; 23/2026 patients) and placebo (1.6%; 32/1956 patients) treatment arms, and similar to what was previously observed during the first review cycle. Based on the data from the placebo-controlled short-term study pool, mean changes from baseline to Week 24 in serum calcium (0.04 ± 0.49 mg/dL vs. -0.01 ± 0.52 mg/dL for dapagliflozin 10 mg and placebo treatment arms respectively), parathyroid hormone (4.07 ± 20.91 pg/dL vs. 1.36 ± 17.12 pg/dL, respectively) and 25-hydroxyvitamin D serum (-0.14 ± 9.26 ng/mL vs. -1.14 ± 8.64 ng/mL, respectively) did not appear to be clinically relevant. In Study D1690C00012, a 25-week placebo-controlled clinical trial with a 78-week extension phase, designed to evaluate the effects of dapagliflozin on bone, the Applicant reported no clinically meaningful changes in bone biomarkers or bone mineral density (lumbar spine, femoral neck and total hip) following up to 102 weeks of exposure to dapagliflozin.

In Study MB102029, a 24-week placebo-controlled trial that included 28- and 52-week extension phases, the effects of dapagliflozin (2:1 dapagliflozin to placebo treatment allocation) were evaluated in patients with moderate renal impairment. In this clinical trial, an apparent imbalance in fracture events (i.e., thirteen patients treated with dapagliflozin [5 in the 5 mg dose cohort and 8 in the 10 mg cohort] versus 0 patients with placebo) was observed over the 104-week treatment period. Eight of these thirteen fractures were in patients who had an eGFR of 30 to 45 mL/min/1.73 m2, and eleven of the thirteen fractures were reported within the first 52 weeks. The Applicant did not identify a pattern with respect to the site of fracture or predisposition due to hypoglycemia or hypotension. However, for seven of the thirteen patients who sustained a fracture, orthostatic hypotension or a history of diabetic neuropathy was also present. Further, the Applicant noted that two patients with fracture reported a fall or coincident trauma. There were small increases in mean serum parathyroid hormone (PTH) concentration without apparent relationship to dose. Markers of bone metabolism (urinary C-telopeptide and deoxypyridinolone excretions, and serum osteocalcin concentration) all increased compared to baseline in patients treated with dapagliflozin. The mean PTH concentrations in all treatment arms (i.e., dapagliflozin 5 and 10 mg and placebo) exceeded the upper laboratory reference limit at baseline. There were also mean increases in the concentrations of serum phosphorus and magnesium in patients receiving dapagliflozin, which remained within laboratory reference limits, and did not lead to discontinuations from study due to hyperphosphatemia or hypermagnesemia. However, one patient receiving dapagliflozin 10 mg had a wrist fracture during a period of marked elevations in inorganic phosphorus.

During the first review cycle, Dr. Marcea Whitaker from the Division of Reproductive and Urologic Products reviewed the data for 10 of the 13 fracture events, as well as the effects of dapagliflozin on bone health for the entire clinical development program. At that time, it was felt

that there was no indication that dapagliflozin exerts a clinically significant effect on bone (either bone loss or increased fracture risk) based on the bone safety data reviewed. Additionally, the imbalance in fracture events that occurred in Study MB102029 was not observed when all patients with moderate renal dysfunction in the Phase 2b and 3 clinical program were pooled during the first review cycle.

The occurrence of bone fractures continues to be followed as an adverse event of special interest in the Applicant's CV outcomes trial (i.e., Dapagliflozin Effect on Cardiovascular Events [DECLARE; TIMI-58; Study D1693C00001]).

SECTION 5. CONCLUSIONS

Dapagliflozin is a new molecular entity in the antidiabetic class known as SGLT2 inhibitors. Through selective and reversible inhibition of SGLT2, dapagliflozin causes renal elimination of glucose. The magnitude of HbA1c reduction observed in the dapagliflozin clinical program is relatively consistent across trials and similar to that of other recently approved antidiabetic drugs, including the SGLT2 inhibitor, canagliflozin. In addition to improvement in glycemic control, dapagliflozin produces modest reductions in body weight and systolic blood pressure. Consistent with the results of previous meta-analyses, the updated meta-analysis of major cardiovascular events in the pool of 21 Phase 2b and Phase 3 clinical trials included in this NDA resubmission continues to meet the December 2008 Guidance, ruling out the unacceptable increase in CV risk of greater than 80% above comparator groups. Furthermore, divergence in the Kaplan-Meier curves, in favor of dapagliflozin, were observed for the primary CV composite endpoint after approximately eight months, suggesting potential benefit with prolonged use. However, there appears to be a numeric imbalance in early MACE events not favoring dapagliflozin. A similar observation of an early imbalance in cardiovascular events was seen with canagliflozin, also not favoring canagliflozin. For dapagliflozin, discordant with the results of the updated meta-analysis, a pool of two large, well-designed clinical trials enriched with individuals at high risks for CV events—and in whom statistically significant reductions in HbA1c, systolic blood pressure, and body weight were observed—achieved a point estimate and upper bound 95% confidence interval for the hazard ratio of the composite MACE endpoint which exceeded 1 and 1.8, respectively.

When considering efficacy of dapagliflozin, potential benefits should be balanced against credible safety concerns identified during clinical development. There continues to be a numeric imbalance in cases of bladder cancer, not favoring dapagliflozin. An imbalance in bladder cancer events was not seen with canagliflozin. Additionally, a potential case of drug-induced liver injury was observed during the first review cycle for which an association with dapagliflozin remains plausible. The Applicant has provided more than three years of follow-up data for this case to support a possible reclassification of the diagnosis. Overall, the occurrence of marked liver laboratory test abnormalities remains relatively balanced between dapagliflozin and the comparator treatment arms.

Similar to canagliflozin, dapagliflozin is associated with adverse events of genital and urinary tract infections, and increased events related to volume depletion and renal impairment. Long-term effects from increased urinary tract and genital infections are unknown, and the risks related to hypovolemia, dehydration, and renal impairment—especially in elderly patients with renal dysfunction and individuals receiving loop diuretics—warrant caution. Additionally, the efficacy of dapagliflozin is limited to patients with normal kidney function or only mild renal insufficiency, and the Applicant recommends that the drug not be used in individuals with moderate or severe renal impairment, which are not uncommon in patients with long-standing type 2 diabetes mellitus. Other safety concerns associated with SGLT2 inhibitors, including dapagliflozin, are the potential to increase low-density lipoprotein-cholesterol, and the unknown risk for fractures with long-term use in vulnerable patient populations. Further, as noted during the previous review cycle, there remains a numeric imbalance of breast cancer cases which favor

the comparator arm. Due to a decline in the incidence risk ratio since the last review, 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 several patients, this imbalance in cancer events may be a spurious finding.

REFERENCES

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2. Hou N, Huo D. A trend analysis of breast cancer incidence rates in the United States from 2000 to 2009 shows a recent increase. Breast Cancer Res Treat 2013;138:633-41.

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APPENDICES

Appendix 1. Clinical Pharmacology Summary

Appendix 1: Clinical Pharmacology Summary

Pharmacokinetic Characteristics:

The pharmacokinetics (PK) of dapagliflozin have been characterized in healthy subjects and T2DM patients, and in relevant specific populations. Following oral administration the absolute bioavailability of dapagliflozin is 78%, and a dose-proportional increase in systemic exposure across a broad range of doses (0.1 to 500 mg) is observed. After oral administration, maximum plasma concentrations (C_{max}) are observed within two hours (h) after administration. The elimination half-life ($t_{1/2}$) of dapagliflozin is around 12 h. Dapagliflozin 3-O-glucuronide (BMS 801576) is the primary metabolite characterized in humans, which accounts for 61% of the dapagliflozin dose. *In-vitro* studies suggest that UGT1A9 is the major enzyme responsible for the formation of dapagliflozin 3-O-glucuronide. In a mass balance study, 96% of the administered dose was recovered in the urine (~75%) and feces (~21%). In urine, 1.2% of the radiolabeled dose was recovered as parent drug and 61% as dapagliflozin-3-O-glucuronide. In feces, 15.4% of the radioactivity was recovered as parent drug. There were no clinically meaningful drug-drug interactions observed with several concomitant medications used by T2DM patients, such as metformin, sitagliptin, digoxin, simvastatin, and warfarin. No drug-drug interactions were observed with drugs that may affect the metabolic pathway of dapagliflozin (e.g., mefenamic acid and rifampin). Drug-drug interaction studies demonstrated that dapagliflozin has little potential either to affect metabolism or to have its metabolism meaningfully affected by co-administration of other drugs. The mean exposure to dapagliflozin in subjects with moderate and severe hepatic impairment was 36 % and 67% higher, respectively, than that of healthy subjects.

Rationale for Phase 3 Dose Selection:

In their Phase 3 clinical program, the Applicant studied doses ranging from 1 mg to 10 mg. The selection of doses was supported by a Phase 2b monotherapy dose-ranging trial, MB102008, in which doses ranging from 2.5 mg to 50 mg were evaluated. In this trial, dose-related changes from baseline in HbA1c, fasting plasma glucose (FPG) and urinary glucose were observed (Figure 1). However, there was no significant improvement in HbA1c levels beyond those observed in the 10 mg dose group. At week 12, the mean change from baseline in HbA1c was -0.85, -0.55 and -0.9 for the 10, 20 and 50 mg dose groups, respectively. Adverse events of genitourinary infections were more common in the 20 mg and 50 mg dapagliflozin groups than in the lower dose groups. There were also increases in the proportion of subjects with a marked laboratory abnormality of hyperphosphatemia, and the mean hematocrit concentrations were increased, in patients assigned to the 20 mg and 50 mg dapagliflozin groups.

Phase 2B – MB102008
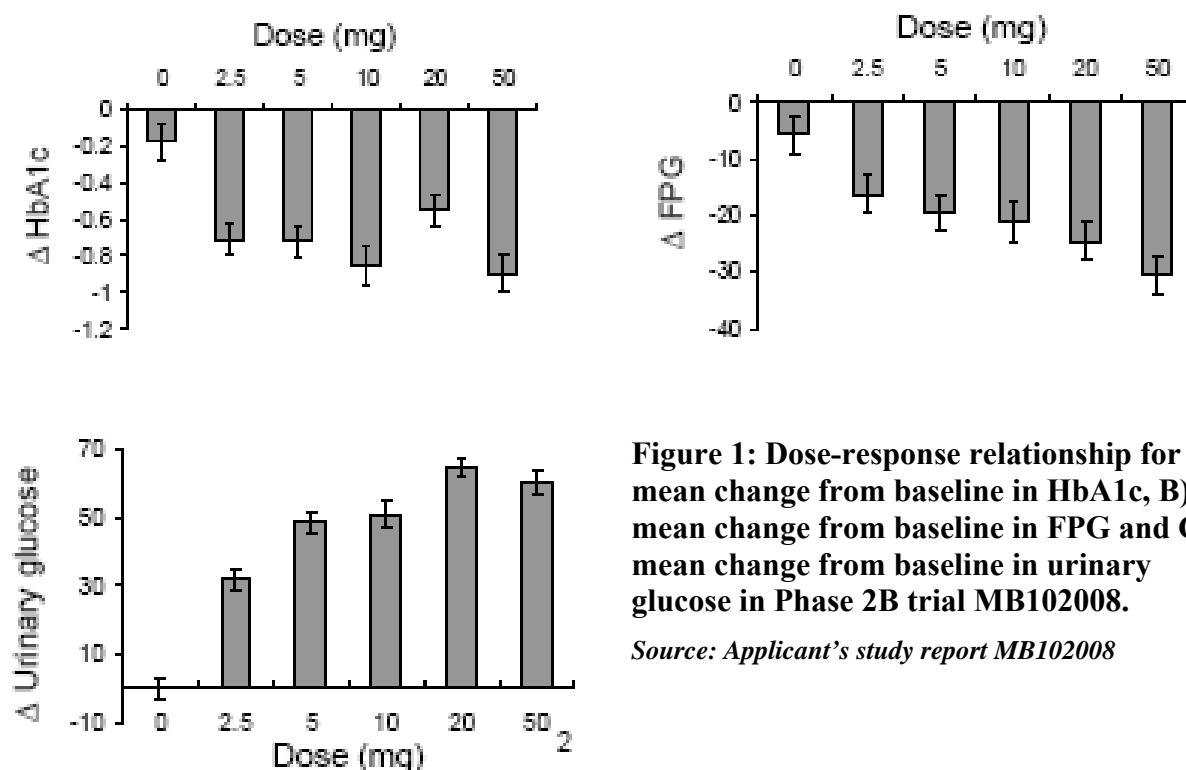
Figure 1: Dose-response relationship for A) mean change from baseline in HbA1c, B) mean change from baseline in FPG and C) mean change from baseline in urinary glucose in Phase 2B trial MB102008.

Source: Applicant's study report MB102008

Dosing in Patients with Renal Impairment:

The Applicant is proposing that dapagliflozin not be used in patients with an eGFR <60 mL/min/1.73 m^2. The results from a PK/PD study in patients with mild, moderate, and severe renal impairment and a dedicated efficacy and safety trial in patients with moderate renal impairment are discussed below.

- **PK/PD in Patients with Renal Impairment:** A single- and multiple-dose PK/PD study was conducted in patients with T2DM and normal, mild, moderate, and severe renal impairment. Following multiple doses of dapagliflozin (20 mg), T2DM patients with mild, moderate, and severe renal impairment had higher exposure compared to those with normal renal function (Figure 2). Since the efficacy of the drug is dependent on renal function, higher systemic exposures of dapagliflozin in patients with moderate and severe renal impairment did not result in a correspondingly higher cumulative amount of glucose excretion (Figure 2).

Figure 2: Effect of Renal Impairment on PK and PD of Dapagliflozin (N=3 For healthy, N=3 for mild, N=6 moderate, N=5 for severe).

PK
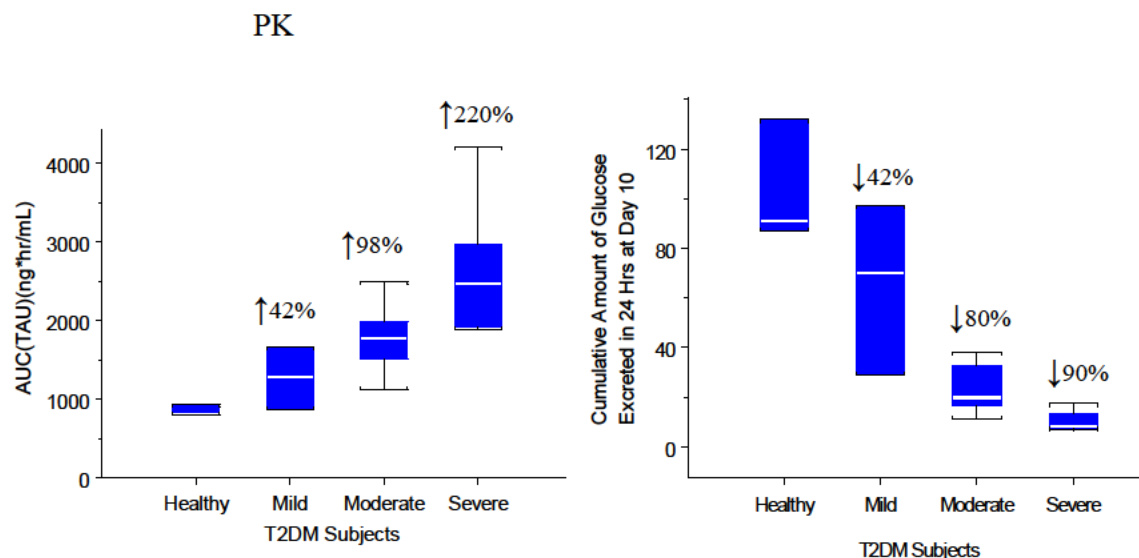
Note: Result's following Reviewer's reanalysis of data from trial MB102007.

- **Mild Renal Impairment (eGFR 60-<90 mL/min/1.73 m^2)**
  Patients with both normal renal function and mild renal impairment were included in most of the pivotal Phase 3 clinical trials. Please refer to the description of efficacy and safety from Phase 3 trials in the main text for discussion on benefits and risks of using dapagliflozin in these patients.

- **Moderate Renal Impairment (eGFR 30-<60 mL/min/1.73 m^2)**
  Efficacy:
  The Applicant evaluated the efficacy of dapagliflozin in a dedicated study (MB102029) that included patients with moderate renal impairment (defined as an eGFR between 30 to <60 mL/min/1.73m^2). This dedicated study in renally impaired subjects was a multicenter, double-blind, placebo-controlled, parallel group, randomized, Phase 2/3 trial to evaluate the glycemic efficacy and renal safety in patients with moderate renal function. Table 1 shows the results for the primary endpoint, change from baseline in HbA1c at Week 24. Both the 5 mg and 10 mg dapagliflozin doses were not superior to placebo, and the observed treatment effects were negligible.

  The Applicant also conducted an "ad-hoc" subgroup analysis in patients with stage 3A moderate renal impairment defined as an eGFR of 45 to 59 ml/min/1.73 m^2, and 3B which was defined as a group with an eGFR of 30 to 44 ml/min/1.73 m^2. The results of the subgroup analysis showed that neither arm was significantly different from placebo (Table 2 and Table 3). Therefore, given the lack of benefit compared to placebo in

73

patients with moderate renal impairment, the Applicant is proposing that dapagliflozin not be used in patients with an eGFR <60 mL/min/1.73 m^2.

Table 1: Results for Primary Endpoint, Study 2029
(Source: Clinical Study Report, Table 7.1)

```
-------------------------------------------------------------------------------------
EFFICACY ENDPOINT                                      Placebo     DAPA 5MG    DAPA 10MG
  STATISTICS                                           N=84        N=83        N=85
-------------------------------------------------------------------------------------

PRIMARY EFFICACY ENDPOINT

HBA1C (%) AT WEEK 24 (LOCF)


  N#                                                   82          83          82
  BASELINE MEAN (SD)                                   8.53 (1.285) 8.30 (1.040) 8.22 (0.973)
  WEEK 24 LOCF MEAN (SD)                               8.18 (1.204) 7.97 (1.150) 7.90 (0.930)
  MEAN CHANGE FROM BASELINE (SD)                       -0.35 (1.260) -0.33 (0.997) -0.32 (0.856)
  ADJ. MEAN CHANGE FROM BSL. (SE)                      -0.32 (0.1701) -0.41 (0.1701) -0.44 (0.1708)
  95% CI FOR ADJ. MEAN CHANGE FROM BSL.                (-0.66, 0.01) (-0.74, -0.07) (-0.77, -0.10)
  DIFFERENCE FROM PLACEBO (SE)                                      -0.08 (0.1448) -0.11 (0.1457)
  95% CI FOR DIFFERENCE FROM PLACEBO                               (-0.37, 0.20) (-0.40, 0.17)
  P-VALUE VS. PLACEBO (*)                                          0.561       0.435

-------------------------------------------------------------------------------------
N is the number of randomized subjects who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with non-missing baseline and Week t (LOCF) values.
(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested
following a sequential testing procedure at alpha=0.05.
Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a
covariate.
```
mean change from baseline at Week 24 (LOCF) in HbA1c was -0.11 (-0.57, 0.35), -0.47 (-0.97, 0.02), and -0.44 (-0.94, 0.07) for placebo, and 5 mg and 10 mg dapagliflozin dose groups, respectively (Table 2).

Table 2: Results for Primary Endpoint in Subjects with Stage 3A Chronic Kidney Disease at Baseline , Study 2029
(Source: Clinical Study Report, Appendix 38)

```
-------------------------------------------------------------------------------------
                                               PLACEBO     DAPA 5MG    DAPA 10MG
                                               N=41        N=35        N=33
-------------------------------------------------------------------------------------

SUMMARY STATISTICS

N#                                             40          35          32
BASELINE MEAN (SD)                             8.78 (1.318) 8.13 (0.928) 8.25 (0.892)
WEEK 24   MEAN (SD)                            8.62 (1.201) 7.93 (1.086) 8.03 (1.002)
MEAN CHANGE FROM BSL (SD)                      -0.16 (1.374) -0.20 (0.941) -0.22 (0.797)

ADJUSTED CHANGE FROM BASELINE

MEAN (SE)                                      -0.11 (0.2339) -0.47 (0.2483) -0.44 (0.2546)
95% 2-SIDED CI                                 [-0.57, 0.35] [-0.97, 0.02] [-0.94, 0.07]

DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS PLACEBO

MEAN (SE)                                                    -0.37 (0.2322) -0.33 (0.2376)
95% 2-SIDED CI                                               [-0.83, 0.10] [-0.80, 0.14]


-------------------------------------------------------------------------------------
N is the number of randomized subjects with baseline eGFR= 45 and <60 mL/min/1.73m^2
who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with baseline eGFR= 45 and <60 mL/min/1.73m^2
and non-missing baseline and Week 24 (LOCF) HbA1c values.
Based on an ANCOVA model with treatment group and stratum as main effects and baseline value as a covariate.
Program Source: /gbs/test/clin/programs/mb/102/029/a0050/rpt/rt-lb-ancovabygfr-v01.sas          08SEP2010:12:09:11
```

For patients with baseline eGFR values included in substratum 3B, the adjusted mean change from baseline at Week 24 (LOCF) in HbA1c was -0.52 (-1.08, 0.03), -0.47 (-1.01, 0.06), and -0.45 (-0.96, 0.05) for placebo, and 5 mg, and 10 mg dapagliflozin dose groups, respectively (Table 3).

Table 3: Results for Primary Endpoint in Subjects with Stage 3B Chronic Kidney Disease at Baseline , Study 2029
(Source: Clinical Study Report, Appendix 39)

```
                                              PLACEBO         DAPA 5MG         DAPA 10MG
                                               N=34            N=41             N=47
--------------------------------------------------------------------------------------------
SUMMARY STATISTICS

N#                                               33              41               45
BASELINE MEAN (SD)                         8.23 ( 1.197)   8.49 ( 1.157)    8.12 ( 1.001)
WEEK 24  MEAN (SD)                         7.79 ( 1.149)   7.97 ( 1.250)    7.78 ( 0.864)
MEAN CHANGE FROM BSL (SD)                 -0.44 ( 1.034)  -0.52 ( 1.069)   -0.34 ( 0.931)

ADJUSTED CHANGE FROM BASELINE

MEAN (SE)                                 -0.52 ( 0.2804) -0.47 ( 0.2712)  -0.45 ( 0.2545)
95% 2-SIDED CI                            [ -1.08,  0.03] [ -1.01,  0.06]  [ -0.96,  0.05]

DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS PLACEBO

MEAN (SE)                                                  0.05 ( 0.2107)   0.07 ( 0.2074)
95% 2-SIDED CI                                            [ -0.37,  0.47]  [ -0.34,  0.48]
--------------------------------------------------------------------------------------------

N is the number of randomized subjects with baseline eGFR>= 30 and <45 mL/min/1.73m^2
who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with baseline eGFR>= 30 and <45 mL/min/1.73m^2
and non-missing baseline and Week 24 (LOCF) HbAlc values.
Based on an ANCOVA model with treatment group and stratum as main effects  and baseline value as a covariate.
Program Source: /gbs/test/clin/programs/mb/102/029/a0050/rpt/rt-lb-ancovabygfr-v01.sas        08SEP2010:12:09:11
```

Safety:

The longitudinal change in eGFR in patients with moderate renal impairment (subgroups 3A and 3B) taking dapagliflozin is shown in Figure 3. The maximum mean reduction in subgroup 3A was 8.87 mL/min/1.73 m^2 and for subgroup 3B was 3.82 mL/min/1.73m^2. Other safety findings for patients with moderate renal impairment are discussed in the main text.

Stage 3A Moderate Renal Impairment	Stage 3B Moderate Renal Impairment

Figure 3: Mean Change from Baseline in Renal Function (eGFR mL/min/1.73m2) with Time (Weeks)
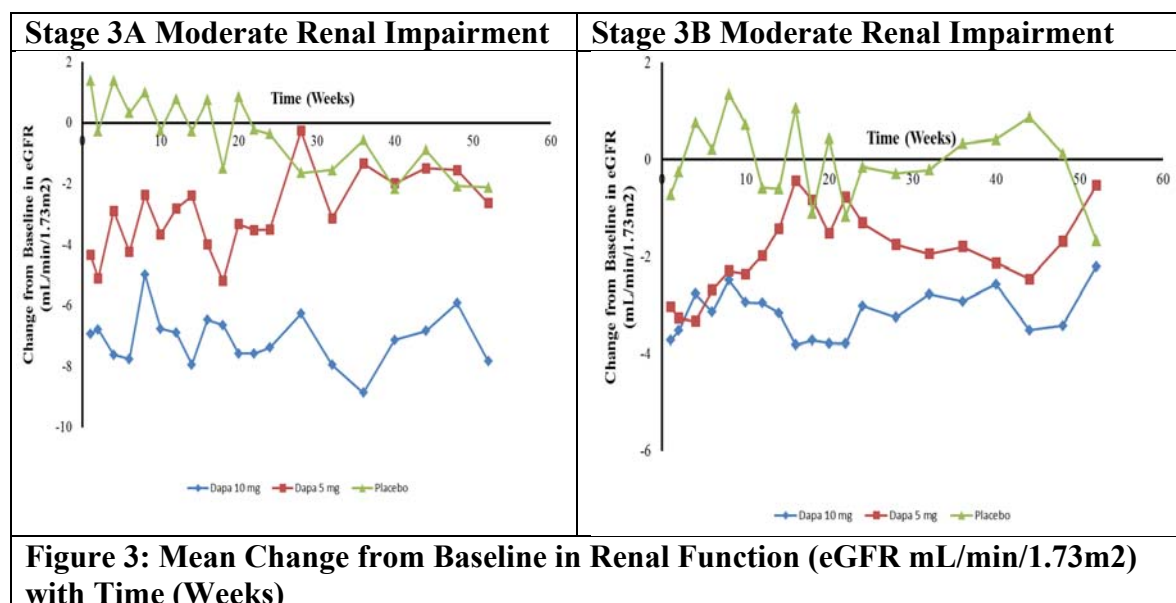
- **Severe Renal Impairment (eGFR <30 mL/min/1.73 m^2)**
  Patients with severe renal impairment were excluded from study participation because the efficacy was expected to be limited with significant renal dysfunction in these patients.

Appendix 2. Bladder Cancer Narratives

(Reproduced from the Applicant's October 20, 2011, Individual Subject Narratives: Events of Bladder Neoplasms)

Please note that these narratives are reproduced verbatim from the Applicant's submissions. They contain many spelling and abbreviation variants, reflective of varying usage across a multinational program.

1   NARRATIVES FOR BLADDER NEOPLASMS

1.1   Malignant and unspecified neoplasms

1.1.1   D1692C00005-1-11

Patient: D1692C00005-1-11 (75 YEARS/MALE/ASIAN) (Japan)
Study Treatment: DAPA 2.5 MG **Date of First Dose:** ▨ (b) (6) (DAY 1)
Event: BLADDER CANCER (Bladder cancer, Moderate, Not related, Day 43)

Relevant Adverse Events during Study: OCCULT BLOOD POSITIVE (occult blood positive, DAY 36)

Disease History: TYPE 2 DIABETES MELLITUS (07AUG2006)

General Medical History: CARDIOVASCULAR (hypertension), ENDOCRINE-METABOLIC (Type2 Diabetes Mellitus, carotid atherosclerosis, hyperlipidemia), DERMATOLOGIC (herpes zoster), OTHER (keratitis), Smoking:FORMER: CIGARETTES 20/DAYS 50YEARS, Alcohol use:1-2 DRINKS WEEKLY

Concomitant Medication(s): BLOPRESS (CANDESARTAN, DAY -89 to -1), BAYASPIRIN (ACETYLSALICYLIC ACID, DAY -89 to 43), HAOPLA (PRANOPROFEN, DAY -89 to 184), XYLOCAINE (LIDOCAINE, DAY 43 to 43), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 43 to 43), AMARYL (GLIMEPIRIDE, DAY 48 to 184), ATOLANT (NETICONAZOLE, DAY -44 to 184), MYSER (DIFLUPREDNATE, DAY -44 to - 30), ACHROMYCIN (TETRACYCLINE, DAY -44 to -30), ALEROFF (EPINASTINA, DAY - 44 to -30), RINDERON VG (BETATP/GENTOP, DAY 51 to 51), ATARAX P (HYDROXYZINE, DAY 51 to 51), HYPO ETHANOL (SODIUM THIOSULFATE, DAY 51 to 51), VEEN F (ACETATED RINGER S SOLUTION) (ELECTROLYTE SOLUTION, DAY 51 to 51), ACTIT (MALTOSE,SODIUM CHLORIDE,POTASSIUM CHLORIDE,MAGNESIUM CHLORIDE,POTASSIUM DIHYDROGEN PHOSPHATE,SODIUM ACETATE) (ELECTROLYTE SOLUTION, DAY 51 to 54), ADRIACIN (DOXORUBICIN, DAY 51 to 51), UROMATIC S (D SORBITOL) (SORBITOL, DAY 51 to 51), ATROPINE SULFATE (ATROPINE, DAY 51 to 51), RASENAZOLIN (CEFAZOLIN, DAY 51 to 54), ISODINE (POVIDONE IODINE, DAY 51 to 51), XYLOCAINE (LIDOCAINE, DAY 51 to 51), XYLOCAINE (LIDOCAINE, DAY 51 to 51), XYLOCAINE (LIDOCAINE, DAY 51 to 51), LACTEC G (LYTESO/SORBTL, DAY 51 to 51), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 51 to 51), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 51 to 54), MARCAIN (BUPIVACAINE, DAY 51 to 51), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 51 to 51), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 52 to 52), LACTEC G (LYTESO/SORBTL, DAY 52 to 54), ISOTONIC SODIUM CHLORIDE SOLUTION (SODIUM CHLORIDE, DAY 53 to 53), BAYASPIRIN (ACETYLSALICYLIC ACID, DAY 55 to 184), KEFRAL (CEFACLOR, DAY 55 to 76), MYSLEE (ZOLPIDEM, DAY 56 to 56), BLOPRESS (CANDESARTAN, DAY 2 to 184)

Clinical Summary:
Hospitalised:'
Action taken, investigational product: DRUG WAS DISCONTINUED'
AE outcome: DID NOT RESOLVE'
Treatment required: YES'

On Day 43, the patient was diagnosed with bladder cancer and study therapy was stopped. In response to' the event, the patient withdrew from study and was scheduled to be hospitalized on Day 50 to undergo' transurethral resection of the bladder on Day 51.'

On the first study visit (Day -79), the patient s urine was noted to be positive for occult blood (2+). On Day -27, the patient's hemoglobin level was 15.4 g/dL (reference range 13.5-17.6). The patient initiated study therapy on Day 1. On Day 6, the patient's urine revealed 3+ for occult blood and hemoglobin was 15.5 g/dL. On Day 29, four weeks after the start of study therapy, the patient complained of anorexia. al occult blood reported positive results. Since the patient's urine for occult blood (2+) continued, endoscopy and urine cytology were conducted. Papillary and broad base elevated lesion from the neck to the trigone of the bladder was noted and bladder cancer was diagnosed. Urinary cytology results revealed Class IV, malignant cells. Glimepiride (1 mg daily) was initiated. On Day 50, the patient was hospitalized to undergo transurethral resection of the bladder tumor, which was performed on Day 51. On Day 52, blood urine persisted and continuous bladder irrigation was performed. On Day 53, blood urine was no longer observed and bladder irrigation was stopped. The Foley catheter was removed on Day 54 and an abdominal computed tomography (CT) revealed negative results for metastasis. The patient resumed aspirin therapy 1 mg/Day and initiated cefaclor 750 mg x 3 per Day on Day 55. On Day 56, microscopical examination revealed prostate infiltration and deep invasion.

Per the investigator, the event potentially existed prior to participation in the study, since the patient s urine was noted to be positive for occult blood on Day -79 (prior to the start of study drug) and bladder cancer was diagnosed on Day 43. Therefore, no causal relationship with the study medication was considered. It was reported that bladder cancer will be followed-up closely and fecal occult blood would be further investigated. Since the complete recovery is hardly expected, further follow-up activity was not performed in this study. The patient will be followed up in the usual care.

Treatment for bladder cancer included parenteral bupivacaine hcl (Day 51), parenteral electrolyte+d sorbitol (Day 52 – Day 54), povidone iodine (Day 51) and oral xolpiden tartrate (Day 56). The event remained unresolved.

Additional follow-up information, received via standardized questionnaire, states that the subject is a former smoker . There were no other reported risk factors known to be associated with bladder cancer.

Anatomical location: Bladder neck
Growth pattern: G2
Histological type: G2, moderately differentiated
TNM classification: T2N0MX
Grade/Stages: G2

The bladder cancer was a new diagnosis. The event was diagnosed after reports of hematuria. Urinary symptoms of decreased stream preceded the event.

The event was treated with surgery, transurethral resection and a total cystectomy and ileal conduit operation. The subject also received medical treatment. The patient is currently treated for lung metastasis.

1.1.2   D1690C00006-1004-6

Patient: D1690C00006-1004-6 (63 years/male/white) (Austria)
Study Treatment: DAPA 5MG + INS   **Date of First Dose:** [redacted] (b) (6)(DAY 1)
Event: Bladder cancer (Carcinoma of the bladder, Moderate, Not related, Day 393 - 399)

Relevant Adverse Events during Study: BENIGN PROSTATIC HYPERPLASIA (benign prostate hyperplasia, Day 136 – C); BLADDER NEOPLASM (suspicious tumor of bladder, Day 358 - C)

Disease History: TYPE 2 DIABETES MELLITUS (01APR1990); MICROALBUMINURIA (01JAN1997); DIABETIC NEUROPATHY (01JAN2000); HYPERTENSION (01JAN1970); CAROTID ARTERY DISEASE (01JAN2002); DYSLIPIDEMIA (01APR1990); NOCTURIA (01JAN2003)

General Medical History: Cataract surgery 1996 right, 1999 left; carotide plaques, hypertension; mild chronic obstructive pulmonary disease; acute pancreatitis 2002; microalbuminuria, nocturia; diabetes mellitus type 2, dyslipidemia; peripheral neuropathy; Allergies: sundermatitis. Smoking: CURRENT; CIGARETTES 40 PER DAY for 50 YEARS. Alcohol use: 1-2 DRINKS WEEKLY.

Concomitant Medications: ACETYLSALICYLIC ACID (Day ≥-90 - C); SIMVASTATIN (Day ≥-90 - C); HYDROCHLOROTHIAZIDE (Day -15 - C); LOSARTAN (Day -15 - C); OMEPRAZOLE (Day 188 - 190); TAMSULOSIN (Day 359 - C)

Background Medications: INSULIN (Day -768 - C); METFORMIN (Day ≥-60 - 350)

Clinical Summary: A suspicious tumor of bladder was diagnosed on Day 358. The patient reported no symptoms. The patient was hospitalised on Day 393. A cystoscopy showed an urothelial carcinoma pTa G2, noninvasive. The treatment of the multicentric urothelial carcinoma consist of transurethral resection. The patient was discharged in recovered condition with sequel on Day 399. No action was taken to study medication in response to the event.

Blood in urine (dipstick) was negative at measurements before/at randomisation (central lab data), but microscopic hematuria since Day ~165 according to follow-up information in questionnaire.

Additional follow-up information received via standardized questionnaire states that the subject is a current smoker with no other reported risk factors known to be associated with bladder cancer.

Anatomical location: Bladder
Growth pattern: unknown
Histological type: G2
TNM classification: pTa
Grade/Stages: unknown

The transitional cell carcinoma was a new diagnosis with no precipitating factor. The subject had microscopic hematuria since March 2009 (~Day 165) and this led to further urological investigations by which the bladder cancer was discovered.

The event was treated with surgery, transurethral resection, and at the time of follow-up there was no recurrence.

1.1.3   MB102014-34-524

Patient: MB102014-34-524 (60 YEARS/MALE/WHITE) (Canada)
Study Treatment: DAPA 5MG + MET   **Date of First Dose:** ▒▒▒ (b) (6) (DAY 1)
Event: BLADDER TRANSITIONAL CELL CARCINOMA (LOW GRADE NON-INVASIVE
PAPILARY UROTHELIAL CARCINOMA BLADDER, MILD, POSSIBLE RELATIONSHIP, DAY 512)

Relevant Adverse Events during Study: CALCULUS URETERIC (SEVERE, NOT RELATED
RELATIONSHIP, DAY 509)

Disease History: TYPE 2 DIABETES MELLITUS (2006); DIABETIC NEUROPATHY (SEP2007)
Medical History: ODEMA LOWER LEGS FOR SEVERAL YEARS WORSE IN MORNINGS;
ARTHRITIS HIPS AND SHOULDERS.LEG CRAMPS (ONSET DATE 06 MAR 2008); DEPRESSION
SINCE 2004 ON ANTIDEPRESSANT MEDS; FEET FEEL COLD FOR SEVERAL YEARS PATIENT
SUSPECTS PERIFHERAL VASCULAR DISEASE; FORMER SMOKER. STOPPED IN 1989; HEAD
INJURY ON MVA 1978 EXCELLENT RECOVERY; MENIERES SINCE 1980 DAILY TINNITAS
AND MILD VERTIGO.BURNING SENZATION TONGUE (ONSET DATE 06 MAR 2008);
TINEACRURA SECONDARY TO OBESITY AND DIABETES; TYPE 2 DIABETES 2006 OBESITY
SINCE 1959 ABDOMINOPLASTY 1999

Concomitant Medication(s): ROSUVASTATIN (DAY -1918 - C); CELECOXIB (DAY -1187 - 122);
METFORMIN (DAY -457 - -16); TRAZODONE (DAY -170 - -19); TRAZODONE (DAY -18 - C);
BENZOCAINE TOPICAL (DAY -3 - C); BUPROPION (DAY 10 - C);
GRMCD/NEMYTP/NYSTOP/TACTOP (DAY 42 - 47); LOPERAMIDE (DAY 92 - 94);
APAP/TRMDOL (DAY 240 - C); TRAMADOL (DAY 290 - 805); DIMENHYDRINATE (DAY 510 -
513); MORPHINE (DAY 510 - 513); CIPROFLOXACIN (DAY 512 - 520); APAP/CODENE (DAY 546 -
549); CIPROFLOXACIN (DAY 546 - 551)

Clinical Summary: On Day 509, the subject reported right renal colic. He was suspected with right
ureteric obstruction. On Day 510, a computed tomography (CT) scan showed a 7 mm stone at the right
upper ureter with proximal mild hydronephrosis which confirmed severe ureteric calculus. On Day 512, he
underwent cystoscopy and retrograde pyelogram and was found to have a low grade non-invasive papillary
urothelial bladder carcinoma. He was diagnosed with transitional bladder cell carcinoma. The urologist was
unable to extract the stone so it was translocated to the renal pelvis and a stent was placed. The obstruction
was cleared following the insertion of a stent, which bypassed the stone.

On Day 546, he underwent right ureteroscopy and retrograde nephrogram. On the same Day (Day 546), he
was noted with post procedural complications, urethral pain and post procedural haematuria (all moderate
in severity). He was treated with ciprofloxacin, dimenhydrinate morphine, and acetaminophen/codeine. The
study medication was interrupted (Day 510-512, Day 525-526, and Day 547) due to the event of ureteric
calculus. The post procedural complication resolved on Day 557 followed by resolution of urethral pain
and post procedural haematuria on Day 550. On Day 568, he underwent cystoscopy and removal of ureteral
stent. The event of ureteric calculus resolved on Day 568. No action was taken with regard to the study
medication due to the event of transitional bladder cell carcinoma. On Day 657, the tumor in the bladder
was excised and a pathology report confirmed non-invasive papillary urothelial carcinoma and the event of
transitional bladder cell carcinoma was considered resolved the same Day (Day 657).

Blood in urine (dipstick) was 2+ and microscopy for red blood cells showed 0-5 RBC/hpf at a measurement
before randomisation.

Additional follow-up information received via standardized questionnaire, states that the subject is a former
smoker (25 cigarettes/Day for 25 years, stopped in 1989). There were no other reported risk factors known
to be associated with bladder cancer.

Anatomical location on bladder: right ureteric orifice.
Growth pattern: papillary.
Histological type: transitional.
TNM classification: pTa, pN0, M0.
Grade/Stages: Stage 0.

The bladder transitional cell carcinoma was a new diagnosis and there were no precipitating factors. The subject did not have a history of neither macroscopic nor microscopic hematuria. There were no urinary symptoms in association with the event.

The event was treated with surgery, transurethral resection, and there was complete response to treatment.

Approved v1.0   930055263 1.0

1.1.4   MB102030-90-880

Patient: MB102030-90-880 (67 YEARS/MALE/WHITE) (Argentina)

Study Treatment: DAPA 5MG + PIO   **Date of First Dose:** ▓▓▓▓ (b) (6) (DAY 1)

Event: TRANSITIONAL CELL CARCINOMA (UROTHELIAL CARCINOMA, MODERATE, NOT RELATED RELATIONSHIP, DAY 144)

Relevant Adverse Events during Study: GENITAL CANDIDIASIS (DAY 19), URINARY TRACT INFECTION (DAY 84), HAEMATURIA (DAY 130), URINARY BLADDER POLYP (DAY 144).

Disease History: TYPE 2 DIABETES MELLITUS (2006); HYPERTENSION (1979)

General Medical History: REPAIRED CARIES, CERVICAL PAIN, ESOPHAGITIS SINCE 10-02-06, CHOLECISTECTOMY AT 45 YEARS OLD, SURGERY OF BILATERAL INGUINAL HERNIA, ARTHROSIS IN LEFT HIP, HYPERTENSION SINCE 1979, DIABETES TYPE II, ERECTIL DISFUNCTION SINCE 2003

Concomitant Medication(s): SILDENAFIL (DAY -2319 - 125); ENALAPRIL (DAY -1223 - 60); PIOGLITAZONE (DAY -1223 - -16); ACETYLSALICYLIC ACID (DAY 5 - 5); ASCORBIC ACID (DAY 5 - 5); BETATP/GENTOP/MICNTP (DAY 20 - 29); ENALAPRIL (DAY 61 - 125); LEVOFLOXACIN (DAY 99 - 103); ENALAPRIL (DAY 126 – C259); APAP/ASTEM/BRMHEX/PSEUD (DAY 160 - 162); CEPHALEXIN (DAY 216 - 232); TERAZOSIN (DAY 216 - 231)   ENALAPRIL (DAY 259 - C)

Clinical Summary: On Day 130, the subject reported mild hematuria which resolved on the same Day. On Day 144, the subject was diagnosed with mild urinary bladder polyp. On Day 214, he was hospitalized and underwent vesical polypectomy. The event urinary bladder polyp was considered resolved the same Day.

The biopsy results from urinary bladder polyp biopsy confirmed high grade, invasive urothelial carcinoma with massive infiltration of the lamina propria and detrusor muscle engagement. Atypical mitotic figures, extensive areas of necrosis with dystrophic calcification and focus of squamous differentiation were observed. He was diagnosed with urothelial carcinoma. Study medication was interrupted from Day 213 to 215 in response to the event. He was discharged on Day 216 on cephalexin and terazosin.

Urine test (dipstick) showed Trace blood (0-5 RBC/hpf) at randomisation and 2+ (9-14/hpf) at week 1, then mostly positive results during the study.

Additional follow-up information received from the investigator via standardized questionnaire, states that the subject is a non-smoker with family history of bladder cancer (brother with malignant bladder cancer, treated with complete cystectomy, no histology available). There were no other reported risk factors known to be associated with bladder cancer.

Anatomical location on bladder: fundus.
Growth pattern: nests and cards.
Histological type: squamous. *Note: the pathology report states urothelial carcinoma*
TNM classification: unknown.
Grade/Stages: unknown.

This was a new diagnosis and there were no precipitating factors. The subject did not have a known history of either macroscopic or microscopic hematuria. Urinary symptoms of urgency and pollakiuria preceded the events.

The event was treated with surgery, cystectomy, and there was complete response to treatment.

Approved v1.0   930055263 1.0

1.1.5   D1690C00004-4916-2

Patient: D1690C00004-4916-2 (76 years/male/white) (Germany)
Study Treatment: DAPA + MET   **Date of First Dose:** [(b) (6)   ] (DAY 1)
Event: Bladder transitional cell carcinoma* (Urothelial carcinoma of the bladder, Moderate, Not related, Day 727 - C)
Note: At the time of 4MSU cut-off, this event was coded as PT 'Bladder neoplasm'

Relevant Adverse Events during Study: BENIGN PROSTATIC HYPERPLASIA (Day 727 – C)

Disease History: TYPE 2 DIABETES MELLITUS (1997); DYSLIPIDEMIA (1997); HYPERTENSION (1997); PREVIOUS MI (1996); PCI (1996); CORONARY ARTERY DISEASE (CAD) (1996)

Medical History: myocardial infarction, left heart hypertrophy, hypertension; Diabetes mellitus type 2, Hypercholesterinaemia, Hyperuricaemia; chronic obstructive pulmonary disease; abdominal aorta aneurysm operation. Smoking: FORMER; 20 PACK YEARS; STOPPED 1980. Alcohol use: <1 DRINK WEEKLY.

Concomitant Medications: ACETYLSALICYLIC ACID (Day ≥ - 90 - C); SIMVASTATIN (Day ≥ - 90 - C); BENAZEPRIL (Day ≥ - 90 - C); TIOTROPIUM (Day ≥ - 90 - C); ALBUTEROL (Day ≥ - 90 - C); PREDNISONE (Day - 10 - C); HYDROCHLOROTHIAZIDE (Day ≥ - 90 - C); MOXIFLOXACIN (Day 63 - 70); ALLOPURINOL (Day ≥ - 90 - C); TAMSULOSIN (Day 735 - C); CIPROFLOXACIN (Day 763 - 767); BUDESI/FORMO (Day 820 - C)

Background Medications: REPAGLINIDE (Day ≥ - 90 - -67); METFORMIN (Day ≥ - 90 - C)

Clinical Summary: The patient was hospitalized on Day 735 with symptoms of macroscopic hematuria. The urine dipstick revealed leukocytes 1+, protein 2+, glucose 1+, blood 2+. A urine culture did not yield any significant bacteriuria. Laboratory results upon admission included leukocytes 14.2/nl and glucose 192 mg/dl; the remaining routine laboratory values were within the normal range. A urinary ultrasound demonstrated a second degree dilatation of the right pelvi-calyceal system with no ectasia on the left; and a large bladder tumor in the region of the right lateral wall of the bladder and bladder floor. The elimination urogram showed a second to third degree dilatation of the kidney with a delayed excretion of the contrast agent. A chest x-ray on Day 735 did not show any signs of intrathoracic metastases.
The patient underwent a transurethral resection of the urinary bladder on Day 736 without any complications. The histology revealed papillary transitional cell carcinoma, pT1, high-grade (formerly G 3) with partial squamous cell differentiation in multiple locations in the region of the right lateral wall, bladder floor. In some locations the grading was low grade (previously G1) and high-grade (previously 2 or 3).

After removing the transurethral indwelling catheter, the patient initially voided urine spontaneously; however, on Day 740, he developed urinary retention. He was discharged from the hospital on Day 740 with a double J-catheter inserted on the right side and a transurethral indwelling catheter. A post-hospitalization trial without the catheter showed that there was no longer any significant amount of residual urine. There was no action taken with study medication in response to the event. The patient was diagnosed with urothelial carcinoma of the urinary bladder pT1, high-grade, multiple locations in the region of the right lateral wall, bladder floor.

On Day 764 the patient underwent a second transurethral resection of the bladder and replacement of the double J catheter. The event is not resolved at the time of this report.
Blood in urine (dipstick) was negative at measurements before/at randomisation.

Additional follow-up information received via standardized questionnaire, states that the subject is an ex-smoker with no other reported risk factors known to be associated with bladder cancer.

Anatomical location: Urinary bladder
Growth pattern: -
Histological type: high-grade, pT1, G3
TNM classification: -
Grade/Stages: -

The transitional cell carcinoma was a new diagnosis and there were no precipitating factors. The subject did not have a history of neither macroscopic nor microscopic hematuria. There were no urinary symptoms in association with the event.

The event was treated with surgery, transurethral resection, and at the time of follow-up there was no recurrence of disease and no metastases.

Approved v1.0   930055263 1.0

1.1.6   D1690C00006-1501-6

Patient: D1690C00006-1501-6 (67 YEARS/MALE/WHITE) (Hungary)
Study Treatment: DAPA 10MG + INS   **Date of First Dose:** [b) (6] (DAY 1)
Event: BLADDER TRANSITIONAL CELL CARCINOMA STAGE II (Carcinoma transitiocellulare
grade II. of the urinary bladder, MODERATE, NOT RELATED, Day 399 - C,)

Relevant Adverse Events during Study: HAEMATURIA (Macroscopic haematuria, Day 372 - C, MILD
/ GRADE I, NOT RELATED)

Disease History: TYPE 2 DIABETES MELLITUS (1990); DIABETIC RETINOPATHY (2004);
DIABETIC NEUROPATHY (2006); DIABETIC NEPHROPATHY (01MAR2008);
MICROALBUMINURIA (01MAR2008); HYPERTENSION (2006); DYSLIPIDEMIA (2006)

General Medical History: status post mastectomiam, diabetic retinopathy; hypertension; diabetic
nephropathy; microalbuminuria; diabetes mellitus type 2, hypoglycemia 08/Oct/2008; hyperlipidaemia;
status after surgery of cystae genu left side; diabetic neuropathy; Allergies: pollen allergy. Smoking:
NEVER. Alcohol use: 1 DRINK ON MOST DAYS.
Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >=-90 - C); ATORVASTATIN (Day >=-
90 - C); CALCIUM DOBESILATE (Day >=-90 - C); CARVEDILOL (Day >=-90 - C); RAMIPRIL (Day
>=-90 - C); ENOXAPARIN (Day 131 - 146); MITOMYCIN (Day 428 - 462)

Background Medication(s): INSULIN (Day -968 - C)

Clinical Summary:
On Day 399 the patient was hospitalised with haematuria. Ultrasonography and CT were done and showed
urinary bladder neoplasm. The tumor was described as located at the posterior wall of vertex and as a 2-3
cm-sized tumor. The final diagnosis was carcinoma transitiocellulare grade II of the urinary bladder.
Transurethral resection and local chemotherapy was done. Study drug was not stopped and patient was
discharged on Day 405 in not yet recovered condition. The patient completed the study on Day 743.

Blood in urine (dipstick) was 1+ and 3+ at measurements before/at randomisation and then intermittently
positive results during the study. Microscopy for red blood cells showed 31–50 rbc/hpf (Day -13) and 0–5
rbc/hpf (Day 1).

Additional follow-up information received via standardized questionnaire, states that the subject is a non-
smoker with no other reported risk factors known to be associated with bladder cancer. There were no
urinary symptoms present.

The event was treated with surgery, transurethral resection, and the patient recovered from the disease
(Day 462) .

Approved v1.0   930055263 1.0

1.1.7   D1690C00006-2206-14

Patient: D1690C00006-2206-14 (66 YEARS/MALE/WHITE) (United States)
Study Treatment: DAPA 10MG + INS   **Date of First Dose:** _____ (b) (6) (DAY 1)
Event: BLADDER TRANSITIONAL CELL CARCINOMA (noninvasive low grade papillary urothelial carcinoma of bladder, MILD, NOT RELATED, Day 581 to 581)

Relevant Adverse Events during Study: HAEMATURIA (painless hematuria, Day 577 to 581)

Disease History: TYPE 2 DIABETES MELLITUS (01JUL1999); DIABETIC NEUROPATHY (2000); HYPERTENSION (1990); CABG (1997); CORONARY ARTERY DISEASE (CAD) (1997); PREVIOUS MI (1997); DYSLIPIDEMIA (1997)

General Medical History: glaucoma; hypertension coronary artery disease myocardial infarction cardiac bypass surgery; cellulitis right leg-history of 06/2003; sleep apnoea chronic obstructive pulmonary disease; hyperlipidemia, diabetes mellitus type 2; peripheral neuropathy; mild depression. Smoking: FORMER; CIGARETTES 30 PER DAY for 42 YEARS; Stopped 2001. Alcohol use: NONE.

Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >=-90 - C); FLUTIN/SALIN (Day >=-90 - C); FUROSEMIDE (Day >=-90 - C); SERTRALINE (Day >=-90 - C); SIMVASTATIN (Day >=-90 - C); TELMISARTAN (Day >=-90 - C); TIOTROPIUM (Day >=-90 - C); NAPROXEN (Day 237 - 331); PREGABALIN (Day 275 - C); CLOPIDOGREL (Day 457 - C); DIPHENHYDRAMINE (Day 457 - 457); FENTANYL (Day 457 - 457); MIDAZOLAM (Day 457 - 457); ACETYLCYSTEINE (Day 463 - 463); BIVALIRUDIN (Day 463 - 463); COLD AND ALLERGY REMEDY (Day 463 - 463); FENTANYL (Day 463 - 463); LIDOCAINE (Day 463 - 463); MIDAZOLAM (Day 463 - 463); THEOPHYLLINE (Day 463 - 463); CEFAZOLIN (Day 581 - 581); FENTANYL (Day 581 - 581); GLYCOPYRROLATE (Day 581 - 581); LIDOCAINE (Day 581 - 581); MIDAZOLAM (Day 581 - 581); PROPOFOL (Day 581 - 581); ROCURONIUM (Day 581 - 581)

Background Medication(s): INSULIN (Day -3429 - C)

Clinical Summary: On Day 581, the patient was diagnosed with low grade, non-invasive, papillary, urothelial carcinoma of bladder. There was no action taken with the study medication.

The patient went to primary care physician with gross painless hematuria on Day 580. He had hematuria from Day 577 to Day 580. The patient had a cystoscope done on Day 581 with removal of small tumor in bladder. The patient had a transurethral resection of bladder tumor on Day 581.

Pathology report showed non-invasive low grade papillary urothelial carcinoma and no further treatment was planned. The event of low grade, non-invasive, papillary, urothelial carcinoma of bladder resolved on Day 581.

Blood urine (dipstick) was negative at measurements before/at randomization, but the patient had positive blood findings in the urine at Days 56, 84, 118 and 377.

Additional follow-up information received via standardized questionnaire, states that there were no previous episodes of hematuria and the patient had no history of urinary tract infections or kidney stones. There is no history of bladder cancer in the family and the patient has no history of any type of cancer. There is no known chemical exposure or radiation exposure related to this event. The patient was in service and worked around chemicals but has no knowledge of specifics.

After removal of the tumor, the patient is followed up yearly with a cystoscopy.

1.1.8   D1690C00018-7831-5

Patient: D1690C00018-7831-5 (48 years/male/white) (United States)
Study Treatment: Dapa 10 mg   **Date of First Dose:** ▮▮▮ (b) (6) (DAY 1)
Event: Bladder transitional cell carcinoma (noninvasive low grade papillary urothelial carcinoma of the urinary bladder, Moderate, Not related, Day 74)

Relevant Adverse Events during Study: Not Applicable

Disease History: TYPE 2 DIABETES MELLITUS (05SEP2005); DIABETIC RETINOPATHY (MAR2009); HYPERTENSION (1976); PERIPHERAL VASCULAR DISEASE (05SEP2005); CORONARY ARTERY DISEASE (CAD) (14JAN2008); HOSPITALIZATION FOR UNSTABLE ANGINA (14JAN2008); PCI (14JAN2008); PREVIOUS MI (14JAN2008); CONGESTIVE HEART FAILURE (31JAN2008); CABG (12FEB2008); AMPUTATION (16NOV2008); DYSLIPIDEMIA (18MAR2006); MALE CIRCUMCISION (16JUN1961); RENAL-URINARY TRACT STONES (18FEB2008)

Medical History: diabetic retinopathy un/MAR/2009; M.I. 14/jan/2008. CABG 12/feb/2008. Angioplasty 14/jan/2008. Congestive heart failure 31/JAN/2008 hypertension un/unk/1996; 5/sep/2005; asthma 18/mar/2010; Haemorrhoids un/aug/2002.; atrophic right kidney nephrolithiasis atrophy of right testicle; DM II 5/Sep/2005 dyslipidemia 18/MAR/2006; anaemia; OA un/oct/1986.; eczema un/uk/1981.; Depression - stable; R big toe amputation 16/nov/2008. Smoking: FORMER; CIGARETTES 20 PER DAY for 34 YEARS; Stopped 14JAN2008. Alcohol use: OCCASIONAL.

Concomitant Medications:
ACETYLSALICYLIC ACID (Day >=-90 - C); ALBUTEROL (Day >=-90 - C); BUPROPION (Day >=-90 - C); CYANOCOBALAMIN (Day >=-90 - C); NIACIN (Day >=-90 - C); SIMVASTATIN (Day >=-90 - C); WARFARIN (Day >=-90 - C); GLUCOSE (Day 31 - 31); GLUCOSE (Day 56 - 56); BCG VACCINE (Day 79 - C); CARVEDILOL (Day >=-90 - C); FUROSEMIDE (Day >=-90 - C); GLIPIZIDE (Day >=-90 - C); METFORMIN (Day > -90 - C); VALSARTAN (Day > -90 - C)

Clinical Summary: The patient was in hospital for CAD when a CT scan was done showing possibility of lesion in bladder. No symptoms were noted. A cystoscopy was done and the subject was diagnosed with non-invasive, low grade, papillary urothelial carcinoma of the urinary bladder. Patient is to begin BCG vaccine treatment and a transurethral resection of the bladder was done.

Investigational product was discontinued due to the event and the event did not resolve.

Blood in urine (dipstick) was negative at measurements before/at randomisation. The patient had a history of renal stones and hematuria starting 2008.

Approved v1.0   930055263 1.0

1.1.9 D1690C00018-7401-9

Patient: D1690C00018-7401-9 (55 years/male/Asian) (Taiwan)
Study Treatment: Dapa 10 mg **Date of First Dose:** [   ] (b) (6) (DAY 1)
Event: Bladder transitional cell carcinoma (UROTHELIAL CARCINOMA OF URINARY BLADDER, Severe, Not related, Day 169)

Relevant Adverse Events during Study: Not Applicable

Disease History: TYPE 2 DIABETES MELLITUS (25MAY2000); CORONARY ARTERY DISEASE (CAD) (21FEB2005); PCI (21FEB2005); DYSLIPIDEMIA (09MAR2005)

Medical History: Chronic hypertrophic rhinitis; Deviation of nasal septum; Anterior epistaxis; Functional gastrointestinal disturbance; Diabetes mellitus, type II; lipid metabolism disorders; Headache after nitrate; Generalized and localized adult periodontitis; periodontal abscess. Smoking: CURRENT; CIGARETTES 5 PER DAY for 36 YEARS. Alcohol use: 1-2 DRINKS WEEKLY.

Concomitant Medications: ACETYLSALICYLIC ACID (Day >=-90 - C); ATORVASTATIN (Day >=-90 - C); CIPROFLOXACIN (Day 183 - 193); CEFAZOLIN (Day 194 - 197); ENEMA (Day 194 - 194); ACETAMINOPHEN (Day 197 - C); ENALAPRIL (Day >=-90 - 13); GLYBURIDE (Day >=-90 - C); METFORMIN (Day >=-90 - C); AMLODIPINE (Day 14 - C); LISINOPRIL (Day 14 - C); FUROSEMIDE (Day 194 - 197)

Clinical Summary: The patient was hospitalised on Day 193 to 197 with suspicion of urothelial carcinoma after suffering from intermittent hematuria for 3 months and persistent hemospermia. Cystoscopy showed three small papillary tumors over the right lateral wall. The pathology report states a diagnosis of low grade, papillary, urothelial carcinoma (papillary transitional cell carcinoma, grade 1). The tumor was confined to the mucosa. The tumours were removed with transurethral resection. There was no action taken to investigational product and the AE resolved on Day 197.
Blood in urine (dipstick) showed Trace blood at enrolment and randomisation and then negative or trace results during the study. Microscopy for red blood cells showed 0-5 RBC/hpf at enrolment and randomisation.

Approved v1.0   930055263 1.0

1.1.10   D1690C00019-1016-7

Patient: D1690C00019-1016-7 (66 years/male/white) (Canada)
Study Treatment: Placebo   **Date of First Dose:** [redacted] (b) (6) (DAY 1)
Event: Bladder cancer (Bladder cancer, Severe, Not related, Day 136)

Relevant Adverse Events during Study: BLOOD URINE PRESENT (Gross Blood in urine, Day 1 to 2); CYSTITIS (Cystitis, Day 32 to 46)

Disease History: TYPE 2 DIABETES MELLITUS (05JUL1993); MICROALBUMINURIA (18MAR1997); HYPERTENSION (16JAN1984); CORONARY ARTERY DISEASE (CAD) (19MAY1994); STABLE ANGINA (22JAN1999); PCI (21JUN1999); DYSLIPIDEMIA (19JAN1988)

Medical History: Microalbuminuria, hematuria; Allergies: Altace. Smoking: CURRENT; CIGARETTES 20 PER DAY for 50 YEARS. Alcohol use: less than 1 DRINK WEEKLY.

Concomitant Medications: ACETYLSALICYLIC ACID (Day >=-90 - C); ISOSORBIDE (Day >=-90 - C); CIPROFLOXACIN (Day 36 - 46); BUDESI/FORMO (Day 73 - 83); MOXIFLOXACIN (Day 73 - 78); INSULIN DETEMIR (Day -235 - 155); BISOPROLOL (Day >=-90 - C); HYDROCHLOROTHIAZIDE (Day >=-90 - C); METFORMIN (Day >=-90 - C); TELMISARTAN (Day >=-90 - C); INSULIN DETEMIR (Day 160 - C)

Clinical Summary: The patient was hospitalised on Day 156 to 159 after a few weeks of non-painful, macroscopic hematuria. A cystoscopy and transurethral resection of multiple bladder cancers and fulguration was done. Diagnosed with high grade, papillary, urothelial carcinoma with microinvasion. The pathology report indicated an area of in situ carcinoma, in addition to a high-grade but superficial tumour.

There was no action taken to investigational product and the event resolved with sequela.

Blood in urine (dipstick) was 3+ or trace at measurements before/at randomisation and then positive results (3+, 2+ and trace) during the study. Microscopy for red blood cells was TNTC (too numerous to count) or 0-5 RBC/hpf before/at randomisation.

Additional follow-up information received via standardized questionnaire, states that the subject is a current-smoker with no other reported risk factors known to be associated with bladder cancer.

Anatomical location: bladder
Growth pattern: papillary, with microinvasion
Histological type: urothelial
TNM classification: -
Grade/Stages: high grade

There were no precipitating factors. The subject had a history of hematuria.

The event was treated with surgery (excision of multiple intra-vesical lesions), transurethral resection, and the current status of the disease is that the patient is scheduled for BCG for six treatments and he will then be scheduled for a follow-up cystoscopy.

Approved v1.0 930069053 1.0

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Page 1 of 4

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I.REACTION INFORMATION

1.PATIENT ID	1.a COUNTRY	2.DATE OF BIRTH			2.a AGE	3.SEX	4-6.REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
D1693C00005 6706-14	SK			(b) (6)	53 Years	F	25	OCT	2012	

7+13 DESCRIBE REACTION(S)(Including relevant tests/lab data)

#1 Bladder cancer

Protocol Title: D1693C00005 - A 24-week, Multicentre, Randomized, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg once daily in Patients with Type 2 Diabetes who have Inadequate glycemic Control on a background combination of metformin and Sulfonylurea.

A clinical investigator reported that a 53-year-old white female patient was hospitalized with the diagnosis of (moderate/grade I) carcinoma of the urinary bladder, considered medically serious while enrolled in a clinical study of dapagliflozin for the treatment of type 2 diabetes. Oral blinded study therapy was initiated on 04-Jul-2012 and consisted of dapagliflozin (10 mg daily) or matching
(Continued)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [x] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II.SUSPECT DRUG(S) INFORMATION

14.SUSPECT DRUG(S)(include generic name)

#1 DAPAGLIFLOZIN
 #2 STADAMET (metformin hcl)

15.DOSE(S)

#1 10 Milligram 1/1 Day
 #2 1500 Milligram

16.ROUTE OF ADMINISTRATION

#1 ORAL
 #2 ORAL

17.INDICATION(S) FOR USE

#1 Type 2 diabetes mellitus
 #2 Type 2 diabetes mellitus

18. THERAPY DATES(from/to)

#1 04JUL2012-11DEC2012
 #2

19. THERAPY DURATION

#1
 #2 Continued

20. DID REACTION ABATE AFTER STOPPING DRUG?

#1 [ ] yes [ ] no [x] na

#2 [ ] yes [ ] no [x] na

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?

#1 [ ] yes [ ] no [x] na

#2 [ ] yes [ ] no [x] na

III.CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION(exclude those used to treat reaction)

#1 AMLODIPINE (amlodipine)
 #2 RAWEL (indapamide)
 #3 LISINOPRIL (lisinopril)
(Continued)

23. OTHER RELEVANT HISTORY(e.g.diagnostics,allergics,pregnancy with last month of period,etc.)

Race: White.
 #1 Drug hypersensitivity "medicamentosa-diolan" #2 Type 2 diabetes mellitus #3 Duodenogastric reflux #4 Hypertension #5 Diabetic neuropathy #6 Hepatic steatosis #7 Hyperlipidaemia #8 Bronchitis chronic #9 Cervicobrachial syndrome cervicotrachial syndrome #10 Tobacco user 20/day for 40 yrs #11 Alcohol use 1-2 drinks/week

IV. MANUFACTURER INFORMATION

24.a NAME AND ADDRESS OF MANUFACTURER

Eileen Leonard
 Bristol-Myers Squibb Company
 GPV HW19-1.01 P.O. Box 5400
 Princeton, NJ 08543-5400
 United States

24b MFR CONTROL NO

17383738

24c. DATE RECEIVED BY MANUFACTURER

12FEB2013

24d REPORT SOURCE

[x] Study [ ] Literature [x] Other
[x] Health Professional   Consumer or

25. DATE OF THIS REPORT

26FEB2013

25a REPORT TYPE

[ ] Initial [ ] Followup

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Page 2 of 4

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26FEB2013   MFR CONTROL NO: 17383738

7+13 DESCRIBE REACTION(S):

placebo. The patient was also treated with background therapy oral metformin HCL 1500

mg daily and background glimepiride 4 mg daily. Both forms were initiated prior to
study participation. Study therapy was completed/prematurely discontinued on
11-Dec-2012, due to safety concerns. The last dose of study drug administration was
on 11-Dec-2012.

On 09-May-2012, the patient's laboratory tests revealed estimated glomerular
filtration rate: 97ml/min/BSA (normal 65-112) and estimated creatinine clearance:
125mL/min (normal >60). The patient's hemoglobin: 15.4g/dL (normal 11.6-16.2) and
hematocrit: 45.3% (normal 35.0-47.0). Special chemistry performed on the same day
revealed fasting plasma glucose: 146mg/dL (normal 68-117) and hemoglobin A1c (NGSP):
8.2% (normal 4.3-6.1). Urinalysis for blood revealed negative results. Creatinine,
urine conconcentrate: 24; microalbumin, urine concentrate: 802 and
microalbumin/creatinine ratio: 3342 mg/g. On 25-Jun-2012, the patient's fasting
plasma glucose was 199 mg/dL and hemoglobin A1c (NGSP) was 8.3%.

On 04-Jul-2012, during randomization, urinalysis results revealed trace hematuria
and bacteria 1+ that were considered indicative of urinary tract infection.
Laboratory data performed on the same day revealed hemoglobin: 14.5 g/dL and
hematocrit: 43.5%. Urine chemistry confirmed est. GFR: 80 ml/min/BSA and est.
creatinine urine clearance: 104mL/min; creatinine, urine concentrate: 36,
microalbumin, urine concentrate: 552 and microalbumin/creatinine ratio: 1533mg/g
creat.

Urine culture performed on 22-Jul-2012 revealed positive results, with eschericia
coli identified as the organism. The colony count was unknown. The overall conclusion
reported that the result was indicative of urinary tract infection. Treatment
required was not specified. The urinary tract infection (considered non-serious
adverse event) resolved on 04-Aug-2012.

On 05-Sep-2013, during study visit 6, urinalysis for blood revealed 1+; epithelial
cells 1+ and bacteria 4+. The patient was asymptomatic. Treatment was required and
the event uroinfection was reported resolved on 22-Sep-2012.

The patient was then referred to urologist for further investigation, who on
25-Oct-2012 (onset date) detected neoplasm of the bladder. Laboratory results
revealed hemoglobin: 16.1 g/dL; hematocrit: 47.5%; alkaline phosphatase: 110 IU/L
(normal 40-100) and GFR: 95ml/min/BSA and estimated creatinine clearance: 121mL/min.
Urinalysis for blood revealed negative results and microalbumin/creatinine ratio:
2993 mg/g creat.

Diagnostic cystoscopy performed on 21-Nov-2012, confirmed a 2.5cm tumor located in
the urinary bladder. Ultrasound of the urinary bladder, performed (date unspecified)
revealed negative results. The event of bladder cancer was confirmed to be a new
diagnosis with the patient having no history of hematuria and no urinary symptoms.

On 12-Dec-2012, laboratory data revealed alkaline phosphatase: 122 IU/L; est. GFR:
83 ml/min/BSA and est. creatinine clearance: 107ml/min.; creatinine urine
concentrate: 52; and microalbumin/creatinine ratio: 2465 mg/g creat.

Laboratory tests performed on 27-Dec-2012, revealed alkaline phosphatase: 110 IU/L;
est. GFR: 83 ml/min/BSA and est. creatinine clearance: 110mL/min. Urinalysis for
blood was negative, creatinine, urine concentrate: 19 and microalbumin/creatinine
ratio: 1879 mg/g creat.

Per the investigator, the patient was confirmed to have no exposure to arsenic,
aromatic amines, phenoacetin, Chinese herbs, chemicals used in manufacturing of dyes,
rubber, leather, textiles, paint products and cyclophosphamide. The patient had no
history of using products or combination products containing pioglitazone and denied
chronic cystitis, indwelling urinary catheter, radiation exposure, and personal
history of bladder cancer or benign bladder neoplasm. Familial risk factors: Negative
history of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome.

The patient was hospitalized on   (b)(6) and admitted to the urology department
to undergo surgical intervention with no symptoms present. On   (b)(6) the
patient underwent transurethral resection of the urinary bladder. Surgery and post
surgery period were without complications. Treatment during hospitalization included
infusion of analgeticum and cefuroxime axetel. Treatment duration was not confirmed.

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26FEB2013   MFR CONTROL NO: 17383738

The patient was released to home on ▒▒▒▒▒ (b)(6) in stable condition. The final
discharge diagnosis: Malignant tumor of urinary bladder, front side.

Final histology results confirmed bladder cancer, (TCC grade 1) without muscle
infiltration. The site confirmed that there was no corrective treatment administered.
The event was resolved on ▒▒▒▒▒ (b)(6). Hospital discharge was performed on the same
day. Additional information was requested.

The patient's medical history included type 2 diabetes mellitus, duodenogastric
reflux, hypertension, hyperlipidemia, diabetic neuropathy, hepatic steatosis, chronic
bronchitis, cervicotrachial syndrome, and status post surgical sterilization. The
patient is a current smoker (20/day for 40 years) with reported alcohol frequency of
1-2 drinks weekly. Allergies included "medcamentosa-diolan".

Concomitant medications: amlodipine, indapamide, lisinopril, salmeterol,
atorvastatin and thioctic acid.

Investigator causality assessment: Carcinoma of the urinary bladder was not related
to the blinded study therapy and not related to background metformin HCL and
glimepiride.

BMS causality assessment: Carcinoma of the urinary bladder was not related to the
blinded study therapy and not related to background metformin HCL and glimepiride.

BMS Medical Comment: This 53-year-old white female patient was diagnosed (mild/grade
I) carcinoma of the urinary bladder approximately four months after the initiation of
the blinded study treatment. The patient had already hematuria on the date of the
treatment start. Based on the very short time to onset in terms of oncogenesis and
early existance of hematuria as a cardinal symptom of bladder cancer, the event is
considered not related to blinded study treatment and background study treatment.

LAB DATA: #1 CREATININE CLEARANCE-09MAY2012 125 ML/MIN Normal , #2 GLOMERULAR
FILTRATION RATE-09MAY2012 97 Normal , #3 HEMOGLOBIN-09MAY2012 15.4 G/DL Normal , #4
HEMATOCRIT-09MAY2012 45.3 % Normal , #5 GLUCOSE FASTING-09MAY2012 146 MG/DL High , #6
HEMOGLOBIN A1C-09MAY2012 8.2 % High , #7 URINALYSIS BLOOD-09MAY2012 Negative , #8
URINE CREATININE-09MAY2012 24 , #9 URINE MICROALBUMIN RATE-09MAY2012 802 , #10 URINE
MICROALBUMIN/CREATININE-09MAY2012 3342 MG/G High , #11 GLUCOSE FASTING-25JUN2012 199
MG/DL High , #12 HEMOGLOBIN A1C-25JUN2012 8.3 % High , #13 URINALYSIS BLOOD-04JUL2012
trace High , #14 BACTERIA URINE-04JUL2012 1+ High , #15 HEMOGLOBIN-04JUL2012 14.5
G/DL Normal , #16 HEMATOCRIT-04JUL2012 43.5 % Normal , #17 URINE CREATININE-04JUL2012
36 , #18 URINE MICROALBUMIN RATE-04JUL2012 552 , #19 URINE
MICROALBUMIN/CREATININE-04JUL2012 1533 MG/G High , #20 GLOMERULAR FILTRATION
RATE-04JUL2012 80 Normal , #21 CREATININE CLEARANCE-04JUL2012 104 ML/MIN Normal , #22
URINE CULTURE-22JUL2012 Positive , #23 EPITHELIAL CELLS-05SEP2012 1+ High , #24
BACTERIA URINE-05SEP2012 4+ High , #25 ALKALINE PHOSPHATASE-05SEP2012 110 IU/L High
#26 URINE MICROALBUMIN/CREATININE-05SEP2012 1444 MG/G High , #27 HEMOGLOBIN-25OCT2012
16.1 G/DL Normal , #28 HEMATOCRIT-25OCT2012 47.5 % High , #29 CYSTOSCOPY-21NOV2012
Abnormal , #30 ULTRASOUND BLADDER-00NOV2012 Negative , #31 URINE
MICROALBUMIN/CREATININE-25OCT2012 2993 MG/G High , #32 ALKALINE PHOSPHATASE-12DEC2012
122 IU/L High , #33 URINE MICROALBUMIN/CREATININE-12DEC2012 2465 MG/G High , #34
GLOMERULAR FILTRATION RATE-12DEC2012 83 Normal , #35 CREATININE CLEARANCE-12DEC2012
107 ML/MIN Normal , #36 URINE MICROALBUMIN/CREATININE-12DEC2012 2465 MG/G High , #37
URINE CREATININE-12DEC2012 52 , #38 URINE MICROALBUMIN/CREATININE-27DEC2012 1879 MG/G
High , #39 HISTOLOGY-10JAN2013 Positive , #40 ALKALINE PHOSPHATASE-25OCT2012 110 IU/L
High , #41 GLOMERULAR FILTRATION RATE-25OCT2012 95 ML/MIN Normal , #42 CREATININE
CLEARANCE-25OCT2012 121 ML/MIN Normal , #43 URINALYSIS BLOOD-25OCT2012 Negative , #44
ALKALINE PHOSPHATASE-27DEC2012 110 IU/L Normal , #45 GLOMERULAR FILTRATION
RATE-27DEC2012 83 ML/MIN Normal , #46 CREATININE CLEARANCE-27DEC2012 110 ML/MIN
Normal , #47 URINALYSIS-27DEC2012 Negative , #48 URINE CREATININE-27DEC2012 19

14.SUSPECT DRUG(S):

#3 MELYD (glimepiride)
#4 PLACEBO

15.DOSE(S):

#3 4 Milligram 1 Day
#4

16.ROUTE OF ADMINISTRATION:

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26FEB2013   MFR CONTROL NO: 17383738

```
  #3 ORAL
  #4 ORAL


  17.INDICATION(S) FOR USE:

  #3 Type 2 diabetes mellitus
  #4 Type 2 diabetes mellitus


  18.THERAPY DATES(from/to):

  #3
  #4 04JUL2012-11DEC2012


  19.THERAPY DURATION:

  #3
  #4


  20.DID REACTION ABATE AFTER STOPPING DRUG?

  #3 Na
  #4 Na


  21.DID REACTION REAPPEAR AFTER REINTRODUCTION?

  #3 Na
  #4 Na


  22. CONCMITANT DRUGS AND DATES OF ADMINISTRATION:


  #4 SEREVENT (salmeterol)
  ATORVASTATIN (atorvastatin) 14MAY2012-UNK
  #6 THIOCTACID (thioctic acid)
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Appendix 3. Serious Liver Event Narratives

CASES MEETING DEFINITION OF: BIOCHEMICAL HY'S LAW (AST/ALT > 3X ULRR AND TBL > 2X ULRR)

(REPRODUCED FROM THE APPLICANT'S JUNE 19, 2013, HEPATIC ADJUDICATION REPORT)

Please note that these narratives are reproduced verbatim from the Applicant's submissions. They contain many spelling and abbreviation variants, reflective of varying usage across a multinational program.

Dapagliflozin
BMS-512148

Table 5: **Listing of Subjects with AST and/or ALT > 3X ULN and Total Bilirubin > 2X ULN Within 14 Days on or After the AT Elevation, Blinded Assessment of Causal Relationship to Study Drug by Hepatic Adjudication Committee, Liver Cases Sent to Committee up to 15 November 2012 (or up to Database Lock for completed studies)**

Treatment Group	Subject (Age/Gender/Race)	Causal Assessment	Last Dose Date
	D1690C00004 4916 16 (67/F/C)	UNLIKELY	02JUL2009
PLACEBO	D1690C00006 1414 2 (62/M/C)	EXCLUDED	25JAN2010
PLACEBO	MB102030 90 905 (29/M/C)	UNLIKELY	05NOV2009
PLACEBO	MB102054 24 498 (63/M/A)	UNLIKELY	24OCT2011
PLACEBO			
	D1690C00004 3104 4 (63/M/C)	UNLIKELY	26NOV2008
DAPA 2.5 MG	D1690C00004 4402 6 (78/M/A)	POSSIBLE	08DEC2008
DAPA 2.5 MG	D1690C00005 7002 4 (60/F/A)	UNLIKELY	22MAR2010
DAPA 2.5 MG			
	D1690C00005 6013 3 (83/M/C)	POSSIBLE	11MAR2009
DAPA 5 MG			
	D1690C00006 2004 6 (62/M/C)	EXCLUDED	09MAR2009
DAPA 10 MG	D1690C00018 201 8 (70/M/C)	UNLIKELY	25AUG2011
DAPA 10 MG	D1690C00018 203 4 (70/M/C)	UNLIKELY	20SEP2012
DAPA 10 MG	MB102029 4 276 (83/M/C)	EXCLUDED	05AUG2009
DAPA 10 MG	MB102030 9 92 (60/M/C)	UNLIKELY	20MAY2009
DAPA 10 MG	MB102077 66 70996 (57/M/A)	EXCLUDED	28FEB2012
DAPA 10 MG			

A=Asian; B=Black/African American; C=White; I=American Indian/Alaska Native; O=Other; P=Native Hawaiian/Other Pacific Islander.
** Event occurred after 30 days of last dose or subjects on dapa 1mg dose.
*** Event occurred prior to first dose date.
**** Event occurred on the first dose day but prior to the first dose.
Include 21 studies in integrated database plus MB102073, MB102077 and D1691C00003.
Program Source: /gbs/prod/clin/programs/mb/102/iss/30msu/rpt/rl hep altbilirelhepeventslt23 v02.sas

Dapagliflozin
BMS-512148

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Patient Identifier: D1690C00004-3104-4

Event: HYPONATRAEMIA (hyponatriamie, Day 1 - C, MILD / GRADE I, NOT RELATED)

Reason(s) for Narrative: (check all that apply)	[ ] Death
	X SAE (regardless of relationship to treatment)
	X AE leading to discontinuation (regardless of relationship to treatment)
	[ ] Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp. event
	YES	YES					YES

Study Medication/Dose: MET 1000MG (DAY -81 - -75); MET 1500MG (DAY -74 - -15);
PLA + MET 1500MG (DAY -14 - -1); DAPA 2.5MG + MET 1500MG (DAY 1 - 9); MET 1500MG (DAY 10 - 21);
MET 2000MG (DAY 22 - 31)

Treatment Group: DAPA + MET	Date of First Dose: (b) (6)

Age: 63 YEARS	Gender: MALE	Race: WHITE	Ethnicity: NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (06AUG2004); HYPERTENSION (03MAY2004); PERIPHERAL VASCULAR DISEASE (17APR2006); PERIPHERAL VASCULAR SURGERY (17APR2006); DYSLIPIDEMIA (06AUG2006); GOUT (01JAN1996)

General Medical History: hypertension; bypass art femoralis; chronic obstructive pulmonary disease; Diabetes mellitus type 2; hypercholesteremia; gout; dry skin/ ichtiosis; ulcus cruris. Smoking: CURRENT; CIGARETTES 20 PER DAY for 42 YEARS; CIGARS 20 PER DAY for 5 YEARS. Alcohol use: 3 OR MORE DRINKS ON MOST DAYS.

Adverse events during study: BLOOD CHLORIDE DECREASED (chloride low, Day 1 - C, MILD / GRADE I, NOT RELATED); BLOOD POTASSIUM DECREASED (potassium low, Day 1 - C, MILD / GRADE I, NOT RELATED)

Concomitant Medication(s): ACENOCOUMAROL (Day >=-90 - C); ENALAPRIL (Day >=-90 - C); SIMVASTATIN (Day >=-90 - C); DOXYCYCLINE (Day -4 - 4); FUSIDATE TOPICAL (Day -4 - -1); SODIUM CHLORIDE (Day 25 - 26)

Background Medication(s): GLIMEPIRIDE (Day >=-90 - -81); METFORMIN (Day >=-90 - C)

Clinical Summary:

Hyponatremia was noted on study day1. On study day14, study drugs were discontinued due to hyponatremia. On study day 25 the patient was hospitalized due to life threatening hyponatremia and discharged on study day 28 with suspicion of SIADH.

Relevant laboratory sodium results included the following (normal range: 132-147 mmol/L): 139 on study day -81, 122 on study day 1, 126 on study day 16, 119 on study day 22 and on study day 56 136 (ref. range 135-145)

On study day 58, 45 days after study medication was discontinued, the patient was hospitalized for life-threatening liver failure (grade 4). Following analysis, the patient was found to have hyperglycemia, and severe liver enzyme impairments with no fever or vomiting. On examination, the patient was found to be pale, somnolent with a blood pressure of 90/60 mm Hg and rectal exam revealed melena. The patient developed increased hemodynamic and respiratory insufficiency.

A computed tomography scan of the abdomen was performed which showed fulminant enlarged liver, speckled appearance (in consultation with the radiologist: unclear image, possible metastasis), adenoma of the adrenal gland right and aortic aneurysm (5 cm), ascites, and no primary tumor was visible.

On study day 59, the patient died due to acute liver failure. The conclusion was bleeding of the digestive tract with differential diagnosis of bleeding from abdominal aneurysm, state of shock with metabolic acidemia and

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severe liver function deficiency.

Investigator's comment: Suspect alcohol induced hepatitis

Autopsy revealed that the death cause was primary small cell lung cancer with massive metastasis in the liver. Further, the report revealed that based on the findings at autopsy, a potential contribution of the use of the oral diabetes medication in the trial to the terminal disease process and thereby the death has been ruled out.

		Time points							
	Date								(b) (6)
	Day (calculated)	-81	1	13	16	22	25	31	58
				IP stopped					
Laboratory data	ref. Range / Unit								E
ALT	6-48 IU/L	27	38		40		50 62*	81	794*
AST	10-45 IU/L	35	46		47		50 68*	69	1604*
ALP	45-145 IU/L	87	89		100	149		149	
bilirubin	3-21 umol/L	9	7		7		10 13*	15	51*
INR							1.8*		PT 26.8*
albumin	35-53 g/L	48	52		50			49	
Sodium	132-147 mmol/L	139	122		126		119 111*		136*
Potassium	3.5-5.5 umil/L	5	5.9		5.8		5.6 4.0*		6.2*
Creatinine	44-115 umol/L	71	63		66		57 59*		174*
Lactate*	0.6-2.4 mmol/L								18.1*
Hb*	8.5-11.0 mmol/L								3.9*

* - not central laboratory measurement

Date								(b) (6)
Day		-81	1	16	22	25	31	58
Range								
ALT(U/L)	(6-48)	27	38	40	50	62*	81	794*
AST(U/L)	(10-45)	35	46	47	50	68*	69	1604*
ALP(U/L)	(45-145)	87	89	100	149		149	
bilirubin(umol/L)	(3-21)	9	7	7	10	13*	15	51*

* indicates local laboratory sample

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00004-4402-6

Event: [1] HEPATITIS ACUTE (Acute hepatitis, Day 183 - C, SEVERE / GRADE III, CERTAIN); [2] Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN (DAY 183); [3] Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN (DAY 189); [4] Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 193); [5] Marked laboratory abnormality - ALT > 10X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 200); [6] Marked laboratory abnormality - ALT > 10X ULN; AST > 5X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 213)

Reason(s) for Narrative: (check all that apply)	[ ] Death
	[ ] SAE (regardless of relationship to treatment)
	[1] AE leading to discontinuation (regardless of relationship to treatment)
	[1]; [2]; [3]; [4]; [5]; [6] Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp. event

Study Medication/Dose: MET 2000MG (DAY -24 - -15); PLA + MET 2000MG (DAY -14 - -1); DAPA 2.5MG + MET 2000MG (DAY 1 - 21); DAPA 5MG + MET 2000MG (DAY 22 - 192); MET 2000MG (DAY 193 - 196)

Treatment Group: DAPA + MET	**Date of First Dose:** 31MAY2008

Age: 78 YEARS	**Gender:** MALE	**Race:** ASIAN	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (26SEP2001); CORONARY ARTERY DISEASE (CAD) (01JUN2000); PCI (01JUN2000); HYPERTENSION (20SEP2004); DYSLIPIDEMIA (20APR2003); BENIGN PROSTATIC HYPERTROPHY (21JUL1999)

General Medical History: Dry eyes; allergic conjunctivitis; see SPECDIS; Repair of inguinal hernia; constipation; Benign prostatic hypertrophy; see SPECDIS. Smoking: NEVER. Alcohol use: NONE.

Adverse events during study: HEADACHE (Headache, Day 79 to 88, MILD / GRADE I, NOT RELATED)

Concomitant Medication(s): ISPAGHULA HUSK (Day -109 - C); SENNA (Day -109 - C); ACETYLSALICYLIC ACID (Day >=-90 - C); ATENOLOL (Day >=-90 - C); ATORVASTATIN (Day >=-90 - 201); CROMOLYN (Day >=-90 - C); HYPROMELLOSE (Day >=-90 - C); LERCANIDIPINE (Day >=-90 - C); PERINDOPRIL (Day >=-90 - C); NAPROXEN (Day -17 - -10); INFLUENZA VACCINE (Day 129 - 129)

Background Medication(s): METFORMIN (Day >=-90 - 196); GLIPIZIDE (Day 201 - C)

Clinical Summary:

The subject had an ALT value just above upper limit of normal and AST and bilirubin within normal range at randomization, study day 1. On study day 85, the subject showed slight increased ALT. On study day 127 ALT was increased further to 117 IU/L (ref. range 6-48) and AST was increased to 72 IU/L (reference range 10-45). On study day 183, severely increased ALT and AST values were recorded which were confirmed at study day 189. The subject was discontinued from study medication at study day 191. By that time, the subject was asymptomatic.

A gastroenterologist consultation on study day 196, noted that the subject was clinically "general well", but had decreased appetite recently, "urine had become darker as well as stool", complained of upper abdominal discomfort and had a "tinge of jaundice but no stigmata of chronic liver disease." On abdominal examination, the liver edge was palpable with slight tenderness in the right fossa.

Atorvastatin was discontinued and non-study glipizide was started on study day 201. The subject

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00004-4402-6

had been on atorvastatin since at least 3 month before the study and atorvastatin was later reinitiated on day 250. A gastroenterologist and hepatologist consult on study day 229 reported the diagnosis of haemochromatosis. By that time, ALT and AST had improved significantly. According to the gastroenterologist, the ultrasound scan was not entirely normal. Ferritin level was elevated at over 4000 (units not reported) and genotyping showed compound heterozygote for haemochromatosis. No treatment was recommended at this point for haemochromatosis.

A liver ultrasound report on study day 263 stated that the liver and gallbladder appeared normal. The common bile duct was dilated throughout its length to 1 mm, with question of an early ampullary tumor. The gastroenterologist was in disagreement with the finding of a questionable ampullary tumor. A liver biopsy was performed on study day 264. The pathology report included "hepatitis with broad inflamed bands connecting portal tracts with liver parenchyma collapse. This could represent chronic inflammation post acute episode of hepatitis which could have been drug related".

A hepatologist and gastroenterologist consult on study day 305, noted the subjects liver function tests continued to improve and that the subject has a "severe drug injury" and particularly in view of his age and underlying haemochromatosis, his hepatic regenerative capacity was diminished, with full recovery likely to take several months.

A second opinion of the liver biopsy was provided on study day 320. The report read "evidence of hepatitis with severe inflammatory activity of relatively short duration. However, the presence of prominent interface hepatitis and the associated pattern of fibrosis in periportal regions favours progression to chronic hepatitis. Underlying etiology is uncertain. Viral agents, drugs and autoimmune hepatitis are three main possibilities to be considered in the differential diagnosis and a number of histological features would favour a diagnosis of autoimmune hepatitis. However, results of other investigations do not appear to support this diagnosis. The clinical presentation appears to favour drug toxicity as a likely cause of liver injury. Siderosis is mild and has a mixed parenchymal/mesenchymal distribution. This finding suggests that there is unlikely to be significant liver injury related to genetic iron overload". The diagnosis as stated on the pathology report was severe hepatitis (acute-on-chronic) with questionable cause.

A follow-up with the consultant physician and gastroenterologist on study day 349 indicated that while there was some subtle improvement in the subject's liver function, there was clearly an ongoing hepatitis. The subject complained of tiredness, weakness and ankle edema. According to the gastroenterologist, the liver biopsy results raised the possibility of an underlying chronic hepatitis in addition to a recent hepatic insult. There were some features, which supported an autoimmune etiology, although this could all be due to the drug reaction. Differential diagnoses at this point included drug induced hepatitis (secondary to trial drug dapagliflozin), haemochromatosis (compound heterozygote for C282Y/H63 D mutation) and possible chronic hepatitis, questionable autoimmune. A trial of prednisolone 20 mg daily for 4 weeks was initiated and furosemide was increased to 40 mg daily for ankle edema.

A gastroenterologist follow-up report on study day 363 stated a marked improvement in the subjects liver enzymes. ALT had decreased to 166 U/L after commencing steroids. The subject developed lower back pain that radiated down his left leg suggestive of sciatica. The subject also experienced weight loss. Bone prophylactic medication was recommended. A magnetic resonance image (MRI) report of the spine lumbar/sacral and pelvis and hips on study day 377 revealed appearances most likely in keeping with osteoporotic fracture collapse, acute at lumbar 3 level and vertebral collapse of thoracic 12 level. There were abnormal signal changes within

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00004-4402-6

the left femoral head and upper shaft. The appearances of the lumbar spine and left femur most likely represented "transient osteoporosis" of the left hip. The possibility of metastatic disease was low. An isotope bone scan has been requested to exclude metastatic disease. A rheumatologist consult was requested at this point.

A gastroenterologist consult on study day 382 stated that the subject's LFTs demonstrated a dramatic improvement one month after the introduction of prednisolone. Prednisolone was tapered to 15 mg once daily and azathioprine 75 mg once daily was added. Additionally the subject was noted to have difficulty mobilizing despite treatment with acetaminpohen+codeine, and tramadol. Administration of calcium carbonate and cholecalciferol was recommended.

A rheumatology consult with a clinic date of study day 389 noted "that there was a possibility that the subject had chronic autoimmune hepatitis, he did have an episode of drug induced hepatitis at the end of 2008 and also his combined heterozygote for haemochromatosis." He had fractures of T 12 and L 3 vertebral bodies which have left him with severe back pain. Additionally it was noted that the subject was Indian and did not take any herbal medications.

At a visit on study day 475, the subject was clinically much better. His liver function was stabilized and his back pain significantly better although he relied on regular analgesia. Prednisolon has subsequently been down titrated and was discontinued on study day 475. Azathioprin 50 mg once a day was continued. The diagnosis recorded in the medical record at the visit were: Drug Hepatotoxicity due to trial drug dapagliflozin, Probable autoimmune hepatitis, Compound heterozygote for C282Y/H63D mutation for heamochromatosis, Type 2 diabetic and Osteoporosis with vertebral crush factors.

At a visit on study day 621, the subject was clinically very well. His liver function test was stable with ALT of 64 U/L. He had a mild thrombocytopenia with platelet count of around 90, but his blood count was otherwise normal. As of June 2012, the patient is still being treated for autoimmune hepatitis with subsequent episodes of ALT increases (ALT 11 x ULN on Day 704, ALT 3.6 x ULN on Day 1132.

Date	Day	ALT		AST		ALP		Bilirubin	
		U/L	xULN	U/L	xULN	U/L	xULN	mg/dL	xULN
07-may-08[a]	-24	47	0.98	35	0.78	73	0.50	0.4	0.33
31-may-08[a]	1	53	1.10	39	0.87	75	0.52	0.3	0.25
19-jul-08[a]	50	32	0.67	27	0.6	54	0.37	0.3	0.25
23-aug-08[a]	85	62	1.29	47	1.04	54	0.37	0.4	0.33
04-okt-08 [a]	127	117	2.44	72	1.60	53	0.37	0.4	0.33
29-nov-08 [a]	183	1204	25.08	825	18.33	103	0.71	0.7	0.58
05-dec-08 [a]	189	1498	31.21	853	18.96	117	0.81	1.2	1.00
09-dec-08 [a]	193	1748	36.42	1060	23.56	120	0.83	2.5	2.08
16-dec-08[b]	200	1858	37.16			128	1.07	4.2	2.80
29-dec-08 [a]	213	805	16.77	374	8.31	133	0.92	2.4	2.00
12-jan-09 [b]	227	431	8.62			98	0.82	1.8	1.20
03-feb-09 [b]	249	729	14.58			149	1.24	2.1	1.40
04-mar-09 [b]	278	439	8.78			162	1.35	1.1	0.73
27-mar-09 [b]	301	524	10.48			216	1.80	1.1	0.73
28-apr-09 [b]	333	498	9.96			302	2.52	1.5	1.00
28-maj-09 [b]	363	166	3.32						

Dapagliflozin
BMS-512148
Hepatic Adjudication Report

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00004-4402-6

Date								
28-maj-09 [b]	363	166	3.32					
16-jun-09 [b]	382	77	1.54		354	2.95	0.8	0.53
07-jul-09 [b]	403	60	1.20		267	2.23	0.8	0.53
13-aug-09 [b]	440	54	1.08		156	1.30	0.6	0.40
02-nov-09 [b]	521	50	1.00		95	0.79	0.5	0.33
10-feb-10 [b]	621	64	1.28		71	0.59	0.5	0.33
18-feb-10 [b]	629	64	1.28					
04-maj-10 [b]	704	563	11.26					
14-maj-10 [b]	714	569	11.38		94	0.78	1.5	0.97
18-jun-10 [b]	749	105	2.10					
10-nov-10 [b]	894	29	0.58		51	0.43	0.3	0.19
16-feb-11 [b]	992	111	2.22		74	0.62	0.3	0.19
10-jun-11 [b]	1106	91	1.82					
06-jul-11 [b]	1132	180	3.60		67	0.56	0.5	0.31
27-sep-11 [b]	1215	40	0.80		45	0.38	0.7	0.47
11-jan-12 [b]	1321	17	0.34		40	0.33	0.4	0.27

a Central laboratory, reference ranges: ALT: 6 48 U/L, AST: 10 45 U/L, ALP 45 145 U/L, Bilirubin: 0.2 1.2 mg/dL

b Local laboratory, reference ranges: ALT: 10 50 U/L, ALP 30 120 U/L, Bilirubin: 0.2 1.5 mg/dL

Viral hepatitis screening was negative for HBsAg, Hepatitis B Core Total Antibody (AHBc) and Hepatitis A IgM and no serological evidence of recent Hepatitis A infection was noted. An elevated IgG 22.4 g/L (reference range 5.3-16.5), IgA 8.93 g/L (0.80-4.00) and IgM 2.90 g/L (reference range 0.50-2.00) were noted on 22-May-2009 (day 357) .

Autoimmune antibody screen was negative for antiliver/kidney microsome type 1, antismooth muscle autoantibody, mitochondrial antibody, antinuclear antibody and Cytomegalovirus (CMV) IgM antinuclear antibody on 01-Jun-2009 (day 365). CMV IgG and Epstein-Barr nuclear antigen (EBNA) IgG antibody were positive. An elevated IgM of 2.92 g /L, IgA 7.55 g/L and IgG 20.2 g/L was also noted. Additionally serum transferrin was 2.3 g/L, transferrin saturation index was 54 % and serum iron level was elevated at 31micromol/L. On 02-Jun-2009 (day 366), results were negative for Hepatitis E IgM and IgG by enzyme immunoassay (reference range not provided).
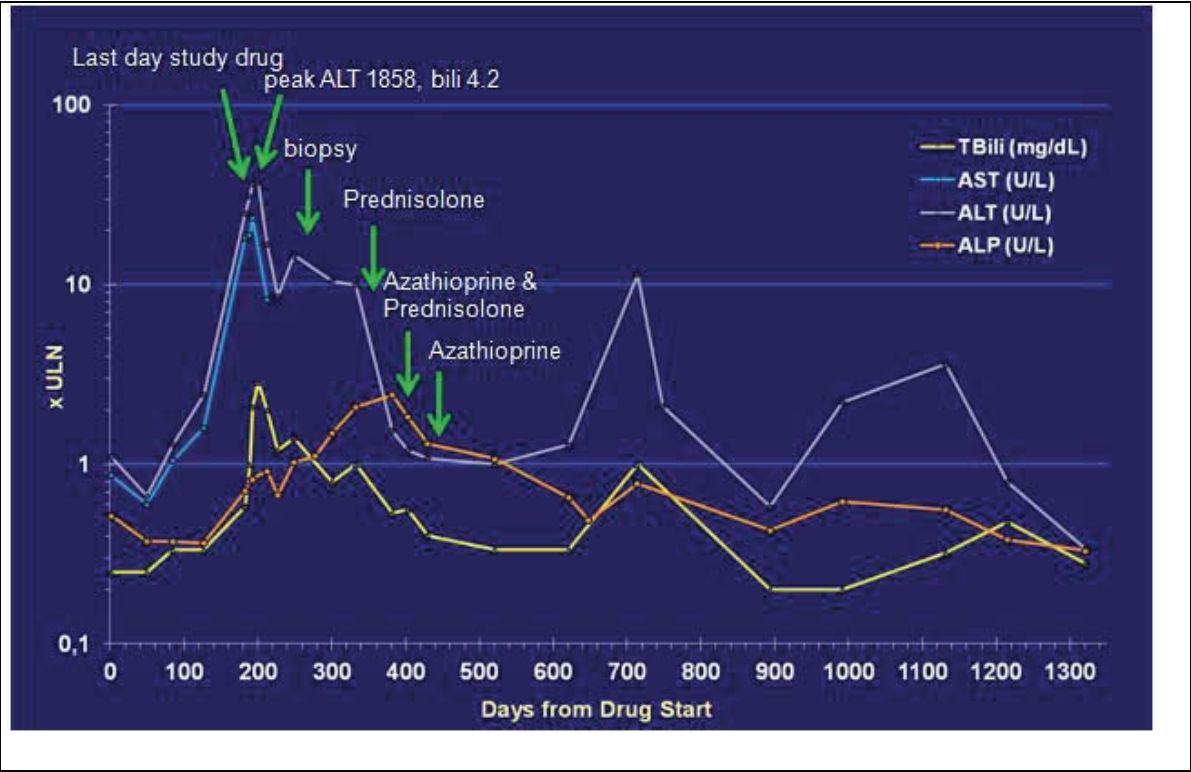
Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00004-4402-6

Dapagliflozin
BMS Compound Number512148   Hepatic Adjudication Report

Patient Identifier: D1690C00005-7002-4

Event: [1] BILE DUCT STONE (Common bile duct stone, Day 333 - C, VERY SEVERE / GRADE IV, NOT RELATED); [2] Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 334); [3] Marked laboratory abnormality - ALT > 5X ULN (DAY 337); [4] LUNG NEOPLASM (Non-enhancing nodules at upper lobes of lung, Day 350 - C, MODERATE / GRADE II, NOT RELATED)

Reason(s) for Narrative: (check all that apply)	[ ] Death
	[1]; [4] SAE (regardless of relationship to treatment)
	[ ] AE leading to discontinuation (regardless of relationship to treatment)
	[2]; [3] Other significant medical event

Serious criteria other than Death:	**Life thr.**	**Hosp.**	**Dis./Incap.**	**Cong. abn.**	**Cancer**	**Dep./Abu.**	**Imp. event**
	[1] YES	[1] YES; [4] YES					[1] YES; [4] YES

Study Medication/Dose: GLI 4 MG (DAY -63 - -1); DAPA 2.5MG + GLI 4 MG (DAY 1 - 230); *DAPA 2.5MG + GLI 4 MG + MET 500 MG (DAY 231 - 262); *DAPA 2.5MG + GLI 4 MG (DAY 263 - 334); *MET 500 MG (DAY 335 - 355)

Treatment Group: DAPA 2.5MG + GLI	**Date of First Dose:** (b) (6)

Age: 60 YEARS	**Gender:** FEMALE	**Race:** ASIAN	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (2003); HYPERTENSION (26JAN2006); DYSLIPIDEMIA (10APR2006); ESTROGEN DEFICIENCY (1998); NOCTURIA (07JUN2006)

General Medical History: Glaucoma, Thyroid nodule; Hypertension; Nocturia; Diabetes Mellitus Type 2, Dyslipidemia, Esteogen deficiency. Smoking: NEVER. Alcohol use: NONE.

Adverse events during study: NASOPHARYNGITIS (cold, Day 80 to 90, MODERATE / GRADE II, NOT RELATED); VOMITING (Nausea with vomiting, Day 173 to 177, MODERATE / GRADE II, NOT RELATED); GASTRITIS (Gastritis, Day 176 to 180, MODERATE / GRADE II, NOT RELATED)

Concomitant Medication(s): ENALAPRIL (Day >=-90 - C); SIMVASTATIN (Day >=-90 - C); ACETAMINOPHEN (Day -42 - -40); LORATADINE (Day -42 - -40); ACETAMINOPHEN (Day 81 - 84); BROMHEXINE (Day 82 - 84); ALOH/MGOH (Day 176 - 180); OMEPRAZOLE (Day 333 - 337); SCOPOLAMINE (Day 333 - C); SIMETHICONE (Day 333 - 337); CIPROFLOXACIN (Day 341 - 347); CEFTRIAXONE (Day 348 - 349); OMEPRAZOLE (Day 348 - C)

Background Medication(s): GLYBURIDE (Day >=-90 - -64); GLIMEPIRIDE (Day -63 - 334); METFORMIN (Day 231 - 262); GLICLAZIDE (Day 335 - C); METFORMIN (Day 335 - C)

Clinical Summary:
[1] Symptoms: Stomachache, fatigue, and anorexia
Diagnostic investigations: U/S upper abdomen: 1.a small cyst at the Lt lobe of liver 2.a small stone at the distal CBD 3. Sludge and multiple sand stones, without evidence the cholicystitis 4. Chronic parenchymal kidney disease.
Treatment: 1. Retest liver function. ultrasound. 2. ERCP on 05 April 2010 but could not remove stone and plan to perform this procedure in the future. 3. Stent insertion.
Other comments: 1.mild tenderness at epigastrium Rt upper quarant 2. Liver: just palpable span 10 cm 3.

Approved v1.0   930070564 1.0

Dapagliflozin
BMS Compound Number512148   Hepatic Adjudication Report

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mild jaundice 4. no fever

Hospitalized: Day 347 to 351

Action taken, investigational product: NONE

AE outcome: DID NOT RESOLVE

[4] Symptoms: No

Diagnostic investigations: Two small non-enhancing nodules at upper lobes associated with adjacent small centrilobular nodules.

Treatment: 1. Performed CT Chest on 07 April 2010 2. Plan to perform bronchoscopy

Other comments: Tree-in-bud appearance is favorable for post primary TB with possible tuberculoma and endobronchail spread

Hospitalized: Day 347 to 351

Action taken, investigational product: NONE

AE outcome: DID NOT RESOLVE

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00005-6013-3

Event: [1] LIVER FUNCTION TEST ABNORMAL (Elevated liver tests, Day 85 - C, MODERATE / GRADE II, NOT RELATED); [2] Marked laboratory abnormality -
(AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 141); [3] Marked laboratory abnormality - ALT > 5X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 148)

Reason(s) for Narrative:	[ ] Death
(check all that apply)	[ ] SAE (regardless of relationship to treatment)
	[1] AE leading to discontinuation (regardless of relationship to treatment)
	[1]; [2]; [3] Other significant medical event

Serious criteria other than Death:	**Life thr.**	**Hosp.**	**Dis./Incap.**	**Cong. abn.**	**Cancer**	**Dep./Abu.**	**Imp. event**

Study Medication/Dose: DAPA 5MG + GLI 4 MG (DAY 1 - 112); GLI 4 MG (DAY 113 - 118); DAPA 5MG + GLI 4 MG (DAY 119 - 141); GLI 4 MG (DAY 142 - 161)

Treatment Group: DAPA 5MG + GLI	**Date of First Dose:** (b) (6)

Age: 83 YEARS	**Gender:** MALE	**Race:** WHITE	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (07JUL2008)

General Medical History: Cataracta of the left eye (operated); crural varices; Suspicion of teniasis chronical gastritis; Calculus of the gallbladder; Type 2 Diabetes Mellitus; spondyloarthrosis. Smoking: NEVER. Alcohol use: OCCASIONAL.

Adverse events during study: DYSPEPSIA (heartburn, Day 50 to 84, MODERATE / GRADE II, NOT RELATED)

Concomitant Medication(s): ALBENDAZOLE (Day >=-90 - C); NUTRITIONAL SUPPLEMENT (Day 1 - C); PANTOPRAZOLE (Day 57 - 84)

Background Medication(s): ANTIDIABETIC (Day -96 - -1); GLIMEPIRIDE (Day 1 - 161); ANTIDIABETIC (Day 162 - C)

Clinical Summary:

[1] Action taken, investigational product: DRUG WAS DISCONTINUED

AE outcome: DID NOT RESOLVE

Treatment required: NO

The subject is a 83 year old white male, overweight with BMI of 27 and type 2 diabetes mellitus since 2008. The relevant medical history consists of obstructive jaundice due to chledocholithiasis in January 2008. Ultrasound in January 2008 showed deposits with diameter 14 mm. The subject was hospitalized 17-19 Jan 2008 in the Surgery Department. The endoscopic papilotomy was performed. Elective cholecystectomy was recommended, but the subject didn´t consent to the surgery. During the study the subject had two episodes of elevated liver tests (on day 85, 93 and on day 141, 148). During the first episode, increased liver enzymes normalized on study medication. During the second episode, the subject was discontinued from the study medication on Day 141. Study medication was stopped temporarily from study day 113 to 119 (stopped the same day as normal LFTs were recorded). The maximal increase to ALT > 5 x ULN (271 U/L) and TBL > 2 x ULN (2.7 mg/dL) was observed on day 148 (7 days after discontinuation of the study drug). After day 148 the liver tests gradually decreased and remained normal during the follow-up. Hepatitis serology was negative. During the episodes of LFT elevation the subject had no symptoms and the ultrasound performed 10 days after discontinuation showed cholecystolithiasis with

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hyperechogenic and thickened wall of the gallbladder and no distension of common bile duct. The subject takes albendazole PRN (due to teniasis) and he drunk herbal tea of St. Johns Wort and fern before day 84 and day 141, the maximal dose was 3 glasses per day. During the follow-up period the liver tests remained normal (local labs were performed in June 2009 and February 2010).

Study Day of Lab Assessment	ALT (U/L)	AST (U/L)	ALP (U/L)	Total Bilirubin (mg/dL)
-9	28	18	85	0.5
1	29	19	86	0.6
29	29	19	75	0.5
57	23	20	83	0.5
85	178#	61	236#	1.5
93	206#	138#	273#	1.5
113	28	25	101	0.8
141	210#	123	128	2.3#
148	271##	125	126	2.7##
162	95	35	115	1.8
176	63	32	152	1.2
484	18.6	18.2		0.68

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00006-2004-6

Event: [1] PANCREATIC CARCINOMA (pancreatic cancer, Day 112 - C, SEVERE / GRADE III, NOT RELATED); [2] Marked laboratory abnormality - (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 131); [3] Marked laboratory abnormality - (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 132); [4] Marked laboratory abnormality - (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 134); [5] Marked laboratory abnormality - ALT > 5X ULN; AST > 5X ULN; (AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 153)

Reason(s) for Narrative: (check all that apply)	[ ] Death
	[1] SAE (regardless of relationship to treatment)
	[1] AE leading to discontinuation (regardless of relationship to treatment)
	[2]; [3]; [4]; [5] Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp. event
		[1] YES			[1] YES		

Study Medication/Dose: INS + MET (DAY -14 - -1); DAPA 10MG + INS + MET (DAY 1 - 130); INS + MET (DAY 131 - 147); INS (DAY 148 - 153)

Treatment Group: DAPA 10MG + INS	Date of First Dose:

Age: 62 YEARS	Gender: MALE	Race: WHITE	Ethnicity: NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (SEP1995); HYPERTENSION (MAR2001); DYSLIPIDEMIA (17JUL2007)

General Medical History: Psoriasis. Smoking: FORMER; CIGARETTES 40 PER DAY for 31 YEARS; Stopped 1993. Alcohol use: 1-2 DRINKS WEEKLY.

Adverse events during study: WEIGHT DECREASED (weight loss, Day 84 - C, MODERATE / GRADE II, NOT RELATED); ABDOMINAL PAIN UPPER (stomachal pain, Day 97 - C, MILD / GRADE I, NOT RELATED); DECREASED APPETITE (lack of appetite, Day 97 - C, MILD / GRADE I, NOT RELATED); DIARRHOEA (diarrhoea, Day 97 - C, MILD / GRADE I, NOT RELATED); ASTHENIA (astenia, Day 130 - C, MODERATE / GRADE II, NOT RELATED); JAUNDICE (ictericia, Day 130 - C, MODERATE / GRADE II, NOT RELATED)

Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >=-90 - 147); AMLODIPINE (Day >=-90 - 147); ATORVASTATIN (Day >=-90 - 147); HYDROCHLOROTHIAZIDE (Day >=-90 - C); IRBESARTAN (Day >=-90 - 147); OMEPRAZOLE (Day 97 - C); ACETAMINOPHEN (Day 147 - C); CHLORQUINALDOL (Day 147 - C); DEXAMETHASONE (Day 147 - C)

Background Medication(s): INSULIN (Day -231 - C); METFORMIN (Day >=-60 - 147)

Clinical Summary:

The subject is a 62 year old male patient, obese with a BMI of 37 and type 2 diabetes mellitus since 1995. The patient is a former smoker and had an alcohol use of one to two drinks weekly.

On day 84 the moderate event of weight decrease started. On day 97 further events of anorexia, upper abdominal pain and diarrhoea started. On day 112 the event of pancreatic cancer started and the patient was hospitalised on day 130. On the same day jaundice and asthenia begun. The final diagnosis was pancreas carcinoma with hepatic metastases. The study drug was stopped on day 130. Treatment with acetaminophen, chlorquinaldol and dexamethasone started on day 147. The patient was discharged on day 147 in not recovered condition. The patient left the study on day 152. Afterwards it was reported that the patient died in day 159.

Lab Test (Unit)	Reference Range	Study Day	Result
Alanine Aminotransferase (ALT) (U/L)	6 - 48	-9	20
		1	25
		8	21
		28	32
		53	32
		84	30
		112	132
	5 - 40	131	§157
		132	§191
		134	§142

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: D1690C00006-2004-6

	6 - 48	153	360
Aspartate Aminotransferase (AST) (U/L)	10 - 45	-9	17
		1	15
		8	18
		28	25
		53	24
		84	17
		112	110
	4 - 50	131	§156
		132	§202
		134	§132
	10 - 45	153	326
Bilirubin, Total (MG/DL)	0.2 - 1.2	-9	0.5
		1	0.4
		8	0.6
		28	0.8
		53	0.6
		84	0.5
		112	2
		131	§8.15
		132	§9.44
		134	§11.28
		153	31.6
§ Indicates spontaneously reported local lab value.			

Patient Identifier: D1690C00018 201 8 Approved v1.0   930070564 1.0

Reason(s) for Narrative: (check all that apply)	[ ] Death
	[X] SAE (regardless of relationship to treatment)
	[X] AE leading to discontinuation (regardless of relationship to treatment)
	[ ] Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp. event
		X					X

Study Medication/Dose: DAPA 10 MG

Treatment Group:	Date of First Dose: (b) (6)

Age:	Gender:	Race:	Ethnicity:
71 YEARS	MALE	WHITE	NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (2009)

General Medical History: Myocardial Infarction (1996), Pacemaker (2009), Hypertension (1996), Coronary heart disease (1996), Appendicular peritonitis. Smoking: Former smoker (20 cigarettes/day for 39 years, quit in May 2009). Alcohol use: Occasional.

Adverse events during study: B12 VITAMIN DEFFICIENCY Day>= 90   C, MODERATE / GRADE II, NOT RELATED); HEPATITIS (Hepatitis, Day 289 297, MODERATE / GRADE II, CERTAIN); INFLUENZA (Flu, Day 3   1, MILD, NOT RELATED); ASPARTATE AMINOTRANSFERASE INCREASED (AST elevation, Day 314   321, MILD / GRADE I, NOT RELATED); BLOOD BILIRUBIN INCREASED (Total Bilirubin elevation, Day 314 321, MILD / GRADE I, NOT RELATED); URINARY TRACT INFECTION (Urinary Infection, Day 328   332, MODERATE / GRADE II, NOT RELATED); AMINOTRANSFERASE INCREASED (AST elevation, Day 326   349, MILD /GRADE I, NOT RELATED); ALANINE AMINOTRANSFERASE INCREASED (AST elevation, Day 326 349, MILD / GRADE I; NOT RELATED)

Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >= 90   C); SCOPOLAMINE (Day 289   289), METOCLOPRAMIDE (Day 289   289); RANITIDINE (Day 289   291, 291 297)

SIMVASTATIN (Day 289   290); CYANOCOBALAMIN (Day 297   C); METFORMIN (Day > = 90   289); INSULIN (Day 297   297, 297 C); LOSARTAN (Day > = 90   289); ATENOLOL (Day > = 90   289); CARVEDILOL (Day 289   C); ENALAPRIL (Day 291   C)

Background Medication(s):

Clinical Summary: On Day 289, the subject was hospitalized in the evening with diffuse abdominal pain (non colic) predominantly in the epigastric and right hypochondrial region, nausea and vomiting since 6 hours. Lab results revealed elevated ALT, AST, ALP and TBL, temperature 38.3 degree. The patient took the last dose of study medication in the morning on Day 289. On Day 290 the subject was significantly improved. Abdominal ultrasound (suboptimal) revealed no signs of obstruction or dilation. Treatment included parenteral hydration, hyoscine, metoclopramide, ranitidin, enoxaparin, simvastatin, vitamin B12 and insulin. Three days before the event the patient had more than 3 drinks at one occasion.

Liver tests peaked on Day 290. On Day 293, the subject had no fever and liver tests had decreased significantly. A repeated abdominal ultrasound revealed steatosis and a pancreas with a pattern of fatty infiltration. No biliary obstruction or dilation. The subject was discharged on Day 297. He was diagnosed with toxic hepatitis with no documented etiology.

On Day 314, a new peak of LT elevations was recorded. By this time, the subject didn't have any symptoms. It was noted that the patient had lost 9.5 kg from baseline to day 314.

On Day 326, the subject was hospitalized with abdominal pain, bradypsychia, dysuria, bad smelling urine, and vomiting. Urine culture revealed E.coli. He was diagnosed with UTI and treated with Ceftriaxone and Ciprofloxacin. Laboratory tests revealed   ALT 149 U/L (reference range 10 49 U/L) and AST 110 U/L (reference range 3 34 U/L).. On Day 329 liver enzymes were ALT 66 U/L, AST 28 U/L ALP, 493 U/L

(reference range 90 360 U/L), Total Bilirubin, 1.14 mg% (reference range 0.3 1.2 mg%) and Direct Bilirubin 0.39 mg% (reference range 0 0.2 mg%). The patient recovered and was discharged on Day 332.

On Day 342, he visited the site. Laboratory results still revealed elevated liver tests.

Since the hospitalization Day 326 to 332 the subject has not had any symptoms from the abdomen or urinary tract. A CT abdomen was performed Day 360 which showed "Discrete thickening of the gallbladder wall with uptake of the IV contrast agent, which may correspond to an inflammatory process", preserved calibre of the intrahepatic and extrahepatic biliary tract and no other abnormalities.

Sponsor causality assessment: hepatitis was not likely to be related to study therapy (pending adjudication).

Subject Identifier	Lab Test (Unit)	Reference Range	Study Day	Result	ULN
D6190C000018-201-8	Alkaline Phosphatase (ALP) (U/L)	Central 45-145 Local -360*	-39	180	1,2
			1	164	1,1
			9	141	1,0
			30	146	1,0
			57	126	0,9
			114	134	0,9
			177	115	0,8
			198	137	0,9
			261	152	1,0
			289ᵃ	547*	1,5
			290	607*	1,7
			291	515*	1,4
			293	547*	1,5
			295	577*	1,6
			300	290	2,0
			314	433	3,0
			316	897*	2,5
			321	338	2,3
			329	493*	1,4
			342	721	5,0
			349	372	2,6
	Alanine Aminotransferase (ALT) (U/L)	Central 6-48 Local -49*	-39	19	0,4
			1	13	0,3
			9	14	0,3
			30	16	0,3
			57	18	0,4
			114	15	0,3
			177	11	0,2
			198	11	0,2
			261	11	0,2
			289ᵃ	150*	3,1
			290	504*	10,3
			291	287*	5,9
			293	133*	2,7
			295	101*	2,1
			300	66	1,4
			314	189	3,9
			316	115*	2,3
			321	48	1
			326	149*	3,0
			329	66*	1,3
			342	233	4,9
			349	53	1,1

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Subject        Lab Test (Unit)        Reference Range    Study      Result    ULN
Identifier                                               Day
D6190C000018-  Alkaline Phosphatase   Central 45-145
201-8          (ALP) (U/L)            Local -360*          -39        180      1,2
                                                             1        164      1,1
                                                             9        141      1,0
                                                            30        146      1,0
                                                            57        126      0,9
                                                           114        134      0,9
                                                           177        115      0,8
                                                           198        137      0,9
                                                           261        152      1,0
                                                           289ᵃ       547*     1,5
                                                           290        607*     1,7
                                                           291        515*     1,4
                                                           293        547*     1,5
                                                           295        577*     1,6
                                                           300        290      2,0
                                                           314        433      3,0
                                                           316        897*     2,5
                                                           321        338      2,3
                                                           329        493*     1,4
                                                           342        721      5,0
                                                           349        372      2,6

               Alanine
               Aminotransferase (ALT)  Central 6-48
               (U/L)                   Local -49*           -39         19      0,4
                                                             1         13      0,3
                                                             9         14      0,3
                                                            30         16      0,3
                                                            57         18      0,4
                                                           114         15      0,3
                                                           177         11      0,2
                                                           198         11      0,2
                                                           261         11      0,2
                                                           289ᵃ       150*     3,1
                                                           290        504*    10,3
                                                           291        287*     5,9
                                                           293        133*     2,7
                                                           295        101*     2,1
                                                           300         66      1,4
                                                           314        189      3,9
                                                           316        115*     2,3
                                                           321         48      1
                                                           326        149*     3,0
                                                           329         66*     1,3
                                                           342        233      4,9
                                                           349         53      1,1
```

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Patient Identifier: D1690C00018-203-4

Event: [1] CHOLELITHIASIS (cholelithiasis, Day 549 to 624, MILD / GRADE I, NOT RELATED);
[2] Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN;
(AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN; Total Bilirubin > 2X ULN
(DAY 549); [3] HYPERGLYCAEMIA (hyperglycemia, Day 625 to 626, MODERATE / GRADE II,
NOT RELATED)

Reason(s) for Narrative: (check all that apply)	[ ] Death [1]; [3] SAE (regardless of relationship to treatment) [ ] AE leading to discontinuation (regardless of relationship to treatment) [2] Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp.event
		[1] YES; **[3] YES**					

Study Medication/Dose: INS (DAY -34 - -29); PLA + INS (DAY -28 - -1); DAPA 10MG + INS
(DAY 1 - 219); *DAPA 10MG + INS (DAY 220 - 268); *#DAPA 10MG + INS + SU
(DAY 269 - 308); *#DAPA 10MG + INS (DAY 309 - 314); *#DAPA 10MG + INS + MET (DAY 315 -
620); *#DAPA 10MG + INS (DAY 621 - 639); *#DAPA 10MG + INS + MET (DAY 640 - 731);
*#INS + MET (DAY 732 - 750)

Treatment Group: DAPA 10 MG	**Date of First Dose:** (b) (6)

Age: 70 YEARS	**Gender:** MALE	**Race:** WHITE	**Ethnicity:** HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (1997); CORONARY ARTERY DISEASE (CAD)
(1988); PREVIOUS MI (1988); HYPERTENSION (2004); BENIGN PROSTATIC HYPERTROPHY
(19APR2006); OVERACTIVE BLADDER (APR2010)

General Medical History: acute myocardial infarction, hypertension; gallstones; erectile dysfunction.
Benign Prostatic Hypertrophy; diabetes type 2, hypothyroidism, osteopenia; spinal osteoarthritis, night
cramps, paresthesias in lower limbs, difficulty with walking. Smoking: NEVER. Alcohol use:
OCCASIONAL.

Adverse events during study: URINE OUTPUT INCREASED (increased urine volume,
Day 1 - C, MILD / GRADE I, NOT RELATED); BALANITIS CANDIDA (Penile candidiasis, Day 4 to
10, MILD / GRADE I, NOT RELATED); FLATULENCE (flatulence, Day 25 to 176, MILD / GRADE
I, NOT RELATED); ANXIETY (Anxiety, Day 47 to 117, MILD / GRADE I, NOT RELATED);
PERIORBITAL CELLULITIS (left periorbital cellulitis, Day 99 to 117, MILD / GRADE I, NOT
RELATED); BALANITIS (balonitis, Day 117 to 177, MILD / GRADE I, CERTAIN); ARTHRALGIA
(bilateral gonartralgia, Day 148 to 367, MILD / GRADE I, NOT RELATED); BALANOPOSTHITIS
(balanopostitis, Day 202 to 228, MILD / GRADE I, NOT RELATED); HYPERTENSION (worsening
of hypertension, Day 269 to 309, MILD / GRADE I, NOT RELATED); HYPERPARATHYROIDISM
SECONDARY (normocalcemic secondary hyperparathyroidism, Day 357 - C, MILD / GRADE I,
CERTAIN)

Concomitant Medication(s): SILDENAFIL (Day >=-90 - C); LEVOTHYROXINE (Day -13 - C);
BETATP/GENTOP/MICNTP (Day 6 - 11); ACETAMINOPHEN (Day 101 - 110); AMOXICILLIN
(Day 101 - 110); CEPHALEXIN (Day 101 - 117); CLAVULANIC ACID (Day 101 - 110);
IBUPROFEN (Day 101 - 110); BETATP/GENTOP/MICNTP (Day 117 - 170); GLUCOSAMINE (Day
163 - 177); MELOXICAM (Day 163 - 177); NUTRITIONAL SUPPLEMENT
(Day 220 - 237); BETATP/GENTOP/MICNTP (Day 221 - 232); CEFADROXIL (Day 221 - 228);
CHOLECALCIFEROL (Day 364 - 425); SCOPOLAMINE (Day 549 - 553)

Background Medication(s): INSULIN (Day -463 - C); AMLODIPINE (Day >=-90 - C);
GLYBURIDE (Day 269 - 308); METFORMIN (Day 315 - 620); METFORMIN (Day 640 - C)

Dapagliflozin
BMS-512148

Hepatic Adjudication Report

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Patient Identifier: D1690C00018-203-4

Clinical Summary:

A 72-year- old male Caucasian treated with dapagliflozin + metformin + insulin experienced MAs of ALT and ALT >10x ULN and TB> 2x ULN on Study Day 549. The subject had a history of gallstones and an abdominal ultrasound performed on Study Day 550 showed multiple mobile gallbladder lithiasis. He got treatment with scopolamine but was not hospitalized and the liver enzyme elevations declined. On Study Day 623 he underwent a cholecystectomy and the AE was reported as resolved. No action was taken regarding the study medication and the subject completed the study.

[1] Symptoms: cholelithiasis was detected on 23-mar-2012 and cholecystectomy was scheduled

Diagnostic investigations: new sonography was performed on 31-may-2012 confirming cholelithisis and cholecystectomy was scheduled to 05-jun-2012

Treatment: cholecystectomy by videolaparoscopy

Other comments: Patient was admitted on ⬛⬛⬛ (b) (6) and surgery was carried out on ⬛⬛⬛ (b) (6).

On ⬛⬛⬛ (b) (6) was discharged

Hospitalized: Day 623 to 626

Action taken, investigational product: NONE

AE outcome: RESOLVED

[3] Symptoms: Patient was hospitalized on ⬛⬛⬛ (b) (6) due to cholelithiasis. During hospitalization, presented hyperglycemia that caused prolongation of hospitalization.

Diagnostic investigations: hyperglycemia was not recorded at medical records

Treatment: regular insulin corrections were indicated from ⬛⬛⬛ (b) (6). Only were administered to patient on ⬛⬛⬛ (b) (6)

Other comments: As per medical records no available data about hyperglycemia was found neither glycemic value or treatment information

Hospitalized: Day 624 to 626

Action taken, investigational product: NONE

AE outcome: RESOLVED

Sponsor causality assessment: Unlikely

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Patient Identifier: D1690C00018-203-4

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-----------------------------------------------------------------------------
Lab Test (Unit)                          Reference Range    Study Day    Result
-----------------------------------------------------------------------------
Alanine Aminotransferase (ALT) (U/L)         6 - 48            -34          23
                                                                1          34
                                                                8          22
                                                               29          23
                                                               57          23
                                                              113          24
                                                              163          15
                                                              197          20
                                                              220          19
                                                              253          22
                                                              309          19
                                                              367          29
                                                              458          26
                                                              549         642
                                                              554         181
                                                              557          92
                                                              591          17
                                                              640          21
                                                              731          24
                                                              750          30


Aspartate Aminotransferase (AST) (U/L)      10 - 45            -34          19
                                                                1          20
                                                                8          23
                                                               29          18
                                                               57          17
                                                              113          18
                                                              163          17
                                                              197          20
                                                              220          20
                                                              253          18
                                                              309          17
                                                              367          25
                                                              458          21
                                                              549         631
                                                              554          57
                                                              557          29
                                                              591          17
                                                              640          15
                                                              731          18
                                                              750          19
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Dapagliflozin
BMS-512148

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Patient Identifier: D1690C00018-203-4

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-------------------------------------------------------------------------------
Lab Test (Unit)                        Reference Range    Study Day    Result
-------------------------------------------------------------------------------
Bilirubin, Total (MG/DL)                 0.2 - 1.2            -34         0.7
                                                               1         1
                                                               8         0.9
                                                              29         0.8
                                                              57         0.8
                                                             113         1
                                                             163         1
                                                             197         0.8
                                                             220         0.6
                                                             253         0.6
                                                             309         0.7
                                                             367         0.8
                                                             458         1.1
                                                             549         3.4
                                                             554         0.7
                                                             557         0.5
                                                             591         1
                                                             640         0.7
                                                             731         0.7
                                                             750         0.9
```

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Patient Identifier: MB102029-4-276

Event: CREATININE >= 1.5X Baseline (DAY 14); HYPOTENSION (SEVERE / GRADE III INTENSITY, POSSIBLE RELATIONSHIP, DAY 14); ALT > 5X ULN (DAY 173); AST > 5X ULN (DAY 173); HEPATIC ENZYME INCREASED (SEVERE / GRADE III INTENSITY, NOT LIKELY RELATIONSHIP, DAY 174); ALT > 5X ULN (DAY 175); AST > 5X ULN (DAY 175)

Reason(s) for Narrative: (check all that apply)	☐ Death X SAE (possibly, probably, or certainly related to treatment) X AE leading to discontinuation (regardless of relationship to treatment) X Other significant medical event

Study Medication/Dose: PLA (DAY -7 - -1); DAPA 10 MG (DAY 1 - 14); DAPA 10 MG (DAY 16 - 66); DAPA 10 MG (DAY 68 - 175)

Treatment Group: DAPA 10 MG	**Date of First Dose:** [(b) (6)]

Age: 83 YEARS	**Gender**: MALE	**Race:** WHITE	**Ethnicity**: NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLI (1992); DIABETIC NEUROPATHY (22OCT1997); DIABETIC RETINOPATHY (2002); DIABETIC NEPHROPATHY (03JUN2003)

General Medical History: DEGENERATIVE LUMOSACRAL SPINAL DISEASE; ARTHRITIS (PRIMARILY OF RIGHT HAND AND LEFT THUMB). SEE OTHER FOR KNEE SURGERY.; DIABETIC NEPHROPATHY; DIABETIC NEUROPATHY; DIABETIC RETINOPATHY; HX OF ACUTE OTITIS MEDIA & EXTERNA; HX OF GLAUCOMA; HX OF CATARACTS. RIGHT EYE CORNEA TRANSPLANT IN NOV. OF 2008. SEE OTHER.; FLUSHING WITH ADVICOR; HX OF ANEMIA; HX OF HYPERKALEMIA INDUCED BY DIAMOX.; HX OF BRONCHITIS; HX OF PNEUMONIA; HX OF ASTHMA; HX OF HEPATITIS (JAUNDICE) IN WORLD WAR II; CAUSE OF THIS HEPATITIS WAS UNDETERMINED, TREATED WITH "LIGHT DUTY", AND RESOLVED ON ITS OWN; EPISODE OF JAUNDICE IN THE 70'S.; HX OF LEG ULCER; HX OF REMOVAL OF SKIN LESION FROM NOSE IN 2006.; HYPERTENSION; HX OF LOWER LEG EDEMA; HX OF HYPOTENSIVE EVENT IN SEPTEMBER 2006.; SURGICAL HX TO INCLUDE THE FOLLOWING: RIGHT EYE CATARACT SURGERY DEC. 1997; GLAUCOMA SURGERY IN JAN. 2001; LEFT EYE CATARACT SURGERY IN OCT. OF 2001; ARTHROSCOPIC LEFT KNEE SURGERY IN MAY OF 2003;; TYPE II DIABETES MELLITUS; HYPERLIPIDEMIA; METABOLIC SYNDROME; HX OF HYPOGLYCEMIC EVENTS

Relevant Concomitant Medication(s): INSULIN (DAY -288 - 15); LISINOPRIL (DAY -288 - 15); LISPRO INSULIN (DAY -288 - 33); PRAVASTATIN (DAY -287 - 175); ACETYLSALICYLIC ACID (DAY -171 - C); GABAPENTIN (DAY -171 - C); NIACIN (DAY -171 - 175); HYDROCHLOROTHIAZIDE (DAY -

Dapagliflozin
BMS-512148

42 - 15); INSULIN (DAY 16 - 33); CYANOCOBALAMIN (DAY 20 - 35); IRON (DAY 20 - 55); INSULIN (DAY 34 - 35); LISPRO INSULIN (DAY 34 - 35); CYANOCOBALAMIN (DAY 36 - 69); INSULIN (DAY 36 - 47); LISPRO INSULIN (DAY 36 - 47); NEMYCN/POLYB (DAY 47 - 62); INSULIN (DAY 48 - 105); LISPRO INSULIN (DAY 48 - 190); CEPHALEXIN (DAY 62 - 72); LEVOFLOXACIN (DAY 75 - 84); SILVER SULFADIAZINE (DAY 75 - 103); LISINOPRIL (DAY 76 - 86); MEDICATED DRESSING (DAY 103 - 245); INSULIN (DAY 106 - 190); APAP/DOXYL/DXMETH/PSEUD (DAY 122 - 131); CEPHALEXIN (DAY 147 - 157); LEVOFLOXACIN (DAY 161 - 170); LEVOFLOXACIN (DAY 175 - 182)

Rescue Medication: N/A

Clinical Summary:

The subject's medical history included hypertension for which he was on lisinopril and hydrochlorothiazide therapy. He had a history of hypotensive event and of hypoglycemic events.

On Day 14, the subject felt dizzy, lightheaded and profoundly weak with bilateral blurred vision. He felt near syncopal, with no loss of consciousness. He was hospitalized. His glucose was checked and he was found to be euglycemic. His blood pressure was 60/40 mmHg (BP at baseline was 141/69 mmHg with a heart rate of 63 bpm) and was 115/65 mmHg in a supine position. His respiratory rate was 16 per minute and not labored. He was fully alert, oriented and cooperative. He was diagnosed with Grade III hypotension. His lungs on auscultation revealed minimal rhonchi at the bases with a slightly prolonged expiratory phase. His lower extremities were negative for the presence of clubbing, cyanosis or edema. Peripheral pulses were palpable. Chronic venous vascular changes were present. Carotids were equal on upstroke bilaterally. Concomitant therapy with lisinopril and hydrochlorothiazide therapy was discontinued. No action was taken with regard to the study medication. Laboratory tests showed elevated creatinine level of 2.2 mg/dL (>= 1.5X baseline) and blood urea nitrogen (BUN) of 30 mg/dL (see table below). He received treatment with intravenous fluids. The hypotensive episode was considered resolved on the same day, Day 14. The subject's BUN and creatinine improved to 28 mg/dL and 1.3 mg/dL respectively on the same day. After hydration, blood pressure normalized (values not available). He was instructed on a low sodium and ADA low cholesterol diet. Study medication was interrupted on Day 15 and restarted on Day 16. His condition was stable and he was discharged on Day 16.

Study Day	Creatinine (0.5–1.3 mg/dL)	BUN (8–23 mg/dL)
Day -7	1.39	34
Day 1	1.43	29
Day 8	1.66	33
Day 14	1.3	32
Day 14	1.57	21
Day 19	1.31	19

On Day 173, the subject's laboratory test results showed elevated aspartate aminotransferase (AST) of 355 IU/L, alanine aminotransaminase (ALT) 419 IU/L (both > 5 X ULN) and alkaline phosphatase (ALP) of 355 IU/L with a normal total bilirubin of 1.0 mg/dL. On Day 174, he was diagnosed with Grade III increased hepatic enzyme. Relevant laboratory test results are shown in the table below.

Study Day	AST (10–45 IU/L)	ALT (6–48 IU/L)	ALP (45–145 IU/L)	Total bilirubin (0.2–1.2 mg/dL)

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Day -7	21	18	81	0.4
Day 1	21	20	72	0.6
Day 62	20	15	77	
Day 118	25	19	76	0.5
Day 133	22	18	73	0.7
Day 147	15	19	84	0.5
Day 156	20	16	92	0.4
Day 173	355	419	355	1.0
Day 175	320	444	410	1.3
Day 197	63	63	445	8.9
Day 239	59	42	410	6.9
Day 252	94	67	601	7.8
Day 272	59	49	469	5
Day 280	68	52	387	2.2
Day 310	45	46	294	1
Day 372	25	24	150	0.4
Day 421	22	25	92	0.6
Day 477	66	78	379	0.8
Day 531	27	21	181	0.7
Day 546	100	64	137	1.1
Day 576	28	25	132	0.7
Day 626	45	64	404	2.9
Day 631	26	41	345	1.4

On Day 175, AST was 320 IU/L (> 5 X ULN), ALT 444 IU/L ((> 5 X ULN), ALP 410 IU/L and total bilirubin was 1.3 mg/dL. The subject did not experience any signs or symptoms at this time. Study medication was discontinued due to the event of increased hepatic enzymes with the last dose administered on Day 175. He was also taken off his pravastatin and nicotinic acid. On Day 177, an abdominal ultrasound was performed which showed an echogenic liver parenchyma, and borderline enlargement of the liver. Intrahepatic vasculature and biliary system appeared normal. Murphy's sign of the gall bladder was positive. Viral serology tests were negative for Hepatitis A IgM antibody, HBsAg screen and Hep B Core IgM antibody. Hepatitis C Virus Ab was < 0.2 titre (reference 0.0-0.9). On Day 185, the subject reported of passing dark urine and was diagnosed with Grade I chromaturia. He underwent ultrasound of the abdomen on Day 187 which showed echogenic liver parenchyma and borderline enlargement of the liver. On Day 197, he was diagnosed with Grade I jaundice. He had underwent magnetic resonance imaging (MRI) of the abdomen on Day 247 and was noted to have significant intra-hepatic duct dilatation with no common duct dilatation and the finding indicative of stricture or mass in the portal hepatitis. He was then seen by a gastroenterologist (GI) on Day 257. He underwent endoscopic retrograde cholangiopancreatography (ERCP) on Day 268 which showed stricture of the common hepatic duct as well as the bifurcation of the left and right systems that was highly suspicious of cholangiocarcinoma. Cytology brushings were performed of the stricture and a stent was placed at that time. Cytology studies, performed on the biliary brushings showed benign ductal epithelial cells that were negative for malignancy. On Day 276, the subject

presented to the hospital with weakness and fever. Blood cultures on the same day were positive for gram negative bacteria. He was diagnosed with Grade II urinary tract infection and Grade II urosepsis. He received hydration therapy and antibiotic therapy with levofloxacin and piperacillin+tazobactam. On the morning of Day 277, he developed shortness of breath and diaphoresis. A chest x-ray revealed interval development of subtle bilateral peri-hilar patchy alveolar infiltrates. On Day 278, echocardiogram performed showed mild cardiomyopathy, overall ejection fraction (EF) of 55% to 60% with mild mitral regurgitation and mild tricuspid regurgitation. His hepatic enzymes were elevated and were carefully monitored. He was diagnosed with Grade III congestive cardiac failure and non Q wave Grade III myocardial infarction (MI). The subject was initially treated with fluid resuscitation. He was then treated with diuretics, with noted improvement. His creatine phosphokinase (CPK) was elevated at 727 U/L, myocardial bands (MB) 145.7, and troponin level was 47.88 ng/mL. His CPK peaked to 861 U/L. Ammonia level was elevated at 44 μmol/L but his status improved after receiving fluid resuscitation. Electrocardiogram, performed on Day 281, showed right bundle branch block, left anterior hemiblock, and nonspecific ST-T wave changes. His troponin level declined to 6.48 ng/mL. He was stabilized and he was then transferred to the telemetry floor and his condition improved. The subject was instructed on appropriate low sodium, and low cholesterol diet. He underwent stress testing, which revealed an area of infarction, an area of ischemia for which medical therapy was recommended. He was placed on hypolipidemic therapy and placed on ace- inhibitor. On Day 282, he was stable and the events of congestive cardiac failure, MI, urinary tract infection and urosepsis resolved. The subject was discharged from the hospital on Day 282, the same day. He was first seen at a cancer center on Day 301. His laboratory data on Day 301 were remarkable for a CA-19.9 of 168 with a CEA of 2.8. His bilirubin level reduced and was 1.1 mg/dL on the same day (Day 301) after his biliary stent. He underwent PET scanning on Day 302 and CT scanning Day 306. Both of these showed no evidence of any measurable malignancy. He again underwent CT scanning on Day 369 and PET scanning Day 370 which showed no evidence of malignancy. He was clinically stable and feeling well in general. He underwent lab testing on Day 364. He had some mild anemia; however, his bilirubin was normal at 0.6 mg/dL. His ALT and AST were normal. His alkaline phosphatase was minimally elevated at 138 U/L. He noted no other specific medical events and was considered to be stable clinically. His previous labs from Day 298 and Day 301 were reviewed to look at his clinical trend. It was noted that his CA19-9 was still elevated at 86.6 with a normal CEA. This was thought to possibly be related to his obstruction. He was to be closely monitored with repeat PET and CT scanning in six months. He will be continued to be monitored for anemia. He was clinically stable and did not require intervention at the time of this report. The event of jaundice resolved on Day 342 and the event of increased hepatic enzymes was continuing at the time of reporting. The ALT and AST levels returned to normal level by Day 631 (as per lab results).

Dapagliflozin
BMS-512148

Hepatic Adjudication Report

Patient Identifier: MB102030-9-92

Event: ABDOMINAL PAIN UPPER (MILD / GRADE I INTENSITY, NOT RELATED RELATIONSHIP, DAY 164); AST > 5X ULN (DAY 165); (ALT or AST) > 3X ULN and TB > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION (DAY 165 of ALT or AST elevation); HEPATIC ENZYME INCREASED (MILD / GRADE I INTENSITY, NOT RELATED RELATIONSHIP, DAY 165)

Reason(s) for Narrative: (check all that apply)	☐ Death
	X SAE (regardless of relationship to treatment)
	X AE leading to discontinuation (regardless of relationship to treatment)
	X Other significant medical event

Study Medication/Dose: PIO 30 MG (DAY -91 - -16); PLA + PIO 30 MG (DAY -15 - -1); DAPA 10 MG + PIO 30 MG (DAY 1 - 166); DAPA 10 MG (DAY 167 - 167)

Treatment Group: DAPA 10MG + PIO	**Date of First Dose:** (b) (6)

Age: 60 YEARS	**Gender:** MALE	**Race:** WHITE	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (JUN2007); HYPERTENSION (1991); GOUT (1995)

General Medical History: ALLERGIC RHINITIS 2006; SOCIAL DRINKER LESS THAN 2 GLASSES WINE PER MONTH

Relevant Concomitant Medication(s): ALLOPURINOL (DAY -5087 - C); VALSARTAN (DAY -3201 - C); MULTIVITAMIN (DAY -1069 - C); ACETYLSALICYLIC ACID (DAY -553 - C); METFORMIN (DAY -553 - -92); HERBS (DAY -492 - C); APAP/HYDCOD (DAY 165 - 166); HYDROMORPHONE (DAY 165 - 165); IBUPROFEN (DAY 165 - 165); ONDANSETRON (DAY 165 - 165)

Rescue Medication: N/A

Clinical Summary: On Day 164, early morning, the subject reported right upper quadrant abdominal pain (severe, 10/10 at maximum), nausea, loss of appetite, and vomiting (all Grade 1 in severity). On Day 165, he was hospitalized and upon admission vital sign examination included a temperature of 97.6 degrees, blood pressure 146/74 mmHg, and heart rate 130 beats per minute (BPM), respirations 24/minute, and oxygen saturation 94% on room air. On physical examination, his abdomen was soft with moderate tenderness in the right upper quadrant and epigastric area. No masses were noted. Diagnostic procedures on Day 165 included a urinalysis which was negative. Cardiac enzymes were within normal limits with a creatine kinase-MB of 1.0 ng/mL and a troponin of < 0.04 ng/mL; an electrocardiogram performed showed tachycardia (heart rate of 120 BPM). On the same day (Day 165), the subject's laboratory test results showed elevated AST level of 240 U/L (> 5X ULN). In addition, total bilirubin was elevated 1.5X ULN on Days 162, 166, and 168 (2.0, 7.6, a d 2.0 mg/dL, respectively; see table). Gallbladder ultrasound was without visible abnormality; however, the study was limited with the pancreas reported as being completely obscured by bowel gas, the liver mildly obscured and the aorta obscured, the right kidney, gall bladder and common bile duct had appeared normal with the common bile duct measuring 4.6 mm in the porta hepatis. Laboratory test results were performed and the results were as shown in table below:

Study Day	Aspartate transaminase (AST) (8−42 U/L)	Alanine transaminase (ALT) (0−65 U/L),	Alkaline phosphate (ALP) (37−107 U/L)	Creatinine (0.5−1.2 mg/dL)	Total bilirubin (0.2−1.0 mg/dL),
Day 1	25	28	74	0.98	0.7
Day 26	16	18	73	0.96	0.5
Day 84	17	15	67	1.04	0.6
Day 140	25	18	70	1.15	0.6

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Day 165	240	139	120	1.40	2.0
Day 166	156	203	106	1.29	7.6
Day 168	57	133	110	1.12	2.0
Day 175	35	56	87	0.94	0.9
Day 238	28	21	87	–	0.5
Day 298	28	22	62	–	0.5

Study Day	Amylase (34−122 U/L)	Lipase (114−286 U/L	White blood count (WBC) (5.1−10.8 thou/mcL)	Neutro-phils (50−70%),	Platelet count (150−400 thou/mcL)	Glucose (70−99 mg/dL).	Prothrombin time (8.7−11.5 sec).
Day 165	57	176	7.6	89.7	108	158	
Day 166	36	17	8.5	80	110		12.2

He was diagnosed with Grade 1 upper abdominal pain and Grade 1 hepatic enzyme increased. Treatment included the administration of intravenous normal saline, hydromorphone and ondansetron for nausea and upper abdominal pain. Later in the morning of Day 165, he was pain free but continued to experience mild nausea. Few hours later, his temperature increased to 102.1 and he was diagnosed with Grade 1 fever. He was given oral ibuprofen (400 mg) as treatment. He was started on a clear liquid diet which was to be advanced as tolerated. His condition was stable and he was discharged home that same morning with prescriptions for hydrocodone tartrate + acetaminophen and ondansetron. His pain level at the time of discharge was described as 3/10. The etiology of the abdominal pain was uncertain. A follow-up gastrointestinal consult was recommended. A hepato-iminodiacetic acid (HIDA) scan was scheduled. On Day 166, serology results were negative. No treatment was provided for the event of hepatic enzyme increased. Treatment with the study therapy was discontinued due to the event hepatic enzyme increased and upper abdominal pain with the last dose of the blinded study therapy on Day 167 and the last dose of pioglitazone HCl on Day 166. On Day 168, fever resolved and he had no additional symptoms and he was negative for jaundice. Repeat liver enzyme test showed normalized results. A gastrointestinal consultation was performed with recommendation for an endoscopic retrograde cholangiopancreatography (ERCP). Results of a hepatobiliary scan were normal with no findings to suggest cystic or common duct obstruction. On Day 175, the subject´s hepatitis panel confirmed negative results for Hep A Ab (IgM); HBS Ag screen and Hep B core Ab (IgM). The test results for Hep C virus Ab was <0.2 s/co ratio (normal range 0.0−0.9). The elevated AST level normalized on Day 175. The event of elevated liver enzymes resolved on Day 176. He underwent magnetic resonance cholangiopancreatography (MRCP) on Day 202. Results revealed suspicion of gallstones within the gallbladder neck. No biliary calculi were noted in the common bile duct or in the common hepatic duct. The test results also reported a diffused atrophy of the pancreas. He was asymptomatic. The event of upper abdominal pain and nausea resolved on Day 208.

Patient Identifier: MB102077_0088_70996			
Event: Acute viral hepatitis E **Severity:** Severe/Grade 3		**Relationship:** Not related	**Action Taken:** None
Reason(s) for Narrative:	☐Death ☒ SAE ☐AE leading to discontinuation ☐ Other significant medical event		
Study Medication: Blinded	**First Active Dose:** 05-Dec-2011		**Last Dose:** 28-Feb-2012
Age: 57 years	**Gender:** Male	**Race:** Asian	**Ethnicity:** Not Hispanic/Latino
Disease History: Type 2 diabetes mellitus (2008) and hypertension (2008)			
General Medical History: Medical history was not provided.			
Concomitant Medication(s) at Baseline: Metformin hydrochloride (30-Oct-2008), losartan potassium (30-Oct-2008), metoprolol (25-Jul-2011), glimepiride (09-Mar-2012),			
Relevant Concomitant Medication(s): Acetaminophen (27-Feb-2012)			
Other Post Randomization Adverse Events: Fever (study Day 85)			

Clinical Summary:

On study Day 87, the subject was reported to have acute viral hepatitis E and was shown to have an abnormal AST result > 5xULN (248 IU/L) and an abnormal ALT result (107 IU/L); normal range: 10 to 45 IU/L for AST and 6 to 48 IU/L for ALT. Previously, the hepatobiliary symptom of fever was reported on study Day 85. The investigator assessed the Adverse Event (AE) of fever to be mild (Grade 1) in severity and not related to study medication. The subject was treated with acetaminophen and the AE was considered resolved the same day. The investigator assessed the event of acute viral hepatitis E to be severe (Grade 3) in severity and not related to study medication. No treatment was required for the event and no action was taken with the study medication. Risk factors for liver injury such as recreational/narcotic drug use, occupational/environmental exposure, alcohol intake, smoking, recent unaccustomed physical exertion, and ≥ 4g/day acetaminophen intake were not reported. On study Day 90, the subject was reported to have abnormal AST and ALT results > 3xULN (2269 IU/L and 4316 IU/L, respectively) and an abnormal total bilirubin result > 1.5xULN (50 μmol/L). On study Day 96, the subject reported to have an abnormal AST result (49 IU/L) and an abnormal ALT results > 5xULN (520 IU/L), and a normal total bilirubin result (17 μmol/L). On study Day 100, the subject was reported to have an abnormal ALT result >3xULN (195 IU/L) and a normal AST result (32 IU/L). Also on study Day 100, a sonography of the abdomen showed cholelithiasis and acute parenchymal disease. On study Day 108, a hepatitis E IgM antibody test confirmed acute viral hepatitis E. On study Day 130, the AST and ALT results (20 IU/L and 20 IU/L, respectively) returned to normal range and the event of acute viral hepatitis E was considered resolved.

Relevant laboratory results are provided in the table below:

Laboratory Parameter (Units)	Normal Range	STUDY DAYS						
		-47	-28	1	31	62	87	90
ALT (IU/L)	6 - 48	24	24	27	24	21	107 H	4316 H2
AST (IU/L)	10 - 45	21	20)	22	19	17	248 H	2269 H2
Total Bilirubin (mg/L)	0.2 – 1.2	7	10	7	5	5	10	50 H2
Albumin (g/dL)	3.5 – 5.3	49	49	7	5	47	46	43
ALP (IU/L)	40 - 100							

Laboratory Parameter (Units)	Normal Range	STUDY DAYS						
		96	100	130				
ALT (IU/L)	6 - 48	512 H2	195 H1	20				
AST (IU/L)	10 - 45	49 H	32	20				
Total Bilirubin (µmol/L)	3-21	17	17	7				
Albumin (g/L)	35 – 53	42	43	45				
GGT (IU/L)	7-51	148 H1						

CASES MEETING DEFINITION OF: AST/ALT > 10X ULRR

REPRODUCED FROM THE APPLICANT'S JUNE 19, 2013 HEPATIC ADJUDICATION REPORT

Please note that these narratives are reproduced verbatim from the Applicant's submissions. They contain many spelling and abbreviation variants, reflective of varying usage across a multinational program.

Dapagliflozin
BMS-512148

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Patient Identifier: D1690C00006-1511-6

Event: [1] CHOLELITHIASIS (cholelithiasis, Day 216 to 218, SEVERE / GRADE III, NOT RELATED); [2]
Marked laboratory abnormality - ALT > 5X ULN; AST > 10X ULN;
(AST > 3X ULN or ALT > 3X ULN) and Total Bilirubin > 1.5X ULN (DAY 222)

Reason(s) for Narrative: (check all that apply)	[ ] Death
	[1] SAE (regardless of relationship to treatment)
	[ ] AE leading to discontinuation (regardless of relationship to treatment)
	[2] Other significant medical event

Serious criteria other than Death:	**Life thr.**	**Hosp.**	**Dis./Incap.**	**Cong. abn.**	**Cancer**	**Dep./Abu.**	**Imp. event**
		[1] YES					

Study Medication/Dose: INS (DAY -14 - -1); DAPA 10MG + INS (DAY 1 - 216);
NS (DAY 217 - 217); DAPA 10MG + INS (DAY 218 - 225); INS (DAY 226 - 230);
DAPA 10MG + INS (DAY 231 - 729); INS (DAY 730 - C)

Treatment Group: DAPA 10MG + INS	**Date of First Dose:** (b) (6)

Age: 61 YEARS	**Gender**: FEMALE	**Race:** WHITE	**Ethnicity**: NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (1990); DIABETIC NEUROPATHY (AUG2002);
HYPERTENSION (1990); PERIPHERAL VASCULAR DISEASE (2002); AMPUTATION (17FEB2003);
DYSLIPIDEMIA (DEC2007); RECURRENT GENITAL YEAST INFECTION (2002); RECURRENT URINARY
TRACT INFECTION (2002); NOCTURIA (MAY2005)

General Medical History: right side hearing decrease after virus infection; often headache, vertigo; hypertension;
angiopathy; varicosity; phlebitis 16-23.09.2008; cystitis acuta occasionally nocturia recurrent genital yeast infection;
diabetes mellitus type 2 dyslipidaemia; Dupuytren contractura; amputation of leg finger arthrosis; onychomycosis;
diabetic neuropathy; Allergies: pollen allergy; obesity. Smoking: NEVER. Alcohol use: OCCASIONAL.

Adverse events during study: INFLUENZA (flu, Day 13 to 24, MILD / GRADE I, NOT RELATED); COUGH (a
specific cough, Day 24 to 26, MILD / GRADE I, NOT RELATED); DERMATITIS (dermatitis in external ear, Day
27 to 34, MILD / GRADE I, NOT RELATED); BACK PAIN (low back pain, Day 50 to 75, SEVERE / GRADE III,
NOT RELATED); REFLUX OESOPHAGITIS (reflux oesophagitis, Day 57 to 75, MILD / GRADE I, NOT
RELATED); ABDOMINAL DISCOMFORT (abdominal discomfort, Day 109 to 217, MODERATE / GRADE II,
NOT RELATED); GASTRITIS (gastritis, Day 109 to 110, MODERATE / GRADE II, NOT RELATED);
CHOLELITHIASIS (gall stone, Day 119 to 217, MODERATE / GRADE II, NOT RELATED); MENIERE'S
DISEASE (Meniere's disease, Day 119 to 125, MODERATE / GRADE II, NOT RELATED); INFLAMMATION
(inflammation on right toe, Day 134 to 169, MODERATE / GRADE II, NOT RELATED); BILIARY COLIC
(biliary colic, Day 180 to 180, MODERATE / GRADE II, NOT RELATED); LIVER FUNCTION TEST
ABNORMAL (elevated liver function values, Day 222 to 281, SEVERE / GRADE III, NOT RELATED); NECK
PAIN (spastic pain in neck, Day 226 to 233, MILD / GRADE I, NOT RELATED); DIABETIC NEUROPATHY
(worsening of diabetic neuropathy, Day 246 - C, MODERATE / GRADE II, NOT RELATED); DYSURIA (burning
during urination, Day 433 to 438, MILD / GRADE I, NOT RELATED); ABDOMINAL PAIN (abdominal pain,
Day 443 to 447, MILD / GRADE I, NOT RELATED); INFLAMMATION (Imflammation right toe IV., Day 523 to
711, MODERATE / GRADE II, NOT RELATED); DYSURIA (burning during urination, Day 683 to 686, MILD /
GRADE I, NOT RELATED); ARTHRALGIA (hip pain, Day 714 to 726, MODERATE / GRADE II, NOT
RELATED); HYPERTENSION (Worsening of hypertension, Day 714 to 729, MILD / GRADE I, NOT RELATED)

Dapagliflozin
BMS-512148

Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >=-90 - C); AMINOPHENAZONE (Day >=-90 - C); ATORVASTATIN (Day >=-90 - C); CALCIUM DOBESILATE (Day >=-90 - C); CHONDROITIN (Day >=-90 - C); ENALAPRIL (Day >=-90 - 27); PENTOSAN POLYSULFATE (Day >=-90 - C); PENTOXIFYLLINE (Day >=-90 - C); TETRAHYDROZOLINE (Day >=-90 - C); THIOCTIC ACID (Day >=-90 - C); ANTIFUNGAL TOPICAL (Day -72 - 82); FLUCONAZOLE (Day -55 - 82); ANTACID (Day 24 - 26); MOMETASONE (Day 27 - 34); VALSARTAN
(Day 27 - C); ANTACID (Day 57 - 75); DICLOFENAC (Day 57 - 75); BETAHISTINE
(Day 125 - 215); DIMENHYDRINATE (Day 125 - 126); METOCLOPRAMIDE (Day 125 - 125); PYRIDOXINE (Day 125 - 125); VINPOCETINE (Day 125 - 491); NUTRITIONAL SUPPLEMENT
(Day 128 - 132); CLINDAMYCIN (Day 140 - 144); MELOXICAM (Day 229 - 233); TOLPERISONE (Day 229 - 233); DULOXETINE (Day 259 - 279); GINKGO BILOBA (Day 495 - C); GUCOSAMINE (Day 495 - C); CLINDAMYCIN (Day 686 - 700); DICLOFENAC (Day 714 - 721); DILTIAZEM (Day 716 - C); NON STEROID ANTIINFLAMMATORY (Day 719 - C); TOLPERISONE (Day 719 - C)

Background Medication(s): LISPRO INSULIN (Day -1899 - C); INSULIN (Day -650 - C)

Clinical Summary:

Patient suffered from biliary colic and epigastrial pain since January 2009 and cholecystectomy was planned for end of April. Pre-operative lab sampling on study day 209 revealed ALT, AT and Bilirubin within normal range, ALP 291 U/L (ref. range 98-279 U/L) and GGT 96 U/L (ref. range 7-32 U/L). Abdominal ultrasound on study day 209 showed: Cholelithiasis, Hepatic steatosis, cystae renis, artheriosclerosis aortae abd, otherwise negative abdominal and pelvic status. The patient was hospitalized from study day 216 until study day 218 due to severe cholelithiasis. Investigational product was temporarily stopped during this period. She underwent laparoscopic cholecystectomy on study day 217, and in the description of the laparoscopy, it's mentioned that the surgeon considered that the bladder contained stones. Following the procedure, the patient was observed without any complaints, inflammation and fever. During the hospitalization, no sampling for liver function tests was done. It was noted that jaundice couldn't be seen.

On study day 222, the next regular study visit, ALT, AST and total bilirubin were increased. The patient had no symptoms. Investigational product was temporarily stopped study day 225 to 231. Re-test on study day 229 show normal total bilirubin and AST and ALT was decreasing. According to the investigator the LFT elevation was caused by the cholelithiasis and the cholecystectomy.

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Patient Identifier: D1690C00018-2608-6

Event: Marked laboratory abnormality - ALT > 10X ULN; AST > 10X ULN (DAY 359)

Reason(s) for Narrative: (check all that apply)	[ ] Death [ ] SAE (regardless of relationship to treatment) [ ] AE leading to discontinuation (regardless of relationship to treatment) **X** Other significant medical event

Serious criteria other than Death:	Life thr.	Hosp.	Dis./Incap.	Cong. abn.	Cancer	Dep./Abu.	Imp.event

Study Medication/Dose: MET (DAY -36 - -30); PLA + MET (DAY -29 - -1); DAPA 10MG + MET (DAY 1 - 359); MET (DAY 360 - 387)

Treatment Group: DAPA 10 MG	**Date of First Dose:** 11AUG2010

Age: 58 YEARS	**Gender:** MALE	**Race:** WHITE	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (17JAN2001); HYPERTENSION (16JAN2001); CABG (24MAY2007); CORONARY ARTERY DISEASE (CAD) (24MAY2007); PREVIOUS MI (24MAY2007)

General Medical History: cardiopathy, posterior wall infarction; renal insufficiency; Diabetes mellitus Type 2, Obesity Grade 3, hypercholesterolemia, art. Hypertension; Sleep apnoea -syndrome. Smoking: FORMER; CIGARETTES 25 PER DAY for 29 YEARS; Stopped 20AUG1996. Alcohol use: less than 1 DRINK WEEKLY.

Adverse events during study: BACK PAIN (backache, Day 51 to 72, MILD / GRADE I, NOT RELATED); DEPRESSION (mild depression, Day 51 to 55, MILD / GRADE I, NOT RELATED); BACK PAIN (lumbago, Day 66 to 72, MILD / GRADE I, NOT RELATED); TRANSAMINASES INCREASED (increased transaminases, Day 359 to 373, MILD / GRADE I, NOT RELATED)

Concomitant Medication(s): ACETYLSALICYLIC ACID (Day >=-90 - C); SIMVASTATIN (Day >=-90 - C); DICLOFENAC (Day 66 - 72); CETIRIZINE (Day 336 - 358)

Background Medication(s): BISOPROLOL (Day >=-90 - C); ENAL/HCTZ (Day >=-90 - C); METFORMIN (Day >=-90 - C)

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Patient Identifier: D1690C00018-2608-6

Clinical Summary:
On the end of treatment visit on Study Day 359 ALT and AST elevations >10xULN were observed. At follow up the values were reversed to near normal/normal values. No AE was reported.

Sponsor causality assessment: Unlikely

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-----------------------------------------------------------------------------
Lab Test (Unit)                        Reference Range   Study Day    Result
-----------------------------------------------------------------------------
Alanine Aminotransferase (ALT) (U/L)        6 - 48          -36          42
                                                              1          51
                                                             10          45
                                                             38          51
                                                             56          45
                                                            114          41
                                                            175          27
                                                            198          28
                                                            251          29
                                                            304          32
                                                            359        1115
                                                            373          96
                                                            387          60


Aspartate Aminotransferase (AST) (U/L)     10 - 45          -36          33
                                                              1          44
                                                             10          35
                                                             38          41
                                                             56          28
                                                            114          27
                                                            175          19
                                                            198          23
                                                            251          19
                                                            304          27
                                                            359         614
                                                            373          45
                                                            387          39


Bilirubin, Total (MG/DL)                   0.2 - 1.2        -36         0.2
                                                              1         0.4
                                                             10         0.4
                                                             38         0.3
                                                             56         0.5
                                                            114         0.5
                                                            175         0.3
                                                            198         0.4
                                                            251         0.5
                                                            304         0.5
                                                            359         0.6
                                                            373         0.5
                                                            387         0.6
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Dapagliflozin
BMS-512148   Hepatic Adjudication Report

Patient Identifier: MB102030-90-706	~~Approved v1.0 930070564 1.0~~

Event: ALT > 10X ULN (DAY 345); ALT > 5X ULN (DAY 345); AST > 10X ULN (DAY 345); AST > 5X ULN (DAY 345)

Reason(s) for Narrative: (check all that apply)	☐ Death
	☐ SAE (regardless of relationship to treatment)
	☐ AE leading to discontinuation (regardless of relationship to treatment)
	X Other significant medical event

Study Medication/Dose: PIO 30 MG (DAY -69 - -15); PLA + PIO 30 MG (DAY -14 - -1); DAPA 10 MG + PIO 30 MG (DAY 1 - 48); PIO 30 MG (DAY 49 - 49); DAPA 10 MG + PIO 30 MG (DAY 50 - 149); DAPA 10 MG + PIO 30 MG (DAY 151 - 345)

Treatment Group: DAPA 10MG + PIO	**Date of First Dose:** 29APR2009

Age: 60 YEARS	**Gender**: FEMALE	**Race:** WHITE	**Ethnicity**: N/A

Disease History: TYPE 2 DIABETES MELLITUS (JUL2008); HYPERTENSION (2004); PERIPHERAL VASCULAR DISEASE (2000)

General Medical History: LONG-SIGHTEDNESS, USE GLASSES; RENAL LEFT PYELONEPHRITIS DIAGNOSED IN 13-JAN-2009; RIGHT SHOULDER PAIN SINCE DEC-2008; VARICOSE VEINS IN BOTH LOWER LIMBS SINCE 2000; FOOT MYCOSIS

Relevant Concomitant Medication(s): ENALAPRIL (DAY -1945 - C); METFORMIN (DAY -302 - -70); ACETAMINOPHEN (DAY -149 - C); AMOXICILLIN (DAY -85 - -82); CLAVULANIC ACID (DAY -85 - -82); ATORVASTATIN (DAY 10 - 166); SCOPOLAMINE (DAY 48 - 48); PIROXICAM (DAY 169 - 185); ATORVASTATIN (DAY 174 - 201); ATORVASTATIN (DAY 345 - 348); PANTOPRAZOLE (DAY 345 - 350)

Rescue Medication: N/A

Clinical Summary: On Day 345, the subject's laboratory test results showed elevated ALT level of 805 U/L (> 10X ULN, > 5X ULN) and elevated AST level of 941 U/L (> 10X ULN, > 5X ULN). She also had elevated total bilirubin and ALP at the time of elevated ALT and AST. Relevant laboratory test results were as shown in the table below:

Study Day	ALT (6–37 U/L)	AST (10–36 U/L)	Total bilirubin (0.2–1.2 mg/dL)	ALP (40–100 U/L)
Day -14	18	16	0.3	104
Day 1	18	17	0.3	97
Day 10	16	15	0.3	108
Day 29	20	15	0.3	98
Day 57	21	15	0.3	103
Day 114	22	17	0.3	101
Day 142	20	15	0.2	96
Day 171	21	19	0.3	96
Day 259	17	17	0.3	104
Day 345	805	941	1.4	306
Day 351	102	20	0.3	170

She was diagnosed with Grade I increased hepatic enzyme. She also had upper abdominal pain and cholelithiasis at the time of the ALT, and AST elevation. No treatment was required and no action was taken with regard to the study medication due to the elevated ALT and AST values. The elevated ALT was continuing at the time of reporting and AST level normalized on Day 351. The event upper abdominal pain resolved on Day 347 and increased hepatic enzyme was considered resolved on Day 351. The event cholelithiasis was continuing at the time of reporting.

Dapagliflozin
BMS-512148

Approved v1.0   930070564 1.0

Patient Identifier: MB102073-182-1152
Protocol: MB102073

Event: CHOLECYSTITIS ACUTE (MILD / GRADE I INTENSITY, NOT RELATED RELATIONSHIP, DAY 76); ALT > 10X ULN (DAY 77); ALT > 5X ULN (DAY 77); AST > 10X ULN (DAY 77); AST > 5X ULN (DAY 77)	

Reason(s) for Narrative: (check all that apply)	[ ] Death [X] SAE) [ ] AE leading to discontinuation (regardless of relationship to treatment) [X] Other significant medical event

Study Medication/Dose: BMED(GLP+LOS+MET) (DAY -41 - -28); PLA+BMED(GLP+LOS+MET) (DAY -27 - -1); DAPA 5MG+BMED(GLP+LOS+MET) (DAY 1 - 12); BMED(GLP+LOS+MET) (DAY 13 - 14); DAPA 5MG+BMED(GLP+LOS+MET) (DAY 15 - 34); DAPA 10MG+BMED(GLP+LOS+MET) (DAY 35 - 35); DAPA 5MG+BMED(GLP+LOS+MET) (DAY 36 - 58); PLA+BMED(GLP+LOS+MET) (DAY 59 - 59); DAPA 5MG+BMED(GLP+LOS+MET) (DAY 60 - 75); BMED(GLP+LOS+MET) (DAY 76 - 78); DAPA 5MG+BMED(GLP+LOS+MET) (DAY 79 - 86); BMED(GLP+LOS+MET) (DAY 87 - 100)

Add on Rescue Therapy and Study Day Started: N/A

Treatment Group: DAP 5 MG + ACEI/ARB	**Date of First Dose:** (b) (6)

Age: 64 YEARS	**Gender:** MALE	**Race:** WHITE	**Ethnicity:** NOT HISPANIC/LATINO

Disease History: TYPE 2 DIABETES MELLITUS (2000) ; CORONARY ARTERY DISEASE (03MAY2010); HYPERTENSION (2000); HOSPITALIZATION FOR UNSTABLE ANGINA (03MAY2010); STABLE ANGINA (04MAY2010); DYSLIPIDEMIA (2000); CABG (03MAY2010)

General Medical History: ERECTILE DYSFUNCTION; HIATAL HERNIA; HYPERLIPIDEMIA; MACULAR DEGENERATION; MILD BILATERAL HEARING LOSS; RIGHT VENTRICULAR HYPERTROPHY

Relevant Concomitant Medication(s): ACETYLSALICYLIC ACID (DAY -4281 - 581); GLIPIZIDE (DAY -4281 - -41); METFORMIN (DAY -4281 - -41); LOSARTAN (DAY -3185 - -41); SIMVASTATIN (DAY -3185 - 581); NUTRITIONAL SUPPLEMENT (DAY -1724 - 581); TESTOSTERONE (DAY -47 - 581); ACETAMINOPHEN (DAY 76 - 77); APAP/OXYCOD (DAY 76 - 99); ATORVASTATIN (DAY 76 - 76); ERTAPENEM (DAY 76 - 76); NITROGLYCERIN (DAY 76 - 76); ONDANSETRON (DAY 76 - 76); PHOSPHATE (DAY 76 - 76); POTASSIUM (DAY 76 - 76); LACTOBACILLUS ACIDOPHILUS (DAY 81 - 581); LEVOFLOXACIN (DAY 81 - 88); METRONIDAZOLE (DAY 81 - 88)

Clinical Summary:

This subject had a past medical history of hyperlipidemia.

On Day 76 the subject was hospitalized due to chest and abdominal pain. He was treated with glyceryl trinitrate, potassium phosphate, sodium biphosphate, atorvastatin, potassium chloride, and oxycodone/paracetamol. He was evaluated for possible aneurysm and dissection and the results were negative. On Day 77, he had elevated levels of alanine aminotransferase (ALT) of 229 U/L (baseline: 60 U/L, reference range: 6-48 U/L) and aspartate aminotransferase (AST) of 216 U/L (baseline: 31 U/L; reference range: 10-45 U/L) (>10X the upper limit of normal (ULN) and > 5x ULN). The subject was diagnosed with infected gall bladder and Grade I cholecystitis. Relevant laboratory test results are shown in the table below. The subject underwent a laparoscopic cholecystectomy with suppurative gallbladder removed. The study medication was interrupted from Days 76-78 and resumed on Day 79. He was treated with intravenous ondansetron, ertapenem and later he was switched to oral antibiotics of levofloxacin, metronidazole, and lactobacillus acidophilus/bulgaricus. The event of cholecystitis was considered resolved on Day 81 and the subject was discharged from the hospital on the same day (Day 81). The subjects' AST and ALT were normalized on Day 86, and Day 99, respectively. The subject's hepatic enzymes improved over time. The elevated AST was normalized on Day 86 whereas elevated ALT was ongoing at the time of this report.

	AST	ALT	ALP	TBILI
Units	U/L	U/L	U/L	mg/dL

Dapagliflozin
BMS-512148

	10 - 45	6 - 48	45 - 145	.2 - 1.2
Range	10 - 45	6 - 48	45 - 145	.2 - 1.2
Day-42	31	**60**	111	1.1
Day-28	**46**	**70**	103	0.8
Day1	38	**60**	108	0.9
Day34	45	**62**	100	0.9
Day57	28	48	96	0.7
Day77	**229**	**216**	132	NULL
Day86	35	**59**	**170**	**1.4**
Day99	31	**50**	112	0.8

The subject completed the study and the last dose was received on Day 86.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences

Office of Biostatistics

STATISTICAL Review

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON
Dapagliflozin

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory
Committee, December 12, 2013

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Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Document Date: November 7, 2013

1.   Regulatory Background

At the last meeting of the Endocrinologic and Metabolic Drugs Advisory Committee held on July 19, 2011, the cardiovascular safety of dapagliflozin was evaluated through a meta-analysis of 14 trials. The primary endpoint of the meta-analysis was a composite of CV death, myocardial infarction (MI), stroke and hospitalization for unstable angina. The meta-analysis included 78 subjects with an event (48 of 4287 randomized to dapagliflozin and 30 of 1941 randomized to comparators). The estimated hazard ratio and 98% confidence interval for this endpoint associated with dapagliflozin was 0.67 (0.38, 1.18). The 1.18 upper bound of this confidence interval was smaller than the margin of 1.8 established in the FDA Guidance for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (2008)[1]. This 98% confidence interval was pre-specified (instead of a 95% interval) as part of a two part sequential testing strategy. Following this Advisory Committee meeting additional data on cardiovascular safety was obtained from new trials and trials that were ongoing at that time. This document discusses the updated meta-analysis based on these data.

2.   Trial Database

On July 11, 2013, Bristol-Myers Squibb and Astra Zeneca submitted an updated meta-analysis of cardiovascular events conducted in 21 randomized clinical trials for dapagliflozin as part of their application package for NDA 202293. Table 1 shows a summary of the trials in the updated meta-analysis. Seven new trials were included in this meta-analysis, that were not presented during the 2011 AC meeting: MB102035, MB102045, D1690C00010, D1690C00018, D1690C00019, D1692C00006 and MB102054. Trials D1692C00006 and MB102054 are regional trials conducted in Japan and China respectively. Trials D1690C00018 and D1690C00019 were conducted in a population with cardiovascular disease and hypertension. For simplicity, trials D1690C00018 and D1690C00019 will be referred to as '18' and '19' respectively. Note that the 2011 meta-analysis did not include trials such as 18 and 19 for which high baseline cardiovascular risk was part of the trials' inclusion criteria. The updated meta-analysis also included additional data from trials that were ongoing at the time of the 2011 AC meeting: D1690C00012, D1690C00006, D1690C00004 and MB102029.

The data cutoff date for the updated meta-analysis was 15 November 2012. At that time, all trials in the meta-analysis had been completed except for trial D1690C00004, which had completed its short term period, but was undergoing its long term extension period. This trial was completed in January 2013.

The updated meta-analysis includes 3111 additional subjects (1649 on dapagliflozin and 1462 on comparators) and 4232 additional patient-years (2250 on dapagliflozin and 1982 on comparators) from the meta-analysis presented at the 2011 Advisory Committee meeting. A total of 5936 subjects randomized to dapagliflozin and 3403 subjects randomized to comparators were included in the updated 2013 meta-analysis.

Table 1. List of Trials Included in the Meta-Analysis

Trial ID	Duration in Weeks Short Term + (Long Terms)	Total Sample Size	Dapagliflozin (N)	Placebo[1] (N)	Active Control (N)	Rescue Treatment
Core Phase 2b Studies						
MB102008	12	389	279	54	56	None
MB102009	12	71	48	23	-	Insulin up-titration
MB102035	**12**	75	24	25	26	Metformin or sulfonylurea
MB102045	**12**	44	23	21	-	None
D1692C00005[2]	12	220	166	54	-	None
Core Phase 2b Studies						
MB102013[3]	24 + (78)	485	410	75	-	Metformin
MB102032	24	210	142	68	-	Metformin
Add-on Studies (Placebo-controlled)						
MB102014	24 + (78)	546	409	137	-	Pioglitazone, acarbose
D1690C00012	24 + **(78)**	182	91	91	-	Sitagliptin
D1690C00006	24 + (24) + **(56)**	807	610	197	-	Insulin up-titration
MB102030	24 + (24)	420	281	139	-	Metformin or sulfonylurea
D1690C00005	24 + (24)	596	450	146	-	Metformin or TZD
D1690C00010	**24 + (24)**	451	225	226	-	Glimeperide
Active Comparator Study vs. Sulfonylurea						
D1690C00004	52 + (52) + **(104)**	814	406	-	408	Allowed after 104 weeks
Initial Combination Study with Metformin (Active Comparator vs. Metformin)						
MB102034	24	638	430	-	208	Pioglitazone, acarbose or sitagliptin
Initial Combination Study with Metformin						
MB102021	24	598	397	-	201	Pioglitazone, acarbose or sitagliptin
Special Populations						
MB102029	24 + (28) + **(52)**	252	168	84	-	Any except Metformin
D1690C00018	**24 + (28) +(52)**	922	460	462	-	Discretion of investigator
D1690C00019	**24 + (28) +(52)**	965	482	483	-	Discretion of investigator
Regional Phase 3 Studies						
D1692C00006	**24**	261	174	87	-	Metformin or Glimeperide
MB102054	**24**	393	261	132	-	Metformin

Source: Created by reviewer from meta-analysis report and dataset adcv5.xpt

*Bold type denotes information added or updated since the 2011 Advisory Committee Meeting.

[1] Placebo arm with or without background medication.

[2] Trial randomized some subjects to Dapagliflozin 1 mg. These subjects are excluded from this table and from all analyses in this document.

[3] Trial included an uncontrolled group randomized to dapagliflozin only. These subjects are excluded from this table and from all analyses in this document.

3. Statistical Methods

3.1 Endpoints

The agreed upon **primary composite endpoint** to assess CV safety was defined as the time until the first of the following adjudicated events:

- ❑ CV death
- ❑ Myocardial infarction (MI)
- ❑ Stroke
- ❑ Hospitalization for unstable angina.

A **secondary composite endpoint** was defined as the time until the first of the following adjudicated events:

- ❑ CV death
- ❑ MI
- ❑ Stroke
- ❑ Hospitalization for unstable angina
- ❑ Unplanned coronary revascularization
- ❑ Hospitalization for heart failure

Analyses were also conducted on Major Adverse Cardiovascular Endpoints (**MACE**), defined as the composite of CV death, MI and Stroke.

The time to event analyses for all endpoints used the following censoring rules. Subjects without an event in AstraZeneca studies (studies with a 'D' in the beginning of the study code) were censored at the earliest of the date of last contact or date of death. Subjects without an event in BMS studies (studies with a 'MB' in the beginning of the study code) were censored at the earliest of the following: end of treatment + 30 days, date of death, date of discontinuation due to loss of follow-up.

3.2 Populations

The primary meta-analysis population consisted of the randomized, controlled, short term plus long term periods of the 21 trials in Table 1. The analyses included data following initiation of any rescue therapy.

Per request from the FDA, a secondary analysis was conducted that incorporated only data from the two trials conducted in a population of subjects with cardiovascular disease and hypertension (trials 18 and 19). This analysis was intended to assess the cardiovascular risk of dapagliflozin in the two trials with the largest sample size, longest follow-up, and increased cardiovascular risk.

The sponsors conducted a secondary analysis in the population of subjects with prior CV disease in the 21 trials, including trials 18 and 19. Prior CV disease was defined as history of any of the following at baseline: MI, congestive heart failure (CHF), hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular accident, carotid artery. Table 2 shows that trials 18 and 19 had a different distribution of cardiovascular risk factors than the subjects with a history of CV disease in the other trials in the program. The secondary analyses in this document were conducted in these two populations separately:

- Trials 18 and 19 alone, and
- Subjects with a history of CV disease in other trials.

Table 2. Baseline Cardiovascular Risk Factors in Subjects with Prior CV Disease

	Subjects with history of CV disease in other trials ($N = 1336$)	Trials 18 and 19 ($N = 1878$)
History of Hypertension (%)	83.8%	96.2%
History of Dyslipidemia (%)	66.8%	84.4%
History of Congestive HF (%)	9.8%	14.4%
Smokers (current or former) (%)	47.5%	59.7%
Statin Use[1]	60.7%	81.3%
SBP ≥ 140 mmHg	34.7%	37.7%
Diabetes Duration ≥ 10 years	36.7%	58.2%
Baseline eGFR (ml/min)		
< 60	21.6%	17.4%
61 – 90	54.6%	59.4%
≥ 90	23.8%	23.3%

Source: Created by reviewer. Dataset: adcv5.xpt
[1]Statin Use was defined as use at any time during the trial. Therefore statin use may be associated with randomized treatment and may not be representative of baseline use.

3.3   Analysis Methods

The pre-specified primary analysis used a Cox proportional hazards model stratified by trial to estimate the hazard ratio (HR) of the primary composite endpoint, and its 95% confidence interval, comparing dapagliflozin (all doses) to all comparators. The model included a single covariate for treatment (dapagliflozin vs. comparators).

A similar Cox proportional hazards model was fit to estimate the hazard ratio (HR) and 95% confidence interval for the secondary composite endpoint and for MACE.

All analyses in this document were repeated separately in the primary population of all trials, the secondary population of trials 18 and 19 alone, and the secondary population of subjects with prior CV disease excluding trials 18 and 19.

A secondary pre-specified analysis estimated the Mantel-Haenszel incidence rate ratio of events associated with dapagliflozin. The results of this secondary analysis were similar to the results obtained from the primary Cox proportional hazards model and are not discussed any further in this document.

The FDA review team estimated the odds ratio of the primary composite event associated with dapagliflozin through a random effects model to account for the possible heterogeneity of the trials in the meta-analysis. This model was not pre-specified in the statistical analysis plan. The results were also consistent with the primary Cox proportional hazards model and are not discussed any further in this document.

4. Results

4.1 Descriptive Statistics of the Primary Composite Endpoint

Table 3 shows the observed number of subjects who experienced an adjudicated primary composite event (CV death, MI, stroke, and hospitalization for unstable angina) in the 21 trials in the updated meta-analysis. A total of 97 events were observed among 5936 subjects randomized to dapagliflozin and 81 events were observed among 3403 subjects randomized to comparators. The two trials with the largest number of observed primary events were trials 18 and 19. These two trials contributed 54% of the total events among subjects randomized to comparators (44/81), and 44% of the total events among subjects randomized to dapagliflozin (43/97).

Table 3. Subjects with Primary Composite Event by Treatment and Trial

Trial	Comparators N = 3403, PY =3831		Dapagliflozin N = 5936, PY = 6594	
	events / N	%	events / N	%
D1690C00004	10 / 408	2.45%	8 / 406	1.97%
D1690C00005	1 / 146	0.68%	6 / 450	1.33%
D1690C00006	6 / 197	3.05%	11 / 610	1.80%
D1690C00010	1 / 226	0.44%	1 / 225	0.44%
D1690C00012	1 / 91	1.10%	1 / 91	1.10%
D1690C00018	18 / 462	3.90%	21 / 460	4.57%
D1690C00019	26 / 483	5.38%	22 / 482	4.56%
D1692C00005	0 / 54	-	1 / 166	0.60%
D1692C00006	1 / 87	1.15%	0 / 174	-
MB102008	0 / 110	-	1 / 279	0.36%
MB102009	0 / 23	-	0 / 48	-
MB102013	0 / 75	-	6 / 410	1.46%
MB102014	6 / 137	4.38%	5 / 409	1.22%
MB102021	1 / 201	0.50%	2 / 397	0.50%
MB102029	8 / 84	9.52%	7 / 168	4.17%
MB102030	0 / 139	-	1 / 281	0.36%
MB102032	0 / 68	-	0 / 142	-
MB102034	1 / 208	0.48%	2 / 430	0.47%
MB102035	0 / 51	-	0 / 24	-
MB102045	0 / 21	-	0 / 23	-
MB102054	1 / 132	0.76%	2 / 261	0.77%
Pooled	**81**		**97**	

*Primary composite event: CV death, MI, stroke and hospitalization for unstable angina.
Source: Created by reviewer. Dataset: adcv5.xpt

4.2   Analysis of the Primary Cardiovascular Composite Endpoint

The primary Cox proportional hazards model stratified by trial obtained an estimated hazard ratio and 95% confidence interval of **0.81 (0.59, 1.09)** for the risk of the primary composite endpoint associated with dapagliflozin. These results are summarized in Table 4 and in the forest plot in Figure 1. These data show no evidence of increased cardiovascular risk associated with dapagliflozin in the 21 trials. The upper bound of the 95% confidence interval for the hazard ratio is smaller than the margin of 1.8 established in the FDA Guidance.

**Table 4. Analysis of the Primary Composite Endpoint in
All Trials in the Meta-Analysis**

	Comparators N = 3403 PY = 3831	Dapagliflozin N= 5936 PY = 6594	Hazard Ratio (95% CI)
Events (rate per 1000 PY)[1]	**81 (23.8)**	**97 (16.3)**	**0.81 (0.59, 1.09)**

[1]Unadjusted rate of events pooled across all trials
Source: Created by reviewer. Dataset: adcv5.xpt

Figure 1. Forest Plot of Estimated HR and 95% CI for the Primary Composite Endpoint
Source: Created by reviewer. Dataset: adcv5.xpt

Trial	Comparators Events / N	Dapagliflozin Events / N		Hazard Ratio (95% CI)
D1690C00004	10 / 408	8 / 406		0.78 (0.31, 1.97)
D1690C00005	1 / 146	6 / 450		1.93 (0.23, 16)
D1690C00006	6 / 197	11 / 610		0.54 (0.2, 1.46)
D1690C00010	1 / 226	1 / 225		0.97 (0.06, 15.44)
D1690C00012	1 / 91	1 / 91		1.05 (0.07, 16.72)
D1690C00018	18 / 462	21 / 460		1.17 (0.62, 2.2)
D1690C00019	26 / 483	22 / 482		0.84 (0.48, 1.49)
D1692C00005	0 / 54	1 / 166		
D1692C00006	1 / 87	0 / 174		
MB102008	0 / 110	1 / 279		
MB102009	0 / 23	0 / 48		
MB102013	0 / 75	6 / 410		
MB102014	6 / 137	5 / 409		0.25 (0.08, 0.82)
MB102021	1 / 201	2 / 397		1.01 (0.09, 11.15)
MB102029	8 / 84	7 / 168		0.39 (0.14, 1.06)
MB102030	0 / 139	1 / 281		
MB102032	0 / 68	0 / 142		
MB102034	1 / 208	2 / 430		0.97 (0.06, 15.44)
MB102035	0 / 51	0 / 24		
MB102045	0 / 21	0 / 23		
MB102054	1 / 132	2 / 261		1.01 (0.09, 11.11)
Pooled	**81 / 3403**	**97 / 5936**		**0.81 (0.59, 1.09)**

4.2.1 Analysis of the Individual Components of the Primary Cardiovascular Composite Endpoint in the Population of All Trials

Table 5 shows counts for each of the individual components of the primary composite endpoint: CV death, MI, stroke, and hospitalization for unstable angina. The estimated hazard ratios for the risk of these endpoints associated with dapagliflozin are consistent with the analysis of the composite endpoint and show no evidence of increased cardiovascular risk associated with dapagliflozin.

Table 5. Analysis of the Individual Components of the Primary Composite Outcome

| | Events | | Estimated HR (95% CI) |
	Comparators N = 3403	Dapagliflozin N = 5936	
CV Death	18	20	0.71 (0.37, 1.37)
MI	33	31	0.59 (0.35, 0.97)
Stroke	18	25	1.00 (0.54, 1.86)
Hospitalization for unstable angina	20	27	0.91 (0.50, 1.66)

Source: Created by reviewer. Dataset: adcv5.xpt

4.2.2 Analysis of the Primary Cardiovascular Composite Endpoint in Secondary Populations

Table 6 and Table 7 show the estimated hazard ratios and 95% confidence intervals for the primary composite endpoint in the secondary populations. For trials 18 and 19 alone the estimated HR associated with dapagliflozin was **0.98** with 95% CI (**0.64, 1.19**), and in subjects with a history of CV disease excluding trials 18 and 19 the estimated HR was **0.53** with 95% CI (**0.28, 1.02**). These results show no evidence of increased cardiovascular risk associated with dapagliflozin.

Table 6. Analysis of the Primary Composite Endpoint in Trials 18 and 19 (Stratified)

	Comparators N = 945 PY = 1119	Dapagliflozin N= 942 PY = 1118	Hazard Ratio (95% CI)
Events (rate per 1000 PY)[1]	**44 (39.3)**	**43 (38.5)**	**0.98 (0.64, 1.49)**

[1]Unadjusted rate of events across both trials
Source: Created by reviewer. Dataset: adcv5.xpt

Table 7. Analysis of the Primary Composite Endpoint in Subjects with a History of CV Disease, Excluding Trials 18 and 19

	Comparators N = 417 PY = 510	Dapagliflozin N= 919 PY = 1166	Hazard Ratio (95% CI)
Events (rate per 1000 PY)[1]	**17 (33.3)**	**25 (21.4)**	**0.53 (0.28, 1.02)**

[1]Unadjusted rate of events pooled across all trials
Source: Created by reviewer. Dataset: adcv5.xpt

4.3 Analysis of the Secondary Cardiovascular Composite Endpoints

Table 8 summarizes the analyses of the secondary composite endpoint and MACE in the three analysis populations (all trials, subjects with CV disease, trials 18 and 19 only). Overall, these analyses are consistent with results of the primary endpoint and show no evidence of an increased cardiovascular risk associated with dapagliflozin.

Table 8. Analysis of the Secondary Composite Endpoint and MACE in All Populations

Population	Events		Estimated HR
endpoint	Comparators	Dapagliflozin	(95% CI)
All Trials in the Meta-Analysis	**N = 3403**	**N = 5936**	
Secondary composite endpoint	111	126	0.76 (0.59, 1.00)
MACE	62	73	0.78 (0.55, 1.11)
Trials 18 and 19 (stratified)	**N = 945**	**N = 942**	
Secondary composite endpoint	63	56	0.89 (0.62, 1.27)
MACE	29	32	1.11 (0.67, 1.83)
Subjects with a history of CV disease, excluding Trials 18 and 19	**N = 417**	**N = 919**	
Secondary composite endpoint	24	38	0.57 (0.33, 0.97)
MACE	16	18	0.41 (0.20, 0.84)

*Secondary composite event: CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization and hospitalization for heart failure
*MACE composite endpoint: CV death, MI, stroke
Source: Created by reviewer. Dataset: adcv5.xpt

4.4 Cardiovascular Endpoints Observed within the First 30 Days after Randomization in the Dapagliflozin Program

A post-hoc analysis was conducted to examine the risk of cardiovascular events associated with dapagliflozin within the first 30 days after randomization in the 21 trials in the meta-analysis. This analysis was motivated by an imbalance of early cardiovascular events observed in the development program for canagliflozin, the only SGLT2 inhibitor currently approved in the United States. Canagliflozin was approved in March 2013 in the United States under NDA 204042, as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus. Section 4.5 discusses the early imbalance of cardiovascular events observed in the canagliflozin program as presented at the January 10, 2013 Advisory Committee meeting.

An imbalance of cardiovascular events was observed within the first 30 days of treatment with dapagliflozin in the meta-analysis as shown in Table 9. There were 8 primary events observed among 5936 subjects randomized to dapagliflozin (0.13%) and 2 primary events (plus 2 secondary events) among 3403 subjects randomized to comparators (0.06%). Four of the 8 events in the dapagliflozin arm occurred within the first week after randomization. The corresponding estimated hazard ratio and 95% confidence interval for primary events associated with dapagliflozin within the first 30 days in the 21 trials was 2.77 (0.57, 13.33).

Table 9. List of Primary and Secondary Composite Cardiovascular Events within the First 30 Days after Randomization in the Dapagliflozin Program

Trial	Treatment	Days to Event	Type of Event	Gender	Age	History of CV Disease
D1690C00018	Dapagliflozin	2	CV death	Female	77	Yes
D1690C00006	Dapagliflozin	3	Stroke	Female	43	No
D1690C00018	Dapagliflozin	3	Stroke	Male	58	Yes
D1690C00018	Dapagliflozin	4	Hospitalization for unstable angina	Female	59	Yes
MB102021	Dapagliflozin	9	MI	Female	55	No
D1690C00006	Placebo	12	Stroke	Female	64	Yes
D1690C00004	Glipizide	13	MI	Male	69	No
D1690C00019	Placebo	15	Hospitalization for heart failure	Male	56	Yes
MB102021	Dapagliflozin	19	MI	Male	68	Yes
MB102034	Dapagliflozin	22	Hospitalization for unstable angina	Male	55	No
D1690C00019	Dapagliflozin	28	Stroke	Male	70	Yes
D1690C00005	Glipizide	29	Hospitalization for heart failure	Male	61	Yes

*Pooled sample size = 5936 on dapagliflozin, 3403 on comparators
*Pooled sample size with history of CV disease, including trials 18 and 19: 1856 on dapagliflozin, 1358 on comparators.
The two subjects highlighted in gray experienced the secondary composite outcome but no the primary composite outcome.
Source: Created by reviewer. Dataset: adcv5.xpt

In trials 18 and 19 alone, there were 4 primary events observed among 942 subjects randomized to dapagliflozin and 0 primary events (plus 1 secondary) among 945 subjects randomized to placebo within the first 30 days after randomization. Figure 2 shows the Kaplan-Meier plots of the observed cumulative probability of primary composite events in trials 18 and 19 alone. The plot shows the imbalance of early events in favor of the comparator arm. However, throughout the full duration of these two trials, both treatment arms showed a comparable risk profile**:** HR 0.98 (0.64, 1.49), logrank test p-value 0.92.

Figure 2. Observed Cumulative Probability of Primary Composite Endpoint in Trials 18 and 19

Source: Created by reviewer. Dataset: adcv5.xpt
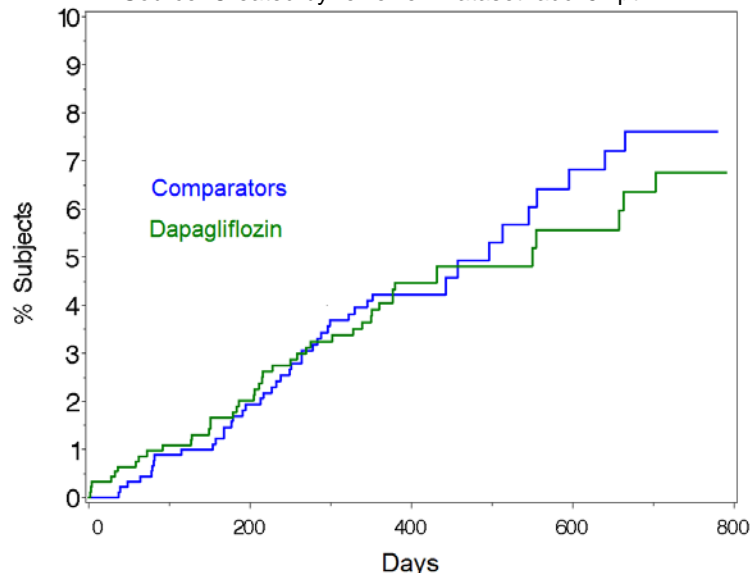
It is not clear whether the early imbalance of cardiovascular events observed in the canagliflozin and dapagliflozin programs may be associated with the use of these products or may be attributable to chance.

4.5 Cardiovascular Endpoints Observed within the First 30 Days after Randomization in the Canagliflozin Program (NDA 204042)

On 31 May 2012, Janssen submitted a meta-analysis of cardiovascular events conducted in nine randomized clinical trials for canagliflozin as part of their application package for NDA 204042. The meta-analysis included one Phase 2 trial, seven Phase 3 trials and one ongoing Phase 3 dedicated cardiovascular safety trial, 'CANVAS'. CANVAS enrolled subjects with history or high risk of CV disease defined as either (1) age $\geq$ 30 with documented symptomatic atherosclerotic CV disease or (2) age $\geq$ 50 with 2 or more risk factors for CV disease at the time of screening.

The pre-specified primary Cox proportional hazards model in the meta-analysis obtained an estimated hazard ratio and 95% confidence interval of 0.91 (0.68, 1.22) for the risk of MACE-plus comparing canagliflozin to all comparators. MACE-plus was defined as the composite of cardiovascular death, MI, stroke and hospitalized unstable angina. The results of this meta-analysis were discussed at an Advisory Committee Meeting held on January 10, 2013.

An imbalance of MACE-plus was observed within the first 30 days after randomization in the dedicated cardiovascular safety trial CANVAS: 13 MACE-plus were observed among 2886 subjects randomized to canagliflozin (0.45%) and 1 MACE-plus was observed among 1441 subjects randomized to placebo (0.07%). Seven of the events in the canagliflozin arm were observed within the first week after randomization. A summary of these events is shown in Table 10.

The early imbalance of MACE-plus was not observed in the non-CANVAS trials in the meta-analysis. During the first 30 days after randomization, 2 events were observed in 3510 subjects randomized to canagliflozin (0.057%) and 4 events were observed in 1886 subjects randomized to comparators (0.21%). Therefore, although there were only 6 MACE-plus observed within the first 30 days in the non-CANVAS trials, a higher proportion of events was observed in the comparator arm than in the canagliflozin arm (0.21% vs. 0.057%).

The imbalance of early MACE-plus observed in CANVAS may have been caused by an early increased cardiovascular risk associated with canagliflozin among subjects with high background risk or it may have been attributable to chance.

**Table 10. List of MACE-plus in CANVAS during the
First 30 Days After Randomization**

Treatment	Day of Event	Type of Event
Cana 300 mg	2	Nonfatal Stroke
Cana 100 mg	2	Hospitalized Unstable Angina
Cana 100 mg	2	Nonfatal Stroke
Cana 300 mg	6	Nonfatal Myocardial Infarction
Cana 300 mg	6	Nonfatal Myocardial Infarction
Cana 300 mg	7	Cardiovascular Death
Cana 100 mg	7	Nonfatal Stroke
Cana 300 mg	12	Nonfatal Myocardial Infarction
Cana 100 mg	14	Hospitalized Unstable Angina
Cana 100 mg	21	Nonfatal Myocardial Infarction
Placebo	23	Nonfatal Myocardial Infarction
Cana 100 mg	24	Nonfatal Myocardial Infarction
Cana 100 mg	26	Nonfatal Stroke
Cana 300 mg	29	Nonfatal Stroke

*Sample size = 2886 on canagliflozin and 1441 on placebo.
Source: Briefing package for Advisory Committee meeting on canagliflozin
held on 10/10/2013.

5. Summary of Findings

The pre-specified primary analysis estimated a hazard ratio and 95% confidence interval of **0.81 (0.59, 1.09)** for the risk of the primary composite cardiovascular outcome (CV death, MI, stroke, and hospitalization for unstable angina) associated with dapagliflozin relative to all comparators. The upper bound of the 95% confidence interval for the hazards ratio was smaller than the margin of 1.8 specified in the FDA Guidance. The estimated hazard ratio and 95% confidence interval for the risk of primary endpoint associated with dapagliflozin in the high risk population of trials 18 and 19 was **0.98 (0.64, 1.49).** Analyses of secondary endpoints, including MACE, and in secondary populations produced consistent results. These analyses found no evidence of increased cardiovascular risk associated with dapagliflozin throughout the full duration of the trials.

During the first 30 days after randomization, a higher proportion of subjects randomized to dapagliflozin experienced an adverse cardiovascular event than subjects randomized to comparators. A similar imbalance of early cardiovascular events was observed in CANVAS, a dedicated cardiovascular outcomes trial for canagliflozin. Canagliflozin is the only SGLT2 inhibitor currently approved in the United States. The analyses of the first 30 days after randomization in the dapagliflozin and canagliflozin programs were not pre-specified in the corresponding Statistical Analysis Plans. Based on these findings, it is possible that the class of SGLT2 inhibitors may be associated with an early increased cardiovascular risk. However, the small total number of events observed within the first 30 days in these two programs does not preclude the possibility that the early imbalance of cardiovascular events may be attributable to chance.

References

1. Food and Drug Administration. Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Briefing Document - Efficacy

NDA/BLA #:	NDA 202293
Drug Name:	dapagliflozin
Indication(s):	Treatment of patients with type 2 diabetes mellitus
Applicant:	Bristol-Myers Squibb
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	Mark D. Rothmann, Ph.D. (Team Leader)
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino, M.D. Karen Mahoney, M.D. (Team Leader)
Project Manager:	Abolade Adeolu

Table of Contents

LIST OF TABLES

1 OVERVIEW OF STUDIES

The Applicant, Bristol-Myers Squibb, has resubmitted the new drug application NDA 202-293 on 11-July-2013 in response to the Complete Response Letter (CRL) dated 17-Jan-2012 for the use of dapagliflozin (BMS-512148, DAPA) in adult patients with type 2 diabetes mellitus and inadequate glycemic control. There are original/updated and new data of phase 3 efficacy and safety studies in this submission. The efficacy of DAPA in the original submission was presented in the first AC meeting held on 19-Jul-2011. This briefing document summarizes the overall efficacy of DAPA, including new efficacy data from three studies, D1690C00010 (add-on to sitagliptin), MB102-073, and MB102-077 (patients with hypertension). The efficacy data from two studies that were previously reviewed but not presented in the AC meeting in 2011, D1690C00018 (patients with cardiovascular disease and hypertension) and D1690C00019 (patients with cardiovascular disease), are also included in this briefing document.

The overview of the phase 3 clinical studies in the Applicant's resubmission for evaluating the efficacy and safety of DAPA in T2DM patients are shown in Table 1. The studies reviewed by FDA statisticians are italicized in the table.

Table 1. Overview of Phase 3 Trials

Study ID (Brief Name)	Population	Dose (mg)	Background Tx (Rescue)	Comparator	Weeks
Monotherapy					
MB102013[1,2] *(2013)*	Drug-naïve	DAPA 2.5, 5, 10	None (MET)	Placebo	24+ext.
MB102032[1,2] (2032)	Drug-naïve	DAPA 1, 2.5, 5	None (MET)	Placebo	24
Combination Therapy					
MB102014[1,2] *(2014)*	Inadequate control on background	DAPA 2.5, 5, 10	MET (Pioglitazone or acarbose)	Placebo	24+ext.
D1690C00005[1,2] (C00005)	Inadequate control on background	DAPA 2.5, 5, 10	Glimepiride (MET or TZD)	Placebo	24+ext.
MB102030[1,2] *(2030)*	Inadequate control on background	DAPA 5, 10	Pioglitazone (MET or SU)	Placebo	24+ext.
D1690C00006[1,2] *(C00006)*	Inadequate control on background	DAPA 2.5, 5, 10	Insulin and up to two OAD (Insulin up-titration)	Placebo	24+ext.
D1690C00004[1,2] *(C00004)*	Inadequate control on background	DAPA 2.5, 5, 10 (titrated)	MET (None)	Glipizide*	52+ext.
D1690C00012[1] (C00012)	Inadequate control on background	DAPA 10	MET (Sitagliptin)	Placebo**	24+ext.
D1690C00010 (C00010)#	Drug-naïve or inadequate control on background	DAPA 10	Sitagliptin and/or MET (glimepiride)	Placebo	24+24
MB102021[1,2] (2021)	Drug-naïve with higher HbA1c	DAPA 5+ MET	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 5 mg, MET	24
MB102034[1,2] *(2034)*	Drug-naïve with higher HbA1c	DAPA 10 + MET	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 10 mg, MET	24
Special Populations					
MB102029[1,2] (2029)	Moderate renal impairment	DAPA 5, 10	Any except MET (Any except MET)	Placebo	24+ext.
MB102-073 (2073)	Hypertension	DAPA 10	OAD and/or insulin (anti-hypertension)	Placebo	12
MB102-077 (2077)	Hypertension	DAPA 10	OAD and/or insulin (anti-hypertension)	Placebo	12
D1690C00018 (C00018)	Cardiovascular disease and hypertension	DAPA 10	OAD and/or insulin (Various)	Placebo	24+ext.
D1690C00019 (C00019)	Cardiovascular disease	DAPA 10	OAD and/or insulin (Various)	Placebo	24+ext.

Notes: DAPA = dapagliflozin. Proposed once daily doses are 5, 10 mg. OAD = oral anti-diabetic drug. SU = sulfonylurea, MET=metformin, TZD = thiazolidinedione. *Italics = focus of review.* # Add-on to sitagliptin.

[1] In the original submission.

[2] In the review briefing of the first AC meeting

*Noninferiority comparison; other studies used superiority comparison.

**Primary endpoint is change in body weight; other studies used change in HbA1c.

2   EVALUATION OF EFFICACY

2.1   *Efficacy Results*

There were 16 Phase 3 studies that evaluated the efficacy of DAPA at doses 1 mg, 2.5 mg, 5 mg, and 10 mg in this briefing. Results from 11 of the phase 3 studies in the original submission on 28-Dec-2010 were reviewed in the AC meeting held on 19-Jul-2011. After the AC meeting, the data of 2 phase 3 studies (D1690C00018 and D1690C00019,) were submitted on 20-Oct-2011, 2-Nov-2011, and 9-Nov-2011, respectively. Additional data of three new studies, D1690C00010 (add-on to sitagliptin), MB102-073, and MB102-077 (patients with hypertension), were included in the resubmission on 11-July-2013. In all these phase 3 studies, the key efficacy findings reported by the Applicant were consistent with FDA analyses. All superiority comparisons of DAPA versus placebo in HbA1c change from baseline to the end of planned treatment period for efficacy (the primary efficacy endpoint in all studies except study C00012), were statistically significant.

The primary efficacy findings in the monotherapy and add-on placebo-controlled studies are summarized in Table 2. These results were from the Applicant's primary analysis of HbA1c change from baseline, which used an analysis of covariance (ANCOVA) model with the last observation carried forward (LOCF) method for missing observations. The analyses disregarded observations recorded after receiving rescue treatment. In general, the ANCOVA model included terms for treatment as fixed effect and the corresponding baseline HbA1c value as a covariate with pre-specified additional fixed effects covariates. Sensitivity analyses by the Applicant using Mixed Model Repeated Measure (MMRM) methods (using the same factors as the ANOVA model along with factors for visit and treatment-by-visit interaction) were consistent with the primary analysis results.

There are issues involving the bias and reliability of an estimate of a treatment difference when carrying forward an intermediate measurement and treating it as an actual measurement at the end point. Additionally, the MMRM analysis has those excluded HbA1c measurements from patients who receive rescue therapy represented by the corresponding measurements of patients on the same treatment arm that did not receive rescue treatment.

Table 2. Primary Efficacy Results for Dapagliflozin versus Placebo in Patients with Type 2 Diabetes (Phase 3 Studies-Monotherapy and add-on Placebo-Controlled Studies) (Fall Analysis Set/LOCF)

Study		Placebo	Dapagliflozin Dose			
			1 mg	2.5 mg	5 mg	10 mg
Monotherapy						
2013[1,2]	Adj. Mean (SE)	-.23 (.10)		-.58 (.11)	-.77 (.11)	-.89 (.11)
	DAPA- Placebo	--		-.35 (.15)*	-.54 (.15)**	-.66 (.15)**
2032[2]	Adj. Mean	.02 (.12)	-.68 (.12)	-.72 (.12)	-.82 (.12)	N.A.
	DAPA- Placebo	--	-.69(.17)**	-.74 (.17)**	-.84 (.17)**	N.A.
Combination Therapy						
2014[2]	Adj. Mean	-.30 (.07)		-.67 (.07)	-.70 (.07)	-.84 (.07)
	DAPA- Placebo	--		-.38 (.10)**	-.41 (.10)**	-.54 (.10)**
C00005[2]	Adj. Mean	-.13 (.06)	N.A.	-.58 (.06)	-.63 (.06)	-.82 (.06)
	Diff. vs. Placebo	--	N.A.	-.44 (.09)**	-.49 (.09)**	-.68 (.09)**
2030[2]	Adj. Mean	-.42 (.08)		N.A.	-.82 (.08)	-.97 (.08)
	DAPA- Placebo	--		N.A.	-.40 (.12)**	-.55 (.12)**
C00006[2]	Adj. Mean	-.30 (.05)		-.75 (.05)	-.82 (.05)	-.90 (.05)
	DAPA- Placebo	--		-.45 (.07)**	-.52 (.07)**	-.60 (.07)**
C00010	Adj. Mean	.04 (.05)	--	--	--	-.45 (.05)
	DAPA- Placebo					-.48 (.07)**

[1] AM dosing
[2] Reviewed by FDA statistical reviewer in the first AC meeting.
*$p < .05$ vs. placebo **$p < .001$ vs. placebo   (Statistical adjustments for multiplicity were not applied.)

There were two studies that compared DAPA + metformin to DAPA alone and to metformin, respectively. The results from these studies are provided in Table 3 below. The primary analyses were based on similar ANOVA models as described above (as described before Table 2). Sensitivity analyses were based on MMRM methods similar to those described above. Each sensitivity analysis provided similar results as the corresponding primary analysis. Previous comments on the issues of these approaches apply.

Table 3: Change in HbA1c from Baseline at Week 24 by Treatment, Studies 2021 and 2034*

	Treatment Arm		
Study 2021	Dapa. 5 mg + Metf.	Dapa. 5 mg	Metf.
Adj. Mean	-2.05 (.09)	-1.19 (.09)	-1.35 (.09)
Diff. from Combin.	--	-.86 (.12)**	-.70 (.12)**
Study 2034	Dapa. 10 mg + Metf.	Dapa. 10 mg	Metf.
Adj. Mean	-60.4 (2.5)	-46.4 (2.5)	-34.8 (2.5)
Diff. from Combin.	--	-13.9 (3.6)**	-25.5 (3.6)**

* Reviewed by FDA statistical reviewer in the first AC meeting.
**p < .001 vs. the combination

The following two studies were also reviewed by FDA statistician in the first AC meeting.

The glipizide-controlled study, C00004, also showed a positive result on the primary endpoint as. Both the dapagliflozin (N=400) and the glipizide (N=401) arms showed an

estimated reduction from baseline to Week 52 of 0.52%. The 95% confidence interval for the difference between treatment arms was (-0.11%, 0.11%). The upper bound of this interval is well within the planned noninferiority margin of 0.35%, and this margin is consistent with the advice given in the guidance for industry cited previously.

For the placebo-controlled Study C00012, the primary endpoint was change in body weight at Week 24. The Applicant reports that subjects in the dapagliflozin 10 mg + metformin arm lost an additional 2.08 kg compared to those in the metformin-only arm (p < .0001).

There were five Phase 3 studies that evaluated the efficacy of DAPA 10 mg in special populations. The key efficacy findings of these studies reported by the Applicant were consistent with FDA analyses. Superiority comparisons of DAPA versus placebo in the primary efficacy endpoint (change from baseline in HbA1c, or HbA1c and 3-item endpoint of clinical benefit), were statistically significant in all studies. For studies 2029, C00018, and C00019, the Applicant's pre-specified primary analyses of HbA1c used an ANCOVA model with LOCF imputation similar to the ANCOVA models described earlier. Sensitivity analyses using MMRM method by the Applicant were consistent with the primary results from the ANCOVA model using LOCF imputation. Studies C00018 and C00019 had a second primary endpoint of the, proportion of responders for a 3-item endpoint of clinical benefit at Week 24 (defined as: (1) an absolute drop of 0.5% or more from baseline in HbA1c, and (2) a relative drop of 3% or more from baseline in total body weight, and (3) an absolute drop of 3 mmHg or more from baseline in seated SBP after 24 weeks of oral administration of double-blind treatment). A Cochran-Mantel-Haenszel method with age category, insulin use, and the time from most recent qualifying CV event group as stratification factors and LOCF used for missing measurements. For studies 2073 and 2077, the Applicant's pre-specified primary analyses of both seated SBP and HbA1c used an MMRM method with fixed categorical effects of treatment, week, treatment-by-week interaction, and randomization factors and continuous fixed covariates of baseline and baseline by week interaction, and excluded post-rescue data. The statistical issues are same as those described previously (before Table 2). The primary efficacy results of the five studies are summarized in Table 4.

Table 4. Primary Efficacy Results for Dapagliflozin 10 mg versus Placebo in Patients with Type 2 Diabetes (Phase 3 Studies-Special populations) (Full Analysis Set)

Study (Weeks)	Primary endpoint Arm	n	Baseline Mean (SD)	LSMean change ± SE	DAPA minus control (95% CI)	p-value
Add-on to Various OADs and/or insulin						
2029[a] (12)	HbA1c					
	DAPA 10 mg	2	7.9 (0.8)	-0.44 ± 0.17	-0.11 (-0.40, 0.17)	0.435
	DAPA 5 mg	2	7.9 (0.7)	-0.41 ± 0.17	-0.08 (-0.37, 0.20)	0.561
	Placebo			-0.32 ± 0.17		
2073[b] (12)	Seated SBP					
	DAPA 10 mg	280	149.8 (7.5)	-10.40±0.88	-3.05 (-4.78, -1.24)	0.0010
	Placebo	279	149.5 (8.0)	-7.34 ± 0.88		

	HbA1c					
	DAPA 10 mg	278	8.09 (1.00)	-0.56 ± 0.06	-0.46 (-0.59, -0.33)	<.0001
	Placebo	279	8.02 (0.91)	-0.10 ± 0.06		
2077 [b] (12)	Seated SBP					
	DAPA 10 mg	205	151.0 (7.9)	-11.90±1.06	-4.28 (-6.54, -2.02)	0.0002
	Placebo	199	151.3 (6.7)	-7.62 ± 1.07		
	HbA1c					
	DAPA 10 mg	204	8.09 (0.91)	-0.63 ± 0.07	-0.61 (-0.76, -0.46)	<.0001
	Placebo	197	8.00 (0.96)	-0.02 ± 0.07		
C00018[a] (24)	HbA1c [d]					
	DAPA 10 mg	448	8.18 ± 0.84	-0.38 ± 0.04	-0.46 (-0.56, -0.37)	<.0001
	Placebo	451	8.08 ± 0.80	0.08 ± 0.04		
	Responders[c, d]					
	DAPA 10 mg	444		52, 11.7%	9.9% (7.0%,12.9%)	<.0001
	Placebo	451		4, 0.9%		
C00019[a] (24)	HbA1c [d]					
	DAPA 10 mg	474	8.04 ± 0.76	-0.33 ± 0.04	-0.40 (-0.50, -0.30)	<.0001
	Placebo	471	8.07 ± 0.79	0.07 ± 0.04		
	Responders[c,d]					
	DAPA 10 mg	468		47, 10.0%	7.0% (4.3%, 9.8%)	<.0001
	Placebo	469		9, 1.9%		

Note: HbA1c: glycosylated hemoglobin; DAPA: dapagliflozin; OAD: oral anti-diabetic drugs; LOCF: last observation carried forward; SBP: systolic blood pressure; SE: standard error.

[a] using LOCF in ANCOVA for HbA1c excluding data after rescue medication (in C00018 and C00019 including data after anti-hypertensive rescue)

[b] MMRM excluding data after rescue medication

[c] Proportion of responders for a 3-item endpoint of clinical benefit at Week 24, using LOCF in Cochran-Mantel-Haenszel method

[d] Significant p-value: the primary endpoints were tested at $\alpha = 0.025$ (two-sided); otherwise they were tested following a sequential testing procedure at $\alpha = 0.05$ (two-sided).

All superiority comparisons of dapagliflozin versus placebo, except study MB102029, were significant, indicating consistency in results across different populations.

2.2   *Efficacy of Integrated Data*

2.2.1   Integrated Analysis of Efficacy

In order to provide information on the efficacy of DAPA in a larger group of T2DM subjects, this reviewer performed efficacy analyses based on pooled phase 3 Placebo-controlled studies with endpoints of 24 weeks stratified by study. This assessment of efficacy includes the Phase 3 placebo-controlled studies (except the renal impairment study MB102029, cohort 1 of Study MB102009 and group 2 of Study MB102013, both of which were uncontrolled, and the two 12-week studies MB102073 and MB102077 for hypertension patients) plus selected data from the initial combination studies (the dapagliflozin plus metformin and placebo plus metformin arms of Studies MB102021 and MB102034).

Two doses, DAPA 5 mg and 10 mg, are selected for the meta-analyses of the pooled 13 phase 3 data. Analyses were stratified by study. The efficacy results of the pooled 13 phase 3 placebo-controlled studies (PC) after 24 weeks of treatment is shown in Table 5. The mean changes in systolic blood pressure from placebo of the pooled studies after 24 weeks of treatment are similar to that of the two studies MB102073 and MB102077 in hypertension patients after 12 weeks of treatment.

The efficacy of DAPA (5 mg and 10 mg) versus placebo is observed in the integrated analysis for the primary efficacy endpoint HbA1c. Additionally, the Applicant appears to be emphasizing positive effects on blood pressure and body weight as additional potential benefits of the drug. Also, there may be a concern that DAPA increases LDL, which is an undesirable effect. Integrated analyses were performed to verify the effect/affect of DAPA on these secondary efficacy endpoints (LDL, seated systolic blood pressure, body weight, and FPG). Caution should be taken when interpretating the results, as it is difficult to account for multiplicity. Mainly, these analyses are done for descriptive purposes. As shown in Table 5, the results support that DAPA is efficacious in reducing FPG, systolic blood pressure, and body weight at Week 24 relative to placebo for both doses of 5 mg and 10 mg. The observed mean level of LDL was greater after 24 weeks treatment in patients treated with DAPA (5 mg and 10 mg) compared to baseline while the mean LDL level in placebo patients remained close to the baseline level.

Table 5. Efficacy Parameters After 24 Weeks of Treatment in Pooled Placebo-Controlled Studies for DAPA 5 mg and 10 mg in Patients with Type 2 Diabetes (FAS/LOCF)

Endpoint	Placebo		DAPA 5 mg		DAPA 10 mg	
	n		n		n	
HbA1c (%)						
Baseline mean (SD)	2274	8.26 (1.03)	996	8.44 (1.13)	2085	8.21 (0.97)
Adj. Mean Change from baseline±SE		-0.37 ± 0.02		-0.88 ± 0.03		-0.90 ± 0.02
DAPA−P, adjusted LS Mean				-0.51		-0.52
(95% CI)				(-0.58, -0.43)		(-0.58, -0.47)
p-value				<.0001		< 0.0001
HbA1c <7%, (%)	325 (14%)		202 (20%)		418 (20%)	
FPG (mg/dL)						
Baseline mean (SD)	2377	168.2 (47.8)	1009	175.2 (51.9)	2182	165.5 ± (46.7)
Adj. Mean Change from baseline		-4.23 ± 0.86		-26.36 ± 1.32		-28.75 ± 0.93
±SE DAPA−P, adjusted LS Mean				-22.12		-24.51
(95% CI)				(-25.27, -18.98)		(-26.77, -22.25)
p-value				<.0001		< 0.0001
LDL (mg/dL)						
Baseline mean (SD)	1906	103.9 (38.5)	899	113.3 (38.3)	1856	101.3 (38.2)
Adj. Mean Change from baseline±SE		-0.11 ± 0.64		2.36 ± 0.93		3.23 ± 0.69
DAPA−P, adjusted LS Mean				2.47		3.34
(95% CI)				(0.19, 4.74)		(1.65, 5.03)
p-value				0.0337		0.0001
Body Weight (Kg)						
Baseline mean (SD)	2395	90.1(19.2)	1016	86.8 (18.9)	2203	90.9 (19.5)
Adj. Mean Change from baseline±SE		-0.66 ± 0.07		-2.07 ± 0.10		-2.48 ± 0.07
DAPA−P, adjusted LS Mean				-1.40		-1.82
(95% CI)				(-1.64, -1.16)		(-1.99, -1.65)
p-value				<.0001		<.0001
Systolic Blood Pressure (mmHg)						
Baseline mean (SD)	1471	129.8 (15.1)	1015	129.3 (15.8)	1278	129.9 (16.0)
Adj. Mean Change from baseline±SE		-0.91 ± 0.31		-3.19 ± 0.39		-4.08 ± 0.35
DAPA−P, adjusted LS Mean				-2.28		-3.17
(95% CI)				(-3.25, -1.32)		(-4.05, -2.29)
p-value				<.0001		< 0.0001

Note: SD – standard deviation

2.2.2　Integrated Analysis of HbA1c by Subgroups in Patients Based on Their Baseline eGFR Levels in Placebo-Controlled Studies

Since dapagliflozin acts via the kidney, the efficacy of the drug may be affected by renal function. Therefore, analyses within different eGFR ranges on HbA1c change from baseline to Week 24 were performed. To evaluate the efficacy of dapagliflozin in a larger group of T2DM subjects based on their renal function, integrated analyses were performed, which included data from study MB102029 of patients with moderate renal impairment and data from the placebo-controlled studies. The integrated analysis of change in HbA1c from baseline to 24 weeks was carried out by the following subgroups:

- baseline eGFR <30 mL/min/1.73m^2
- baseline eGFR <45 mL/min/1.73m^2
- baseline eGFR 30 to <45 mL/min/1.73m^2
- baseline eGFR 45 to <60 mL/min/1.73m^2
- baseline eGFR 60 to <90 mL/min/1.73m^2
- baseline eGFR ≥90 mL/min/1.73m^2

The integrated analysis of the primary endpoint HbA1c (at Week 24) of the fourteen placebo-controlled studies was performed using ANCOVA analyses (stratified by study) using LOCF method for dealing with missing values. This analysis method is the pre-specified method for the primary endpoint. No statistical adjustments for multiplicity were applied.

This reviewer also computed the percentage of patients who achieved an HbA1c <7% at Week 24 for these subgroups.

The subgroup analysis results are summarized in Table 6. Across the eGFR categories, the observed treatment effect on HbA1c change from baseline to Week 24 decreased as eGFR decreased for both doses of dapagliflozin. For the eGFR subgroups of 45 to <60 mL/min/1.73 m^2 or higher, the 95% confidence intervals for the treatment effect on HbA1c change from baseline to Week 24 ruled out no effect or negative effect on HbA1c. For the eGFR <45 mL/min/1.73 m^2 subgroup the results are consistent with no or little improvement by dapagliflozin on on HbA1c change from baseline to Week 24. There is no clear dose response of dapagliflozin (DAPA 5 mg and 10 mg) versus placebo in HbA1c reduction from baseline to Week 24. HbA1c reduction in the eGFR 45 to <60 mL/min/1.73m^2 subgroup was smaller than seen overall, with mean difference -0.23 and -0.32 from placebo for the 5 mg and 10 mg, respectively, with similar percentage of patients achieving HbA1c <7% at Week 24 in all three arms.

Table 6. Subgroup Analaysis in HbA1c for Dapagliflozin (5 mg and 10 mg) in Patients with Type 2 Diabetes by eGFR Levels (FAS/LOCF)

Endpoint	Placebo		Dapagliflozin			
			5 mg		10 mg	
HbA1c (%)	n		n		n	
eGFR <30 mL/min/1.73 m^2						
Baseline mean ± SE Adj. Mean Change from baseline±SE DAPA−P, adjusted LS Mean (95% CI)	5	--	4	--	3	--
eGFR <45 mL/min/1.73 m^2						
Baseline mean ± SE	60	8.24 ± 0.14	57	8.40 ± 0.16	83	8.16 ± 0.10

Adj. Mean Change from baseline±SE		-0.40 ± 0.19		-0.34 ± 0.18		-0.47 ± 0.18
DAPA−P, adjusted LS Mean (95% CI)				0.06 (-0.30, 0.42)		-0.07 (-0.38, 0.24)
HbA1c <7%, (%)	8 (15%)		5 (9%)		5 (6%)	
eGFR 30 to < 45 mL/min/1.73 m^2						
Baseline mean ± SE	55	8.20 ± 0.015	53	8.45 ± 0.16	80	8.16 ± 0.10
Adj. Mean Change from baseline±SE		-0.36 ± 0.20		-0.38 ± 0.19		-0.44 ± 0.18
DAPA−P, adjusted LS Mean (95% CI)				-0.02 (-0.39, 0.36)		-0.08 (-0.40, 0.24)
HbA1c <7%, (%)	8 (15%)		5 (9%)		5 (6%)	
eGFR 45 to <60 mL/min/1.73 m^2						
Baseline mean ± SE	278	8.16 ± 0.06	123	8.20 ± 0.09	234	8.20 ± 0.06
Adj. Mean Change from baseline±SE		-0.35 ± 0.07		-0.57 ± 0.10		-0.66 ± 0.08
DAPA−P, adjusted LS Mean (95% CI)				-0.23 (-0.44, -0.01)		-0.32 (-0.47, -0.16)
HbA1c <7%, (%)	32 (12%)		15 (12%)		33 (14%)	
eGFR 60 to <90 mL/min/1.73 m^2						
Baseline mean ± SE	1309	8.23 ± 0.03	543	8.39 ± 0.05	1183	8.17 ± 0.03
Adj. Mean Change from baseline±SE		-0.34 ± 0.03		-0.87 ± 0.05		-0.84 ± 0.04
DAPA−P, adjusted LS Mean (95% CI)				-0.53 (-0.63, -0.43)		-0.50 (-0.57, -0.43)
HbA1c <7%, (%)	183 (14%)		111 (20%)		242 (20%)	
eGFR ≥ 90 mL/min/1.73 m^2						
Baseline mean ± SE	707	78.40 ± 0.04	356	8.58 ± 0.06	666	8.30 ± 0.04
Adj. Mean Change from baseline±SE		-0.36 ± 0.08		-0.91 ± 0.09		-0.99 ± 0.08
DAPA−P, adjusted LS Mean (95% CI)				-0.55 (-0.68, -0.42)		-0.64 (-0.74, -0.53)
HbA1c <7%, (%)	106 (15%)		76 (21%)		142 (21%)	

3.   SUMMARY

The resubmitted data of phase 3 studies provide convincing evidence that dapagliflozin is efficacious for both of the proposed once daily doses, 5 mg and 10 mg. For majority of the phase 3 studies, the efficacy analyses were based on LOCF as the primary method for accounting for missing data, disregarding observations recorded after any rescue treatment. Results from analyses using MMRM performed by this reviewer to selected studies were consistent with the primary analysis results with LOCF. However, the efficacy of dapagliflozin based on HbA1c reduction is modest.

In all the placebo-controlled studies but study MB102029, both the 5 mg and 10 mg doses of dapagliflozin were shown to be superior to placebo on the primary endpoint, using the planned primary analysis. As reviewed in the first AC meeting, the active-controlled study showed that titrated doses of dapagliflozin and glipizide yielded quite similar results at Week 52. Although dapagliflozin was statistically non-inferior at Week 52, it should be noted that glipizide was clearly superior at some earlier time points.

The efficacy of DAPA (5 mg and 10 mg) versus placebo is observed in the meta analysis of the integrated placebo-controlled data for the primary efficacy endpoint HbA1c and interested secondary efficacy endpoints (seated systolic blood pressure, body weight, and FPG) without

family-wise type 1 error control. However, the results in the LDL change after 24 weeks treatment suggested elevated LDL levels in patients treated with DAPA (5 mg and 10 mg) while the LDL level in placebo arm remained close to the baseline level. This may raise a safety concern.

Subgroups analyses of HbA1c were conducted based on a pooled patient population from the 13 Phase 3 placebo-controlled studies with the primary endpoint at Week 24. The subgroup analysis suggests that dapagliflozin (5 mg and 10 mg) is effective only in subjects with normal renal function or mild impairment (eGFR $\geq$45 mL/min/1.73m^2). The size of the treatment effect should be considered when considering whether treatment with dapagliflozin is appropriate. There is no clear dose response of dapagliflozin (DAPA 5 mg and 10 mg) versus placebo in HbA1c reduction from baseline to Week 24.

Advisory Committee Nonclinical Briefing Document

Application: Dapagliflozin, NDA 202293 Complete Response
Drug Class: SGLT2 inhibitor
Clinical Indication: Type 2 Diabetes
Reviewers: Mukesh Summan, Ph.D., DABT, and Todd Bourcier, Ph.D., Division of Metabolism and Endocrinology Products

Non-Clinical Assessment of Carcinogenic Risk for Dapagliflozin

The non-clinical studies submitted in the original NDA did not identify a carcinogenic hazard for dapagliflozin. This conclusion was driven primarily by the lack of drug-related tumors observed in the two-year bioassays conducted in rats and mice at drug exposures reaching ~160x and 90x the clinical dose, respectively. Non-clinical studies indicated that dapagliflozin is unlikely to be genotoxic at clinically relevant doses, consistent with the 'clean' result from the two-year rodent studies. Pre-neoplastic alterations were also not observed in tissues, including the mammary and bladder tissues, with the exception of the kidney tubules. An increased incidence and severity of atypical hyperplasia of the renal tubules (considered a preneoplastic change) was observed at all doses of dapagliflozin in rats, though there was no increase in renal tubule adenoma or carcinoma as observed for other members of the SGLT2 inhibitor class.

Two-year rodent bioassays remain the contemporary standard by which the carcinogenic potential of most investigational pharmaceuticals intended for chronic use is addressed, though these studies are not perfect predictors of human cancer risk. An investigational compound that tests negative for neoplasms in the rat and mouse two-year bioassays, particularly at the multiples of clinical exposure achieved with dapagliflozin, is typically viewed as having low or negligible carcinogenic potential for human subjects. Common factors that would confound interpretation of a negative result were not present in this case (e.g., differences in metabolism or pharmacological activity).

In light of the numerical imbalance in bladder cancer from the clinical trials, additional concern was raised that dapagliflozin may act as a tumor promoter possibly as a consequence of changes in urinary volume, flow, and composition. Spontaneous primary bladder tumors were completely absent in the control (placebo) groups of rats and mice, and only three control rats showed transitional epithelial hyperplasia in the two-year studies with dapagliflozin (combined, n=520 rodents). Thus, it can be argued that a putative tumor promoting effect of dapagliflozin was inadequately addressed due to the lack of pre-existing pre-neoplastic or neoplastic bladder lesions in the two-year studies. As such, the FDA suggested that the Sponsor conduct additional non-clinical studies focused on evaluating potential tumor promotion with dapagliflozin. Central to the additional studies, FDA suggested evaluating dapagliflozin in a rodent model of bladder tumor promotion.

In their resubmission, the Sponsor submitted several nonclinical studies that addressed whether dapagliflozin or its major metabolite (dapagliflozin 3-O-glucuronide) directly promoted tumor growth of human bladder tumor cell lines *in vitro* or *in vivo* (xenograft studies).

Dapagliflozin and dapagliflozin 3-O-glucuronide did not promote growth of several human bladder transitional cell carcinoma (TCC) cell lines after 72 hour incubation with various concentrations of drug. Results from this study are consistent with what FDA had already concluded: that dapagliflozin itself is not a direct tumor promoter or inducer and that tumor promotion, if it occurs, would be secondary to changes in urinary volume, flow, and composition within the bladder.

The sponsor demonstrated that dapagliflozin did not induce a transcriptional profile 'typical' of tumor promoters from various rat tissues, retrospectively assessed. However, the bladder was not among the tissues profiled, and therefore these results are of marginal additional interest.

Hyperplastic bladders were not observed in 15-month old SGLT2 knockout mice, despite having a glucosuric phenotype. The absence of bladder tumors in these mice is reassuring and adds to the weight of evidence for a lack of carcinogenic activity. However, these observations do not address the current question of potential promotion of pre-existing bladder lesions with dapagliflozin- they are simply consistent with the observation that bladder tumors were also absent in normal mice or rats regardless of treatment with dapagliflozin in the two-year bioassays.

The Sponsor also demonstrated that varying the glucose concentration in growth medium had no effect on growth in the TCC cell lines for up to 145 hours of incubation. However, the focus on glucose in isolation cannot account for the spectrum of changes secondary to SGLT2 inhibition beyond a higher glucose load within the bladder *in vivo*, thus limiting the utility of this experiment.

Citing nonclinical studies conducted with Prasugrel[1], the Sponsor used a xenograft tumor promotion model wherein human bladder TCC cell lines were subcutaneously injected/transplanted into the flank of immunodeficient mice. Administering dapagliflozin at pharmacologically effective doses for 14 days did not result in enhanced tumor growth relative to untreated control mice. The xenograft model that the Sponsor chose, while appropriate for the situation with Prasugrel, was not relevant to the situation with dapagliflozin. The primary deficiency of the model is that the transplanted human bladder cells were not exposed to the variables of most concern: changes in urinary volume, flow, and composition within the microenvironment of the bladder. There are several models that allow evaluation of dapagliflozin on transitional cell tumor growth within the bladder, such as transplanting human bladder tumor cells to mouse bladders (e.g., orthotopic models). Another is the hydroxybutyl nitrosamine (BBN) model wherein bladder tumors are selectively induced in rodents administered a genotoxic agent, followed by administration of test promoters of interest. The limitations of the orthotopic or BBN models are far outweighed by their advantage of best reflecting the human

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[1] Buckley LA, et al. (2012) Nonclinical assessment of carcinogenic risk and tumor growth enhancement potential of prasugrel, a platelet-inhibiting therapeutic agent. Int J Toxicol; 31:317.

clinical experience: a change in urinary composition and renal function from dapagliflozin and transitional tumors in the bladder. The limitations of the xenograft model chosen by the sponsor do not have an outweighing benefit. The FDA recommended that the Sponsor consider using the BBN model or other orthotopic models on no fewer than five occasions following issuance of the Complete Response. Results from the Sponsor's chosen xenograft model are acceptable, but must be interpreted with consideration given to the relevance of the model.

In summary, results of the new nonclinical studies add to the weight-of-evidence and confirm but do not substantially extend what the FDA already concluded: that dapagliflozin by itself does not act as a carcinogen. Any putative human bladder risk from dapagliflozin would likely be related to tumor promotion secondary to changes in the microenvironment of the bladder *in vivo.*

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I.   INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.[2] Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

In March 2008, the FDA issued the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.[3] Concerns related to cardiovascular risk will be addressed in the final version of that guidance. In the meantime, we are issuing this final guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs. We will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

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[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For discussion of general issues of clinical trial design or statistical analysis, see the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

Contains Nonbinding Recommendations

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II.   BACKGROUND

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although several drug treatments currently are available, we recognize the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs and therapeutic biologics).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure). Both type 1 and type 2 diabetes have a heritable basis. Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.[4] Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.[5]

There are also compelling data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control. Glycemic control in these studies has been based on changes in HbA1c. This endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. Therefore, reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus. However, diabetes mellitus is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. Although this excess cardiovascular risk is present in both type 1 and type 2 diabetes, the

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[4] See N Engl J Med, 1993, 329:977-986.

[5] See Diabetes, 2006, 55:3556-3565.

absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. For type 2 diabetes, the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings. After considering the discussion at this meeting as well as other available data and information,[6] we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.

III.   RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

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[6] See Lancet, 1998, 352:837-853 and 854-865.

3

Contains Nonbinding Recommendations

controlled trials, and to preserve the study level randomized comparison but include, when possible in the meta-analysis, important identifiers of study differences or other factors (e.g., dose, duration of exposure, add-on drugs). It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.

- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.[7]

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary.

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[7] See the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901. This section will become section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A).

Contains Nonbinding Recommendations

- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings.

Sponsors are encouraged to contact the division to discuss specific issues that arise during the development of a new antidiabetic therapy to treat type 2 diabetes.