

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**202293Orig1s000**

**MEDICAL REVIEW(S)**

**CLINICAL REVIEW**  
**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**  
**(DMEP)**

Application Type	New Drug Application (NDA)
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Division / Office	DMEP / Office of New Drugs II
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	12/22/13
Established Name	Dapagliflozin
Trade Name(s)	Farxiga
Therapeutic Class	Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor
Applicant	Bristol-Myers Squibb
Formulation(s)	Oral tablets
Dosing Regimen	5 mg & 10 mg
Indication(s)	Type 2 Diabetes Mellitus (T2DM)
Intended Population(s)	Adults with T2DM

Template Version: March 6, 2009

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## Abbreviations

<b>4MSU</b>	4-Month Safety Update	<b>eGFR</b>	Estimated glomerular filtration rates
<b>30-MU</b>	30-Month Safety Update	<b>FDA</b>	Food and Drug Administration
<b>AC</b>	Advisory Committee	<b>FPG</b>	Fasting Plasma Glucose
<b>ACE</b>	Angiotensin-Converting Enzyme	<b>GCP</b>	Good Clinical Practice
<b>AD</b>	Antidiabetic	<b>GLP-1</b>	Glucagon-like Peptide-1
<b>ADA</b>	American Diabetes Association	<b>HAC</b>	Hepatic Adjudication Committee
<b>ADAM</b>	Analysis Data Model	<b>HCTZ</b>	Hydrochlorothiazide
<b>AE</b>	Adverse Event	<b>HDL-C</b>	High Density Lipoprotein-Cholesterol
<b>ALT</b>	Alanine Aminotransferase	<b>HbA1c</b>	Hemoglobin A1c
<b>ANCOVA</b>	Analysis of Covariance	<b>HER2</b>	Human Epidermal Growth Factor Receptor
<b>ARB</b>	Angiotensin Receptor Blocker	<b>HR</b>	Hazard Ratio
<b>AST</b>	Aspartate Aminotransferase	<b>HTN</b>	Hypertension
<b>BBN</b>	Hydroxybutyl nitrosamine	<b>ICH</b>	International Conference on Harmonization
<b>BMD</b>	Bone Mineral Density	<b>IND</b>	Investigational New Drug
<b>BMI</b>	Body Mass Index	<b>IR</b>	Immediate-Release
<b>BP</b>	Blood Pressure	<b>IRR</b>	Incidence Risk Ratio
<b>CABG</b>	Coronary Artery Bypass Graft	<b>IRS</b>	Insulin Receptor Substrate
<b>CAD</b>	Coronary Artery Disease	<b>LAD</b>	Left Anterior descending
<b>CBC</b>	Complete Blood Count	<b>LDL-C</b>	Low-Density Lipoprotein Cholesterol
<b>CFR</b>	Code of Federal Regulations	<b>LOCF</b>	Last Observation Carried Forward
<b>CI</b>	Confidence Interval	<b>LS</b>	Least Squares
<b>C<sub>MAX</sub></b>	Maximum plasma concentrations	<b>LT</b>	Long-Term
<b>CMC</b>	Chemistry, Manufacturing and Controls	<b>MA</b>	Marked Laboratory Abnormality
<b>CrCl</b>	Creatinine Clearance	<b>MACE</b>	Major Adverse CV Events
<b>CRF</b>	Case Report Form	<b>Max</b>	Maximum
<b>CRL</b>	Complete Response Letter	<b>MDRD</b>	Modification of Diet in Renal Disease Study
<b>CSR</b>	Clinical Study Report	<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>CV</b>	Cardiovascular	<b>MEN2</b>	Multiple Endocrine Neoplasia
<b>CVA</b>	Cerebrovascular Accident	<b>MI</b>	Myocardial Infarction
<b>CVD</b>	Cardiovascular Disease	<b>Min</b>	Minimum
<b>CVOT</b>	Cardiovascular Outcome Trial	<b>MMRM</b>	Mixed Model Repeated Measures
<b>DAPA</b>	Dapagliflozin	<b>MRHD</b>	Maximum Recommended Human Dose
<b>DGCPC</b>	Division of Good Clinical Practice Compliance	<b>MTC</b>	Medullary Thyroid Carcinoma
<b>DILI</b>	Drug-Induced Liver Injury	<b>N</b>	Number
<b>DMEP</b>	Division of Metabolism and Endocrinology Products	<b>NDA</b>	New Drug Application
<b>DOP</b>	Division of Oncology Products	<b>NME</b>	New Molecular Entity
<b>DPP4</b>	Dipeptidyl Peptidase-4 Inhibitor	<b>NYHA</b>	New York Heart Association
<b>DPV I</b>	Division of Pharmacovigilance I	<b>OAD</b>	Oral Antidiabetic Drug
<b>DVT</b>	Deep Vein Thrombosis	<b>OSE</b>	Office of Surveillance and Epidemiology
<b>OSI</b>	Office of Scientific Investigations	<b>OSI</b>	Office of Scientific Investigations
<b>P-Y</b>	Patient-years	<b>SGLT2</b>	Sodium-Glucose Co-Transporter 2
<b>PCI</b>	Percutaneous Coronary Intervention	<b>SMQ</b>	System MedDRA Query
<b>PD</b>	Pharmacodynamics	<b>SOC</b>	System Organ Class
<b>PDUFA</b>	Prescription Drug User Fee Act	<b>ST</b>	Short-Term
<b>PeRC</b>	Pediatric Research Committee	<b>SU</b>	Sulfonylurea
<b>PK</b>	Pharmacokinetics	<b>T1DM</b>	Type 1 Diabetes Mellitus

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<b>PPG</b>	Post Prandial Glucose	<b>T2DM</b>	Type 2 Diabetes Mellitus
<b>PREA</b>	Pediatric Research Equity Act	<b>TBL</b>	Total Bilirubin
<b>PT</b>	Preferred Term	<b>TCC</b>	Transitional Cell Carcinomas
<b>PVD</b>	Peripheral Vascular Disease	<b>TEAE</b>	Treatment-Emergent Adverse Event
<b>QD</b>	Daily	<b>TZD</b>	Thiazolidinediones
<b>SAE</b>	Serious Adverse Event	<b>UGT1A9</b>	UDP-glucuronosyltransferases 1A9
<b>SAP</b>	Statistical Analysis Plan	<b>ULRR</b>	Upper Laboratory Reference Range
<b>SBP</b>	Systolic Blood Pressure	<b>US</b>	United States
<b>SCS</b>	Summary of Clinical Safety	<b>UTI</b>	Urinary Tract Infection
<b>SD</b>	Standard Deviation	<b>VS</b>	Versus
<b>SDTM</b>	Study Data Tabulation Model	<b>XR</b>	Extended-Release
<b>SE</b>	Standard Error	<b>ZDF</b>	Zucker Diabetic Fatty

## 1 Recommendations/Risk Benefit Assessment

This document contains the clinical review for a New Drug Application (NDA) submitted on July 11, 2013, under NDA 202293 for FARXIGA (dapagliflozin). This Application is being reviewed for a second cycle under a six-month review clock. The original NDA was submitted on December 28, 2010. During the first review cycle, a Complete Response Letter (CRL) was issued on January 17, 2012, which outlined a benefit-risk assessment of modest efficacy but with concerns regarding cardiovascular (CV) safety, a numeric imbalance in bladder cancer (i.e., nine cases in dapagliflozin-treated patients and one in the control arm), and a single case of apparent dapagliflozin-induced liver injury deemed “probable” in causality. An analysis of the stratified hazard ratio (HR) for major adverse CV events (i.e., MACE) of CV death, nonfatal myocardial infarction (MI) and nonfatal stroke from a pool of two large Phase 3 clinical trials (D1690C00018 and D1690C00019), which had been enriched with individuals at high CV risk, resulted in a point estimate greater than one with a 95% upper bound greater than 1.8 (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.69 to 2.31). These results were discordant with those reported in the meta-analysis of the larger pool of the 19 overall studies (HR, 0.861; 95% CI, 0.534 to 1.388). For a path forward, it was recommended that the Applicant submit additional clinical trial data (at least for 52-week completers from trials D1690C00018 and D1690C00019), and the analyses should include updated information on bladder cancer events and hepatic safety, along with an updated CV meta-analysis.

On July 11, 2013, the Applicant resubmitted their NDA, which now includes a 30-month safety update (30-MU) with additional and updated nonclinical and clinical efficacy and safety data. The clinical review for this Application will focus primarily on the updated clinical safety information provided in the 30-MU pertaining to bladder cancers and hepatic and CV safety, as well as new Phase 3 clinical trial data provided by the Applicant in support of the overall safety and efficacy of dapagliflozin.

### 1.1 Recommendation on Regulatory Action

I recommend approval of this NDA pending agreement on product labeling.

Dapagliflozin is a new molecular entity in the oral antidiabetic class known as selective sodium glucose co-transporter 2 (SGLT2) inhibitors. Through selective and reversible inhibition of SGLT2, dapagliflozin causes renal elimination of glucose. 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). To establish clinical efficacy, the Applicant submitted data from sixteen core Phase 2b and Phase 3 clinical trials, eleven of which included long-term extensions up to 156 weeks. These trials evaluated the use of dapagliflozin as monotherapy and as add-on or in combination with other antidiabetic medications, including metformin, insulin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP4) inhibitors. Across

these clinical trials, the Applicant was able to demonstrate modest but consistent improvement in the primary efficacy outcome of placebo-adjusted change from baseline to Week 24 in hemoglobin A1c (HbA1c). The magnitude of the HbA1c reductions was similar to those of other recently approved antidiabetic drugs, including the SGLT2 inhibitor, canagliflozin. Although efficacy results for the 5 mg dapagliflozin dose were statistically significant and similar, the dapagliflozin 10 mg treatment arm consistently resulted in numerically greater reductions in HbA1C concentrations for trials that included both dapagliflozin doses. Secondary glycemic endpoints, including reduction in fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG) concentrations, and the proportion of patients achieving HbA1c of less than 7% all were supportive of the primary efficacy endpoint. Additionally, modest reductions in body weight and systolic blood pressure were reported.

The statistical reviewer for this Application, Dr. Wei Liu, conducted integrated analyses based on a pool of 12 of the placebo-controlled clinical trials. Since no adjustments were made for multiplicity, these analyses should be considered exploratory and are included for descriptive purposes. In concurrence with the Applicant's efficacy findings, statistically significant reductions in HbA1c (i.e., placebo-adjusted changes from baseline to Week 24) were reported for both the 5 and 10 mg dapagliflozin dose groups, respectively. Additionally, in subgroup analyses based on baseline estimated glomerular filtration rates (eGFR), dapagliflozin (i.e., 5 or 10 mg doses) appears to be result in a clinically meaningful reduction in HbA1c only for patients with an estimated glomerular filtration rate [eGFR]  $\geq 60$  mL/min/1.73 m<sup>2</sup>. This may limit the use of dapagliflozin in patients with long-standing T2DM, for whom renal impairment is a common comorbidity.

The major safety considerations with the product are addressed in the risk-benefit assessment below.

## **1.2 Risk Benefit Assessment**

The potential clinical benefits of dapagliflozin should be balanced against credible safety concerns identified during clinical development. Overall, the review of this Application did not identify new or unexpected safety signals, and serious adverse events (AEs) with fatal and nonfatal outcomes were relatively balanced between dapagliflozin and control treatment arms.

Common AEs, occurring in  $\geq 2\%$  of dapagliflozin-treated patients which were at least 1% greater than placebo, included genital infection, urinary tract infection, back pain, and polyuria.

As per the advice in the CR letter, the Applicant conducted an updated CV meta-analysis of a pool of 21 Phase 2b and Phase 3 clinical trials. Consistent with the results of the last

meta-analysis (i.e., the pool of 19 studies evaluated during the first review cycle), the HR point estimates for both the primary composite endpoint of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (MACE-plus) and secondary composite MACE endpoint (CV death, myocardial infarction or stroke) for the updated meta-analysis, are now 0.82 (95% CI, 0.59 to 1.14) and 0.79 (95% CI, 0.54 to 1.17), respectively. These results continue to meet the December 2008 Guidance,<sup>1</sup> ruling out the unacceptable increase in CV risk of greater than 80% above comparator groups.

It should be noted that an imbalance of CV events was observed within the first 30 days of treatment with dapagliflozin, with seven primary events (plus one secondary) observed among 5936 subjects randomized to dapagliflozin (0.12%) and two primary events (plus two secondary events) among 3403 subjects randomized to comparators (0.06%). For the dapagliflozin-treated patients, the majority of these early events occurred in patients with established peripheral and/or cardiovascular disease, of whom four were enrolled in Trials D1690C00018 and D1690C00019, (i.e., the trials enriched with individuals at high risks for CV events). A similar observation of an early imbalance in CV events was also observed with canagliflozin.

The updated CV safety analyses also included a new meta-analysis of the pool of Trials D1690C00018 and D1690C00019, which was updated to include data from individuals who had continued in the controlled extension phases of these two trials. In these trials, statistically significant reductions in HbA1c, systolic blood pressure, and body weight were reported. Although the point estimate and upper bound 95% CI for the HR of the composite MACE endpoint were lower than those reported in the previous analysis, they nonetheless continued to exceed 1 and 1.8, respectively (i.e., HR 1.11; 95% CI, 0.67 to 1.83). This raises a question as to whether dapagliflozin could produce a cardiovascular benefit with prolonged use in patients with established CV disease or conversely increase CV risk in a subset of these patients.

With this NDA resubmission, there continues to be a numeric imbalance in cases of bladder cancer, not favoring dapagliflozin (i.e., 10 cases/6045 [0.17%] dapagliflozin-treated patients and 1/3512 [0.03%] in the control arm). A similar imbalance in bladder cancer events was not seen with canagliflozin. Although the number of bladder cancer events is relatively small, with only one additional case reported since the last review—which now includes 40% more patient-years (p-y) of exposure—the estimated incidence risk ratio [IRR] of 6.11 (95% CI, 0.827 to 272) should not be disregarded. The potential for detection bias (i.e., resulting from more frequent monitoring of dapagliflozin treatment arms due to higher rates of urogenital AEs) cannot be ruled out. The consultant from the Division of Oncology Products (DOP), Dr. Yang-Min Ning, recommended that the potential risk for bladder cancer be further studied, carefully monitored, and possibly labeled as a Warning or Precaution if dapagliflozin were to be approved. In this regard, the Applicant has proposed several postmarketing safety measures to include enhanced surveillance in their clinical program, pharmacoepidemiologic studies, and blinded adjudication of bladder cancer events in their long-term CV outcome trial. These



safeguards may be acceptable, pending further review and input from the Office of Surveillance and Epidemiology (OSE).

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

A potential case of dapagliflozin-induced liver injury was observed during the first review cycle; for this case, an association with dapagliflozin cannot be excluded entirely. The Applicant has now provided more than three years of additional follow-up data for this individual to support a possible reclassification of the diagnosis as an autoimmune hepatitis. Dr. John Senior, the consulting hepatologist from OSE, concurs with two experienced hepatologists on the Hepatic Adjudication Committee (HAC) that this case likely represents autoimmune hepatitis. However, he noted that it cannot be determined whether liver disease in this 79-year-old patient would have occurred if he were not exposed to low-dose dapagliflozin. Overall, the occurrence of marked liver laboratory test abnormalities remains relatively balanced between dapagliflozin and the comparator treatment arms. The majority of cases of transaminase and total bilirubin elevations of greater than three and two times the upper laboratory reference limits, respectively, had other diagnoses that were more likely than dapagliflozin to have caused the test abnormalities.

Similar to canagliflozin, dapagliflozin relative to comparators is associated with adverse events of genital and urinary tract infections, and events related to polyuria, volume depletion and renal impairment. Although long-term effects from increased urinary tract and genital infections are unknown, these events are usually not recurrent and can typically be managed with antimicrobial therapy. Caution is warranted regarding the potential for hypovolemia, dehydration, and renal impairment — especially in elderly patients with renal dysfunction and perhaps in individuals receiving loop diuretics. Other safety concerns include the potential to increase low-density lipoprotein cholesterol (LDL-C), and the unknown risk for fractures with long-term use in vulnerable patient populations. These potential adverse effects are known for this pharmacologic class and can be mitigated with adequate patient monitoring and careful management of adverse effects as described in the proposed product labeling.

The incidence of hypoglycemia in the pool of thirteen short-term placebo-controlled studies was similar but slightly higher, for dapagliflozin-treated patients (i.e., 13.7% and 12.4% for the dapagliflozin and placebo treatment arms, respectively). Hypoglycemic

events were more common when dapagliflozin was used in combination with insulin or a sulfonylurea.

In summary, the data provided in this resubmission are generally supportive of previous findings of efficacy across the Phase 2b and Phase 3 clinical program. Additionally, no new or unexpected safety signals have emerged. While taking into consideration the safety concerns that were identified during the first review cycle, the totality of evidence from the updated efficacy and safety databases appears to support approval of this Application.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

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

### **1.4 Recommendations for Postmarket Requirements and Commitments**

During the first review cycle, the Applicant was informed that they would be required to conduct a dedicated cardiovascular outcome trial (CVOT) as a postmarketing requirement. This clinical trial would need to assess the CV safety of dapagliflozin in high-risk patients and be designed in accordance with the recommendations of the 2008 FDA *Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.<sup>1</sup> In response, the Applicant is currently conducting a randomized, controlled CVOT (i.e., DECLARE, [TIMI 58, Study D1693C00001]). This clinical trial will randomize 17,150 patients with T2DM with either established CV disease or at least two CV risk factors in addition to T2DM to dapagliflozin or placebo as add-on to background antidiabetic therapy. The primary efficacy objective will be to determine whether dapagliflozin will result in a reduction in the adjudicated major adverse CV event (MACE) composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke, compared to placebo. The study is cardiovascular event-driven with an anticipated total duration of six years to accrue sufficient events to demonstrate superiority of dapagliflozin compared to placebo. The primary safety objective will be to determine whether the upper bound of the two-sided 95% confidence interval (CI) for the estimated hazard ratio (HR) for the MACE composite endpoint observed with dapagliflozin is less than 1.3 when compared to placebo. In this study, the Applicant also plans to assess AEs of special interest (i.e., serious urinary tract infections [UTIs], serious genital infections, hepatic events, renal events, fractures, events related to volume depletion, and malignancies), with blinded adjudication of hepatic events and malignancies. The Agency also plans to require that bladder cancer be included as an adverse event of special interest in this trial.

Besides the CVOT, the Applicant also proposes to conduct additional postmarketing safety surveillance, including routine and enhanced pharmacovigilance, pharmacoepidemiology studies, and clinical trials in other geographic locations. The Agency plans a postmarketing requirement for enhanced pharmacovigilance for bladder cancer, serious hepatic adverse events, and adverse pregnancy outcomes. The Applicant's planned pharmacoepidemiology studies are intended to assess the occurrence of selected AEs (e.g., malignancies, acute liver injury, acute renal injury, and severe complications of urinary tract infections) associated with dapagliflozin compared to other antidiabetic medications.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. During the first review cycle, the Applicant requested a waiver from the Pediatric Research Equity Act (PREA) requirements for the use of dapagliflozin in pediatric patients with T2DM who are less than 10 years of age and a deferral to assess the use of dapagliflozin in pediatric patients with T2DM who are 10 to 17 years of age until a positive benefit/risk is established in adults. For SGLT2 inhibitors, these requests are acceptable. The Applicant is currently conducting a single-dose pharmacokinetic (PK) and pharmacodynamic (PD) clinical trial (i.e., MB102091) in pediatric patients with T2DM. Four patients have been enrolled into this clinical trial, and no deaths, serious adverse events (SAEs) or withdrawals due to AEs have been reported.

## **2 Introduction and Regulatory Background**

Dapagliflozin is an orally active, selective 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 proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

### **2.1 Product Information**

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., glycosuria).

The proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The proposed dose of dapagliflozin is 5 mg or 10 mg taken once daily at any time of the day regardless of meals. These doses were selected for evaluation in the Phase 2b/3 clinical development program based on the

results of a Phase 2 dose-ranging clinical trial (i.e., MB102008) in which dapagliflozin doses ranging from 2.5 mg to 50 mg were evaluated. In this trial, doses larger than 10 mg did not result in further reductions in HbA1c levels at 12 weeks (i.e., mean changes from baseline were -0.71%, -0.72%, -0.85%, -0.55% and -0.90% for the 2.5, 5, 10, 20 and 50 mg dose groups, respectively; all p-values  $\leq 0.008$ ). Compared to placebo, larger reductions from baseline to Week 12 in FPG were also achieved in the four higher dose dapagliflozin treatment arms (i.e., 5, 10, 20, and 50 mg; all p-values  $\leq 0.005$ ), while the comparison between dapagliflozin 2.5 mg and placebo did not reach statistical significance (as prespecified using a Dunnett adjusted significance level). Although overall efficacy was similar among the dapagliflozin treatment arms, genitourinary infections, elevations of hematocrit, and marked clinical laboratory abnormalities of hyperphosphatemia were more common in the 20 mg and 50 mg dapagliflozin groups.

Because dapagliflozin causes an increase in urinary volume excretion, the Applicant's proposed dose for patients at risk for volume depletion due to coexisting conditions is 5 mg once daily.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and one or more of the drug products presented in Table 1 (a detailed listing of available products and associated safety concerns is presented in Table 38, Appendix 9.4). Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, many of these drug classes may not be tolerated or have limited usefulness in certain populations. For example, thiazolidinediones (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and the approved sodium-glucose co-transporter 2 (SGLT2) inhibitor are contraindicated in patients with severe renal dysfunction. Use of insulin and insulin analogues, meglitinides and sulfonylureas (SU) may be associated with hypoglycemia and weight gain. Amylin mimetics, alpha-glucosidase inhibitors, biguanides, bile acid sequestrants, and GLP-1 receptor agonists may be associated with intolerable gastrointestinal side effects, and pancreatitis and allergic reactions have been reported with dipeptidyl peptidase-4 [DPP4] inhibitors and GLP-1 receptor agonists. Further, progressive  $\beta$ -cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and reliance on the use of combination therapies.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend initiating anti-diabetic therapy for the management of T2DM with monotherapy.<sup>2</sup> Should a single agent alone fail to achieve/maintain the HbA1c target over three months, the next step would be to add a second oral agent.<sup>2</sup>

Several studies have also reported advantages from adding a third noninsulin agent to a two-drug combination that has not yet or is no longer achieving the glycemic target.<sup>3-6</sup>

In this NDA, the Applicant provided data from 21 Phase 2b/3 clinical trials intended to support the use of dapagliflozin for adjunct to diet and exercise to improve glycemic control in adults with T2DM. These clinical trials evaluated the effects of dapagliflozin as monotherapy and in combination with other antidiabetic medications, including metformin, SU, pioglitazone, DPP4 inhibitor, and insulin.

**Table 1: Available Therapeutic Options for the Management of T2DM**

Pharmacologic Class	Antidiabetic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Exenatide; Liraglutide
INSULINS AND INSULIN ANALOGUES	Insulin Aspart; Insulin Detemir; Insulin Glargine; Insulin Glulisine; Insulin Isophane (NPH); Insulin Isophane and Regular; Insulin Lispro; Insulin Regular (human), Pre-mixed (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

### 2.3 Availability of Proposed Active Ingredient in the United States

The drug substance, dapagliflozin, is not approved in the United States (U.S.).

## **2.4 Important Safety Issues with Consideration to Related Drugs**

Canagliflozin is the only other SGLT2 inhibitor approved for use in the U.S. The Warnings and Precautions section of product labeling (Section 5) warns of possible renal impairment and intravascular volume contraction, especially in the elderly, patients with impaired renal function and concomitant use of antihypertensive medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and diuretics).<sup>7</sup> Hyperkalemia may also occur in patients with moderate renal impairment who are taking medications that interfere with potassium excretion or the renin-angiotensin-aldosterone system. Additionally, hypersensitivity reactions (e.g., generalized urticaria), some serious, and fractures (including the occurrence of upper extremity fractures at a higher incidence than comparator) have been reported with canagliflozin.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

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 hepatotoxicity, cardiovascular (CV) safety, and a possible increase in cancer risk (i.e., bladder cancer).

The original Application for dapagliflozin was submitted on December 28, 2010. The key milestone meetings and regulatory actions for this product are outlined in Table 2. 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) with a relationship to dapagliflozin deemed “probable”. Further, the analysis of the stratified 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 (overall 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

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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 submitted a Formal Dispute Resolution Request, requesting that the CV data from studies D1690C00018 and D1690C00019 be viewed in the context of the overall CV risk assessment of dapagliflozin and not as stand-alone studies; and that the overall benefit/risk assessment of dapagliflozin recognize the demonstrated benefits of dapagliflozin on glycemic control, weight loss and reduction in blood pressure (BP), as well as the “questionable and scientifically improbable” risks pertaining to bladder cancer and liver safety. Further, the Applicant 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.

On September 14, 2012, the Agency issued a Dispute Appeal Denied Letter to the Applicant stating that the proposed path forward was denied. The Agency instead recommended the following path forward:

1. **“The path forward as written in the CR letter is reasonable under the circumstances posed by the data in the NDA and stands as written.** This includes the request for updated safety analyses of the NDA database, including at least 52 weeks of data from Studies 18 and 19, but given information that you shared with the review team about event rates at 52 weeks, the full study data, which are expected to be completed with two years of data are imminent and would be far preferable. Even if there are many patients who have left the study, it is important that as much data from it as possible be brought to consideration, as should additional information about the patient with concerning liver disease, which was included in this FDRR but is considered new data so has not been reviewed by me.
2. **A resubmitted NDA should be brought before an Advisory Committee (AC).** A second AC meeting on this drug is important because data and the overall spectrum of risk have shifted since their first meeting. Additional data about liver toxicity and breast cancer were brought to bear in the major amendment from the first cycle of the NDA, lessening the concern for some risk signals that were of concern when the AC convened and those data have continued to accumulate. More importantly, the CV data and how it evolved to shift expectations for dapagliflozin, from having hope for CV benefit to concern about a signal of CV risk, warrants discussion. It raises questions about how to factor in new data to a meta-analysis that has already been used to make a decision that the FDA Guidance on CV risk for diabetes drugs does not fully address. Also, how should clinical trials that are highly enriched for CV risk be considered in the overall premarketing risk

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assessment for a diabetes treatment? If they are to play a major role, should such enriched trials be required earlier in development than was planned for dapagliflozin? Should they carry more weight than studies in patients with fewer CV risk factors? These questions, being raised in the context of this NDA, should not be answered without public discussion.

3. **You must conduct a preclinical toxicology study to address the issue of tumor promotion of bladder cancer, even in light of the reduced number of cases of concern in the database.** The balanced rates of baseline hematuria across dapagliflozin patients and controls diminish the light of the reduced number of cases of individual concern in the database. This study is reasonable to conduct in the postmarketing period, unless the review of the resubmitted NDA raises new concerns about bladder cancer. Per FDA pharmacology/toxicology experts, the most relevant model would be one that evaluates the effect of dapagliflozin on transitional cell tumor growth within the bladder. There are several models that would allow for this, as they best reflect the human clinical experience – a change in urinary composition and renal function from dapagliflozin and transitional tumors in the bladder. I believe that if such a study is negative it may serve to greatly lessen residual concerns about bladder cancer risk.”

**Table 2: Key Meetings and Regulatory Actions**

Date	Meeting/ Submission Type	Comments
09/01/2007	End-of-Phase 2	<ul style="list-style-type: none"><li>• Inclusion of dapagliflozin doses &lt;2.5 mg and patients with renal impairment in the Phase 3 clinical program recommended by the Agency</li></ul>
12/28/2010	Original NDA submitted	<ul style="list-style-type: none"><li>• NDA filed: 03/04/2011</li><li>• PDUFA date: 10/28/2011</li></ul>
07/19/2011	EMDAC Meeting	<ul style="list-style-type: none"><li>• The EMDAC voted not to support approval of dapagliflozin based on the current data</li><li>• More data are needed regarding the risks of bladder cancers and liver injury</li></ul>
10-20-2011	Major Amendment submitted	<ul style="list-style-type: none"><li>• Requested by the Agency</li><li>• Trigger PDUFA date shift</li><li>• Additional data from studies D1690C00018 and D1690C00019, and updated analyses for CV safety, malignancy, and hepatic safety submitted</li></ul>



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Date	Meeting/ Submission Type	Comments
01/17/2012	CRL issued	<ul style="list-style-type: none"> <li>CV safety data from studies D1690C00018 and D1690C00019 were discordant with the CV safety data submitted in the initial NDA</li> <li>An unmet need could not be identified to offset the potential risks of bladder cancer and hepatic toxicity</li> <li>Path Forward <ul style="list-style-type: none"> <li>Applicant should submit additional clinical trial data (at least for 52-week completers from Trials D1690C00018 and D1690C00019)</li> <li>Analyses should include updated information on bladder cancer events, hepatic safety, and the CV meta-analysis</li> </ul> </li> </ul>
08/15/2012	Dispute Resolution Request Meeting	<ul style="list-style-type: none"> <li>Applicant requested to discuss the issues surrounding the appeal</li> <li>09/14/2012: Agency issued a Dispute Appeal Denied Letter</li> <li>Path forward: <ul style="list-style-type: none"> <li>As written in the CRL is reasonable</li> <li>NDA resubmission should be brought before an AC</li> <li>Conduct a preclinical toxicology study to address tumor promotion of bladder cancer</li> </ul> </li> </ul>
07/11/2013	NDA resubmission	<ul style="list-style-type: none"> <li>PDUFA date: 01/11/2014</li> </ul>

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; EMDAC, Endocrinology and Metabolic Advisory Committee; 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 safety 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 (CSRs) 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 clinical review will focus primarily on the updated safety information pertaining to bladder cancers, hepatic AEs and CV 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 risk, hepatotoxicity, genital infections, renal impairment or failure, volume depletion, polyuria, fractures and hypoglycemia). Please refer to Dr. Eugenio Andraca-Carrera's CV safety review for detailed statistical information regarding CV outcomes, and to Dr. Wei Liu's review for detailed statistical information regarding efficacy.

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The overall quality of the submission was acceptable, and no irregularities were identified.

During the first review cycle, the Division requested site inspections from the Division of Good Clinical Practice Compliance (DGCPC)/Office of Scientific Investigations (OSI) for two Canadian, two Argentinian, and three U.S. sites where six pivotal clinical trials were conducted. At that time, there were no protocol violations that would have been expected to substantially influence the overall study results. No additional inspections were requested with this NDA resubmission. Please refer to the Clinical Site Inspection Review by Dr. Susan Leibenhaut (dated September 2, 2011) from the first review cycle for further details.

### **3.2 Compliance with Good Clinical Practices**

The Applicant states that internal quality control measures and audit programs provided reassurance that the clinical study program was carried out in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) standards and the U.S. Food and Drug Administration (FDA).

### 3.3 Financial Disclosures

For this NDA resubmission, financial disclosure information was reported for the investigators of 21 core studies, Data Monitoring/Adjudication Committee members and subject matter expert consultants. The Applicant submitted Form FDA 3454 (i.e., Certification: Financial Interests and Arrangements of Clinical Investigator), certifying that they had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could affect the outcome of the study as defined in 21 CFR 54.2(a). No response was received for 28 investigators, most of whom were sub-investigators, accounting for 193 subjects out of all core studies. During the first review cycle, there were two individuals for whom the Applicant reported significant payments of other sorts (i.e., payments of a monetary value of more than \$25,000, exclusive of the costs of conducting the clinical study or other clinical studies). One investigator, (b) (6) previously received (b) (6) in excess of \$25,000, but now had no financial information to disclose. He enrolled (b) (6) subjects in protocol (b) (6). Additionally, (b) (6) previously (i.e., 2010) received (b) (6) in excess of \$25,000, but now had no information to disclose. It is unlikely that the financial relationships between the Applicant and these two individuals would significantly affect the overall integrity of the studies conducted under this NDA.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

At the time of this review, several of the other review disciplines had not yet submitted their final reviews. However, there were no significant efficacy or safety issues identified by these disciplines at the time of this review that would influence the approval of this NDA.

### 4.1 Chemistry Manufacturing and Controls

There is no new Chemistry, Manufacturing and Controls (CMC) information in this application that applies to this section.

### 4.2 Clinical Microbiology

Clinical microbiology data were not required or submitted for this application.

### 4.3 Preclinical Pharmacology/Toxicology

During the first review cycle, the nonclinical studies did not identify a carcinogenic hazard associated with dapagliflozin. However, due to an imbalance in bladder cancer that did not favor dapagliflozin in the Applicant's clinical program, the Agency recommended that the Applicant conduct additional nonclinical studies focused on evaluating potential bladder tumor promotion with dapagliflozin in a rodent model. In this NDA resubmission, the Applicant submitted additional 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). Although the Applicant retrospectively demonstrated that dapagliflozin did not induce a transcriptional profile typical of tumor promoters in various rat tissues, the bladder was not among the tissues profiled. Additionally, the Applicant demonstrated that varying glucose concentrations in growth medium did not alter the growth in transitional cell carcinoma cell lines, and that hyperplastic bladders were not observed in a SGLT2 knockout mouse model. The results of these studies were consistent with what the Agency had already concluded (i.e., dapagliflozin did not appear to be a direct tumor promoter or inducer). However, these studies did not address whether dapagliflozin may act as a tumor promoter through changes in urinary volume, flow, and composition within the microenvironment of the bladder. Since the CRL, the Agency has repeatedly recommended acceptable models for evaluating transitional cell tumor growth within the bladder (e.g., transplanting human bladder tumor cells to mouse bladders [orthotopic models] or selectively inducing bladder tumors in rodents in which a genotoxic agent had been administered, such as hydroxybutyl nitrosamine [BBN]). These studies were never conducted. However, at the December 12, 2013 EMDAC meeting, the Applicant stated that they are currently working with experts in the field, and are committed to conducting these studies. For further details regarding the nonclinical findings, please refer to the Pharmacology/Toxicology review by Dr. Mukesh Summan.

### 4.4 Clinical Pharmacology

During the first review cycle, the Office of Clinical Pharmacology had reviewed the clinical pharmacology data submitted, and found it acceptable. There is no new information in this NDA resubmission that applies to this section. A brief review is provided below. Refer to the Clinical Pharmacology Review for the original NDA submission (dated 12/27/2010) by Dr. Ritesh Jain for detailed information related to Sections 4.4.1 through 4.4.3 below.

#### 4.4.1 Mechanism of Action

Through selective and reversible inhibition of SGLT2 expressed in the kidney, dapagliflozin reduces renal glucose reabsorption, resulting in glycosuria over a 24-hour

dosing interval. Dapagliflozin does not inhibit other glucose transporters important for glucose transport in the gut (e.g., SGLT1) and peripheral tissues.

#### **4.4.2 Pharmacodynamics**

In patients with T2DM, approximately 70 grams of glucose may be excreted in the urine per day following 10 mg daily doses of dapagliflozin. Urinary volume is increased as a result of osmotic diuresis associated with glycosuria.

#### **4.4.3 Pharmacokinetics**

Following oral administration, the bioavailability of dapagliflozin is approximately 78%, reaching maximum plasma concentrations (C<sub>max</sub>) within approximately two hours (T<sub>max</sub>) under fasting state. The T<sub>max</sub> may be delayed approximately one hour when dapagliflozin is administered with a high-fat meal. Dose-proportional increases in systemic exposure are observed across a wide range of doses from 0.1 to 500 mg. Dapagliflozin is approximately 91% protein-bound, which is not altered by renal or hepatic impairment. It is inactivated by UDP-glucuronosyltransferase 1A9 (UGT1A9), an enzyme present in the liver and kidney, to an inactive glucuronidated metabolite (dapagliflozin 3-O-glucuronide) and has an elimination half-life of approximately 12 hours. Approximately 75% of a dose is recovered in the urine following oral administration.

Compared to healthy subjects, exposure to dapagliflozin in patients with moderate and severe hepatic impairment was 36% and 67% higher, respectively. No dose adjustment is recommended for patients with hepatic impairment (mild to severe) in the proposed product labeling. There is also no dose adjustment based on renal function. However, the efficacy of dapagliflozin is dependent on the filtered load of glucose, which in turn is dependent on GFR. The Applicant proposes that dapagliflozin should not be taken by patients with moderate renal impairment (defined estimated glomerular filtration [eGFR] rate <60 mL/min/1.73 m<sup>2</sup> or creatinine clearance [CrCl<sub>B</sub>] <60 mL/min).

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

Please refer to the Clinical Pharmacology Review by Dr. Ritesh Jain for further details on the pharmacokinetic characteristics of dapagliflozin.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

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 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 3. 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 (referred to as the All Phase 2b/3 study pool from this point forward) comprises the main safety review for this NDA resubmission. These trials are identified in the table below.

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

Study Number	Study Phase / Description	Patient Population	Duration	Dapa (mg) / Background Therapy (Rescue)	Number of Patients per Arm (dose—N)
<i>Core Studies Included in the Summary of Clinical Safety</i>					
MB102008 (30-MU)*	Phase 2b / Monotherapy vs. placebo vs. metformin XR 750/1500 mg	Drug-naïve Baseline HbA1c $\geq 7$ to $\leq 10\%$	12 weeks	Dapa 2.5, 5, 10, 20, 50 (none)	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 $\geq 7.5$ to $\leq 10\%$	12 weeks	Dapa 10, 20 / 50% on original insulin dose + metformin or TZD (insulin up-titrated)	Dapa 10 mg-24, 20 mg-24 / placebo-23
MB102064 D1692C00005 (30-MU)*	Phase 2b / Monotherapy vs. placebo	Drug-naïve Japanese patients Baseline HbA1c $\geq 7$ to $\leq 10\%$	12 weeks	Dapa 1, 2.5, 5, 10 (none)	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 $\pm$ insulin secretagogue vs. placebo	On metformin $\pm$ insulin secretagogue (SU, DPP4, or glinide) Baseline HbA1c $\geq 7$ to $\leq 10\%$	12 weeks	Dapa 5 / metformin $\pm$ insulin secretagogue (none)	Dapa 5 mg-23 / placebo-21
MB102013 (30-MU)*	Phase 3 / Monotherapy vs. placebo	Drug-naïve Baseline HbA1c $\geq 7.5$ to $\leq 10\%$ or $>10$ to $\leq 12\%$	24 weeks + 78 week extension	Dapa 2.5, 5, 10 (metformin)	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 $\geq 7.5$ to $\leq 10\%$	24 weeks	Dapa 1, 2.5, 5 (metformin)	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 $\geq 1500$ mg Baseline HbA1c $\geq 7$ to $\leq 10\%$	24 weeks + 78 week extension	Dapa 2.5, 5, 10 / metformin $\geq 1500$ mg (pioglitazone or acarbose)	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 $\geq 7.5$ to $\leq 12\%$	24 weeks	Dapa 5 mg / metformin up to 2000 mg (pioglitazone, acarbose or sitagliptin)	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 $\geq 7.5$ to $\leq 12\%$	24 weeks	Dapa 10 mg / metformin up to 2000 mg (pioglitazone, acarbose or sitagliptin)	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 $\geq 30$ mg (metformin or SU)	Dapa 5 mg-141, 10 mg-140 / placebo-139

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Study Number	Study Phase / Description	Patient Population	Duration	Dapa (mg) / Background Therapy (Rescue)	Number of Patients per Arm (dose—N)
MB102028 D1690C00005 (30-MU)*	Phase 3 / Add-on to SU vs. placebo	On SU Baseline HbA1c $\geq 7$ to $\leq 10\%$	24 weeks + 24 week extension	Dapa 2.5, 5, 10 / glimepiride 4 mg (metformin or TZD)	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 $\geq 7$ to $\leq 11\%$	24 weeks + 28 week extension + 52 week extension	Dapa 5, 10 / any AD combination except metformin (any AD 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 $\geq 1500$ mg Baseline HbA1c $\geq 6.5$ to $\leq 10\%$	52 weeks + 52 week extension + 104 week extension	Dapa 2.5, 5, 10 / metformin $\geq 1500$ mg vs. glipizide 10 or 20 mg (none $\leq 104$ weeks)	Dapa 2.5 to 10 mg-400 glipizide-401
MB102033 D1690C00006 (30-MU)*	Phase 3 / Add-on to insulin vs. placebo	On insulin $\geq 30$ units $\pm$ maximum 2 OAD Baseline HbA1c $\geq 7.5$ to $\leq 10.5\%$	24 weeks + 24 week extension + 56 weeks extension	Dapa 2.5, 5, 10 / insulin $\geq 30$ units $\pm$ maximum 2 OAD (insulin up-titration)	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 $\geq 1500$ mg BMI $\geq 25$ kg/m <sup>2</sup> Baseline HbA1c $\geq 6.5$ to $\leq 8.5\%$	24 weeks 78 week extension	Dapa 10 / metformin $\geq 1500$ mg/day (sitagliptin)	Dapa 10 mg-91 / placebo-91
<b>Additional Core Studies Completed Since the Original Summary of Clinical Safety</b>					
MB102061 D1690C00010 (30-MU)*	Phase 3 / Add-on to DPP4 inhibitor $\pm$ metformin vs. placebo	Inadequate glycemic control on background AD Baseline HbA1c $\geq 7$ to $\leq 10\%$	24 weeks + 24 week extension	Dapa 10 / sitagliptin 100mg/day and/or metformin $\geq 1500$ mg/day (glimepiride)	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 $\geq 7$ to $\leq 10\%$	24 weeks + 28 week extension + 52 week extension	Dapa 10 / OAD and/or insulin (AD at discretion of investigator)	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 $\geq 7$ to $\leq 10\%$	24 weeks + 28 week extension + 52 week extension	Dapa 10 / OAD and/or insulin (AD at discretion of investigator)	Dapa 10 mg-480 / placebo- 482
MB102035 (30-MU)*	Phase 2b / Effect on GFR as add-on to metformin $\pm$ SU	On metformin $\pm$ SU HTN Baseline HbA1c $\geq 6.6$ to $\leq 9.5\%$	12 weeks	Dapa 10 vs. HCTZ / metformin $\pm$ SU (initiation or up-titration of metformin or SU)	Dapa 10 mg-24 / placebo-51



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Study Number	Study Phase / Description	Patient Population	Duration	Dapa (mg) / Background Therapy (Rescue)	Number of Patients per Arm (dose—N)
MB102073	Phase 3 / Dedicated BP study	HTN On OAD and/or insulin Baseline HbA1c $\geq 7$ to $\leq 10.5\%$	12 weeks	Dapa 10 / OAD and/or insulin (antihypertensive medication)	Dapa 10 mg-302 / placebo-311
MB102077	Phase 3 / Dedicated BP study	HTN On OAD and/or insulin Baseline HbA1c $\geq 7$ to $\leq 10.5\%$	12 weeks	Dapa 10 / OAD and/or insulin (antihypertensive medication)	Dapa 10 mg-225 / placebo-224
<b>Completed Supportive Phase 2/3 Studies: Other Indications</b>					
MB102072 (30-MU)*	Phase 2b / Add-on to insulin vs. placebo	T1DM Baseline HbA1c $\geq 7$ to $\leq 10\%$	14 days	Dapa 1, 2.5 / insulin (none)	Dapa 1 mg-13, 2.5 mg-15, 5 mg-14, 10 mg-15 / placebo-13
<b>New Regional Studies</b>					
MB102106 D1692C00006	Phase 3 / Japan monotherapy vs. placebo	Japanese drug-naïve Baseline HbA1c $\geq 6.5$ to $\leq 10\%$ or on AD with Baseline HbA1c $\leq 8\%$	24 weeks	Dapa 5, 10 (metformin or glimepiride)	Dapa 5 mg-86, 10 mg-88 / placebo-87
D1692C00012	Phase 3 / Japan monotherapy or OADs	Japanese with or without OADs Baseline HbA1c $\geq 6.5$ to $\leq 10\%$	52 weeks	Dapa 5 titrated to 10 / none or selected OADs (AD at discretion of investigator)	Dapa 5-10 mg-728
MB102054 (30-MU)*	Phase 3 / Multinational Asia (primarily China) Monotherapy	Asian drug-naïve Baseline HbA1c $\geq 7.5$ to $\leq 10.5\%$	24 weeks	Dapa 5, 10 (metformin)	Dapa 5 mg-128, 10 mg-133 / placebo-132
<b>Studies to Support Dapagliflozin/Metformin IR and XR FDC</b>					
D1691C00003	Phase 3 / BID Dosing Study	Baseline HbA1c $\geq 6.5$ to $\leq 10\%$	24 weeks	2.5 BID, 5 BID, 10 QD / metformin IR BID ( $\geq 1500$ mg/day) (glimepiride)	Dapa 2.5 mg-100, 5 mg-100, 10 mg-99 / placebo-101
<b>TOTAL NUMBER OF PHASE 2B AND 3 STUDIES: 26 (15 from SCS/4MSU and 10 from 30-MU)</b>					

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, 4-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.

## 5.2 Review Strategy

This review evaluated the updated efficacy and safety data provided by the Applicant for this NDA resubmission. For more detailed information related to the original NDA submission (dated December 28, 2010) and the Major Amendment (dated October 20, 2011), please refer to the clinical reviews by Dr. Soma Dunn, dated September 2, 2011, and November 21, 2011, respectively and the statistical reviews by Dr. Jonathan Norton, dated September 8, 2011, and November 21, 2011, respectively.

The updated safety information was evaluated primarily using the analysis datasets for the current (i.e., 30-MU) and previous (i.e., 4MSU) submissions:

### 30-MU:

[url:gs:PAAAAAUBAAqmrqOu9lqCAACDAa4CgwEDAATDpgEBAAIAAASuAqYDAAQAAASuA6YFAAYAAAABAgIHAAgACRJEYXRhIEFuYWx5c2lzIERhdGEKSW5kaWNhdGlvbhbBUeXBIIeIJIERpYWJldGVzC1N0dWR5IFRpdGxlFjMwIE1vbnRoIFNhZmV0eSBVcGRhdGUiU3R1ZHkgSUQUc2FmZXR5LXVwZGF0ZS0zMCI3UGMjAyMjkzA25kYQA%3d](gs:PAAAAAUBAAqmrqOu9lqCAACDAa4CgwEDAATDpgEBAAIAAASuAqYDAAQAAASuA6YFAAYAAAABAgIHAAgACRJEYXRhIEFuYWx5c2lzIERhdGEKSW5kaWNhdGlvbhbBUeXBIIeIJIERpYWJldGVzC1N0dWR5IFRpdGxlFjMwIE1vbnRoIFNhZmV0eSBVcGRhdGUiU3R1ZHkgSUQUc2FmZXR5LXVwZGF0ZS0zMCI3UGMjAyMjkzA25kYQA%3d)

### 4MSU:

[url:gs:QAAAAAUBAAQuAq4DrvdaggAAgwGuAoMBAwAErgSuAgEAAgAABK4FrgIDAAQAAASuBq4CBQAGAAAAAQICBwAIAAkXQW5hbHlzaXMgRGF0YXNldCBMZWhY3kKSW5kaWNhdGlvbhbBUeXBIIeIJIERpYWJldGVzC1N0dWR5IFRpdGxlGEZvdXlGTW9udGggU2FmZXR5IFVwZGF0ZQhTdHVkeSBjRA5zYWZldHktdXBkYXRlcwYyMDIyOTMDbmRhAA%3d%3d](gs:QAAAAAUBAAQuAq4DrvdaggAAgwGuAoMBAwAErgSuAgEAAgAABK4FrgIDAAQAAASuBq4CBQAGAAAAAQICBwAIAAkXQW5hbHlzaXMgRGF0YXNldCBMZWhY3kKSW5kaWNhdGlvbhbBUeXBIIeIJIERpYWJldGVzC1N0dWR5IFRpdGxlGEZvdXlGTW9udGggU2FmZXR5IFVwZGF0ZQhTdHVkeSBjRA5zYWZldHktdXBkYXRlcwYyMDIyOTMDbmRhAA%3d%3d)

A separate biostatistics analysis and review was conducted by Wei Liu to confirm the primary and major secondary efficacy analyses for the additional Phase 2b/3 clinical trials (i.e., D1690C00010 [add-on to sitagliptin], MB102-073, and MB102-077 [patients with hypertension]) submitted in the 30-MU. He also performed integrated analyses of relevant Phase 2b/3 clinical trials included in this NDA. Refer to his review (dated December 13, 2013) for details regarding the statistical evaluation of these clinical trials.

Additionally, Dr. Eugenio Andraca-Carrera reviewed the cardiovascular (CV) safety and data for the updated CV meta-analysis of the All Phase 2b/3 study pool using the analysis datasets (i.e., adv5.xpt), and Dr. John Senior reviewed hepatic safety and data (i.e., eDISH datasets) for hepatic adverse events. Please refer to their reviews for further information related to the CV and hepatic safety of dapagliflozin.

## 5.3 Discussion of Individual Studies/Clinical Trials

Many of the Phase 2b/3 clinical trials for this Application had been previously reviewed by Drs. John Norton, the statistical reviewer for the original NDA submission, and

Somya Dunn, the previous clinical reviewer. Please refer to their reviews for detailed discussion related to the overall design of these studies. There were several additional Clinical Study Reports (CSRs) for Phase 2b/3 clinical trials submitted with this Application. Top-line efficacy findings of the overall Phase 2b/3 clinical program are presented below (Section 6 – Review of Efficacy).

## **6 Review of Efficacy**

### **Efficacy Summary**

To establish clinical efficacy, the Applicant submitted data from sixteen of the 21 core Phase 2b/3 clinical trials (N=9412 patients), eleven of which included long-term extensions up to 156 weeks. These trials evaluated the use of dapagliflozin as monotherapy and as add-on or in combination with other antidiabetic medications, including metformin, insulin, sulfonylureas, thiazolidinediones, and DPP4 inhibitors. Across these clinical trials, the Applicant was able to demonstrate modest but consistent improvement in the primary efficacy outcome of placebo-adjusted change from baseline to Week 24 in HbA1c. The magnitude of the HbA1c reductions was similar to those of other recently approved antidiabetic drugs, including the SGLT2 inhibitor, canagliflozin. Although efficacy results for the 5 mg dapagliflozin dose were statistically significant and similar to that of 10 mg, the dapagliflozin 10 mg treatment arm consistently resulted in numerically greater reductions in HbA1C and FPG concentrations.

In an active-comparator study, titrated doses of dapagliflozin and glipizide yielded similar results (non-inferior) at Week 52 for change from baseline in HbA1c concentrations. However, the magnitude of HbA1c reductions with glipizide was greater at several earlier time points.

Secondary glycemic endpoints, including reduction in FPG, 2-hour PPG concentrations, and the proportion of patients achieving HbA1c of less than 7% all were supportive of the primary efficacy endpoint. Additionally, modest reductions in body weight and SBP were reported.

It should be noted that for majority of the phase 2b/3 studies, the efficacy analyses were performed using a last-observation-carried-forward (LOCF) statistical approach for handling (i.e., imputing) missing data, disregarding observations recorded following rescue therapy. Dr. Wei Liu, the statistical reviewer for this Application, noted that 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. However, efficacy results for selected studies from analyses performed by Dr. Liu using a mixed model repeated measures (MMRM) statistical method were consistent with the primary analysis results observed using a LOCF approach.

In an integrated analysis that included a pool of 12 of the Phase 3 placebo-controlled trials, Dr. Liu also reported statistically significant reductions ( $p < 0.0001$ ) in HbA1c (i.e., placebo-adjusted changes from baseline to Week 24) for both the 5 mg (0.51%; 95% CI, -0.58 to -0.43) and 10 mg (-0.52%; 95% CI, -0.58 to -0.47) dapagliflozin dose groups. Secondary endpoints for the 5 mg and 10 mg dose groups, including the proportion of patients achieving a HbA1c of less than 7% (20% for both dapagliflozin dose arms vs. 14% in control arm), and placebo-subtracted reductions in FPG (-22.12 and -24.51 mg/dL, respectively), body weight (-1.4 and -1.82 kg, respectively), and systolic blood pressure (-2.28 and -3.17, respectively), were again supportive (all  $p < 0.0001$ ). Additionally, in subgroup analyses using the same study pool, it appears that dapagliflozin may be effective (i.e., reduction in HbA1c from baseline to Week 24) only in patients with normal renal function or mild renal impairment ( $\text{eGFR} \geq 45 \text{ mL/min/1.73m}^2$ ). However, the effect size in patients with mild renal impairment is relatively small. The Applicant proposes that the drug not be used in individuals with moderate or severe renal impairment (i.e., an  $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ ). This may limit the use of dapagliflozin in patients with long-standing T2DM in whom renal impairment is a common comorbidity. As stated above, results for these subgroup analyses should be considered exploratory as no statistical adjustments for multiplicity were applied.

## 6.1 Indication

The proposed indication for FARXIGA (dapagliflozin) is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The Phase 2b/3 clinical trials submitted to this Application are intended to provide efficacy findings to support this indication.

### 6.1.1 Methods

Most of the efficacy data for this resubmission were previously evaluated during the first review cycle. Recently completed clinical trials which the Sponsor intends to include in the proposed product labeling for this NDA resubmission include the following updated and new 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 DPP4 inhibitor)
- MB102073 (dedicated blood pressure [BP] study)
- MB102077 (dedicated BP study).

Refer to Table 3 for information related to the study design of these trials. For a detailed summary of the new (primarily Trials MB102061, MB202073, and MB102077) and

previous efficacy data submitted to this Application, please refer to the statistical reviews by Drs. Norton and Liu and the previous clinical reviews by Dr. Dunn. To inform the overall benefit to risk assessment of dapagliflozin, this section provides a summary of the efficacy data (i.e., glycemic efficacy, weight and BP) for the sixteen core efficacy studies included in product labeling (summarized in the Efficacy Statistical Briefing Document and Statistical Review submitted by Dr. Liu).

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. Across these 16 trials, 5952 patients received dapagliflozin.

In his reviews, Dr. Liu sub-classified the sixteen core Phase 2b/3 controlled trials based on the evaluation of dapagliflozin as monotherapy, combination therapy or use in special populations (Table 4). These studies are described in further detail in Table 3 above. The results for thirteen of these clinical trials (identified by footnotes in the table), were previously reviewed by Agency statisticians. 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.

**Table 4. Summary Table of Sixteen Core Placebo-Controlled Clinical Trials**

Study ID (Brief Name)	Population	Dose (mg)	Background Tx (Rescue)	Comparator	Treatment Duration (Weeks)
<b>Monotherapy</b>					
1. MB102013 <sup>1,2</sup>	Drug-naïve	Dapa 2.5, 5, 10	None (metformin)	Placebo	24 + extension
2. MB102032 <sup>1,2</sup>	Drug-naïve	Dapa 1, 2.5, 5	None (metformin)	Placebo	24
<b>Combination Therapy</b>					
3. MB102014 <sup>1,2</sup>	Inadequate control on background	Dapa 2.5, 5, 10	Metformin (pioglitazone or acarbose)	Placebo	24 + extension
4. MB102028 <sup>1,2</sup> (D1690C00005)	Inadequate control on background	Dapa 2.5, 5, 10	Glimepiride (metformin or TZD)	Placebo	24 + extension

Study ID (Brief Name)	Population	Dose (mg)	Background Tx (Rescue)	Comparator	Treatment Duration (Weeks)
5. MB102030 <sup>1,2</sup>	Inadequate control on background	Dapa 5, 10	Pioglitazone (metformin or SU)	Placebo	24 + extension
6. MB102033 <sup>1,2</sup> (D1690C00006)	Inadequate control on background	Dapa 2.5, 5, 10	Insulin and up to two OAD (insulin up-titration)	Placebo	24 + extension
7. MB102022 <sup>1,2</sup> (D1690C00004)	Inadequate control on background	Dapa 2.5, 5, 10 (titrated)	Metformin (none)	Glipizide*	52 + extension
8. MB102047 <sup>1</sup> (D1690C00012)	Inadequate control on background	Dapa 10	Metformin (sitagliptin)	Placebo**	24 + extension
9. MB102061# (D1690C00010)	Drug-naïve or inadequate control on background	Dapa 10	Sitagliptin ± metformin (glimepiride)	Placebo	24 + 24
10. MB102021 <sup>1,2</sup>	Drug-naïve with higher HbA1c	Dapa 5 + metformin	None (pioglitazone, acarbose, or sitagliptin)	Dapa 5 mg, MET	24
11. MB102034 <sup>1,2</sup>	Drug-naïve with higher HbA1c	Dapa 10 + metformin	None (pioglitazone, acarbose, or sitagliptin)	Dapa 10 mg, metformin	24
<b>Special Populations</b>					
12. MB102029 <sup>1,2</sup>	Moderate renal impairment	Dapa 5, 10	Any except metformin (Any except metformin)	Placebo	24 + extension
13. MB102073	Hypertension	Dapa 10	OAD and/or insulin (antihypertensives)	Placebo	12
14. MB102077	Hypertension	Dapa 10	OAD and/or insulin (antihypertensives)	Placebo	12
15. MB102067 <sup>3</sup> (D1690C00018)	Cardiovascular disease and hypertension	Dapa 10	OAD and/or insulin (various)	Placebo	24 + extension
16. MB102080 <sup>3</sup> (D1690C00019)	Cardiovascular disease	Dapa 10	OAD and/or insulin (various)	Placebo	24 + extension

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu, (page 155 of 175, labeled as Table 1).

Abbreviations: Dapa, dapagliflozin; OAD, oral antidiabetic drug; SU = sulfonylurea; TZD = thiazolidinedione.

# Add-on to sitagliptin.

<sup>1</sup> Reviewed in the original submission (December 2010).

<sup>2</sup> In the review briefing of the first EMDAC meeting (July 2011).

<sup>3</sup> Reviewed in the Major Amendment (October 2011).

\*Noninferiority comparison; other studies used superiority comparison.

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

## 6.1.2 Demographics

The three study pools used in the efficacy and safety assessments were: the Placebo-Controlled Pool (ST) pool (i.e., includes all placebo-controlled clinical 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 from the North American region (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<sup>2</sup>, a mean HbA1c of approximately 8.1%, and a mean duration of T2DM of >7 years. Approximately 11.5% of patients in the All Phase 2b/3 Pool had moderate to severe renal insufficiency (i.e., eGFR <60 mL/min/1.73 m<sup>2</sup>). As noted during the first review cycle, there continues to an underrepresentation of black/African American patients (i.e., <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	
	Dapa 10 mg (N=2360)	Placebo (N=2295)	Dapa 10 mg (N=2026)	Placebo (N=1956)	Dapa Total (N=5936)	All Control (N=3403)
<b>Age (y), Mean ± SD (Range)</b>	58.4 ± 10.0 (20-84)	58.9 ± 10.0 (21-86)	59.3 ± 9.7 (22-84)	59.8 ± 9.6 (22-86)	56.9 ± 10.4 (18-92)	58.1 ± 10.3 (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)
<b>Gender (%)</b>						
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)
<b>Race (%)</b>						
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)
<b>Geographic Region (%)</b>						
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)

Patient Characteristics	Placebo-Controlled Pool (ST)		Placebo-Controlled Pool (ST+LT)		All Phase 2b/3 Pool	
	Dapa 10 mg (N=2360)	Placebo (N=2295)	Dapa 10 mg (N=2026)	Placebo (N=1956)	Dapa Total (N=5936)	All Control (N=3403)
<b>Body Mass Index (kg/m<sup>2</sup>), (%)</b>						
Mean ± SD (Range)	32.2 ± 5.7 (16.6-66.6)	32.1 ± 5.8 (17.5-62.4)	32.4 ± 5.6 (18.5-66.6)	32.3 ± 5.8 (18.8-62.4)	31.6 ± 5.8 (15.9-62.4)	31.3 ± 5.7 (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)
<b>Blood Pressure (mmHg)</b>						
SBP, Mean ± SD (Range)	131.7 ± 15.3 (87-195)	131.6 ± 14.9 (82-199)	132.1 ± 15.2 (87-195)	131.9 ± 14.9 (82-181)	130.4 ± 15.7 (85-195)	131.1 ± 14.9 (82-199)
DPB, Mean ± SD (Range)	78.5 ± 9.1 (41-108)	78.6 ± 9.0 (46-113)	78.3 ± 9.2 (41-108)	78.4 ± 9.1 (46-113)	78.8 ± 9.1 (41-120)	78.8 ± 8.9 (46-113)
<b>Duration of T2DM (y),</b>						
Mean ± SD (Range)	8.9 ± 8.0 (0.0-54.4)	8.8 ± 8.0 (0.0-48.0)	9.8 ± 8.1 (0.0-54.4)	9.8 ± 7.9 (0.0-48.0)	7.0 ± 7.5 (0.0-54.4)	7.6 ± 7.7 (0.0-48.0)
<b>HbA1c (%), Mean ± SD (Range)</b>	8.2 ± 0.9 (5.3-12.2)	8.2 ± 0.9 (5.6-13.3)	8.1 ± 0.9 (5.3-12.2)	8.1 ± 0.9 (5.6-10.9)	8.2 ± 1.0 (5.3-13.0)	8.1 ± 1.0 (5.6-13.3)
<b>Fasting Plasma Glucose (mg/dL),</b>						
Mean ± SD (Range)	164.8 ± 46.6 (38.0-498.0)	165.4 ± 45.3 (43.0, 382.0)	162.8 ± 45.1 (38.0, 498.0)	163.3 ± 43.7 (43.0, 382.0)	167.2 ± 48.8 (32.0-498.0)	165.3 ± 46.5 (43.0-436.0)
<b>GFR (mL/min/1.73 m2)</b>						
Mean ± SD (Range)	82.7 ± 20.3 (19.0-201.6)	82.2 ± 20.2 (12.0-236.5)	81.0 ± 19.1 (19.0-177.0)	80.7 ± 19.2 (12.0-190.0)	83.6 ± 21.1 (12.0-236.5)	83.9 ± 21.3 (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.

### 6.1.3 Subject Disposition

Summary tables that included patient disposition were not provided with this NDA resubmission, but instead were derived from the analysis datasets. The disposition of patients in the All Phase 2b/3 Pool and Placebo-Controlled Pools (ST and ST+LT) are presented in Table 6. Overall, across all three study pools, there did not appear to be an imbalance between dapagliflozin and placebo treatment arms for patients who discontinued study. Also, discontinuations due to AEs, deaths, lack of efficacy (except in the Placebo-Controlled ST Pool, which favored dapagliflozin), safety and withdrawal of consent were similar between treatment arms.



**Table 6: Subject Disposition for the All Phase 2b/3 and Placebo-Controlled Study Pools**

Disposition	Placebo-Controlled Pool (ST)		Placebo-Controlled Pool (ST+LT)		All Phase 2b/3 Pool	
	Dapa 10 mg N (%)	Placebo N (%)	Dapa 10 mg N (%)	Placebo N (%)	Dapa Total N (%)	All Control N (%)
<b>Patients randomized</b>	2360	2295	2026	1956	5936	3403
<b>Discontinued</b>	583 (24.7)	658 (28.7)	967 (28.3)	605 (30.9)	1489 (25.1)	1035 (30.4)
<b>Reason for discontinuation</b>						
Administrative	3 (0.1)	9 (0.4)	7 (0.2)	9 (0.5)	9 (0.2)	9 (0.3)
Adverse event	92 (3.9)	88 (3.8)	153 (4.5)	78 (4.0)	276 (4.7)	163 (4.8)
Death	18 (0.8)	13 (0.6)	24 (0.7)	12 (0.6)	33 (0.6)	21 (0.6)
Incorrect enrollment	12 (0.5)	11 (0.5)	16 (0.5)	11 (0.6)	17 (0.3)	12 (0.4)
Lack of efficacy	22 (0.9)	47 (2.1)	75 (2.2)	41 (2.1)	80 (1.4)	53 (1.6)
Lost to follow up	52 (2.2)	56 (2.4)	80 (2.3)	49 (2.5)	141 (2.4)	77 (2.3)
No longer meets trial criteria	107 (4.5)	97 (4.2)	122 (3.6)	91 (4.7)	213 (3.6)	224 (6.6)
Patient requests to discontinue from trial					74 (1.3)	38 (1.1)
Poor/non-compliance	34 (1.4)	32 (1.4)	55 (1.6)	32 (1.6)	0	1 (<0.1)
Pregnancy	0	1 (<0.1)	0	1 (0.1)	4 (0.1)	6 (0.2)
Safety	2 (0.1)	6 (0.3)	3 (0.1)	5 (0.3)	6 (0.1)	9 (0.3)
Withdrew consent	200 (8.5)	234 (10.2)	320 (9.4)	216 (11.0)	481 (8.1)	330 (9.7)
Other	41 (1.7)	64 (2.8)	112 (3.3)	60 (3.1)	155 (2.6)	92 (2.7)

Source: Derived from the ADCV5 dataset available at:

<url:gs:PAABAAUBAAqmrqKu9lqCAACDAa4CgwEDAATDpgEBAIAAAASuAqYDAAQAAASuA6YFAAYAAAABAgIHAAgACRJEYXRhIEFuYWw5c2l2IERhdGEKSW5kaWNhdGlybHBUeXBIIIEUJERpYWJldGVzC1N0dWR5IFRpdGxIMURhcGFnbGlmbG96aW4gQ2FyZGlvdmlFzY3VsYXl2TWV0YS1BbmFseXNpcyBSZXBXbvcnQIU3R1ZHZkeSUQNbWV0YS1hbmFseXNpcwYyMDIyOTMDbmRhAA%3d%3d>

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for the majority of placebo-controlled clinical trials was the change from baseline to Week 24 in HbA1c (%). Hemoglobin A1c is considered an appropriate efficacy endpoint, and a positive result would indicate a clinically meaningful benefit for the following reasons:

- Hemoglobin A1c is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months.<sup>8</sup>
- The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5%.<sup>9,10</sup>

- c. Hemoglobin A1c has excellent reliability, predicts some of the diabetes-specific complications, and provides a basis for treatment decisions in patients with T2DM.<sup>11,12</sup>
- d. Lowering HbA1c reduces microvascular complications in patients with T1DM and T2DM,<sup>13-15</sup> and may lower macrovascular complications in patients with T1DM.<sup>16</sup>

For these reasons, the FDA draft guidance entitled *Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* states, “for purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control.”<sup>17</sup>

For the Applicant’s primary analysis of HbA1c change from baseline, an analysis of covariance (ANCOVA) model was used, with the LOCF method for imputing missing data. All observations recorded after rescue therapy were disregarded. The model included terms for treatment as fixed effect and the corresponding baseline HbA1c value as a covariate with pre-specified additional fixed effects covariates. Additionally, the Applicant conducted sensitivity analyses using Mixed Model Repeated Measures (MMRM) methods. Results using this approach were consistent with those reported using the prespecified primary statistical analysis approach. In the efficacy section of the Briefing Document, Dr. Liu noted the following limitations to the Applicant’s statistical analysis plan (SAP):

“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.”

### **Monotherapy and Combination Controlled Trials**

The efficacy results for the trials that evaluated the use of dapagliflozin as monotherapy, combination therapy, and in special populations are presented below (Table 7-9). For the placebo-controlled monotherapy and combination therapy trials, placebo-subtracted changes in HbA1c from baseline to Week 24 ranged from -0.4 to -0.84% and -0.48 to -0.66% for the 5 mg and 10 mg dapagliflozin dose groups, respectively (Table 7). Although modest, this magnitude of change is considered clinically meaningful, and is consistent with that of other recently approved oral antidiabetic medications. The Applicant stated that the 2.5 mg dose (data not shown) was not consistently effective for glycemic control. Further, for the 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 (Table 7), while safety of the 5 mg dose was considered comparable.

**Table 7: Change from Baseline to Week 24 in HbA1c for Dapagliflozin vs. Placebo (Monotherapy and Add-On Phase 2b/3 Placebo-Controlled Trials)**

Study (Background Therapy)		Placebo	Dapagliflozin Dose	
HbA1c (%)			5 mg	10 mg
Monotherapy				
MB102013 <sup>1,2</sup>	Adj. Mean (SE)	-0.23 (0.10)	-0.77 (0.11)	-0.89 (0.11)
	Dapa - Placebo	—	-0.54 (.15) **	-0.66 (.15) **
MB102032 <sup>2</sup>	Adj. Mean (SE)	0.02 (0.12)	-0.82 (0.12)	N.A.
	Dapa - Placebo	—	-0.84 (0.17) **	N.A.
Combination Therapy				
MB102014 <sup>2</sup> (Metformin)	Adj. Mean (SE)	-0.30 (0.07)	-0.70 (0.07)	-0.84 (0.07)
	Dapa - Placebo	—	-0.41 (0.10) **	-0.54 (0.10) **
MB102028 <sup>2</sup> D1690C00005 (Glimepiride)	Adj. Mean	-0.13 (0.06)	-0.63 (0.06)	-0.82 (0.06)
	Diff. vs. Placebo	—	-0.49 (0.09) **	-0.68 (0.09) **
MB102030 <sup>2</sup> (Pioglitazone)	Adj. Mean (SE)	-0.42 (0.08)	-0.82 (0.08)	-0.97 (0.08)
	Dapa - Placebo	—	-0.40 (0.12) **	-0.55 (0.12) **
MB102033 <sup>2</sup> D1690C00006 (Insulin + ≤2 OAD)	Adj. Mean (SE)	-0.30 (0.05)	-0.82 (0.05)	-0.90 (0.05)
	Dapa - Placebo	—	-0.52 (0.07) **	-0.60 (0.07) **
MB102061 D1690C00010 (Sitagliptin ± Metformin)	Adj. Mean (SE)	0.04 (0.05)	—	-0.45 (0.05)
	Dapa - Placebo			-0.48 (0.07) **

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (pages 156-7 of 175, labeled as Table 2).

Abbreviations: Adj., adjusted; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; OAD, oral antidiabetic drugs; and SE, standard error.

<sup>1</sup> AM dosing

<sup>2</sup> Reviewed by Agency statistical reviewer at the first EMDAC meeting.

\*p < 0.05 vs. placebo \*\*p < 0.001 vs. placebo (Note: statistical adjustments for multiplicity were not applied)

In the two clinical trials that compared dapagliflozin plus metformin to metformin or dapagliflozin alone, combination therapy was superior to both dapagliflozin and metformin monotherapy treatment arms for both the dapagliflozin 5 mg and 10 mg dose groups (Table 8).

**Table 8: Change from Baseline to Week 24 in HbA1c for Dapagliflozin Plus Metformin vs. Metformin Monotherapy and Dapagliflozin Monotherapy**

Study		Treatment Arm		
HbA1c (%)		Dapa 5 mg + Metformin	Dapa 5 mg	Metformin
MB102021	Adjusted Mean (SE)	-2.05 (0.09)	-1.19 (0.09)	-1.35 (0.09)
	Difference from Combination	—	-0.86 (0.12)**	-0.70 (0.12)**
		Dapa 10 mg + Metformin	Dapa 10 mg	Metformin
MB102034	Adjusted Mean	-2.01 (1.08)	-1.44 (1.31)	-1.42 (1.41)
	Difference from Combination	—	-0.53 (0.11)**	-0.54 (0.11)**

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (pages 157 of 175, labeled as Table 3).

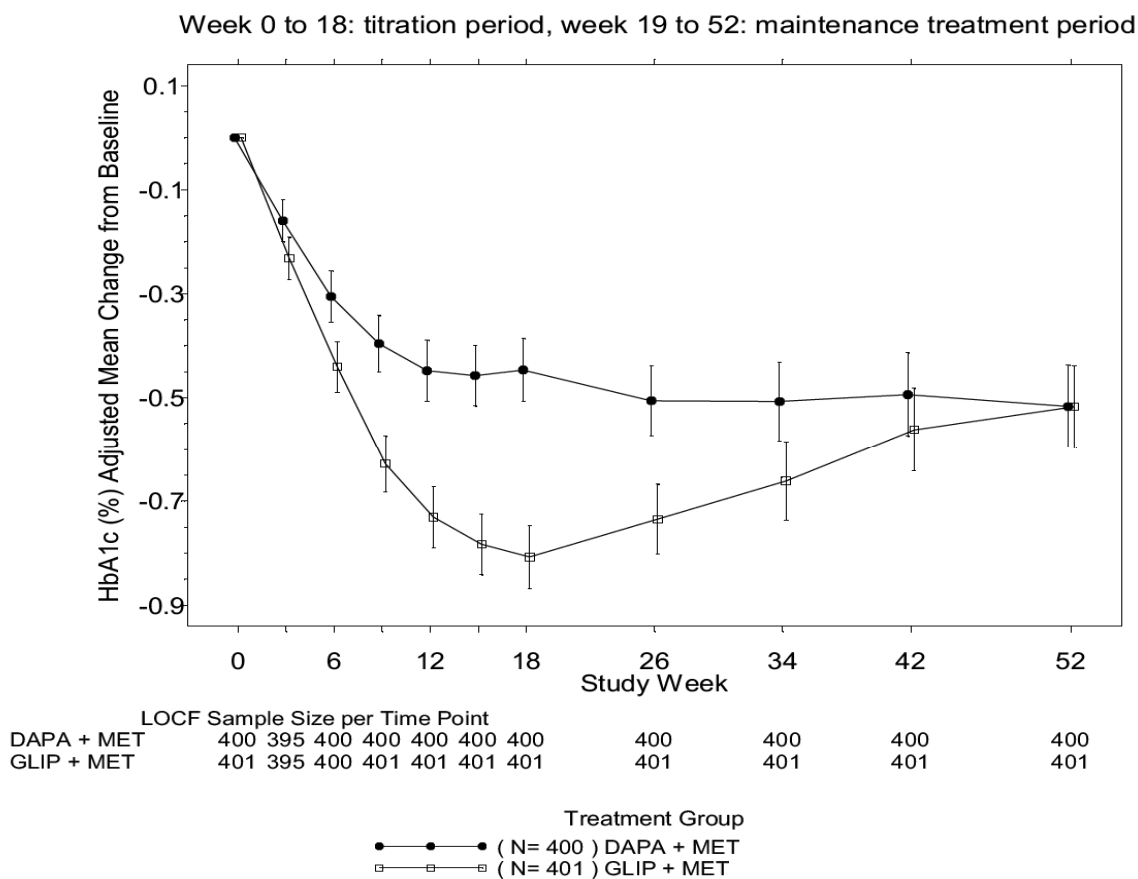
Abbreviations: Dapa, dapagliflozin; HbA1c, glycosylated hemoglobin; and SE, standard error.

\* Reviewed by FDA statistical reviewer in the first AC meeting.

\*\*p < 0.001 vs. the combination

During the first review cycle, two additional trials, MB102022 (D1690C00004) and MB102047 (D1690C00012), were also reviewed. Trial MB102022 was a noninferiority trial comparing dapagliflozin to glipizide. Both treatment arms resulted in a 0.52% reduction from baseline to Week 52 in HbA1c, and the upper bound of the confidence interval (95% CI; -0.11%, 0.11% for the difference between arms) was within the accepted noninferiority margin of 0.3 to 0.4%.<sup>17</sup> However, during several earlier time points (Figure 1), the magnitude of HbA1c reduction was greater in the glipizide treatment arm. For Trial MB102047, the primary endpoint was change in body weight from baseline to Week 24. In this study, dapagliflozin 10 mg plus metformin resulted in an additional 2.08 kg reduction in body weight compared the metformin-only treatment arm (p < 0.0001).

**Figure 1: D1690C00004 (Active Control vs. Glipizide) Adjusted Mean Change from Baseline Over time in HbA1c (%) for 52-Week Treatment Period, Full Analysis Set**



Source: Applicant's 52-Week Clinical Study Report, D169C00004, (page 86 of 28,208, labeled as Figure 3).

### **Phase 3 Controlled Clinical Trials Conducted in Special Populations**

The results of the five clinical trials conducted in special populations are presented in Table 9 below. For all but one of these clinical trials (i.e., MB102029, conducted in patients with renal insufficiency), dapagliflozin was superior to placebo in the primary efficacy endpoint(s) (i.e., change from baseline in HbA1c, or HbA1c and 3-item endpoint of clinical benefit), and results were consistent with analyses conducted by the Agency statisticians. Trials MB102067 (D1690C00018) and MB102080 (D1690C00019), which were trials conducted in patients at higher cardiovascular risk (i.e., patients with established CVD with and without hypertension, respectively), both had a second primary endpoint of proportion of patients meeting three-item composite endpoint criteria at Week 24. The three-item composite endpoint criteria was defined as reductions from baseline to Week 24 in HbA1c  $\geq 0.5\%$ , total body weight  $\geq 3\%$ , and seated SBP  $\geq 3$  mmHg. For Trials MB102073 and MB102077, the Applicant prespecified seated SBP and HbA1c as co-primary endpoints.

**Table 9: Change from Baseline to Week 24 in HbA1c for Dapagliflozin vs. Placebo (Phase 3 Placebo-Controlled Trials – Special Populations)**

Study Duration (Wks) Population	Primary Endpoint Arm	n	Baseline Mean (SD)	LS Mean Change ± SE	DAPA Minus Control (95% CI)	p-value
<i>Add-On to Various Oral Antidiabetic Drugs and/or Insulin</i>						
MB102029 <sup>a</sup> (12) <i>Dedicated Renal Trial</i>	HbA1c					
	DAPA 10 mg	82	8.22 (0.97)	-0.44 ± 0.17	-0.11 (-0.40, 0.17)	0.435
	DAPA 5 mg	83	8.30 (1.04)	-0.41 ± 0.17	-0.08 (-0.37, 0.20)	0.561
	Placebo	82	8.53 (1.29)	-0.32 ± 0.17		
MB102073 <sup>b</sup> (12) <i>Dedicated HTN Trial</i>	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)	<0.0001
	Placebo	279	8.02 (0.91)	-0.10 ± 0.06		
MB102077 <sup>b</sup> (12) <i>Dedicated HTN Trial</i>	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)	<0.0001
	Placebo	197	8.00 (0.96)	-0.02 ± 0.07		
MB102067 <sup>a</sup> (D1690C00018) (24) <i>CVD + HTN Trial</i>	HbA1c <sup>d</sup>					
	DAPA 10 mg	448	8.18 ± 0.84	-0.38 ± 0.04	-0.46 (-0.56, -0.37)	<0.0001
	Placebo	451	8.08 ± 0.80	0.08 ± 0.04		
	Responders <sup>c, d</sup>					
	DAPA 10 mg	444		52, 11.7%	9.9% (7.0%, 12.9%)	<0.0001
	Placebo	451		4, 0.9%		
MB102080 <sup>a</sup> (D1690C00019) <sup>a</sup> (24) <i>CVD Trial</i>	HbA1c <sup>d</sup>					
	DAPA 10 mg	474	8.04 ± 0.76	-0.33 ± 0.04	-0.40 (-0.50, -0.30)	<0.0001
	Placebo	471	8.07 ± 0.79	0.07 ± 0.04		
	Responders <sup>c, d</sup>					
	DAPA 10 mg	468		47, 10.0%	7.0% (4.3%, 9.8%)	<0.0001
	Placebo	469		9, 1.9%		

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (pages 158-9 of 175, labeled as Table 4).

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; Dapa, dapagliflozin; HbA1c, glycosylated hemoglobin; HTN, hypertension; LOCF, last-observation-carried-forward; LS, least squares; n, sample size; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; and Wks, weeks.

LOCF: last observation carried forward; SBP: systolic blood pressure; SE: standard error.

<sup>a</sup> Using LOCF in ANCOVA for HbA1c excluding data after rescue medication (in C00018 and C00019 including data after anti-hypertensive rescue)

<sup>b</sup> MMRM excluding data after rescue medication

<sup>c</sup> Proportion of responders for a 3-item endpoint of clinical benefit at Week 24, using LOCF in Cochran-Mantel-Haenszel method

<sup>d</sup> 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).



### **Integrated Analyses of Phase 3 Clinical Trials**

An independent integrated analysis (i.e., meta-analysis) of a pool of twelve of the placebo-controlled trials was conducted by Dr. Wei Liu. Statistically significant reductions ( $p < 0.0001$ ) in HbA1c (i.e., placebo-adjusted changes from baseline to Week 24) for both the 5 mg and 10 mg dapagliflozin dose groups were observed (Table 10). Since no adjustments were made for multiplicity, these results were done for descriptive purposes.

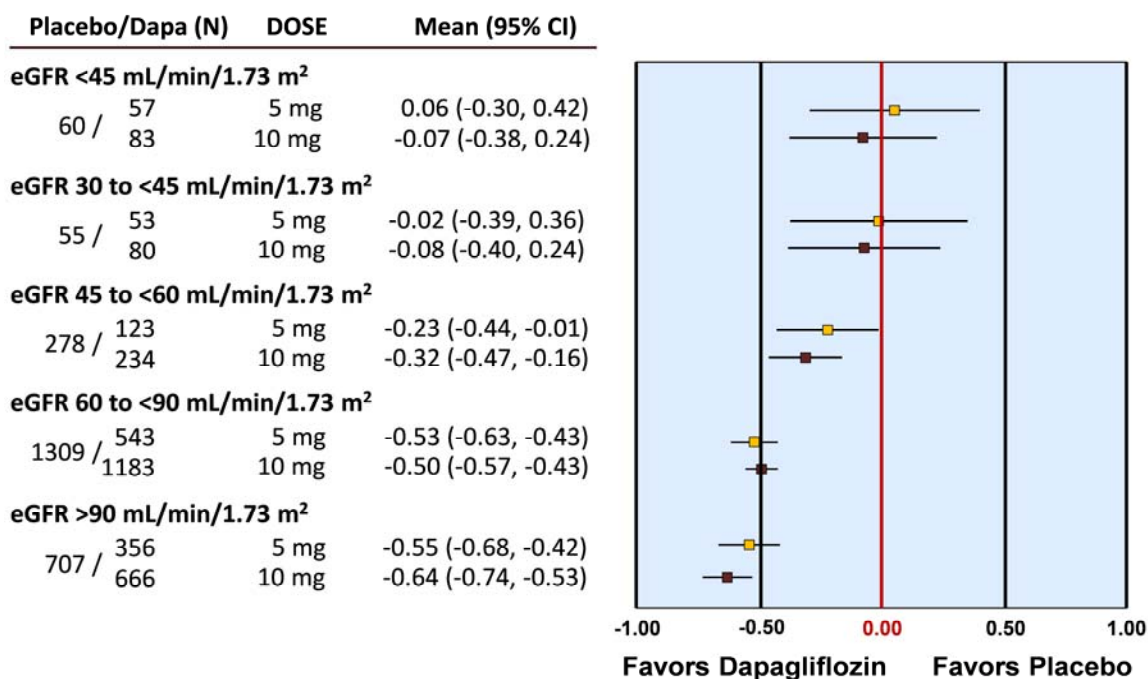
**Table 10: Integrated Analysis of HbA1c Change from Baseline to Week 24  
(Pool of 13 Phase 2b/3 Placebo-Controlled Trials)**

Endpoint	Placebo		DAPA 5 mg		DAPA 10 mg	
	n		n		n	
<b>HbA1c (%)</b>						
Baseline mean (SD)	2274	8.26 (1.03)	996	8.44 (1.13)	2085	8.21 (0.97)
Adj. Mean Change from baseline $\pm$ SE		-0.37 $\pm$ 0.02		-0.88 $\pm$ 0.03		-0.90 $\pm$ 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

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (page 161 of 175, labeled as Table 5).  
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; and N, sample size.

Additionally, in subgroup analyses conducted by Dr. Liu using the same pooled patient population of 13 placebo-controlled studies (Figure 2), it appears that dapagliflozin (i.e., 5 or 10 mg doses) is effective (i.e., reduction in HbA1c from baseline to Week 24) only in patients with normal renal function or mild impairment ( $\text{eGFR} \geq 45 \text{ mL/min/1.73m}^2$ ). However, the effect size in with mild renal impairment is relatively small. The proportions of patients achieving a HbA1c  $< 7\%$  appeared to differ from placebo for the dapagliflozin 5 mg and 10 mg dose groups for patients with baseline  $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$  (data not shown). The Applicant proposes that the drug not be used in individuals with moderate or severe renal impairment (i.e., an estimated glomerular filtration rate [ $\text{eGFR}$ ]  $< 60 \text{ mL/min/1.73 m}^2$ ). This may limit the use of dapagliflozin in patients with long-standing T2DM in whom renal impairment is a common comorbidity. As stated above, results for these subgroup analyses should be considered exploratory as no statistical adjustments for multiplicity were applied.

**Figure 2: Placebo-Subtracted Mean Change in HbA1c from Baseline to Week 24 Based on Baseline eGFR (Integrated Subgroup Analyses of 13 Phase 2b/3 Placebo-Controlled Trials)**



Source: Derived from data presented in the Efficacy Statistical Briefing Document by Dr. Wei Liu (pages 162-3 of 175, labeled as Table 6).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; and N, sample size.

### 6.1.5 Analysis of Secondary Endpoints(s)

Key secondary glycemic control parameters included change from baseline to Week 24 in the 2-hour PPG and the FPG, and the proportion of patients achieving HbA1c concentrations <7% at Week 24 compared with placebo. Additionally, changes in body weight and blood pressure were also assessed. In general, reductions in FPG and 2-hour PPG concentrations, and mean daily insulin dose, as well as the proportion of patients achieving HbA1c concentrations <7%, were usually supportive of the primary efficacy findings (data not shown). Additionally (b) (4) modest reductions in body 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) (b) (4)

In the integrated analyses of the pool of 13 placebo-controlled clinical trials conducted by Dr. Wei Liu, secondary endpoints, including the proportion of patients achieving a HbA1c of less than 7%, and reductions in FPG, body weight, and systolic blood pressure were again supportive (Table 11 and Figure 3). However, placebo-adjusted low-density lipoprotein-cholesterol (LDL-C) changes from baseline were increased in both the 5 mg



and 10 mg dapagliflozin dose cohorts with percent changes of 2.1% and 3.2% respectively (Figure 3), while LDL-C concentrations for the placebo treatment arm remained close to baseline determinations.

**Table 11: Integrated Analyses of Changes from Baseline to Week 24 in Secondary Endpoints (Pool of 13 Phase 2b/3 Placebo-Controlled Trials)**

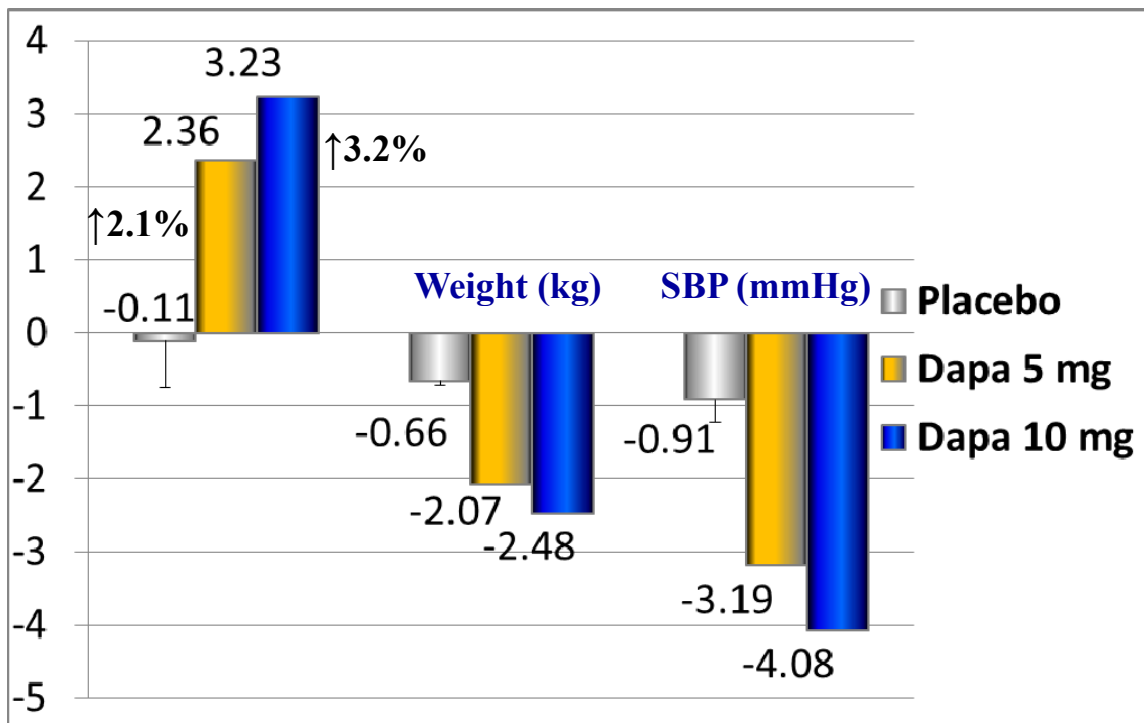
Endpoint	Placebo		Dapa 5 mg		Dapa 10 mg	
	n		n		n	
HbA1c <7%, (%)	325 (14%)		202 (20%)*		418 (20%)*	
FPG (mg/dL)						
Baseline mean (SD)	2377	168.2 (47.8)	1009	175.2 (51.9)	2182	165.5 ± (46.7)
Adj. Mean Change from baseline ± SE		-4.23 ± 0.86		-26.36 ± 1.32		-28.75 ± 0.93
DAPA-P, adjusted LS Mean				-22.12		-24.51
(95% CI)				(-25.27, -18.98)		(-26.77, -22.25)
p-value				<0.0001		< 0.0001
LDL-C (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				<0.0001		<0.0001
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				<0.0001		< 0.0001

Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (page 161 of 175, labeled as Table 5).

Abbreviations: Adj, adjusted; CI, confidence interval; Dapa-P, placebo-subtracted change; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LS, least squares; n, sample size; and SD, standard deviation.

\*P-value <0.0001 dapagliflozin 5 mg or 10 mg vs. placebo.

**Figure 3: Integrated Analyses of Mean Change in LDL-C, Weight and Systolic Blood Pressure from Baseline to Week 24 (Pool of 13 Phase 2b/3 Placebo-Controlled Trials)**



Source: Modified from the Efficacy Statistical Briefing Document by Dr. Wei Liu (page 161 of 175, labeled as Table 5).

Abbreviations: Dapa, dapagliflozin; placebo-subtracted change; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LS, least squares; n, sample size; and SD, standard deviation.

### 6.1.6 Other Endpoints

Please refer to the original clinical reviews by Dr. Dunn for other endpoints assessed in the dapagliflozin clinical development program related to pharmacokinetic, pharmacodynamic and efficacy endpoints.

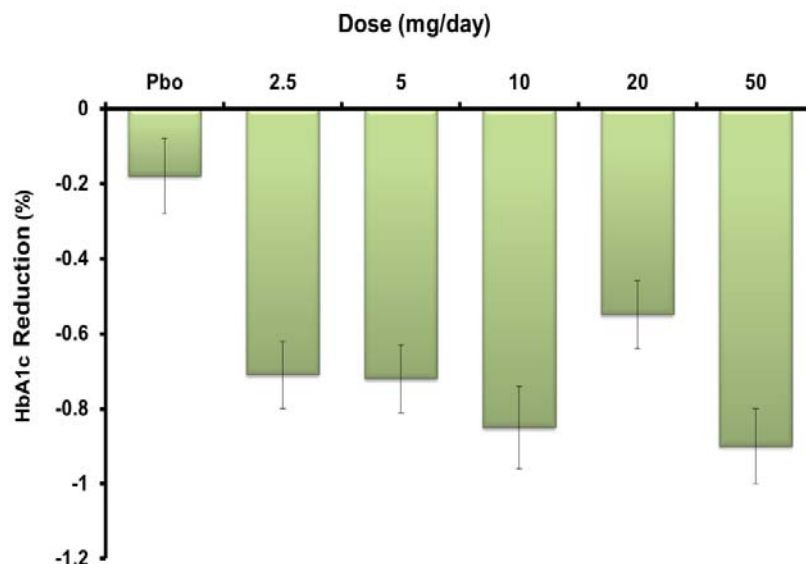
### 6.1.7 Subpopulations

Subpopulations were not specifically examined in this submission except as they pertain to the independent integrated efficacy analyses conducted by Dr. Wei Liu based on baseline eGFR categories (refer to Section 6.1.4 Analysis of Primary Endpoint(s) above).

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No new clinical information relevant to dosing recommendations was included in this NDA resubmission. Refer to the original reviews by Drs. Dunn, Jain, and Norton for additional information. In the original NDA submission, the results of a twelve-week Phase 2 dose-ranging study (i.e., MB102008) were reviewed. This study evaluated dapagliflozin daily doses ranging from 2.5 mg to 50 mg. The results of this trial suggest that additional HbA1c lowering is not observed with doses greater than 10 mg (Figure 4). However, genitourinary infections and laboratory abnormalities, such as hyperphosphatemia and increases in hematocrit, were more common in the 20 and 50 mg dapagliflozin treatment arms. Further, in the integrated analyses, Dr. Liu provided additional support for the use of the 5 and 10 mg doses of dapagliflozin for glycemic control (Table 10).

**Figure 4: Phase 2 Study (MB102008) — Dapagliflozin Dose Range of 2.5 to 50 mg Once Daily Studied Over 12 Weeks in Treatment-Naïve Patients with T2DM**



Source: Modified from Dr. Ritesh Jain's Clinical Pharmacology Review.  
Abbreviations: HbA1c, hemoglobin A1c.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the Phase 2b/3 clinical program, eleven of the clinical trials included 24 to 80 week long-term extension phases. The persistence of efficacy was reviewed during the first

review cycle of this NDA. In the Applicant's placebo-controlled clinical trials with long-term extension phases, HbA1c reductions were maintained for up to 104-week treatment phases. In her clinical review, Dr. Dunn concluded the dapagliflozin, in the proposed to-be-marketed doses of 5 and 10 mg, appears to have lasting effects to 102 weeks.

#### **6.1.10 Additional Efficacy Issues/Analyses**

Additional primary and secondary efficacy analyses were conducted by the Agency. Refer to the integrated analyses of a pool of 12 placebo-controlled clinical trials performed by Dr. Liu (Sections 6.1.4 Analysis of Primary Endpoint(s) and 6.1.5 Analysis of Secondary Endpoints(s) above).

## **7 Review of Safety**

### **Safety Summary**

This section reviews the safety information pertaining to this NDA resubmission, and will focus primarily on the updated safety information provided in the 30-MU pertaining to bladder cancers, risk for DILI and CV safety, as well as the additional Phase 2b/3 clinical trial data included in the Application to support the safety of this product.

Overall, the review of this Application did not identify new or unexpected safety signals, and serious adverse events (AEs) with fatal and nonfatal outcomes were relatively balanced between dapagliflozin and control treatment arms. The incidence of hypoglycemia in the pool of thirteen short-term placebo-controlled studies was similar but slightly higher, for dapagliflozin-treated patients (i.e., 13.7% and 12.4%% for the dapagliflozin and placebo treatment arms, respectively). Hypoglycemic events were more common when dapagliflozin was used in combination with insulin or a sulfonylurea. Common AEs, occurring in  $\geq 2\%$  of dapagliflozin-treated patients greater than placebo, included genital infection (5.5%), urinary tract infection (3.9%), back pain (3.5%), dizziness (2.3%), pollakiuria (2.1%) and influenza (2.0%).

As per the advice in the CRL, the Applicant conducted an updated CV meta-analysis of a pool of 21 Phase 2b and Phase 3 clinical trials. Consistent with the results of the last meta-analysis (i.e., the pool of 19 studies evaluated during the first review cycle), the HR point estimates for both the primary composite endpoint of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina (MACE plus) and secondary composite MACE endpoint for the updated meta-analysis, are now 0.82 (95% CI, 0.59 to 1.14) and 0.79 (95% CI, 0.54 to 1.17), respectively. These results continue to meet the December 2008 Guidance,<sup>1</sup> ruling out the unacceptable increase in CV risk of greater than 80% above comparator groups. Additionally, divergence in the Kaplan-Meier curves, in favor of dapagliflozin, were observed for the primary CV composite endpoint after approximately eight months, suggesting potential CV benefit with prolonged use.

It should be noted that an imbalance of CV events was observed within the first 30 days of treatment with dapagliflozin, with seven primary events (plus one secondary) observed among 5936 subjects randomized to dapagliflozin (0.12%) and two primary events (plus two secondary events) among 3403 subjects randomized to comparators (0.06%). For the dapagliflozin-treated patients, the majority of these early events occurred in patients with established peripheral and/or cardiovascular disease, of whom four were enrolled in Trials D1690C00018 and D1690C00019 (i.e., the trials enriched with individuals at high risks for CV events). A similar observation of an early imbalance in CV events was also observed with canagliflozin.

The updated CV safety analyses also included a new meta-analysis of the pool of Trials D1690C00018 and D1690C00019, which was updated to include data from individuals who had continued in the controlled extension phases of these two trials. In these trials, statistically significant reductions in HbA1c, systolic blood pressure, and body weight were reported. Although the point estimate and upper bound 95% CI for the HR of the composite MACE endpoint were lower than those reported in the previous analysis, they nonetheless continued to exceed 1 and 1.8, respectively (i.e., HR 1.11; 95% CI, 0.67 to 1.83). This raises a question as to whether dapagliflozin could produce a cardiovascular benefit with prolonged use in patients with established CV disease or conversely increase CV risk in a subset of these patients.

With this NDA resubmission, there continues to be a numeric imbalance in cases of bladder cancer, not favoring dapagliflozin (i.e., 10 cases in dapagliflozin-treated patients and one in the control arm). A similar imbalance in bladder cancer events was not seen with canagliflozin. Although the number of bladder cancer events is relatively small, with only one additional case reported since the last review— which now include 40% more patient-years (p-y) of exposure — the estimated incidence risk ratio [IRR] of 6.1 (95% CI, 0.827 to 272) should not be disregarded. The potential for detection bias (i.e., resulting from more frequent monitoring of dapagliflozin treatment arms due to higher rates of urogenital AEs) cannot be ruled out. The consultant from the Division of Oncology Products (DOP), Dr. Yang-Min Ning, recommended that the potential risk for bladder cancer be further studied, carefully monitored, and possibly labeled as a Warning or Precaution if dapagliflozin were to be approved. In this regard, the Applicant has proposed several postmarketing safety measures to include enhanced surveillance in their clinical program, pharmacoepidemiologic studies, and blinded adjudication of bladder cancer events in their long-term CVOT. The EMDAC concurred that additional evaluation should be conducted by the Applicant to further assess potential safety concerns (i.e., malignancies, renal function, and serious hepatic events). These safeguards may be acceptable, pending input and recommendations from the Office of Surveillance and Epidemiology (OSE).

As noted during the previous review cycle, there remains a numeric imbalance of breast cancer cases (i.e., 0.45% and 0.21% for dapagliflozin and comparator arms, respectively) which favors the comparator arm (IRR 2.472; 95% CI, 0.636 to 14.095). Due to a decline in the IRR since the original review (i.e., the IRR was 4.41; 95% CI 0.57 to 200.86 at the

time of the 2011 EMDAC meeting), the lack of screening mammography prior to study entry in a population at risk for breast cancer, and a diagnosis within the first year of exposure to dapagliflozin for the majority of patients, Dr. Genevieve Schechter, the consultant from the DOP, acknowledged that this imbalance in cancer events may be a spurious finding.

A potential case of dapagliflozin-induced liver injury was observed during the first review cycle for which an association with dapagliflozin remains plausible. The Applicant has now provided more than three years of additional follow-up data for this individual to support a possible reclassification of the diagnosis as an autoimmune hepatitis. Dr. John Senior, the consulting hepatologist from OSE, concurs with two experienced hepatologists on the Hepatic Adjudication Committee that this case likely represents autoimmune hepatitis. However, it cannot be determined whether liver disease in this 79-year-old patient would have occurred if he were not exposed to low-dose dapagliflozin. Overall, the occurrence of marked liver laboratory test abnormalities remains relatively balanced between dapagliflozin and the comparator treatment arms. The majority of cases of transaminase and total bilirubin elevations of greater than three and two times the upper laboratory reference range (ULRR), respectively, had other diagnoses that were more likely than dapagliflozin to have caused the test abnormalities.

Similar to canagliflozin, dapagliflozin relative to comparators is associated with adverse events of genital and urinary tract infections, and events related to polyuria, volume depletion and renal impairment. Although long-term effects from increased urinary tract and genital infections are unknown, these events are usually not recurrent and can typically be managed with antimicrobial therapy. Caution is warranted regarding the potential for hypovolemia, dehydration, and renal impairment—especially in elderly patients with renal dysfunction and perhaps in individuals receiving loop diuretics. Other safety concerns include the potential to increase LDL-C, and the unknown risk for fractures with long-term use in vulnerable patient populations. These potential adverse effects are known for this pharmacologic class and can be mitigated with adequate patient monitoring and careful management of adverse effects as described in the proposed product labeling.

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The safety evaluation plan included routine assessments, as well as a focus on potential risks associated with SGLT2 inhibitors. Additionally, clinical study report and analysis datasets were reviewed for safety. Selected AEs and laboratory abnormalities were cross-checked with those provided with the NDA documents. The Applicant was also requested to provide updated information related to malignancies, as well as confirm safety data across their current and previous submission.

### 7.1.2 Categorization of Adverse Events

All the serious and non-serious AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) for classification of adverse event data into system organ classes (SOC) and preferred terms (PTs). MedDRA version 13.0 was used for the analyses in the Summary of Clinical Safety for the original NDA submission and the CV safety meta-analysis, and versions 10.0 through 13.0 were used for the Phase 2b/3 Clinical Study Reports (CSRs).

The Applicant used several versions of MedDRA, but provided an Appendix with a summary of apparent discrepancies. Review of these discrepancies did not reveal significant revisions which would alter or influence the safety evaluation of this NDA. Comparisons were also made between the verbatim terms (i.e., AE Case Report Form [CRF] text and analysis datasets) provided by the investigators and the MedDRA Preferred Terms (PTs) for which these AEs were coded. The classifications of these data appeared appropriate.

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

The Applicant's pooling strategy for the evaluation of safety in their integrated safety datasets included the following two major study pools (Table 12):

- 1) All Phase 2b/3 Pool, consisting of 21 clinical trials (including both the short- and long-term extension phases of these studies)
- 2) Placebo-Controlled Pool, 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 was 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

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Frank Pucino, PharmD, MPH  
NDA 202293; FARXIGA (dapagliflozin)

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 12: Pooling Strategy of the Applicant for Clinical Evaluation of Safety**

All Phase 2b and 3 Pool (N=21)	Placebo-Controlled Pool	
	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).



## 7.2 Adequacy of Safety Assessments

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

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 13 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 four 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 report submitted by the Applicant.

**Table 13: 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
<b>Cumulative Exposure (p-y)</b>	979.1	1372.5	3864.7	6247.2	3637.6
<b>Duration (days)</b>					
	n (%)	n (%)	n (%)	n (%)	n (%)
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)

	Dapa 2.5 N=1220	Dapa 5 mg N=2048	Dapa 10 mg N=3417	Dapa Total N=5936	All Control N=3403
<b>Summary Statistics (days)</b>					
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; and p-y, patient-years.

## 7.2.2 Explorations for Dose Response

Explorations for dose response were not performed in this NDA resubmission. However, dose-response was evaluated as part of the original NDA submission. In general, the incidence of events for the proposed 5 and 10 mg once daily dapagliflozin doses were similar.

## 7.2.3 Special Animal and/or In Vitro Testing

Please refer to Section 4.3 Preclinical Pharmacology/Toxicology, as well as the review by Dr. Mukesh Summan, the Pharmacology/Toxicology reviewer for this Application.

## 7.2.4 Routine Clinical Testing

Safety assessment included collection of adverse events, physical examination, vital signs, body weight, electrocardiograms (ECGs), and clinical laboratory testing. Routine clinical laboratory safety studies included blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase), hematology (including complete blood count [CBC], differential, and absolute neutrophil count), urinalysis, creatine kinase and urine pregnancy testing (performed in women of childbearing potential).

## 7.2.5 Metabolic, Clearance, and Interaction Workup

Additional metabolic clearance and interaction data were not submitted to this NDA. For detailed information on the metabolic, clearance and interaction assessments for dapagliflozin, refer to the original NDA and to the Clinical Pharmacology Review by Dr. Jain. In general, it appears that dose adjustment is not necessary for intrinsic and extrinsic factors, such as age, gender, hepatic function, co-administered drugs, or food intake.

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

Based on findings observed in their nonclinical and Phase 1 and 2 programs, the Applicant considered AEs identified at the beginning of their Phase 3 clinical program, as well as those related to the mechanism of action of dapagliflozin as an SGLT2 inhibitor, to be AEs of clinical interest. These events included dyslipidemia, hypoglycemia, genital and urinary tract infections, renal impairment/failure, polyuria, volume depletion, and fractures.

### **7.2.7 Adequacy of Specific Testing Intended to Assess Certain Expected or Observed Reactions**

The Applicant stated that all safety data (e.g., AEs, clinical laboratory tests, vital signs, electrocardiograms [ECG]) included in the Clinical Summary of Safety were collected and reported according to Good Clinical Practice guidelines. The safety evaluations included a fairly comprehensive program to monitor (e.g., monitoring algorithms and establishment of independent data monitoring/adjudication committees) and collect additional information on selected AEs that were of particular clinical interest and related to specific organ systems or syndromes intended to complement the standard safety monitoring of the dapagliflozin clinical program.

## **7.3 Major Safety Results**

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 14 and Table 15. 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 slightly 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.

### **7.3.1 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 14). 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 16). 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 CVD. 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 (eight 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).

**Table 14: 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 15: 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 16: Frequency Table of Causes of Death for the All Phase 2b/3 Pool**

MedDRA Preferred Term	30-MU						Original NDA Database Lock	
	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)
<b>TOTAL PATIENTS WITH AN EVENT OF DEATH</b>	<b>0</b>	<b>1</b>	<b>17</b>	<b>13</b>	<b>37 (0.6)</b>	<b>24 (0.7)</b>	<b>18 (0.4)</b>	<b>9(0.5)</b>

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.

### 7.3.2 Nonfatal 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 14). For the placebo-controlled pools (Table 15), the proportions of patients experiencing an SAE were also similar between treatment arms for 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 17.

Although the numbers were small, SAEs in the Infections and Infestations SOC occurred more commonly in dapagliflozin-treated patients than in the control arm. Of note, there were four SAEs of sepsis (3 males and 1 female, ages 69-73) and six of septic shock (4 males and 2 females, ages 51-70) that occurred in dapagliflozin-treated patients, compared to none in the comparator arms. Of the four SAEs of sepsis, only one was reported since the 4MSU. For these four patients, the events involved septicemia unconfirmed by culture in a patient with recurrent events of lower extremity cellulitis (n=1), a recent prostate biopsy (n=1), respiratory sepsis associated with pneumonia (n=1), and a UTI in a patient with an indwelling catheter (n=1, urine culture was negative). For the six cases of septic shock, three were newly reported since the 4MSU. Of the six events, five were fatal, and were associated with pneumonia (n=2), colitis treated by colectomy and ileostomy (n=1), gastrointestinal bleed with antithrombotic therapy (n=1), and MI (n=1).

Additionally, SAEs of angioedema were reported in four dapagliflozin-treated patients (3 males and 1 female, ages 44-78) and none in the control arm. Of these patients, three events occurred following at least six months of exposure, with two patients receiving ACE inhibitors, known to be associated with angioedema. One patient experienced angioedema on Day 46, which was felt to be associated with salicylates.

### 7.3.3 Dropouts and/or Discontinuations

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 15). 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 17: 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 (%)
<b>TOTAL NUMBER (%) PATIENTS WITH SAEs</b>	<b>602 (10.14)</b>	<b>408 (12.00)</b>	<b>139 (11.39)</b>	<b>105 (7.22)</b>	<b>116 (7.75)</b>	<b>363 (8.42)</b>	<b>184 (9.38)</b>
<b><i>CARDIAC DISORDERS</i></b>	<b>139 (2.34)</b>	<b>106 (3.11)</b>	<b>30 (2.46)</b>	<b>28 (1.93)</b>	<b>16 (1.07)</b>	<b>74 (1.72)</b>	<b>44 (2.24)</b>
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
<b><i>INFECTIONS AND INFESTATIONS</i></b>	<b>102 (1.72)</b>	<b>55 (1.62)</b>	<b>21 (1.72)</b>	<b>17 (1.17)</b>	<b>23 (1.54)</b>	<b>61 (1.42)</b>	<b>24 (1.22)</b>
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
<b><i>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</i></b>	<b>82 (1.38)</b>	<b>45 (1.32)</b>	<b>20 (1.64)</b>	<b>15 (1.03)</b>	<b>17 (1.14)</b>	<b>53 (1.23)</b>	<b>17 (0.87)</b>
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)
<b><i>NERVOUS SYSTEM DISORDERS</i></b>	<b>62 (1.04)</b>	<b>51 (1.50)</b>	<b>21 (1.72)</b>	<b>2 (0.14)</b>	<b>13 (0.87)</b>	<b>36 (0.84)</b>	<b>22 (1.12)</b>
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)
<b><i>GASTROINTESTINAL DISORDERS</i></b>	<b>53 (0.89)</b>	<b>33 (1.00)</b>	<b>12 (0.98)</b>	<b>8 (0.55)</b>	<b>9 (0.60)</b>	<b>29 (0.67)</b>	<b>13 (0.66)</b>
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)



Clinical Review  
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NDA 202293; FARXIGA (dapagliflozin)

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 (%)
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
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	<b>43 (0.72)</b>	<b>26 (0.76)</b>	<b>10 (0.82)</b>	<b>7 (0.48)</b>	<b>9 (0.60)</b>	<b>26 (0.60)</b>	<b>15 (0.76)</b>
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)
INTERVERTEBRAL DISC PROTRUSION	4 (0.07)	1 (0.03)	3 (0.25)	1 (0.07)	0	4 (0.09)	1 (0.05)
<b>VASCULAR DISORDERS</b>	<b>37 (0.62)</b>	<b>19 (0.59)</b>	<b>5 (0.41)</b>	<b>9 (0.62)</b>	<b>9 (0.60)</b>	<b>23 (0.53)</b>	<b>3 (0.15)</b>
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
<b>METABOLISM AND NUTRITION DISORDERS</b>	<b>25 (0.42)</b>	<b>14 (0.41)</b>	<b>4 (0.27)</b>	<b>8 (0.55)</b>	<b>4 (0.27)</b>	<b>16 (0.37)</b>	<b>7 (0.36)</b>
HYPERGLYCEMIA	4 (0.07)	1 (0.03)	0	2 (0.14)	2 (0.13)	8 (0.19)	4 (0.20)
<b>HEPATOBIILIARY DISORDERS</b>	<b>21 (0.35)</b>	<b>13 (0.38)</b>	<b>6 (0.49)</b>	<b>3 (0.21)</b>	<b>1 (0.07)</b>	<b>10 (0.23)</b>	<b>5 (0.25)</b>
CHOLELITHIASIS	11 (0.19)	4 (0.12)	4 (0.33)	2 (0.14)	1 (0.07)	8 (0.19)	1 (0.05)
<b>RENAL AND URINARY DISORDERS</b>	<b>21 (0.35)</b>	<b>13 (0.38)</b>	<b>3 (0.25)</b>	<b>6 (0.41)</b>	<b>3 (0.20)</b>	<b>12 (0.28)</b>	<b>10 (0.51)</b>
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)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	<b>20 (0.34)</b>	<b>17 (0.50)</b>	<b>5 (0.41)</b>	<b>5 (0.34)</b>	<b>1 (0.07)</b>	<b>11 (0.26)</b>	<b>9 (0.46)</b>
DYSPNEA	3 (0.05)	1 (0.03)	0	3 (0.21)	0	3 (0.07)	1 (0.05)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	<b>12 (0.2)</b>	<b>4 (0.1)</b>	<b>3 (0.25)</b>	<b>2 (0.14)</b>	<b>0</b>	<b>5 (0.12)</b>	<b>1 (0.05)</b>
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 Safety 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.

### 7.3.4 Significant Adverse Events

The review of this NDA resubmission focused primarily on cancer, hepatic safety and CV risks, which were identified as significant safety concerns during the first review cycle. This section will discuss the updated safety information provided by the Applicant related to these concerns.

#### 7.3.4.1 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, all males, 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 in males only 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. The stratified IRR is now 5.428 (95% CI, 0.712 to 245.10) for males only (i.e., 9 per 1626 dapagliflozin-treated males vs. 1/1150 males in the control arm of trials with at least one event). 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  $\geq 100 \times$  human C<sub>max</sub> 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 Zucker Diabetic Fatty (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*. The Applicant's nonclinical studies to date do not entirely rule out a possibility of bladder tumor promotion.

Since the integrated database lock for the 30-MU, one additional case of bladder cancer was reported 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. Inclusion of this patient and the entire All Phase 2b/3 Pool (i.e., 2923 dapagliflozin-treated patients vs. 1989 controls for studies that reported at least one event) results in a stratified IRR of 6.111 (95% CI, 0.827, 272.02), which is similar to that reported previously in the male only population. 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 no additional cases between two and four years exposure (i.e., 428 p-y of exposure). Six of the ten cases had hematuria at baseline prior to the diagnosis of bladder cancer, with an additional three patients developing hematuria within six months of exposure to dapagliflozin, also prior to diagnosis. 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. Yang-Min 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 18 (presented below) summarizes key information about bladder cancer cases diagnosed in the pooled analysis.

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%

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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.

**Table 18: Index Bladder Cancer Cases in Phase 2b/3 Clinical Program**

Study ID (Country)	Dapa Dose (mg)	Age (y)	Gender	Exposure (Days)	Tumor Type/Stage*†/Grade#	Tobacco Use	Prior Pioglitazone Use	Baseline Hematuria **
<b>DAPAGLIFLOZIN TREATMENT ARMS</b>								
D1692C00005-1-11 (Japan)	2.5	75	Male	43	Papillary/T2/G2	50 pack-years	No	Positive, Occult
D1690C00006-1004-6 (Austria)	5	63	Male	358	TCC/Ta/G2	100 pack-years	No	Negative
MB102014-34-524 (Canada)	5	60	Male	512	TCC/Ta/Low	25 pack-years	No	Positive: Occult (w/ureteric calculus)
MB102030-90-880 (Argentina)	5	67	Male	144	TCC/T2/Mod	No	Yes	Positive: Trace
D1690C00004-4916-2 (Germany)	10	76	Male	727	TCC/T1/G3	20 pack-years	No	Negative
D1690C00006-1501-6 (Hungary)	10	67	Male	399	TCC/NA/G2	No	No	Positive: Occult
D1690C00006-2206-14 (United States)	10	66	Male	581	TCC/NA/Low	53 pack-years	No	Negative
D1690C00018-7831-5 (United States)	10	48	Male	74	TCC/Noninvasive/Low	34 pack-years	No	Negative**
D1690C00018-7401-9 (China)	10	55	Male	169	TCC/Noninvasive/NA	No	No	Positive: Trace
<b>CONTROL ARMS</b>								
D1690C00019-1016-7 (Canada)	—	66	Male	136	Papillary/ Microinvasive/High	50 pack-years	No	Positive: Occult
<b>BLADDER CANCER CASES OCCURRING AFTER THE NOVEMBER 2012 INTEGRATED DATABASE LOCK</b>								
D1693C00005-6706-14 (Slovakia)	10	53	Female	114	TCC/G1	40 pack-years	No	Positive: Trace

Source: Modified from the October 3, 2013, DOP/OHOP Memorandum of Consultation.

Abbreviations: GNA, not available; 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.

† Primary Tumor Stage: Ta and T1, non-muscle-invasive (superficial); and T2, muscle invasive; and NA, not available.

# Grade: G1 or Low (well-differentiated); G2 (moderately differentiated); and G3, High (poorly differentiated).

### **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 in 38 countries outside of the United States (i.e., the European Union, Australia, Mexico, New Zealand, Brazil, and Argentina), Vigibase, the World Health Organization global individual case safety report database system, was also searched. A total of 113 FAERS reports for all adverse events 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 (mean age among five patients with bladder cancer was 73 years; range 64-79), and therefore inference on causality from spontaneous reports is severely limited. No cases were identified in the medical literature 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.

The limited postmarketing data and medical literature do not provide reassurance that there isn't a causal association between dapagliflozin and bladder cancers. In concurrence with the oncology consultant, the risk for bladder cancer should be further studied and carefully monitored. The Applicant proposes to do so in the postmarketing setting, with additional long-term clinical trial safety data, including blinded adjudication of bladder cancer events, and heightened pharmacovigilance. On December 12, 2013, the EMDAC concurred that additional studies are warranted. The safeguards proposed by the Applicant may be acceptable, pending further review and input from OSE. Additionally, in Section 6.3 (Risk Mitigation) of the Applicant's Background Document (dated November 4, 2013) it states that "potential risks for dapagliflozin will be clearly described in the proposed label, package insert, and medication guide for patients with instructions and recommendations to ensure safe use." (b) (4)

The Warnings and Precautions section of product labeling will need to adequately inform prescribers and patients of these events and the uncertain association with dapagliflozin. Further, the informed consent documents for clinical studies conducted with dapagliflozin should also appropriately inform potential study participants.

#### **7.3.4.2 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; all treated patients)
- Breast: 0.45% vs. 0.21%; IRR 2.47 (95% CI, 0.64 to 14.10; females only)
- 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 twelve 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 patients were typically overweight/obese, Caucasian females over age 50, with a current or past history of smoking. Study days of diagnoses for the 12 breast cancer cases occurring in patients receiving dapagliflozin ranged from six to 722 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 19) and by study across the pool of 2b/3 clinical trials (

Table 20) are provided below. Two of the 12 dapagliflozin-treated patients were diagnosed with invasive ductal breast cancer on study days six and sixteen, and therefore temporal association with dapagliflozin was unlikely. Two patients were diagnosed by mammography, although only three patients appear to have had routine screening. The tumors for nine of the twelve cases in patients who received dapagliflozin were estrogen receptor positive (i.e., suggestive of relatively slow-growing tumors), and progesterone receptor positivity also was reported in seven.

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); the IRR had been 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%).<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup>

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,<sup>18</sup> 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

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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.”

In the Summary Basis for Regulatory Action, dated January 17, 2012, Dr. Curtis Rosebraugh stated the following:

“I do not think that the breast cancer risk identified for dapagliflozin is at the level of magnitude that would require further pre-marketing evaluation and I found the updated safety data reassuring. If this were the only issue we faced, I would allow marketing and have postmarketing study for further reassurance. This decision is based on a relatively low risk ratio generated by few events, which decreased with additional exposure data and experience that we have had in the past where signals of this magnitude eventually were disproven.”

The Applicant proposes to continue to evaluate the occurrence of all malignancies, including breast cancers, in their ongoing CV outcomes trial and pharmacoepidemiology study, as well as through enhanced pharmacovigilance in countries where dapagliflozin is already approved. Based on the recommendations of the oncology consultant, as well as previous and updated information and data, this approach may be reasonable, but will also require further review and input from OSE.

In summary, there did not appear to be an obvious imbalance in the overall incidence of malignancies between dapagliflozin and the all comparator treatment arms (Table 20). Several tumor types were diagnosed more frequently in dapagliflozin-treated patients, of which an imbalance in breast cancers was a concern during the first review cycle. However, the risk ratio has declined, and several other factors are not suggestive of a causal relationship. The lack of screening mammography prior to study entry in a population at risk for breast cancer, and a diagnosis within the first year of exposure to dapagliflozin for the majority of patients, make an association with dapagliflozin less likely.

**Table 19: Malignant Breast Cancer Events**

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

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Patient ID Age/Sex/Race/Smoking Status/BMI/Estrogen Use Prior to Randomization	Treatment	Tumor Type	Grade	TNM <sup>a</sup>	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Weight Change (kg)	Study Day of Diagnosis
<b>D1690C00010-2009-3</b> 73/F/White/Never/28/No	Comparator	Invasive, lobular carcinoma	2	T3, N3a	Positive	Positive	Negative	-4.7	57
<b>D1690C00018-7841-5</b> 60/F/Asian/White/Former/40/No	Comparator	Infiltrating ductal breast cancer	1-2	T1c, N0, M0	Positive,	Positive,	Negative	-2.5	113
<b>D1690C00019-7833-2</b> 60/F/White/Former/49/No	Comparator	Ductal carcinoma in situ <sup>f</sup>	1	T1, N0, M0	Positive	Positive	NA	-3.1	347
<b>NEW EVENTS AFTER 15-JULY-2011 DATABASE CUT-OFF</b>									
<b>D1690C00019-3315-11</b> 75/F/White/Former/33/No	Dapa 10 mg	Invasive ductal carcinoma	1	T2, N0	Positive	Positive	Positive	-0.2	687
<b>D1690C00019-7841-9</b> 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; HER2/neu, human epidermal growth factor receptor 2; 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. T, primary tumor size (Tx, Tis, T0-T4); N, absence/presence of regional lymph node involvement (Nx, N0-N3); and M, absence/presence of distant metastasis (M0-M1).

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.

**Table 20: 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‡	
		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

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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‡	
		Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)
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
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	51	12/2693 Females	3/1439 Females	9/1626 Males	1/1150 Males
								IRR = 1.030 (95% CI, 0.711, 1.506) ¶		IRR = 2.472 (95% CI, 0.636, 14.095) ¶		IRR = 5.428 (95% CI, 0.712, 245.10) §	

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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)
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.

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

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

\* Median or range of medians across treatment arms.

\*\* Cohort 1 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).

§ The IRR based on all treated patients for trials with at least one event (i.e., 2814 dapagliflozin-treated patients vs. 1880 controls) is 5.168 (95% CI, 0.677 to 233.55); 30-MU, Part 3 (page 16745/18333, labeled as Appendix 322). 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: 10/2923 v. 1/1989; **IRR = 6.111 (95% CI, 0.827, 272.02)** with inclusion of both genders.

### 7.3.4.3 Hepatic Safety

Dr. John Senior of the Drug-Induced Liver Disease (DILI) Team/OSE was consulted on August 22, 2013, to review the hepatic safety of dapagliflozin clinical program. This section includes some of the findings and recommendations from this consultation.

During the first review cycle, no imbalances in the numbers of patients experiencing marked transaminase elevations were observed between dapagliflozin and control treatment arms. However, hepatic safety of dapagliflozin was initially questioned following a single case of biochemical Hy's Law, defined as a serum ALT  $\geq 3$ x ULRR with serum total bilirubin (TBL)  $\geq 2$ x the ULRR. This case involved a 78-year-old Indian male exposed to 2.5 mg of dapagliflozin. The patient had been diagnosed with compound heterozygous hemochromatosis, and his baseline ALT values were mildly elevated. Transaminases began to increase approximately 3 months after initiating drug, and peaked at an ALT of over 1800 IU/L at Day 200, associated with a TBL of 4.2 mg/dL. Dapagliflozin was discontinued on Day 192. The patient subsequently developed abdominal pain, nausea and jaundice. A liver biopsy was performed on Day 264. The biopsy report had features suggestive of autoimmune hepatitis but other laboratory tests to support this diagnosis were negative. Serology did not support a viral etiology. The patient was treated with high-dose corticosteroids starting on Day 349, at which point, hepatic enzymes had already been declining. The opinions of three hepatology consultants to the Applicant were mixed concerning the cause of the patient's abnormal liver tests.

In the first review cycle, following a thorough review by Agency hepatologists for alternative etiologies, this event was classified as "probable" drug-induced liver disease 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.

In the Dispute Appeal-Denied Letter, 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 current Response to CRL, the Applicant has 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 experienced hepatologists resulted in



reclassification of the event as “probable” autoimmune hepatitis, although possible drug-associated autoimmune hepatitis could not be ruled out. The updated case summary from the Hepatic Adjudication Report is provided below.

### **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 across the All Phase 2b/3 safety database, or in patients who exhibited potential hepatocellular injury with liver dysfunction, defined here as an AST or ALT >3x ULRR, and a TBL >3x ULRR. Also, there were no major shifts in proportions of patients experiencing these events since the previous review (Table 21).

The narratives for the dapagliflozin-treated patients meeting criteria of hepatocellular injury with liver dysfunction and for cases of dapagliflozin-treated patients with marked elevations in transaminase concentrations (i.e., >10x the upper laboratory reference limit) were reviewed to assess possible associations with dapagliflozin. For the cases associated with dapagliflozin exposure, a dose-response relationship was not noted. However, this was difficult to assess definitively because the numbers of patients exposed to the 2.5 and 5 mg doses of dapagliflozin were relatively small compared to the number of patients exposed to 10 mg.

**Table 21: Marked Liver Laboratory Test Abnormalities - All Phase 2b/3 Pool**

<b>LFT Abnormality</b>	<b>30-MU Dapa Total N=5936 X/N# (percent)</b>	<b>30-MU All Control N=3403 X/N# (percent)</b>	<b>Major Amendment Dapa Total N=5466 X/N# (percent)</b>	<b>Major Amendment All Control N=3161 X/N# (percent)</b>
Patients with Elevated LFTs	255/5895 (4.3)	152/3380 (4.5)	242/5501 (4.4)	133/3161 (4.2)
<b>AST</b>				
>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)
<b>ALT</b>				
>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)

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<b>LFT Abnormality</b>	<b>30-MU Dapa Total N=5936 X/N# (percent)</b>	<b>30-MU All Control N=3403 X/N# (percent)</b>	<b>Major Amendment Dapa Total N=5466 X/N# (percent)</b>	<b>Major Amendment All Control N=3161 X/N# (percent)</b>
<b>Total Bilirubin &gt; 2x ULRR</b> >2x ULRR	22/5894 (0.4)	11/3379 (0.3)	20/5465 (0.4)	4/3160 (0.1)
<b>Biochemical Hy's Law</b> 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)
<b>ALP</b> >3x ULRR	8/5894 (0.1)	6/3380 (0.2)	—	—

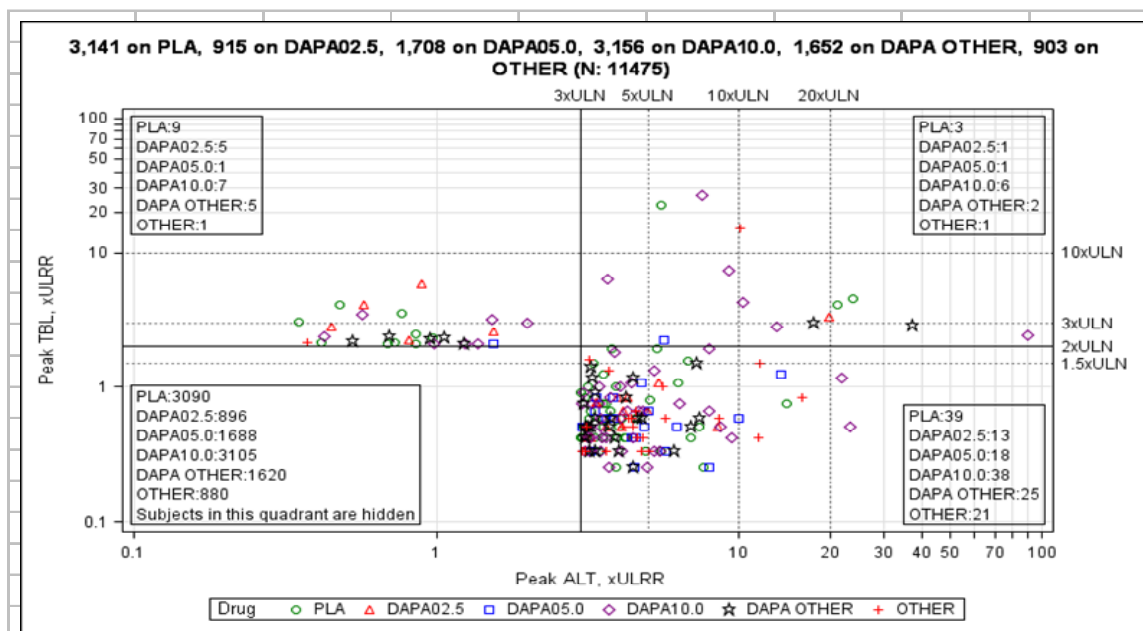
Source: Modified from the Applicant's 30-Month Update, Part 2 (pages 16952-3 of 18920, labeled as Appendix 337) and NDA Major Amendment Clinical Review (page 20 of 42, labeled Table 15).

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.

In this NDA, the Applicant provided a series of datasets for entry into eDISH by Dr. Ted Guo, but only the latest dataset, labeled by the Applicant as DAPN95, was reviewed by Dr. Senior. Since the previous review cycle, there were 4,993 additional patients added (i.e., 2918 receiving various doses of dapagliflozin and 2077 on comparators). The eDISH step 1 graph below (Figure 5) contains a total of 11,475 patients (10,279 of whom were in the left lower quadrant of normal or nearly normal peak ALT and TBL values, and are “hidden” to reduce large computer memory requirements for these data). Dr. Senior noted that there were 28 patients who showed some TBL elevation, but no ALT rise of significance (left upper quadrant). There were considerably more patients for whom ALT peak elevations were observed at some time during study, including two >20x ULRR and >10x but <20x ULRR, with no rise in TBL (right lower quadrant). The patients of most interest were the fourteen patients in the right upper quadrant who had evidence of both hepatocellular injury (ALT >3x ULRR) and liver dysfunction (TBL >2x ULRR). These patients had a time course plot of all available liver test data during the observation period (step 2 of the eDISH program), and the narrative clinical information for each was reviewed for assessment of a potential diagnosis (step 3 eDISH program). Ten of these fourteen patients had been previously evaluated during the first review cycle, and only one patient (Patient D1690C00004-4402-6; right-most star in the right upper quadrant) with an ALT 38.9x ULRR and TBL 3.0x ULRR was felt to have been a probable case of DILI during the first review cycle (updated case narrative provided below).

**Figure 5: eDISH Step 1 Graph**



Source: Reproduced from the Clinical Consultation Review by Dr. John Senior, OPE/OSE (page 5 of 17).

In addition to liver laboratory test abnormalities, it appeared that dapagliflozin-treated patients and controls were relatively balanced for liver AEs (1.6% vs. 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 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 assessment 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 adverse event (SAE/AE) in subjects who prematurely discontinued study treatment due to any AE/SAE

4. Liver-related SAE or liver-related 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 22).

**Table 22: 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 (all adjudicated as “possibly” related to study medication) 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)

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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  $\geq$ 5X ULRR and ALT  $\geq$ 1.5X baseline (Study Day 29) possibly related to study drug."

This patient received concomitant acyclovir therapy, which may be associated with liver laboratory test abnormalities. Despite continuation of dapagliflozin therapy, ALT returned to normal by Day 57.

**"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."

This patient had peak elevations of ALT of 145 IU/L (3.9x ULRR) which were slightly above normal by Day 195. No treatment was required.

**"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  $\leq$ 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."

This patient reported excessive alcohol use at the time of ALT elevations. Elevations in ALT resolved without interruption in dapagliflozin therapy.

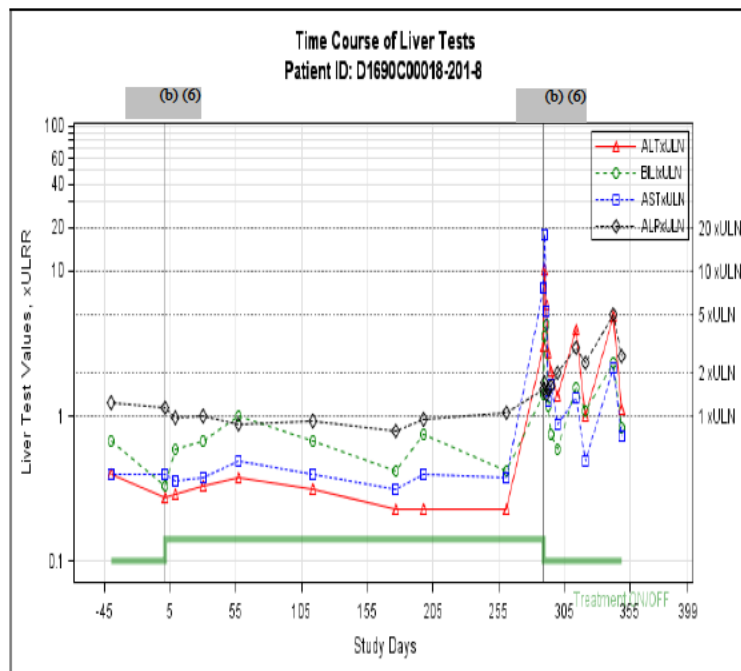
Additionally, 14 adjudicated events (10 in patients receiving dapagliflozin 2.5-10 mg and four in patients treated with placebo) met the combined definition for biochemical Hy's Law (i.e., AST/ALT  $>$ 3x ULRR and TBL  $>$ 2x ULRR) in the Phase 2/3 clinical trials. The HAC classified two events as possibly 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** (Figure 6), 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."

**Figure 6: Time Course of Liver Tests for Patient D169000018-201-8**

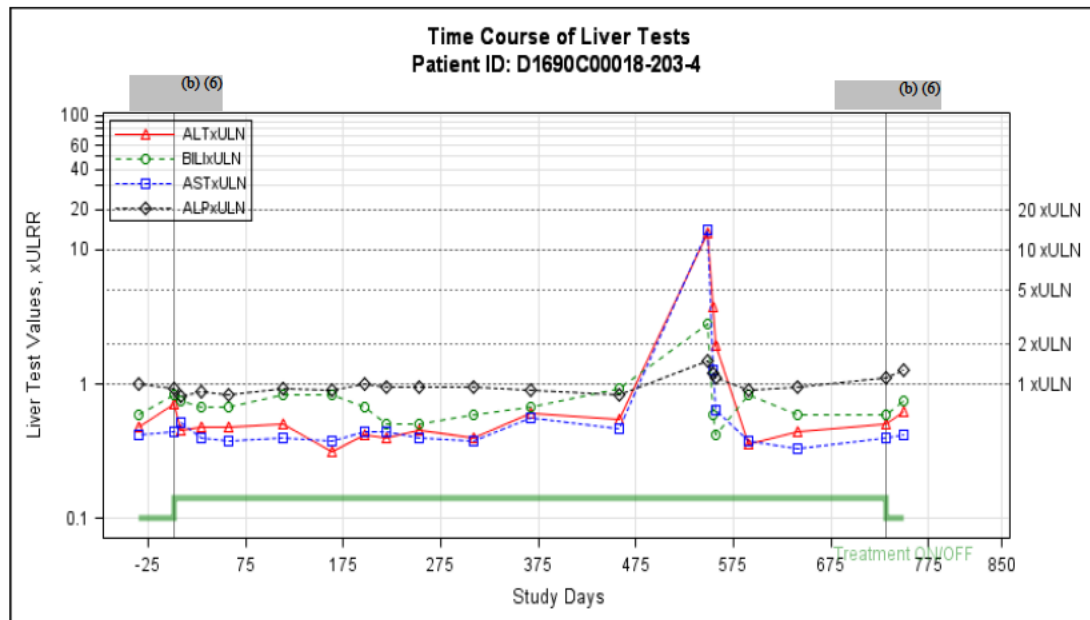


Source: Reproduced from the Clinical Consultation Review by Dr. John Senior, OPE/OSE (page 9 of 16).

Dr. Senior noted that this patient tolerated dapagliflozin for approximately 36 weeks without liver test abnormalities before developing both symptoms and laboratory abnormalities. He noted that biliary tract disease was clinically suspected in this patient, but this was not very well proven.

“**Patient D1690C00018-203-4** (Figure 7), 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.”

**Figure 7: Time Course of Liver Tests for Patient D169000018-203-4**

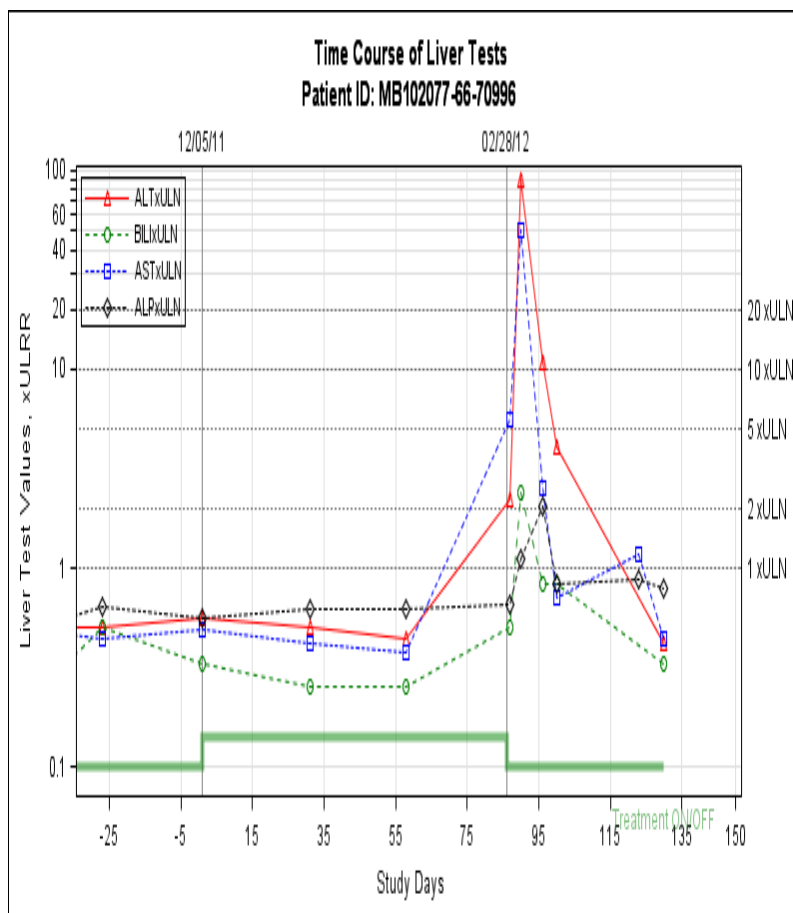


Source: Reproduced from the Clinical Consultation Review by Dr. John Senior, OPE/OSE (page 6 of 16).

Dr. Senior noted that liver tests had remained within the normal range for approximately 1.5 years before markedly rising on Day 549 (ALT 13.4x ULRR, AST 14x ULRR, ALP 1.5x ULRR, and TBL 3.4x ULRR). This patient had a history of gallstones, and ultrasound examination on Day 550 revealed multiple gallbladder lithiasis, ultimately requiring cholecystectomy. Dapagliflozin therapy was not interrupted, and the patient was managed with scopolamine. The liver tests abnormalities improved without dechallenge of study medication.

“**Patient MB102077-88-70996** (Figure 8), 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.”

**Figure 8: Time Course of Liver Tests for Patient MB102077-66-70996**



Source: Reproduced from the Clinical Consultation Review by Dr. John Senior, OPE/OSE (page 10 of 16).

Dr. Senior felt that this was clearly not a drug-induced problem but an acute viral infection that is fairly prevalent in India. He concurred with the actions of the investigators and opinion of the HAC that concluded this was almost certainly due to viral hepatitis E and not dapagliflozin-induced.

In summary, Dr. Senior considered that all three dapagliflozin-treated patients who showed both ALT >3x ULRR and TBL >2x ULRR, had other diagnoses that were considerably more likely than dapagliflozin to have caused the test abnormalities. Additionally, Dr. Leonard Seef had also previously evaluated all other cases that met the criteria of an ALT >3x ULRR and TBL >2x ULRR, and for these cases it was felt that another etiology was more likely than dapagliflozin exposure. Dr. Senior also noted that no increases in minor ALT elevations of clinical consequence due to dapagliflozin have been found.



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

“**Patient D1690C00004-4402-6** (Figure 9), 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. 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. 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.”

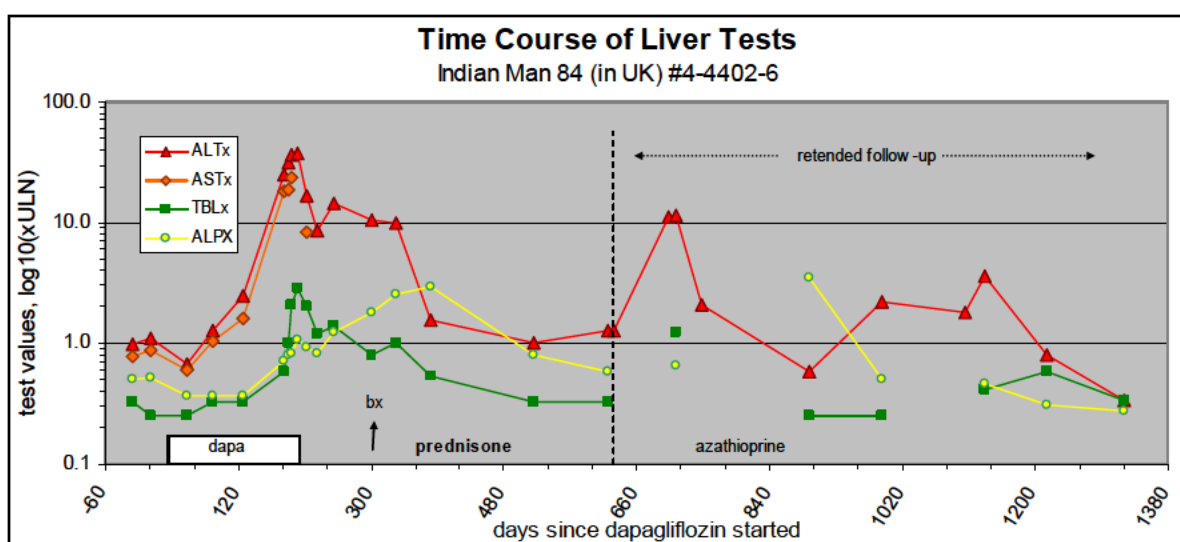
Based on the additional follow-up information provided for this case, the following excerpt is reproduced from the clinical consultation review of Dr. John Senior:

“Case D1690C00004-4402-6, the Indian male living and followed in the UK at site 4402, is now 84, and is still being followed more than 5.5 years since he started dapagliflozin, and almost five years since it was stopped. He has continued to have smoldering liver disease with occasional flares, and has been treated with azathioprine and occasional steroids for autoimmune hepatitis. The most recent data on liver tests was on (b) (6) January 2012, eighteen months before the resubmission of NDA 202293. Consultations were requested from Drs. Paul Watkins and Willis Maddrey, who had much more data than did Dr. Seeff or the other consultants when the NDA was

originally submitted in 2011, as stated in the Hepatic Adjudication Report of 13 June 2013. With the much longer follow-up and clinical responses to treatment, it has become clear that the patient has autoimmune hepatitis. Whether it was coincidental that the first serious manifestation was triggered by exposure to dapagliflozin is controversial, and is complicated by his low-grade underlying hemochromatosis.”

The graphic plot of the time course of liver tests for patient D1690C00004-4402-6 is depicted in Figure 9 below. Dr. Senior noted that this time course shows recurring peaks of liver inflammation not associated with dapagliflozin, and characteristic of autoimmune hepatitis.

**Figure 9: Clinical Follow-up of Patient D1690C00004-4402-6**



Source: Reproduced from the Clinical Consultation Review by Dr. John Senior, OPE/OSE (page 6 of 16).

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 23.

**Table 23: 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 <sup>a</sup> (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	Unlikely (UPDATED) <sup>e</sup>

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Patient ID(Age/Gender/Race)	Treatment Group	Criteria Meeting Adjudication	Final Adjudicated Causality Assessment
		discontinued	
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 <sup>b</sup> (59/M/Asian)	Placebo	AST and/or ALT > 5X ULN	Excluded (UPDATED) <sup>e</sup>
D1690C00018-2608-6 (58/M/White)	Dapagliflozin 10 mg	AST and/or ALT > 5X ULN	Unlikely
D1690C00018-6109-11 <sup>c</sup> (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) <sup>e</sup>
D1692C00006-4307-6 (59/M/Asian)	Dapagliflozin 5 mg	Liver-related SAE/AE in patient who discontinued	Unlikely
D1692C00012-8-8 <sup>*</sup> (51/F/Asian)	Dapagliflozin 5-10 mg	Liver-related SAE/AE in patient who discontinued	Possible
D1692C00012-33-11 <sup>*</sup> (61/M/Asian)	Dapagliflozin 5-10 mg	AST and/or ALT > 3X ULN and TBL > 1.5X ULN	Unlikely
D1692C00012-34-30 <sup>*</sup> (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) <sup>e</sup>
MB102073-275-968 <sup>b</sup> (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 <sup>d</sup> (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) <sup>e</sup>
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).

<sup>a</sup> Patient D1690C00012-211-12 diagnosed with cholangiocarcinoma with possible lesion present by MR day -21 prior to study.

<sup>b</sup> Patient D1690C00018-1005-3 was "inconsistently included in the tables and text and the narrative" and was omitted.

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- <sup>c</sup> 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.
- <sup>d</sup> Patient MB102077-66-70996 was diagnosed with Grade II Hepatitis E that the HAC excluded from a relationship with study drug.
- <sup>e</sup> Updated information provided since the previous review cycle.
- <sup>\*</sup> 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

In summary, Dr. Senior recommended that dapagliflozin product labeling should reflect the concerns of the Division, and that patients should be warned of these concerns. He also noted that there is no good justification for requiring any periodic monitoring (e.g., monthly ALT testing). Rather, he suggested that patients should be informed to report any early symptoms of possible liver injury or dysfunction (e.g., anorexia, fatigue, nausea, dark urine, vomiting, yellowish sclera, right upper, epigastric or other abdominal discomfort) to their healthcare providers immediately. Further, with the presence of symptoms, therapy should be temporarily interrupted while prompt investigation is undertaken to assess for possible liver injury due to dapagliflozin therapy.

### **Postmarketing Reports and Medical Literature**

In response to the August 22, 2013 consultation request, Dr. Chamberlain also evaluated postmarketing reports in the 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.

In summary, the majority of patient cases with marked elevations of both serum transaminase and total bilirubin, had other diagnoses that were more likely than dapagliflozin to have caused the test abnormalities. Additionally, elevations in ALT concentrations were generally balanced across treatment groups. The long-term follow-up for the possible case of DILI is supportive of a diagnosis of autoimmune hepatitis; however, an association with dapagliflozin cannot be entirely excluded for this case. No additional safety signals were identified from either postmarketing reports or the medical literature. Overall, a hepatic safety signal was not obvious; however, the Applicant's proposed enhanced pharmacovigilance program in the postmarketing setting to further evaluate the potential hepatotoxicity of dapagliflozin is reasonable.

#### **7.3.4.4 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 (MACE-plus), 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, that is placebo and active controls (Table 24). 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 the findings of a possible risk reduction in CV events, 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

(submitted as a Major Amendment in October 2011) included the same primary composite endpoint, as well as a secondary analysis of 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 (Table 24), 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).<sup>1</sup>

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  $\geq 65$  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 1.27; 95% CI, 0.69 to 2.31) from the pool of these two trials did not favor dapagliflozin, and were discordant with the overall results from the updated meta-analysis (Table 24). 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, for Studies 18 and 19, 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 24), 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 (Figure 10).

**Table 24: Meta-Analysis Results of Composite Primary and MACE Endpoints  
(Original NDA, Major Amendment, 30-Month Safety Update)**

Study Endpoints	Number of CV Events (Dapa/Comparator)	HR (95% CI)
<i>All Phase 2b/3 Study Pool</i>		
<b>ORIGINAL NDA (JULY 2011 EMDAC MEETING)</b> (14 Clinical Trials; N=4287 dapagliflozin vs. N=1941 comparator)		
Primary Composite Endpoint	78 (48/30)	0.67 (95% CI, 0.38, 1.18)



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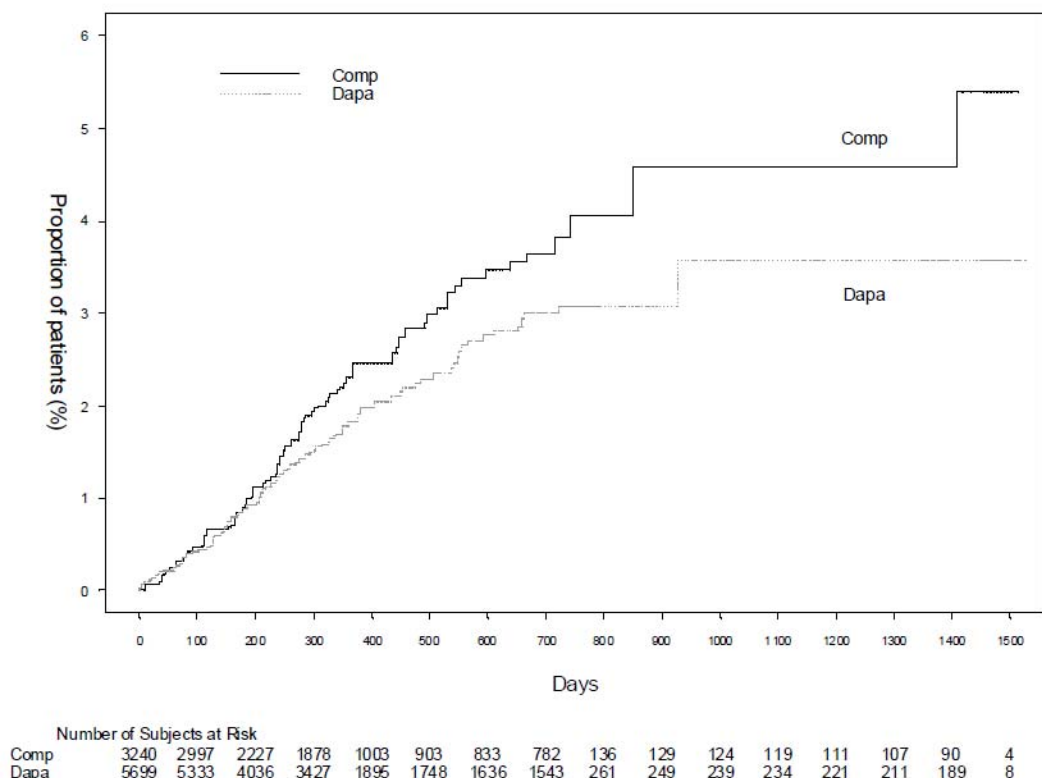
Study Endpoints	Number of CV Events (Dapa/Comparator)	HR (95% CI)
MACE	64 (37/27)	0.60 (95% CI, 0.32, 1.10)
<b>MAJOR AMENDMENT</b> (19 Clinical Trials; N=5498 dapagliflozin vs. N=3184 comparator)		
Primary Composite Endpoint	145 (82/63)	0.82 (95% CI, 0.58, 1.15)
MACE	111 (62/49)	0.79 (95% CI, 0.54, 1.17)
<b>30-MONTH SAFETY UPDATE</b> (21 Clinical Trials; N=5936 dapagliflozin vs. N=3403 comparator)		
Primary Composite Endpoint	178 (97/81)	0.81 (95% CI, 0.59, 1.09)
MACE	135 (73/62)	0.78 (95% CI, 0.55 to 1.11)
<b><i>Patients with a History of CV Disease Excluding D1690C00018 and D1690C00019 (All Phase 2b/3 Study Pool)</i></b>		
<b>30-MONTH SAFETY UPDATE</b> (21 Clinical Trials; N=919 dapagliflozin vs. N=417 comparator)		
Primary Composite Endpoint	42 (25/17)	0.53 (95% CI, 0.28, 1.02)
MACE	34 (18/16)	0.41 (95% CI, 0.20, 0.84)
<b><i>Pool of Studies D1690C00018 and D1690C00019</i></b>		
<b>MAJOR AMENDMENT</b> (19 Clinical Trials; N=942 dapagliflozin vs. N=945 comparator)		
Primary Composite Endpoint	60 (31/29)	1.07 (95% CI, 0.64, 1.77)
MACE	43 (24/19)	1.27 (95% CI, 0.69, 2.31)
<b>30-MONTH SAFETY UPDATE</b> (21 Clinical Trials; N=942 dapagliflozin vs. N=945 comparator)		
Primary Composite Endpoint	87 (43/44)	0.98 (95% CI, 0.64, 1.49)
MACE	61 (32/29)	1.11 (95% CI, 0.67, 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 and Statistical Review and Evaluation by Dr. Eugenio Andraca-Carrera.  
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.

**Figure 10: Cumulative Probability of the Primary CV Composite Endpoint Over Time All Dapagliflozin vs. All Comparator Pools (ST+LT Treatment Period)**



Source: Applicant's Supplemental CV Events Meta-Analysis Report, (page 40 of 990, labeled as Figure 1).  
Abbreviations: Comp, all comparator treatment arm; CV, cardiovascular; Dapa, dapagliflozin; LT, long-term; and ST, short-term.

In his review, Dr. Andraca-Carrera 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 (Table 25). 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 and numerous risk factors, of whom four were enrolled in Studies D1690C00018 and D1690C00019. Review of the narratives did not reveal predisposing risk factors for these events. The Applicant was also unable to identify an etiology or risk factors associated with early events.

**Table 25: Dapagliflozin-Treated Patients with Early ( $\leq 30$  Days) Major Cardiovascular Events**

Patient ID	Event	Treatment	Exposure (Days)	Age/ Race/ Gender	Medical History / Risk Factors
MB102067-201-12 (D1690C00018)	CV death	Dapa 10 mg + Metformin	2	77/W/F	<ul style="list-style-type: none"> <li>Alzheimer disease</li> <li>CAD</li> <li>Diabetic retinopathy</li> <li>HTN</li> <li>MI</li> </ul>
MB102033-1902-7 (D1690C00006)	Stroke	Dapa 10 mg + Insulin + Metformin	3	43/W/F	<ul style="list-style-type: none"> <li>Chronic bronchitis</li> <li>Chronic venous insufficiency</li> <li>Diabetic neuropathy</li> <li>Dyslipidemia</li> <li>Hepatic steatosis</li> <li>HTN</li> <li>Obesity</li> <li>Tobacco use (12.5 pack-year)</li> </ul>
MB102067-8403-7 (D1690C00018)	Stroke	Dapa 10 mg + SU + Metformin	3	58/A/M	<ul style="list-style-type: none"> <li>CVA</li> <li>HTN</li> <li>Tobacco use (22.5 pack-year)</li> </ul>
MB102067-7808-1 (D1690C00018)	Hospitalization for unstable angina	Dapa 10 mg + Insulin + Metformin	4	59/W/F	<ul style="list-style-type: none"> <li>CABG</li> <li>CAD</li> <li>Carotid artery disease</li> <li>Carotid endarterectomy or stenting</li> <li>Diabetic retinopathy</li> <li>Dyslipidemia</li> <li>HTN</li> <li>MI</li> </ul>
MB102021-6-125	MI	Dapa 5 mg	9	55/W/F	<ul style="list-style-type: none"> <li>Dyslipidemia</li> <li>HTN</li> </ul>
MB102021-39-17	MI	Dapa 5 mg	19	68/W/M	<ul style="list-style-type: none"> <li>Carotid calcification</li> <li>DVT</li> <li>Dyslipidemia</li> <li>HTN</li> <li>PVD</li> </ul>
MB102034-34-41	Hospitalization for unstable angina	Dapa 10 mg + Metformin	22	55/W/M	<ul style="list-style-type: none"> <li>Coronary artery stenosis (75% mid-LAD and 95% distal-LAD)</li> <li>Dyslipidemia</li> <li>HTN</li> <li>Tobacco use (23 pack-year)</li> </ul>

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Patient ID	Event	Treatment	Exposure (Days)	Age/ Race/ Gender	Medical History / Risk Factors
MB102080-3301-19 (D1690C00019)	Stroke	Dapa 10 mg	28	70/W/M	<ul style="list-style-type: none"> <li>• Arteriosclerosis universalis</li> <li>• CABG</li> <li>• CAD (stable angina and hospitalization for unstable angina)</li> <li>• Dyslipidemia</li> <li>• HTN</li> <li>• MI</li> <li>• PCI</li> <li>• Tobacco use (12 pack-year)</li> </ul>

Source: Modified from the Statistical Review Background Information from Dr. Eugenio Andraca-Carrera (page 148 of 175, labeled as Table 9), and the Applicant's Cardiovascular Events Meta-analysis Report (pages 285-980 of 990, labeled as Appendix B).

Abbreviations: Afib, atrial fibrillation; A, Asian; B, black; CABG, coronary artery bypass graft; CAD, coronary artery disease; CV, cardiovascular; CVA, cerebrovascular accident; DVT, deep vein thrombosis; F, female; HTN, hypertension; LAD, left anterior descending; M, male; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SU, sulfonylurea; W, white.

In summary, since the original NDA submission, the Applicant has conducted two updated meta-analyses, each with similar results for the primary composite endpoint of MACE-plus and secondary composite endpoint of MACE (i.e., HR point estimates less than 1.0 and an upper bound of the 95% CI excluding both 1.8 and 1.3, consistent with the 2008 FDA Guidance).<sup>1</sup> The updated CV safety analyses also included a new meta-analysis of the pool of Trials D1690C00018 and D1690C00019, which was updated to include data from individuals who had continued in the controlled extension phases of these two trials. In these trials, statistically significant reductions in HbA1c, systolic blood pressure, and body weight were reported. Although the point estimate and upper bound 95% CI for the HR of the composite MACE endpoint were lower in the 30-MU than those reported at the time of the Major Amendment, they nonetheless continue to exceed 1 and 1.8, respectively (i.e., HR 1.11; 95% CI, 0.67 to 1.83). This raises a question as to whether dapagliflozin could produce a cardiovascular benefit with prolonged use in patients with established CV disease or conversely increase CV risk in a subset of these patients.

It should be noted that imbalance of CV events was observed within the first 30 days of treatment with dapagliflozin, with seven primary events (plus one secondary) observed among 5936 subjects randomized to dapagliflozin (0.12%) and two primary events (plus two secondary events) among 3403 subjects randomized to comparators (0.06%). For the dapagliflozin-treated patients, the majority of these early events occurred in patients with established peripheral and/or cardiovascular disease, of whom four were enrolled in Trials D1690C00018 and D1690C00019. A similar observation of an early imbalance in CV events was also observed with canagliflozin. On December 13, 2013, the EMDAC reviewed these data and concluded that dapagliflozin relative to comparators has an acceptable CV risk profile (9.3 Advisory Committee Meeting). However, several members acknowledged that the existing data were not sufficient to rule out a potential risk. The Applicant is currently conducting a CV outcomes trial (i.e., Dapagliflozin Effect

on Cardiovascular Events [DECLARE; TIMI-58; Study D1693C00001]) to provide these data.

### *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-C) (4-5%) and high density lipoprotein cholesterol (HDL-C) (approximately 4% increase). Mean changes in lipid parameters for the placebo-controlled trials at Week 24 (ST Pool) and Week 102 (ST+LT Pool) are presented in Table 26. The LDL-C changes were similar to those reported by Dr. Liu in the integrated analyses (Table 11). Long-term clinical consequences associated with these changes are not known.

**Table 26: 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)
<b>TC (mg/dL)</b>				
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
<b>LDL-C (mg/dL)</b>				
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
<b>HDL-C (mg/dL)</b>				
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

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)
<b>Triglycerides (mg/dL)</b>				
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; N, sample size; SD, standard deviation; SE, standard error; ST, short-term study pool; ST+LT, and short-term plus long-term study pool.

### 7.3.5 Submission Specific Primary Safety Concerns

Adverse events (AEs) of special interest included hypoglycemia, genital and urinary tract infections, renal impairment, volume depletion, polyuria, and fractures. This section will review these events.

#### 7.3.5.1 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 15). 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.

### 7.3.5.2 Genital Infections

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.

Comparison of genital infection 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 27 and Table 28, respectively. As noted during the first review cycle and anticipated with SGLT2 inhibitors, dapagliflozin treatment arms were associated with increased risk for genital infections compared the placebo treatment arms for both the placebo-controlled ST (i.e., 5.5% vs. 0.6%, respectively) and ST+LT (7.7% vs. 1%, respectively) study pools. Also consistent with the previous findings from data submitted during the first review cycle, genital infection events were more common in females (8.4-11.5% vs. 1.2-1.9% in dapagliflozin and control arms, respectively) than in males (3.4-4.9% vs. 0.2-0.3%, respectively) and typically resolved with treatment. Events of vulvovaginal mycotic infections and balanitis were the most common genital infections reported for women and men, respectively. In the ST pool, approximately 5.3% and 0.7% of dapagliflozin-treated and placebo-treated patients received antimicrobial therapy for the treatment of genital infections. Approximately 17% of patients experienced a second infection in the 10 mg dapagliflozin treatment arm, with a total of two patients having three infections each 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).

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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 11). 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 27. Events of Genital Infections in Placebo-Controlled Studies (ST 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 (%)
<b>TOTAL NUMBER (%) PATIENTS WITH GENITAL INFECTION EVENTS</b>	<b>130 (5.5)</b>	<b>14 (0.6)</b>	<b>33 (4.1)</b>	<b>65 (5.7)</b>	<b>57 (4.8)</b>	<b>167 (5.1)</b>	<b>12 (0.9)</b>
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 FOR GENITAL INFECTION	125/2360 (5.3)	12/2295 (0.7)	—	—	—	—	—
RECURRENT INFECTIONS*	22/130 (16.9)	1/15 (7.1)	—	—	—	—	—
<b>PREFERRED TERMS</b>							
VULVOVAGINAL MYCOTIC INFECTION**	34 (3.4)	7 (0.7)	8 (2.0)	13 (2.2)	20 (3.3)	45 (2.7)	5 (0.7)
BALANITIS***	29 (2.1)	0	4 (1.0)	7 (1.2)	7 (1.2)	18 (1.1)	1 (0.1)
VAGINAL INFECTION**	18 (1.8)	1 (0.1)	6 (1.5)	14 (2.4)	10 (1.7)	33 (2.0)	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 (0.8)	1 (0.1)	3 (0.8)	10 (1.7)	4 (0.7)	18 (1.1)	1 (0.1)
BALANITIS CANDIDA***	6 (0.4)	0	2 (0.5)	2 (0.4)	2 (0.3)	7 (0.4)	0
VULVOVAGINITIS**	5 (0.5)	0	2 (0.5)	4 (0.7)	3 (0.5)	9 (0.5)	0
GENITAL CANDIDIASIS	3 (0.1)	0	0	3 (0.3)	2 (0.2)	5 (0.2)	0
VULVITIS**	2 (0.2)	0	2 (0.5)	1 (0.2)	1 (0.2)	4 (0.2)	0
BALANOPOSTHITIS***	1 (0.1)	1 (0.1)	0	1 (0.2)	0	2 (0.1)	0
GENITAL INFECTION MALE***	1 (0.1)	0	0	0	1 (0.2)	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 (0.2)	2 (0.1)	0
POSTHITIS***	1 (0.1)	0	0	1 (0.2)	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 denominator represents the number of patients who had at least one genital infection; \*\*the denominator represents females only; \*\*\* the denominator represents males only.



**Table 28: Events of Genital Infections in Placebo-Controlled Studies (ST+LT Pool)**

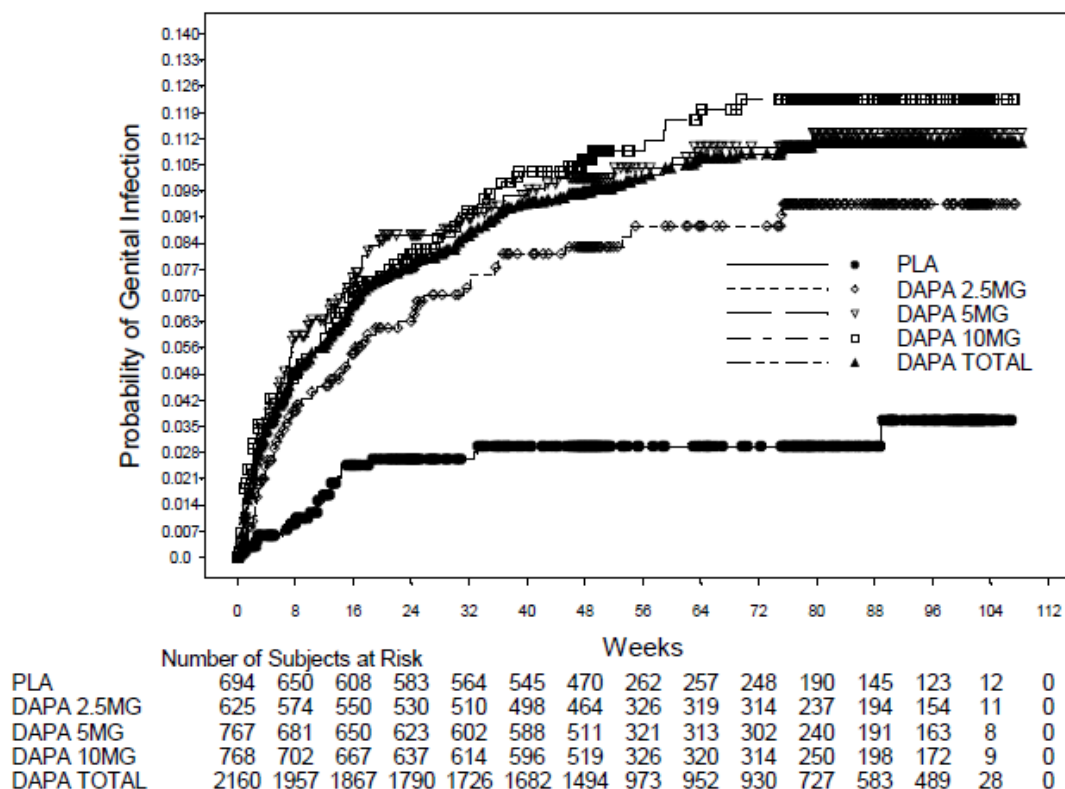
Event	30-MU		4MSU				
	Dapa 10 mg N=2026 (%)	Placebo N=1956 (%)	Dapa 2.5 mg N=625 (%)	Dapa 5 mg N=767 (%)	Dapa 10 mg N=859 (%)	Dapa Total N=2251 (%)	Placebo N=785 (%)
<b>TOTAL NUMBER (%) PATIENTS WITH GENITAL INFECTION EVENTS</b>	<b>156 (7.7)</b>	<b>19 (1.0)</b>	<b>40 (6.4)</b>	<b>68 (8.9)</b>	<b>68 (7.9)</b>	<b>176 (7.8)</b>	<b>10 (1.3)</b>
FEMALES	98/852 (11.5)	15/799 (1.9)	27/313 (8.6)	54/388 (13.9)	45/447 (10.1)	126/1148 (11.0)	10/387 (2.6)
MALES	58/1174 (4.9)	4/1157 (0.3)	13/312 (4.2)	14/379 (3.7)	23/412 (5.6)	50/1103 (4.5)	0/398
<b>PREFERRED TERMS</b>							
VULVOVAGINAL MYCOTIC INFECTION**	38 (4.5)	8 (1.0)	6 (2.0)	16 (4.1)	18 (4.0)	40 (3.5)	6 (1.6)
BALANITIS***	36 (3.1)	0	6 (2.0)	6 (1.6)	12 (2.9)	24 (2.2)	0
VAGINAL INFECTION**	21 (2.5)	1 (0.1)	6 (2.0)	18 (4.6)	12 (2.7)	36 (3.1)	1 (0.3)
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 (0.3)
VULVOVAGINAL CANDIDIASIS**	11 (1.3)	1 (0.1)	5 (1.6)	9 (2.3)	7 (1.2)	21 (1.8)	0
BALANITIS CANDIDA***	8 (0.7)	0	3 (1.0)	1 (0.3)	4 (1.0)	8 (0.7)	0
VULVOVAGINITIS**	8 (0.9)	1 (0.1)	4 (1.3)	5 (1.3)	4 (1.0)	13 (1.1)	0
GENITAL CANDIDIASIS	7 (0.3)	0	0	2 (0.3)	4 (0.5)	6 (0.3)	0
BALANOPOSTHITIS***	4 (0.3)	1 (0.1)	1 (0.3)	1 (0.3)	1 (0.2)	3 (0.3)	0
GENITOURINARY TRACT INFECTION	3 (0.1)	2 (0.1)	0	1 (0.1)	0	1 (<0.1)	0
VULVAL ABSCESS**	3 (0.4)	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.3)
VULVITIS**	3 (0.4)	0	2 (0.6)	1 (0.3)	2 (0.4)	5 (0.4)	0
PENILE INFECTION***	2 (0.2)	0	0	0	1 (0.2)	1 (0.1)	0
GENITAL INFECTION FEMALE	1 (0.1)	0	0	0	1 (0.2)	1 (0.1)	0
GENITAL INFECTION MALE***	1 (0.1)	0	0	0	1 (0.2)	1 (<0.1)	0
PENILE ABSCESS***	1 (0.1)	0	0	0	0	0	0
POSTHITIS***	1 (0.1)	0	1 (0.3)	1 (0.3)	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 denominator represents females only; \*\*\*the denominator represents males only.

**Figure 11: Time to First Event of Genital Infection in the Short-Term plus Long-Term Placebo-Controlled Pool**



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).

In summary, genital infections were more frequent in dapagliflozin treatment arms than for patients randomized to placebo for the placebo-controlled trials. Use of antimicrobial therapy for treating genital infections and recurrent events was also more common among dapagliflozin-treated patients. Females were at greater risk than males for genital infections, with vulvovaginal mycotic infections and balanitis reported as the most common genital infections among females and males, respectively. Withdrawals due to genital infection events were more common in dapagliflozin treatment arms, but no events were considered serious or severe, and infections could be managed adequately with antimicrobial therapy.

### 7.3.5.3 Urinary Tract Infections

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.

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 ST (i.e., 4.7% vs. 3.5%, respectively) and ST+LT (8.6% vs. 6.7%, respectively) study pools (Table 29 and Table 30). 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 ST 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 ST 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 with a UTI 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).

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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 12).

**Table 29: 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 (%)
<b>TOTAL NUMBER (%) PATIENTS WITH UTI EVENTS</b>	<b>110 (4.7)</b>	<b>81 (3.5)</b>	<b>29 (3.6)</b>	<b>65 ( 5.7)</b>	<b>51 (4.3)</b>	<b>158 (4.8)</b>	<b>52 (3.7)</b>
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)
FEMALES	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)
MALES							
<b>PREFERRED TERMS*</b>							
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)

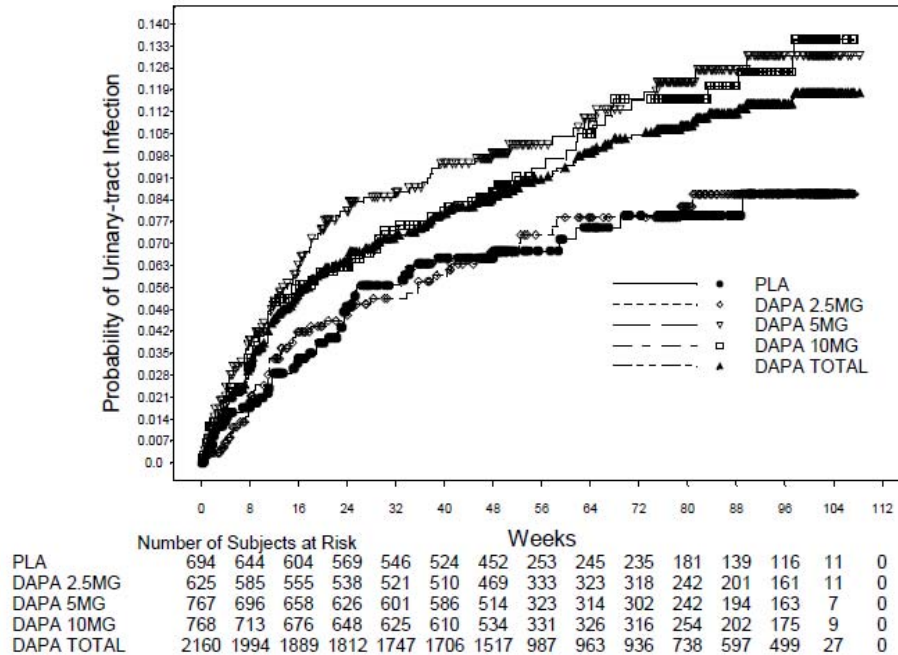
Source: Modified from the Applicant's 30-MU (pages 109-110 of 200, labeled as Tables 38 and 39) and the October 25, 2013 Response to FDA Request for Information.  
Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; N, sample size; and UTI, urinary tract infection.

**Table 30: 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 (%)
<b>TOTAL NUMBER (%) PATIENTS WITH UTI EVENTS</b>	<b>174 (8.6)</b>	<b>121 (6.2)</b>	<b>37 (5.9)</b>	<b>64 ( 8.3)</b>	<b>65 (7.6)</b>	<b>166 ( 7.4)</b>	<b>49 (6.2)</b>
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)
<b><i>PREFERRED TERMS</i></b>							
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.

**Figure 12. Time to First Urinary Tract Infection Event - Placebo-Controlled Short-Term plus Long-term Pool**



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).

As anticipated with the known safety profile of SGLT2 inhibitors, there was an increased risk for UTIs among dapagliflozin-treated patients compared to patients randomized to placebo treatment arms for both the ST and the ST+LT placebo-controlled study pools. Similar to the risk for genital infections, the occurrence of UTIs was higher among females than in males, and was usually managed with antimicrobial therapy. Serious AEs (e.g., pyelonephritis or urosepsis) or withdrawals due to UTIs was limited, with the majority of patients experiencing a single UTI event. Events were manageable with antimicrobial therapy.

### 7.3.5.4 Renal Impairment and Volume Depletion Events

#### Renal Impairment

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 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. The renal impairment/failure events are presented for the All Phase 2b/3 (Table 31), and ST (Table 32) and ST+LT (Table 33) placebo-controlled study pools.

The dapagliflozin clinical development program included 4906 patients with mild renal impairment, defined as an estimated glomerular filtration rate (eGFR)  $\geq 60$  to  $< 90$  mL/min/1.73 m<sup>2</sup>, and 1070 patients with a baseline eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>. Since efficacy is limited with significant renal dysfunction, patients with severe renal impairment, defined as an eGFR  $< 30$  mL/min/1.73 m<sup>2</sup> 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. Across the All Phase 2b and 3 Pool (N=9339), events of renal failure/impairment, as defined based on the MedDRA query described above (of which most preferred terms represented changes in renal function), were similar between dapagliflozin and control arms, and there were fourteen SAEs of renal impairment, nine (0.2%) in dapagliflozin-treated patients (i.e., renal failure n=8; creatinine clearance decreased n=1) and five (0.1%) in the all controls arm (i.e., renal failure n=4; anuria n=1). Compared to placebo, adverse events of renal impairment/failure were reported more frequently in dapagliflozin treatment arms for the ST (3.2% in the dapagliflozin-treated patients vs. 1.8% with placebo) and the ST+LT (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. Across all three study pools, the proportions of patients with marked renal function laboratory abnormalities (defined as blood urea nitrogen  $> 60$  mg/dL or urea  $> 21.4$  mmol/L, serum creatinine  $\geq 1.5$ x pretreatment creatinine or serum creatinine  $> 2.5$  mg/dL) were relatively infrequent for both treatment arms. Of these laboratory abnormalities, serum creatinine elevations of  $\geq 1.5$ x pretreatment creatinine concentrations occurred in the highest proportions of dapagliflozin and all comparator treatment arms, but the frequency of events were relatively small (i.e.,  $< 3.8\%$  and  $< 3.5\%$ , respectively, across all study pools).



In subgroup analyses, dapagliflozin-treated patients from the ST and ST+LT placebo-controlled study pools, as well as the All 2b/3 pool, who were 65 years of age or older 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 observed in the placebo-controlled ST+LT study pool (Figure 13). Events of renal impairment/failure were observed in 14% vs. 7.9% of patients 65 years of age or older, 28% vs. 16.1% for those with moderate renal impairment, and 35.1% and 19.1% for those with both baseline characteristics for dapagliflozin and placebo treatment arms, respectively. 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<sup>2</sup>). However, these data were limited for adequate assessment of dose-response relationships in these patient subsets.

**Table 31: Events of Renal Impairment/Failure and Laboratory Abnormalities in the All Phase 2b/3 Study Pool**

Event	30-MU	
	Dapa 10 mg N=5936 (%)	Placebo N=3403 (%)
NUMBER (%) OF PATIENTS WITH RENAL IMPAIRMENT/FAILURE EVENTS	235 (4.0)	130 (3.8)
<65 years old	101/4512 (2.2)	45/2424 (1.9)
≥65 years old	134/1424(9.4)	85/979 (8.7)
eGFR ≥60 mL/min/1.73 m <sup>2</sup>	27/2094 (1.3)	17/2025 (0.8)
eGFR 30 to <60 mL/min/1.73 m <sup>2</sup>	114/668 (17.1)	58/387 (15.0)
<65 years old and eGFR ≥60 mL/min/1.73 m <sup>2</sup>	55/4188 (1.3)	27/2244 (1.2)
≥65 years old and eGFR 30 to <60 mL/min/1.73 m <sup>2</sup>	69/348 (19.8)	40/211 (19.0)
<b>PREFERRED TERMS</b>		
CREATININE RENAL CLEARANCE DECREASED	66 (1.1)	41 (1.2)
RENAL IMPAIRMENT	66 (1.1)	37 (1.1)
BLOOD CREATININE INCREASED	54 (0.9)	26 (0.8)
GLOMERULAR FILTRATION RATE DECREASED	20 (0.3)	12 (0.4)
RENAL FAILURE	19 (0.3)	10 (0.3)
RENAL FAILURE ACUTE	7 (0.1)	3 (0.1)
CYSTATIN C INCREASED	4 (0.1)	0
CREATININE RENAL CLEARANCE ABNORMAL	3 (0.1)	2 (0.1)
URINE FLOW DECREASED	3 (0.1)	0
RENAL FAILURE CHRONIC	2 (<0.1)	1 (<0.1)
RENAL FUNCTION TEST ABNORMAL	2 (<0.1)	0
URINE OUTPUT DECREASED	2 (<0.1)	1 (<0.1)
ACUTE PRERENAL FAILURE	1 (<0.1)	0
BLOOD CREATININE ABNORMAL	1 (<0.1)	0
GLOMERULAR FILTRATION RATE ABNORMAL	1 (<0.1)	0
OLIGURIA	1 (<0.1)	0
OBSTRUCTIVE UROPATHY	1 (<0.1)	0
ANURIA	0	1 (<0.1)
<b>MARKED LABORATORY ABNORMALITIES – RENAL FUNCTION</b>		
BUN >60 mg/dL or Urea >21.4 mmol/L	29/5879 (0.5)	12/3368 (0.4)
Creatinine ≥1.5X Pre-treatment Creatinine	190/5868 (3.2)	117/3362 (3.5)
Creatinine ≥2.5 mg/dL	29/5868 (0.5)	18/3362 (0.5)

Source: December 11, 2013, Response to FDA Request for Information (pages 1-49).

Abbreviations: 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate by MDRD equation; and N, sample size.

**Table 32: Events of Renal Impairment/Failure and Laboratory Abnormalities in Placebo-Controlled Studies (ST 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 (%)
<b>NUMBER (%) OF PATIENTS WITH RENAL IMPAIRMENT/FAILURE EVENTS</b>	<b>76 (3.2)</b>	<b>42 (1.8)</b>	<b>11 (1.4)</b>	<b>15 (1.3)</b>	<b>11 (0.9)</b>	<b>38 (1.2)</b>	<b>12 (0.9)</b>
<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 <sup>2</sup>	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 <sup>2</sup>	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 <sup>2</sup>	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 <sup>2</sup>	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)
<b>PREFERRED TERMS*</b>							
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)
<b>MARKED LABORATORY ABNORMALITIES – RENAL FUNCTION</b>							
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 mg/dL	2 (0.1)	1 (<0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)

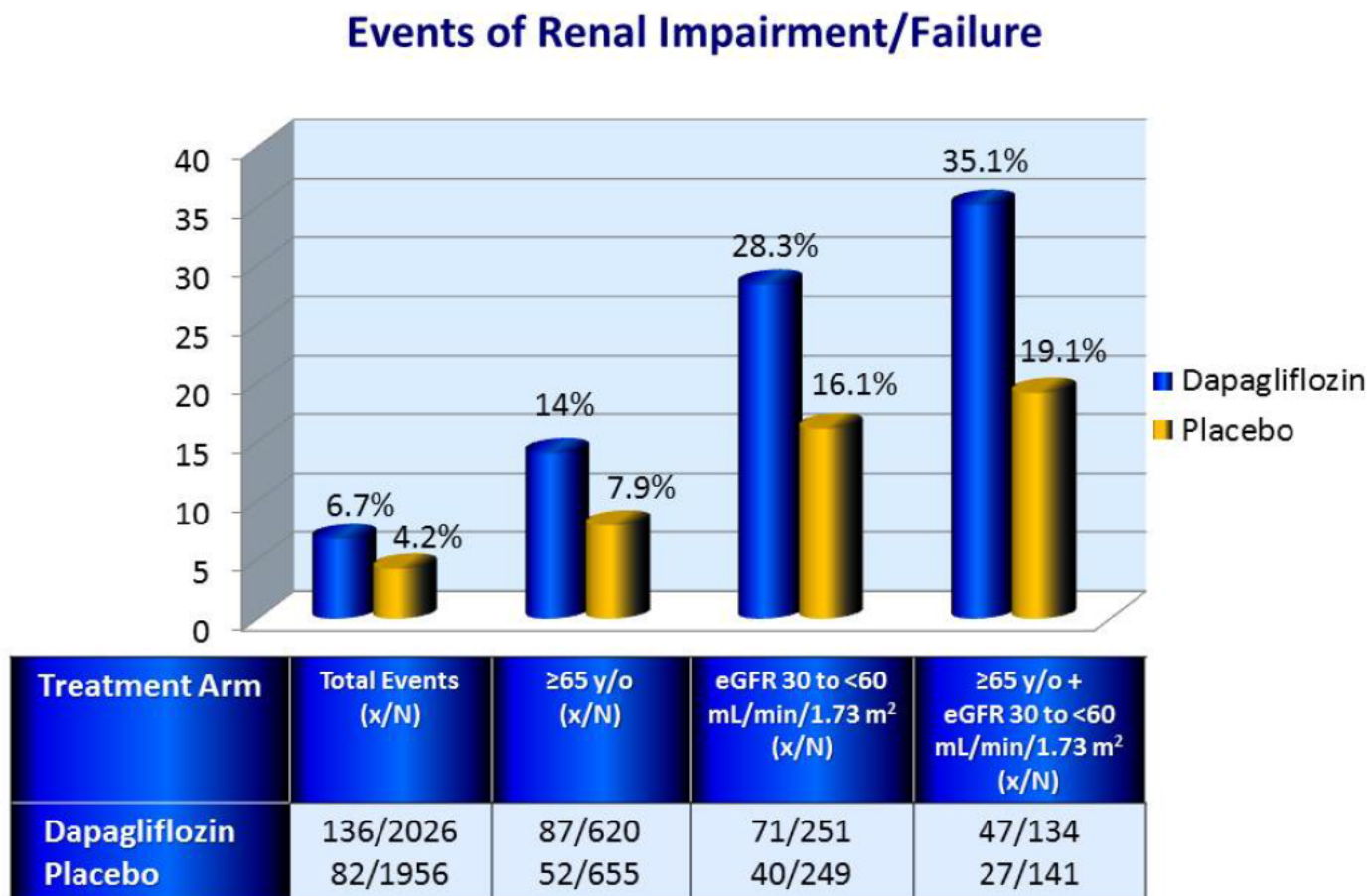
Source: Modified from the Applicant's 30-MU (pages 125-136 of 200, labeled as Tables 46, 47, 49, 50, 51, 52 and 53) and the October 25, 2013 Response to FDA Request for Information. Abbreviations: 4MSU, 4-Month Safety Update; 30-MU, 30-Month Update; Dapa, dapagliflozin; eGFR, estimated glomerular filtration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

**Table 33: Events of Renal Impairment/Failure and Laboratory Abnormalities in Placebo-Controlled Studies (ST+LT 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 (%)
<b>NUMBER (%) OF PATIENTS WITH RENAL IMPAIRMENT/FAILURE EVENTS</b>	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 <sup>2</sup>	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 <sup>2</sup>	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 <sup>2</sup>	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 <sup>2</sup>	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)
<b>PREFERRED TERMS*</b>							
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)
<b>MARKED LABORATORY ABNORMALITIES – RENAL FUNCTION</b>							
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 mg/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.

**Figure 13. Events of Renal Impairment/Failure by Baseline Characteristics in Placebo-Controlled Trials (ST+LT Pool)**



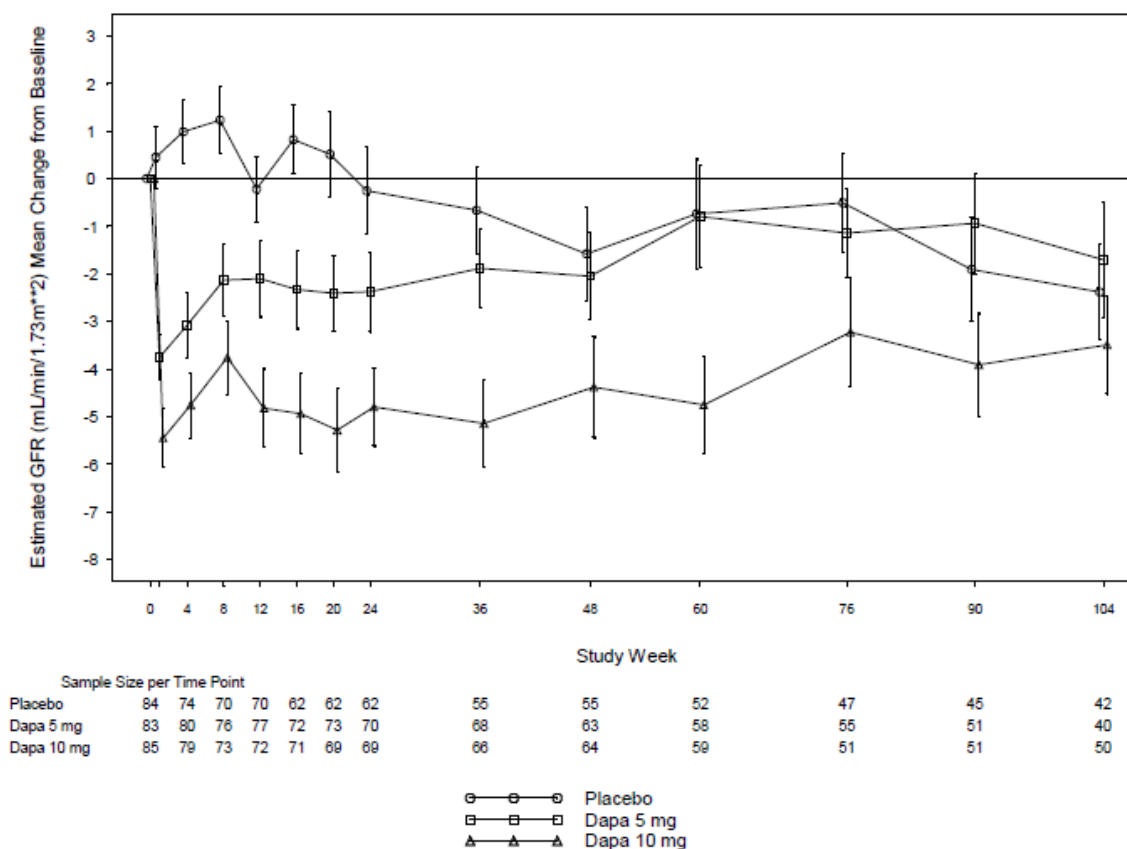
Source: Modified from the Applicant's 30-Month Update (pages 124-36)

MedDRA PTs ≥1% (Dapa ≥ Placebo): Creatinine renal clearance decreased (2.3% vs. 1.4%), renal impairment (1.9% vs. 1.1%)

**Figure Legend:** The Applicant used a customized MedDRA query to search for events of renal impairment and renal failure, which are depicted in the graph. The sets of columns from left to right represent the proportion of patients with renal impairment/failure adverse events for the total population and for the patient subsets who were ≥65 years of age; had estimated glomerular filtration rates (eGFRs) between 30 to <60 mL/min/1.73 m²; and were ≥ 65 years of age with an eGFRs between 30 to <60 mL/min/1.73 m². In subgroup analyses, patients who were over age 65 or had moderate renal impairment at baseline appeared to be at increased risk for renal impairment/failure events, with the highest proportion of events reported in individuals with both baseline characteristics.

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<sup>2</sup>). In this clinical trial, dapagliflozin 10 mg daily was associated with a -4.46 mL/min/1.73 m<sup>2</sup> change from baseline in mean eGFR compared to -2.58 mL/min/1.73 m<sup>2</sup> with placebo. Reductions in eGFR occurred by the first week of treatment and persisted throughout the 104-week treatment period, and were greater in the dapagliflozin 10 mg daily dose group than the dapagliflozin 5 mg and placebo treatment arms throughout the 104 week treatment period (Figure 14). Refer to Clinical Pharmacology Review by Dr. Jain for further details of this study. As noted earlier, the Applicant proposes that dapagliflozin not be used in patients with an eGFR <60 mL/min/1.73 m<sup>2</sup>.

**Figure 14. Mean (SE) Change from Baseline in Estimated GFR (mL/min/1.73m<sup>2</sup>) – Study MB102029 Short-Term plus Long-Term Pool**



**Source:** Source: December 11, 2013, Response to FDA Request for Information (pages 43 of 49, labeled as Figure 16). Abbreviations: Dapa, dapagliflozin; GFR, glomerular filtration rate; and SE, standard error.

In summary, impairment of renal function is a known effect of SGLT2 inhibitors, including dapagliflozin. Because of limited efficacy and increased risk for adverse events (e.g., further renal impairment, volume depletion), the Applicant recommends that dapagliflozin not be initiated in patients with an eGFR of  $<60$  mL/min/1.73 m<sup>2</sup>. Patients over 65 years of age, those with renal impairment, or those who have both of these patient characteristics appear to be at greatest risk for renal impairment/failure AEs. Renal function should be evaluated prior to initiation of dapagliflozin, and monitored periodically thereafter, with discontinuation of therapy for persistent eGFR determinations of  $<60$  mL/min/1.73 m<sup>2</sup>.

### **Volume Depletion (hypotension/ hypovolemia/ dehydration)**

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 (refer to Table 34 and Table 35).

Across the All Phase 2b/3 Study Pool, events of volume depletion were similar between dapagliflozin (i.e., 1.6%; 97/5936) and control (i.e., 1.3%; 43/3403) arms, but were more frequent in dapagliflozin-treated patients receiving loop diuretics (i.e., 6.1% vs. 3.9%, respectively). In the placebo-controlled ST and ST+LT 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  $\geq 65$  years of age, receiving loop diuretics or having moderate renal insufficiency (i.e., eGFR 30 to  $\leq 60$  mL/min/1.73 m<sup>2</sup>). Although there is an imbalance in events among these patient subsets, the total number of events is small, which limits conclusions. 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 suggests that the numbers were limited to adequately assess a 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% (8/1193) and 0.6% (7/1145) of patients who received dapagliflozin 10 mg and 5 mg, respectively, compared with 0.4% (5/1393) 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/1.73m<sup>2</sup> were limited, making any inference regarding dose-response difficult.

In summary, volume depletion events were more common among dapagliflozin-treated patients compared to controls, with higher proportions of events observed for patients older than 65 years and those with renal impairment or who used loop diuretics. However, events were few for both treatment arms, making it difficult to adequately assess at-risk patient populations or a dose-response relationship. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Appropriate monitoring for orthostatic changes in blood pressure and symptoms (e.g., postural dizziness) in potentially vulnerable patient populations is recommended. Additionally, hemoconcentration in patients predisposed to thromboembolic events is an additional safety concern with SGLT2 inhibitors, including dapagliflozin. The Applicant proposes to continue to follow cardiovascular events in their dedicated CVOT, as well as through enhanced pharmacovigilance. These data will be necessary to adequately assess thromboembolic risks for vulnerable patient populations.



**Table 34: Events of Volume Depletion and Polyuria in Placebo-Controlled Studies (ST 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 (%)
<b>NUMBER (%) OF PATIENTS WITH VOLUME DEPLETION EVENTS</b>	<b>27 (1.1)</b>	<b>17 (0.7)</b>	<b>10 (1.2)</b>	<b>7 (0.6)</b>	<b>9 (0.8)</b>	<b>27 (0.8)</b>	<b>5 (0.4)</b>
<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	<b>11/665 (1.7)</b>	<b>6/771 (0.8)</b>	<b>5/193 (2.6)</b>	<b>1/216 (0.5)</b>	<b>3/204 (1.5)</b>	<b>8/631 (1.3)</b>	<b>1/276 (0.4)</b>
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	<b>6/236 (2.5)</b>	<b>4/267 (1.5)</b>	3/37 (8.1)	0/40	<b>3/31 (9.7)</b>	6/114 (5.3)	<b>1/55 (1.8)</b>
eGFR ≥60 mL/min/1.73 m <sup>2</sup>	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 <sup>2</sup>	<b>5/265 (1.9)</b>	<b>4/268 (1.5)</b>	<b>2/74 (2.7)</b>	<b>1/107 (0.9)</b>	<b>1/89 (1.1)</b>	<b>4/277 (1.4)</b>	<b>2/107 (1.9)</b>
<b>PREFERRED TERMS*</b>							
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	3 (0.4)	0	1 (0.1)	4 (0.1)	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)
<b>EVENTS OF POLYURIA**</b>							
<b>NUMBER (%) OF PATIENTS WITH POLYURIA EVENTS</b>	<b>78 (3.3)</b>	<b>27 (1.2)</b>	<b>18 (2.2)</b>	<b>33 (2.9)</b>	<b>45 (3.8)</b>	<b>103 (3.1)</b>	<b>24 (1.7)</b>
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)
<b>HEMATOLOGIC CHANGES FROM BASELINE TO END-OF-STUDY</b>							
<b>Hemoglobin (g/dL)</b> Mean ± SD Change from Baseline	0.62 ± 0.82	-0.14 ± 0.74	—	—	—	—	—
<b>Hematocrit (%)</b> 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	—	—	—	—	—
<b>Number (%) of Patients with Marked Abnormality of Hematocrit (&gt;55%) and/or Hemoglobin (&gt;18 g/dL)</b>	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\*

**Table 35: Events of Events of Volume Depletion and Polyuria in Placebo-Controlled Studies (ST+LT 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 (%)
<b>NUMBER (%) OF PATIENTS WITH VOLUME DEPLETION EVENTS</b>	<b>38 (1.9)</b>	<b>27 (1.4)</b>	<b>9 (1.4)</b>	<b>8 (1.0)</b>	<b>13 (1.5)</b>	<b>30 (1.3)</b>	<b>6 (0.8)</b>
<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 <sup>2</sup>	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 <sup>2</sup>	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)
<b>PREFERRED TERMS*</b>							
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)
<b>EVENTS OF POLYURIA**</b>							
<b>NUMBER (%) OF PATIENTS WITH POLYURIA EVENTS</b>	<b>79 (3.9)</b>	<b>28 (1.4)</b>	<b>17 (2.7)</b>	<b>28 (3.7)</b>	<b>42 (4.9)</b>	<b>87 (3.9)</b>	<b>18 (2.3)</b>
POLAKIURIA	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)
<b>HEMATOLOGIC CHANGES FROM BASELINE TO END-OF-STUDY</b>							
<b>Hemoglobin (g/dL)</b> Mean ± SD Change from Baseline	—	—	—	—	—	—	—
<b>Hematocrit (%)</b> 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
<b>Number (%) of Patients with Marked Abnormality of Hematocrit (&gt;55%) and/or Hemoglobin (&gt;18 g/dL)</b>	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.

### **Polyuria**

The Applicant used a customized MedDRA query for polyuria events using a prespecified list of preferred terms, pollakiuria, polyuria, urine output increased. 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 ST and ST+LT study pools (Table 34 and Table 35). 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 ST study pool, there were small increases in mean hematocrit values beginning at week 1 ( $0.55 \pm 0.05$ ) and continuing up to week 16 ( $2.32 \pm 0.06$ ) 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  $0.62 \pm 0.82$  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 ST (2% vs. 0.6%, respectively) and ST+LT (2.9% vs. 0.8%, respectively) study pools. During the first review cycle, mean ( $\pm$  SE) hematocrit ( $1.81 \pm 0.08\%$  vs.  $2.15 \pm 0.08\%$ ) and hemoglobin ( $0.47 \pm 0.03$  g/dL vs.  $0.58 \pm 0.03$  g/dL) changes from baseline to week 24 were increased with both the 5 and 10 mg dapagliflozin doses, respectively.

In summary, polyuria is a known adverse event associated with SGLT2 inhibitors, with increased adverse events of polyuria associated with dapagliflozin-treated patients in the placebo-controlled study pools. Although the occurrence and complications associated with these events are limited, one potential safety concern associated with these events may include possible nocturia in patients predisposed to falls (e.g., diabetic neuropathy, patients with orthostatic blood pressure changes, immobility).

#### **7.3.5.5 Bone Safety**

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 ( $0.04 \pm 0.49$  mg/dL vs.  $-0.01 \pm 0.52$  mg/dL for dapagliflozin 10 mg and placebo treatment arms respectively), parathyroid hormone ( $4.07 \pm 20.91$  pg/dL vs.  $1.36 \pm 17.12$  pg/dL, respectively) and 25-hydroxyvitamin D serum ( $-0.14 \pm 9.26$  ng/mL vs.  $-1.14 \pm 8.64$  ng/mL, respectively) were small and of uncertain clinical relevance. At Week 24, there was also a small increase in magnesium concentration with dapagliflozin 10 mg ( $0.09$  mEq/L) compared to placebo ( $-0.02$  mEq/L).

In Study D1690C00012, a 24-week placebo-controlled clinical trial with a 78-week extension phase, designed to evaluate the effects of dapagliflozin on bone mineral density (BMD), the Applicant reported no statistically significant changes (all  $p > 0.6$ ) in bone biomarkers (i.e., C-terminal cross-linking telopeptides of Type 1 collagen; N-terminal cross-linking telopeptides of Type 1 collagen; osteocalcin, or procollagen Type 1) or BMD (lumbar spine, femoral neck and total hip) at Week 102 of exposure to dapagliflozin. The mean placebo-subtracted change from baseline to Week 102 in BMD at the lumbar spine, femoral neck and total hip were 0.22 (-0.89, 1.34), -0.94 (95% CI, -2.21, 0.35) and -0.45 (-1.32, 0.43), respectively. It should be noted that a 5% change represents one standard deviation, and was used as a criteria to discontinue patients from study.

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 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 m<sup>2</sup>, 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. In recent correspondence with the Applicant, they stated that all fractures were related to falls. There were small increases in mean serum parathyroid hormone (PTH) concentration without apparent relationship to dose. 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. As previously noted, the Applicant proposes that the drug not be used in patients with an eGFR <60 mL/min/1.73 m<sup>2</sup>.

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.

In summary, the occurrence of fractures was relatively low, and balanced between dapagliflozin and placebo treatment arms in the placebo-controlled ST+LT clinical trials. Additionally, the changes in laboratory parameters associated with bone metabolism were small and of uncertain clinical relevance with long-term use of this product. 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]).

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

In the placebo-controlled ST study pool, treatment-emergent adverse events (TEAEs) reported in at least 2% of patients treated with dapagliflozin and occurring more commonly than in patients treated with placebo for the short-term study pool included hypoglycemia, genital infection, urinary tract infection, back pain, and polyuria (Table 36).

**Table 36: Common Adverse Events ( $\geq 2\%$ ) Occurring More Frequently than Placebo in the Placebo-Controlled Studies (ST Pool)**

Adverse Event	30-MU	
	Dapa 10 mg N=2360 (%)	Placebo N=2295 (%)
HYPOGLYCEMIA	309 (13.1)	242 (10.5)
GENITAL INFECTION	130 (5.5)	14 (0.6)
URINARY TRACT INFECTION	91 (3.9)	61 (2.7)
BACK PAIN	83 (3.5)	56 (2.4)
DIZZINESS	54 (2.3)	42 (1.8)
POLAKIURIA	49 (2.1)	16 (0.7)
INFLUENZA	47 (2.0)	44 (1.5)

Source: Modified from the Applicant's proposed product labeling and the Applicant's EMDAC Background Document, (page 68 of 128, labeled as Table 11).  
Abbreviations: 30-MU, 30-Month Safety Update.

### 7.4.2 Laboratory Findings

Several relevant laboratory abnormalities of interest (e.g., liver tests, renal function tests, blood glucose, lipid parameters, minerals, hemoglobin and hematocrit) have already been presented in other sections of this review. The clinical laboratory data submitted in this

NDA are consistent with what was previously submitted for the first review cycle, and marked laboratory abnormalities (MAs) were limited, and similar between treatment arms for the Placebo-Controlled Pools (ST and ST+LT).

The following criteria were used to define Marked Laboratory abnormalities:

- Creatinine  $\geq 2.5$  mg/dL
- Creatinine  $\geq 1.5$ x baseline
- Potassium (hypokalemia)  $\leq 2.5$  mEq/L
- Potassium (hypokalemia)  $\geq 6.0$  mEq/L
- Sodium (hyponatremia)  $< 120$  mEq/L
- Sodium (hypernatremia)  $> 150$  mEq/L
- Hematocrit  $> 55\%$
- Creatine kinase (CK)  $> 5$ x ULRR
- ALT  $> 5$ x ULRR
- ALT  $> 10$ x ULRR
- ALT or AST  $> 3$ x ULRR and TBL  $> 1.5$ x ULRR
- AST  $> 5$ x ULRR
- AST  $> 10$ x ULRR
- TBL  $\geq 2$ x ULRR

Since hyperkalemia has been associated with canagliflozin, especially in combination with ACE inhibitors, ARBs or potassium-sparing diuretics, the Applicant was asked to provide these same data for dapagliflozin. For the Placebo-Controlled ST Pool, MAs of potassium were reported in 6 (0.3%) vs. 1 ( $< 0.1\%$ ) dapagliflozin-treated patients and placebo, respectively, and in the ST+LT Pool MAs were reported in 6 (0.3%) vs. 5 (0.3%) patients, respectively. In the Applicant's two dedicated BP trials (MB102073 and MB102077) in which all patients received an ACE inhibitor or ARB, MAs of potassium were reported in 1.0% vs. 2.6% and 1.8% vs. 0% of dapagliflozin 10 mg and placebo groups in each study, respectively. Additionally, for patients with baseline eGFR  $< 60$  mL/min/1.73m<sup>2</sup>, MAs of potassium were observed in 3.4 vs. 4.9% and 4.9% vs. 6.1% of dapagliflozin-treated patients and controls in the ST and ST+LT Pools, respectively.

Data for the All Phase 2b/3 Study Pool is presented in Table 37 below.

**Table 37: Events of Hyperkalemia in the All Phase 2b/3 Study Pool**

Event	30-MU	
	Dapa 10 mg N=5936 (%)	Placebo N=3403 (%)
POTASSIUM $\geq 6.0$ MEQ/L	231/5880 (3.9)	137/3368 (4.1)
SUBGROUP WITH AES OF VOLUME DEPLETION	97/5936 (1.6)	43/3403 (1.3)
POTASSIUM $\geq 5.5$ MEQ/L	19/97 (19.6)	7/43 (16.3)
Hypovolemia without ACE/ARB use	2/19 (10.5)	0



Event	30-MU	
	Dapa 10 mg N=5936 (%)	Placebo N=3403 (%)
Hypovolemia with ACE/ARB use	17/19 (89.5)	7/7 (100)
Hypovolemia without potassium-sparing diuretic use	17/19 (89.5)	6/7 (85.7)
Hypovolemia with potassium-sparing diuretic use	2/19 (10.5)	1/7 (14.3)
SUBGROUP WITH AEs WITHOUT VOLUME DEPLETION	5839/5936 (98.4%)	3360/3403 (98.7)
POTASSIUM $\geq$ 5.5 MEQ/L	643/5839 (11.0)	411/3360 (12.2)
Hypovolemia without ACE/ARB use	196/643 (30.5)	108/411 (26.3)
Hypovolemia with ACE/ARB use	447/643 (69.5)	303/411 (73.7)
Hypovolemia without potassium-sparing diuretic use	614/643 (95.5)	367/411 (89.3)
Hypovolemia with potassium-sparing diuretic use	29/643 (4.5)	44/411 (10.7)
SUBGROUP WITH AEs WITH RENAL IMPAIRMENT/FAILURE	235/5936 (4.0)	130/3403 (3.8)
POTASSIUM $\geq$ 5.5 MEQ/L	48/235 (20.4)	29/130 (22.3)
Renal impairment/failure without ACE/ARB use	7/48 (14.6)	3/29 (10.3)
Renal impairment/failure with ACE/ARB use	41/48 (85.4)	26/29 (89.7)
Renal impairment/failure without potassium-sparing diuretic use	46/48 (95.8)	24/29 (82.8)
Renal impairment/failure with potassium-sparing diuretic use	2/48 (4.2)	5/29 (17.2)
SUBGROUP WITH AEs WITHOUT RENAL IMPAIRMENT/FAILURE	5701/5936 (96)	3273/3403 (96.2)
POTASSIUM $\geq$ 5.5 MEQ/L	614/5701 (10.8)	389/3273 (11.9)
Without ACE/ARB use	191/614 (31.1)	105/389 (27.0)
With ACE/ARB use	423/614 (68.9)	284/389 (73.0)
Without potassium-sparing diuretic use	585/614 (95.3)	349/389 (89.7)
With potassium-sparing diuretic use	29/614 (4.7)	40/389 (10.3)

Source: Source: December 11, 2013, Response to FDA Request for Information (pages 1-49).

### 7.4.3 Vital Signs

Mean changes from baseline in vital signs were consistent with those observed in the previous submission. Clinically meaningful changes in vital signs were not typically observed except for the anticipated changes in BP associated with SGLT2 inhibitors. In the Placebo-Controlled ST Study Pool, the mean change in seated SBP from baseline at Week 24 was -3.7 mmHg vs. -0.5 mmHg for the 10 mg dapagliflozin dose group compared to placebo. Mean seated diastolic blood pressure changes were -1.8 mmHg vs. -0.5 mmHg, respectively. Orthostatic hypotension was observed in 13.1% of dapagliflozin-treated patients compared to 11.3% of patients treated with placebo. In the two dedicated BP studies (MB102073 and MB102077), orthostatic hypotension was reported in 3.2% and 1.7% of patients in the dapagliflozin 10 mg and placebo treatment arms, respectively.

#### **7.4.4 Electrocardiograms (ECGs)**

During the first review cycle for this NDA, Dr. Dunn noted that there were limited differences between ECGs recordings at baseline and at weeks 12, 24, or 52, and no clinically relevant rhythm disturbances were observed in ECG recordings. In the Applicant's TQT study (D1690C00001), no clinically meaningful differences in the QTc intervals were observed between placebo and dapagliflozin 20 or 150 mg dose groups in healthy male subjects.

#### **7.4.5 Special Safety Studies/Clinical Trials**

There were no special safety studies submitted to the sNDA.

#### **7.4.6 Immunogenicity**

None

### **7.5 Other Safety Explorations**

No other safety explorations were performed.

#### **7.5.1 Dose Dependency for Adverse Events**

In this NDA resubmission, only data for the 10 mg dapagliflozin dose group was provided, and therefore dose dependency of dapagliflozin for AEs could not be assessed.

#### **7.5.2 Time Dependency for Adverse Events**

Discussion of AEs associated with both short- and long-term exposure to dapagliflozin is presented throughout this review.

#### **7.5.3 Drug-Demographic Interactions**

Limited safety analyses related to drug-demography interactions were performed with this NDA resubmission.



#### **7.5.4 Drug-Disease Interactions**

New safety analyses related to drug-disease interactions were not provided.

#### **7.5.5 Drug-Drug Interactions**

No new data regarding drug-drug interactions were submitted as part of this NDA resubmission. Refer to the original NDA or product labeling for information related to the potential for drug interactions with dapagliflozin.

### **7.6 Additional Safety Evaluations**

No additional safety explorations were performed in the clinical study or submitted to this NDA.

#### **7.6.1 Human Carcinogenicity**

The Applicant provided nonclinical data to provide support that dapagliflozin does not promote bladder tumor growth. Refer to Section 7.3.4.1 Bladder Cancer.

#### **7.6.2 Human Reproduction and Pregnancy Data**

No new reproduction or pregnancy data was provided with this submission. Dapagliflozin is a Pregnancy Category C drug.

#### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Studies in pediatric patients have not been completed. The Applicant is currently conducting a single-dose pharmacokinetic (PK) and pharmacodynamic (PD) clinical trial (i.e., MB102091) in pediatric patients with T2DM. Four patients have been enrolled into this clinical trial, and no deaths, serious adverse events (SAEs) or withdrawals due to AEs have been reported.

#### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

In Dr. Somya Dunn's clinical review, she noted that dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the maximum recommended human dose [MRHD]). In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for two weeks in healthy subjects and patients with T2DM, the incidence of hypoglycemia was slightly higher than

placebo and did not appear to be dose-related. However, dapagliflozin doses greater than 10 mg daily have been associated with increased AEs without additional efficacy.

The abuse potential of dapagliflozin has not been studied.

## 7.7 Additional Submissions / Safety Issues

There was a single 15-Day Safety Report to this NDA of a male patient (age not reported) who was hospitalized due to Stevens-Johnson syndrome (grade not provided). The patient developed a skin reaction while receiving dapagliflozin (duration of exposure not provided) which was diagnosed as Stevens-Johnson-like syndrome. A dermatology assessment was not available at the time of the submission. According to the Applicant, “intensive follow-up has been requested and further data is pending.”

The Applicant noted that as of October 2013, 10,750 patients have been exposed to dapagliflozin during clinical trials, and an additional (b) (4) patients have received dapagliflozin in Europe outside of clinical trials. In a search of the corporate safety database (CARES), they identified one additional case that involved a 68-year-old female who experienced bullous pemphigoid (confirmed by a dermatologist) following four weeks of dapagliflozin therapy for diabetes mellitus. This patient was also receiving vildagliptin. The Applicant assessed the case of pemphigoid as not related to dapagliflozin and possibly related to vildagliptin, based on its known safety profile.

A search of the AE datasets for this NDA, did not reveal any additional cases of Stevens-Johnson syndrome, and Dr. Christine Chamberlain was not able to identify other cases through searches using the FAERS database. Severe hypersensitivity reactions, including Stevens-Johnson syndrome will be included in an enhanced pharmacovigilance plan.

## 8 Postmarket Experience

This product is not approved in the United States. However, dapagliflozin is currently available in the European Union (EU, November 2012), Australia (October 2012), Mexico (March 2013), New Zealand (June 2013), Brazil (July 2013), and Argentina (September 2013). In this NDA resubmission, the Applicant reiterated a previous agreement with the Agency as stated below:

“As agreed with the Agency (NDA 202-293/SN0088 submitted on 26-Oct-2012), postmarketing data from these countries is not included with this resubmission since by the time of the datacut for the Complete Response Letter (CRL) NDA resubmission (15-Nov-2012), dapagliflozin had not yet been marketed in any country.”

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

Labeling negotiations and signatory review for this NDA are still pending at the time of this review, and therefore a detailed outline of all recommended revisions will not be included in this review. However, numerous sections of proposed dapagliflozin labeling will need to be extensively revised to be in alignment with the approved canagliflozin labeling, the only SGLT2 inhibitor currently approved in the U.S. Additionally, promotional statements, and statements that appear to minimize risk messages, will need to be removed throughout labeling. The following sections of proposed dapagliflozin labeling have been identified as needing substantive revisions:

1. **Section 2 Dosage and Administration:** The Applicant recommends the use of either a 5 or 10 mg dapagliflozin daily dose at any time of day, but advises initiating therapy with the 5 mg dose in patients at risk for volume depletion. Since glycemic efficacy has been demonstrated with the 5 mg dose, the preferred dose for initiation of therapy should be 5 mg once daily. This may help to minimize the risk for potential adverse events (e.g., volume depletion and renal impairment) in vulnerable patient populations. Further, it has been questioned whether evening administration of dapagliflozin may be associated with nocturia and the potential for falls in vulnerable patient populations (e.g., patients with diabetic neuropathy, experiencing orthostatic changes, poor mobility).
2. **Section 4 Contraindications:** There were no contraindications for the use of dapagliflozin included in the proposed labeling. We recommend that dapagliflozin be contraindicated for patients with a history of a serious hypersensitivity reaction to dapagliflozin and those with severe renal impairment, end stage renal disease or patients on dialysis. Serious hypersensitivity reactions have been observed in the dapagliflozin clinical program, and patients with severe renal dysfunction have limited efficacy and a predisposition to adverse events.
3. **Section 5 Warnings and Precautions:** The Applicant's proposed language for this section does not include any information regarding the observed imbalance in bladder cancers among patients exposed to dapagliflozin in the Applicant's clinical program. Patients and prescribers should be adequately informed about this potential safety concern.
4. **Section 6 Adverse Reactions:** The Applicant was asked to simplify and make extensive revisions to this section in accordance with the Draft Guidance for Industry: *Guidance for Industry. Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>.

5. **Section 14 Clinical Studies:** In this section, (b) (4)
- 
- if  
prespecified and adjusted for family-wise error control in the statistical analysis plans, it may be possible to consider inclusion of some of this information in the text.

### 9.3 Advisory Committee Meeting

In the Dispute Denied Letter, the Agency informed the Applicant that a second Advisory Committee meeting on this NDA is important because data and the overall spectrum of risk have shifted since their first meeting. The reasons stated in the Dispute Resolution Denied Letter were as follows:

“Additional data about liver toxicity and breast cancer were brought to bear in the major amendment from the first cycle of the NDA, lessening the concern for some risk signals that were of concern when the AC convened and those data have continued to accumulate. More importantly, the CV data and how it evolved to shift expectations for dapagliflozin, from having hope for CV benefit to concern about a signal of CV risk, warrants discussion. It raises questions about how to factor in new data to a meta-analysis that has already been used to make a decision that the FDA Guidance on CV risk for diabetes drugs does not fully address. Also, how should clinical trials that are highly enriched for CV risk be considered in the overall premarketing risk assessment for a diabetes treatment? If they are to play a major role, should such enriched trials be required earlier in development than was planned for dapagliflozin? Should they carry more weight than studies in patients with fewer CV risk factors? These questions, being raised in the context of this NDA, should not be answered without public discussion.”

The EMDAC convened on December 12, 2013 to review the clinical efficacy and safety data for the dapagliflozin clinical program. Below are the questions posed to the Committee and key discussions points.

#### “Cardiovascular Risk Evaluation:

- 1) **DISCUSSION:** Based on the information provided in the briefing package and the presentations at today’s meeting, please address the following with regard to the cardiovascular risk assessment for dapagliflozin.
  - a. 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 cardiovascular disease in Trials 18 and 19.
  - b. Discuss whether you believe the updated cardiovascular risk data derived from Trials 18 and 19 are consistent with the overall findings reported for the pool of 21 clinical trials.
  - c. 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.



- d. Discuss additional concerns, if any, you may have with regard to dapagliflozin and cardiovascular risk.”

The EMDAC did not express particular concern regarding an increased risk for cardiovascular events. However, it was acknowledged that the existing data were not sufficient to rule out a potential risk. Further, it was felt that inclusion or exclusion of the two studies that were enriched with high-risk patients (i.e., established CV disease), did not significantly alter the opinions of the Committee. The observed changes in blood pressure, weight and glycemic control were considered modest, but might improve adherence to therapy in a subset of patients.

“Malignancy:

- 2) **DISCUSSION:** Based on the information provided in the briefing package and the presentations at today’s meeting, discuss your level of concern with regard 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.”

In their deliberation, the EMDAC was somewhat reassured that the IRR for all malignancies was approximately 1 and that there were a limited number of bladder cancer events in a population with known risk factors. In addition, if dapagliflozin was a tumor promoter, more cases of advanced bladder cancer would have been expected. Many expressed the need for additional studies to further assess a possible association between dapagliflozin and bladder cancer events, but felt that these studies could be conducted post approval.

“Liver Toxicity:

- 3) **DISCUSSION:** Based on the information provided in the briefing package and the presentations at today’s meeting, discuss your level of concern with regard 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.”

Much of the discussion focused on a relative lack of evidence across the Applicant’s entire clinical program to suggest an association of serious liver injury with dapagliflozin. Many of the members concurred with the Applicant’s reclassification for the potential case of drug-induced liver injury. It was felt that the available data on hepatic safety did not support a Boxed Warning, however, it was questioned whether the Warnings and Precautions section of product labeling should include information

related to potential hepatotoxicity with dapagliflozin. The EMDAC was informed that labeling negotiations were still ongoing at this time. The hepatologist on the panel recommended against routine monitoring of liver laboratory tests.

**“4) VOTE:** In accordance with FDA’s Guidance for Industry titled “Diabetes Mellitus – Evaluating Cardiovascular 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 cardiovascular risk profile?

- a. If you voted “Yes” to question #4, please provide your rationale.
- b. If you voted “No” to question #4, please provide your rationale.”

Taking into consideration the FDA’s Guidance Document and the evidence provided, the EMDAC voted 10 in favor and 4 against an acceptable CV risk profile of dapagliflozin.

**“5) VOTE:** Based on the information included in the briefing materials and presentations today, 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?

- a. If you voted “Yes” to question #5, please provide your rationale and whether you recommend any additional studies post-approval.
- b. If you voted “No” to question #5, please provide your rationale and discuss what additional data are necessary to support approval.”

The EMDAC voted 13 in favor and 1 against approval of dapagliflozin for the proposed indication. However, many of the members expressed concerns regarding potential safety issues, and reiterated the need for further study in the postmarketing setting.

In summary, the EMDAC concluded that dapagliflozin relative to comparators has an acceptable cardiovascular risk profile and that the benefits of dapagliflozin outweigh potential risks, when considering an indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. However, many of the Committee members expressed a need for further evaluation, in the postmarketing setting, of bladder cancer risk. Regarding liver safety, the EMDAC did not note an association of serious liver injury with dapagliflozin, and concurred with a reclassification of the diagnosis of drug-induced liver injury, reported in a single patient during the first review cycle, to autoimmune hepatitis.

## 9.4 Products Approved in the U.S. for the Management of T2DM

**Table 38: Approved Anti-Diabetic Drugs for T2DM**

Trade Name (Established Name)	NDA #	Original Approval Date	Safety Concerns*
Alpha-Glucosidase Inhibitors			
GLYSET (meglitol)	020682	December 18, 1996	• Contraindications: diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, predisposition to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine
PRECOSE (acarbose)	020482	September 6, 1995	• Contraindications: diabetic ketoacidosis or cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, predisposition to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine
Amylin Mimetics			
SYMLIN (pramlintide)	021332	March 16, 2005	• Product labeling includes a Boxed Warning of increased risk of insulin-induced severe hypoglycemia when used with insulin • Contraindications: confirmed diagnosis of gastroparesis, or hypoglycemia unawareness
Biguanides			
FORTAMET (metformin)	021574	April 28, 2004	• Product labeling includes a Boxed Warning of lactic acidosis • Contraindications: renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females) or abnormal creatinine clearance from any cause, including shock, acute myocardial infarction, or septicemia; acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)
GLUCOPHAGE (metformin)	020357	March 3, 1995	
RIOMET (metformin)	021591	September 11, 2003	
GLUCOPHAGE XR (metformin extended-release)	021202	October 13, 2000	
GLUMETZA (metformin extended-release)	021748	June 3, 2005	
Combination Products GLUCOVANCE (metformin + glyburide)	021178	July 31, 2000	
METAGLIP (metformin + glipizide)	021460	October 21, 2002	
Bile Acid Sequestrants			

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Trade Name (Established Name)	NDA #	Original Approval Date	Safety Concerns*
<b>WELCHOL</b> (colesevelam)	21176	January 18, 2008	<ul style="list-style-type: none"><li>• Postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia, pancreatitis, and increased transaminases</li><li>• Contraindications: history of bowel obstruction, serum triglyceride concentrations &gt;500 mg/dL, hypertriglyceridemia-induced pancreatitis</li></ul>
<b>Dopamine-2 Agonists</b>			
<b>CYCLOSET</b> (bromocriptine)	020866	May 5, 2009	<ul style="list-style-type: none"><li>• Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation</li><li>• Contraindications: syncopal migraines, or lactating female (inhibits lactation, and postmarketing reports of stroke)</li></ul>
<b>DPP-4 Inhibitors</b>			
<b>JANUVIA</b> (sitagliptin)	021995	October 16, 2006	<ul style="list-style-type: none"><li>• Postmarketing reports of fatal and non-fatal hemorrhagic or necrotizing pancreatitis</li><li>• Postmarketing reports of acute renal failure, sometimes requiring dialysis</li><li>• Increased risk of hypoglycemia when added to an insulin secretagogue (e.g., sulfonylurea) or insulin</li><li>• Postmarketing reports of serious allergic and hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome</li></ul>
<b>Combination Products</b> <b>JANUMET</b> (sitagliptin + metformin)	022044	March 30, 2007	
<b>JANUMET XR</b> (sitagliptin + metformin extended-release)	202270	February 2, 2012	
<b>JUVISYNC</b> (sitagliptin + simvastatin)	202343	October 7, 2011	
<b>NESINA</b> (alogliptin)	022271	January 25, 2013	<ul style="list-style-type: none"><li>• Postmarketing reports of acute pancreatitis</li><li>• Postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema and severe cutaneous adverse reactions</li><li>• Postmarketing reports of hepatic failure, sometimes fatal</li><li>• When used in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required</li></ul>
<b>Combination Products</b> <b>KAZANO</b> (alogliptin + metformin)	203414	January 25, 2013	
<b>OSENI</b> (alogliptin + pioglitazone)	022426	January 25, 2013	
<b>ONGLYZA</b> (saxagliptin)	022350	July 31, 2009	<ul style="list-style-type: none"><li>• Postmarketing reports of acute pancreatitis</li><li>• Postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions</li><li>• When used in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required</li></ul>
<b>Combination Products</b> <b>KOMBIGLYZE XR</b> (saxagliptin + metformin extended-release)	200678	November 5, 2010	
<b>TRADJENTA</b> (linagliptin)	201280	May 2, 2011	<ul style="list-style-type: none"><li>• When used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of the insulin secretagogue or insulin may be required</li><li>• Pancreatitis was reported more often in patients treated with linagliptin than for comparator</li></ul>
<b>Combination Products</b> <b>JENTADUETO</b> (linagliptin + metformin)	201281	January 30, 2012	
<b>GLP-1 Receptor Agonists</b>			

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Trade Name (Established Name)	NDA #	Original Approval Date	Safety Concerns*
<b>BYDUREON</b> (exenatide extended-release)	022200	January 27, 2012	<ul style="list-style-type: none"><li>• Product labeling carries a Boxed Warning for risk of thyroid C-cell tumors</li><li>• Postmarketing reports of fatal and non-fatal hemorrhagic or necrotizing pancreatitis</li><li>• Contraindications: personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2)</li></ul>
<b>BYETTA</b> (exenatide)	021773 021919	April 28, 2005 October 30, 2009	
<b>VICTOZA</b> (liraglutide)	022341	January 25, 2010	
<b>Insulins and Insulin Analogues</b>			
<b>APIDRA</b> (insulin glulisine)	021629	April 16, 2004	<ul style="list-style-type: none"><li>• Hypoglycemia</li></ul>
<b>HUMALOG</b> (insulin lispro)	020563	June 14, 1996	
<b>HUMULIN N</b> (insulin isophane)	018781	October 28, 1982	
<b>HUMULIN R</b> (insulin human)	018780	October 28, 1982	
<b>LANTUS</b> (insulin glargine)	021081	April 20, 2000	
<b>LEVEMIR</b> (insulin detemir)	021536	Jun 16, 2005	
<b>NOVOLIN R</b> (insulin human)	019938	June 25, 1991	
<b>NOVOLOG</b> (insulin human)	020986	Jun 7, 2000	
<b>Combination Products</b> <b>HUMALOG MIX</b> (insulin lispro protamine + insulin lispro)	021017 021018	December 22, 1999 December 22, 1999	
<b>NOVOLOG MIX</b> (insulin aspart protamine + insulin aspart)	021172	Nov 1, 2001	
<b>Meglitinides</b>			
<b>PRANDIN</b> (repaglinide)	020741	December 22, 1997	<ul style="list-style-type: none"><li>• Hypoglycemia</li><li>• Contraindications: diabetic ketoacidosis, with or without coma, or co-administration of gemfibrozil</li></ul>
<b>Combination Products</b> <b>PRANDIMET</b> (repaglinide + metformin)	022386	June 23, 2008	

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Trade Name (Established Name)	NDA #	Original Approval Date	Safety Concerns*
STARLIX (nateglinide)	021204	December 22, 2000	<ul style="list-style-type: none"><li>• Hypoglycemia</li><li>• Contraindications: diabetic ketoacidosis</li></ul>
<b>SGLT2 Inhibitors</b>			
INVOKANA (canagliflozin)	204042	March 29, 2013	<ul style="list-style-type: none"><li>• Can cause volume-related AEs, genital mycotic infections and a dose-related decline in the estimated glomerular filtration rate</li><li>• Contraindications: severe renal impairment, ESRD, or on dialysis</li></ul>
<b>Sulfonylureas</b>			
DIABINESE (Chlorpropamide)	011641	January 1, 1982	<ul style="list-style-type: none"><li>• Hypoglycemia</li><li>• Contraindications: diabetes complicated by ketoacidosis, with or without coma, or diabetes complicated by pregnancy (for chlorpropamide, micronized glyburide, and tolazamide)</li></ul>
AMARYL (Glimepiride)	020496	November 30, 1995	
GLUCOTROL (Glipizide)	017783	May 8, 1984	
GLUCOTROL XL (Glipizide extended-release)	020329	April 26, 1994	
GLYNASE (Glyburide) DIABETA (Glyburide)	020051	March 4, 1992	
(Tolazamide)	017532	May 1, 1984	
(Tolbutamide)	A070259 <sup>†</sup>	January 2, 1986	
	A086445 <sup>†</sup>	Prior to January 1, 1982	
<b>Thiazolidinediones</b>			
ACTOS (pioglitazone)	021073	July 15, 1999	<ul style="list-style-type: none"><li>• Product labeling includes a Boxed Warning for risk of congestive heart failure</li><li>• Contraindications: established NYHA Class III or IV heart failure</li></ul>
Combination Products ACTOPLUS MET (pioglitazone + metformin)	021842	August 29, 2005	
ACTOPLUS MET XR (pioglitazone + metformin extended-release)	022024	May 12, 2009	
DUETACT (pioglitazone + glimepiride)	021925	July 28, 2006	
AVANDIA (rosiglitazone)	021071	May 25, 1999	<ul style="list-style-type: none"><li>• Product labeling includes a Boxed Warning of the risk for congestive heart failure and myocardial infarction (available through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program)</li><li>• Contraindications: established NYHA Class III or IV heart failure</li></ul>
Combination Products AVANDAMET (rosiglitazone + metformin)	021410	October 10, 2002	
AVANDARYL (rosiglitazone + glimepiride)	021700	November 23, 2005	

\*Safety concerns reflect single-entity drug substances and not combination products.

<sup>†</sup>Reference Listed Drug (RLD); approved under an Abbreviated New Drug Application (ANDA).

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/s/  
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FRANK PUCINO  
12/22/2013

KAREN M MAHONEY  
12/22/2013



## Summary Basis for Regulatory Action

<b>Date</b>	January 17, 2012
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	202293
<b>Supp #</b>	
<b>Applicant Name</b>	Bristol-Myers Squibb
<b>Proprietary / Established (USAN) Names</b>	Dapagliflozin
<b>Dosage Forms / Strength</b>	5- and 10-mg tablets
<b>Proposed Indication(s)</b>	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
<b>Action:</b>	<i>Complete Response</i>

### 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding dapagliflozin and the reader should review the action package for more detail. Dapagliflozin is a first in class new molecular entity anti-diabetic therapy that inhibits the sodium glucose cotransporter-2 (SGLT2) receptor. Inhibition of this receptor is the proposed mechanism for treating hyperglycemia associated with diabetes as it prevents glucose reabsorption in the proximal tubules of the kidney resulting in glucosuria. This mechanism of action is not dependent upon insulin release or improving insulin sensitivity and the control of hyperglycemia though glucose diuresis results in excess caloric loss and may have other salutary effects such reducing blood pressure and weight loss. Regarding possible salutary blood pressure changes, it is unknown whether a glucose-induced 'diuretic' effect would provide the same beneficial cardiovascular outcome as traditional diuretic medications that exert their effects mainly through sodium balance. Review of the data in the application revealed safety signals of concern: bladder/breast cancer imbalances and a case fulfilling Hy's Law for drug-induced liver injury (DILI).

The clinical review team is not in agreement regarding what action should be taken with this application. Drs. Dunn and Irony have recommended approval with appropriate labeling, whereas Dr. Parks has recommended a Complete Response (CR) action.

There is no question or disagreement within the team that dapagliflozin demonstrated efficacy in improving glycemic control in adults (with normal or mildly impaired renal function) with type-2 diabetes (T2DM). There also is not any disagreement between team members regarding safety signals that warrant further evaluation. Instead the disagreement is in regard to the timing of further evaluation of these signals; e. g. whether further evaluation should occur before approval or after approval. Dr. Dunn and Irony believe that an appropriate risk:benefit ratio exists at present to allow marketing and that these signals can be further



evaluated after approval. Implicit in their recommendation is that they either have come to the conclusion that if these signals are real the benefit of the drug outweighs the risk, or that they do not believe these safety concerns to be real. Dr. Parks believes that we need more information disproving these signals for an appropriate risk-benefit ratio to justify marketing.

I agree with Dr. Parks' assessment and will discuss my reasoning and conclusions below.

### Efficacy

Efficacy has been thoroughly covered by Drs. Dunn, Irony, Parks and Norton and I will not present this in detail as all agree with the amount of HbA1c control exhibited by dapagliflozin.

Depending upon the population studied (i.e. monotherapy vs. add-on etc.), HbA1c changes ranged from 0.4-0.7%. As Dr. Parks has noted, this is in the range (perhaps slightly less in some cases) of HbA1c control exhibited by other recently approved therapies. This is summarized below from Dr. Parks' review (page 7, italicized below):

**Table 7.1. Efficacy of Dapagliflozin Monotherapy**

	Study 102013				Study 102032*		
	pbo	2.5mg	5mg	10mg	pbo	2.5mg	5mg
N	72	64	61	65	68	72	66
Baseline mean HbA1c	7.8	7.9	7.8	8.0	7.8	8.1	7.9
Wk 24 LOCF mean	7.6	7.3	7.1	7.1	7.8	7.3	7.1
Adj mean chg from baseline	-0.23	-0.58	-0.77	-0.89	0.02	-0.72	-0.82
difference from pbo	---	-0.35	-0.54	-0.66	---	-0.74	-0.84
p-value vs pbo		0.02	0.0005	<0.0001		<0.0001	<0.0001

source: Tables 2.5.26 for Studies 2013 and 2032 from CSR Module 5.3.5 (1/5/2011 submission)

\*Study 102032 not reviewed by FDA statistician

### *Add-on Therapy*

- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to metformin background therapy achieved a range of **-0.38 to -0.54** difference from placebo in HbA1c reduction (MB102014)
- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to glimepiride background therapy achieved a range of **-0.44 to -0.68** difference from placebo in HbA1c reduction (D1690C00005)
- Dapagliflozin 5 and 10 mg, added onto pioglitazone background therapy, achieved a **-0.4 to -0.55** difference from placebo in HbA1c reduction (MB102030)
- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to insulin background therapy achieved a range of **-0.45 to -0.60** difference from placebo in HbA1c reduction (D1690C00006)

It is also important to note that dapagliflozin's efficacy wanes as renal function declines (even though serum drug levels increase) such that it has not been convincingly demonstrated to be effective in patients with eGFR less than 60 mL/min.

Therefore, the 5- and 10-mg doses demonstrate reductions in HbA1c as monotherapy or in combination with other commonly prescribed anti-diabetics, in those with renal function of 60 mL/min or greater. Therapy with dapagliflozin would only be indicated in those with normal renal function or mild renal insufficiency and would necessitate monitoring of patient's renal function and removal of dapagliflozin therapy should the patient's renal function decline to moderate or severe insufficiency.

### Safety

There are three main concerns that I will discuss below, possible DILI highlighted by a case fulfilling Hy's Law and cancer signals for breast and bladder cancer. These concerns were noted in the data contained within the original submission. The sponsor also had other data not included in the original submission, including interim data from two large trials (D1690C00018 and D1690C00019, henceforth referred to as Trial 18 and 19) and a few smaller trials, which was submitted during the review cycle to further evaluate these concerns, causing a review extension. The supplemental data increased the existing dapagliflozin exposure database by about 30% and placebo exposure-comparison by about 50%.

I will also discuss what effect the addition of data from Trial 18 and 19 have had on the cardiovascular evaluation of dapagliflozin.

### **Hepatotoxicity**

There were not any pre-clinical animal signals of hepatotoxicity with dapagliflozin. There also is not any evidence of transaminitis 'shifts' indicating that there could potentially be concerns regarding DILI from dapagliflozin as demonstrated by the following table from Dr. Parks' review (page 11).

**Table 8.1. Hepatic Enzyme Elevations in Phase 2b/3 Controlled Trials**

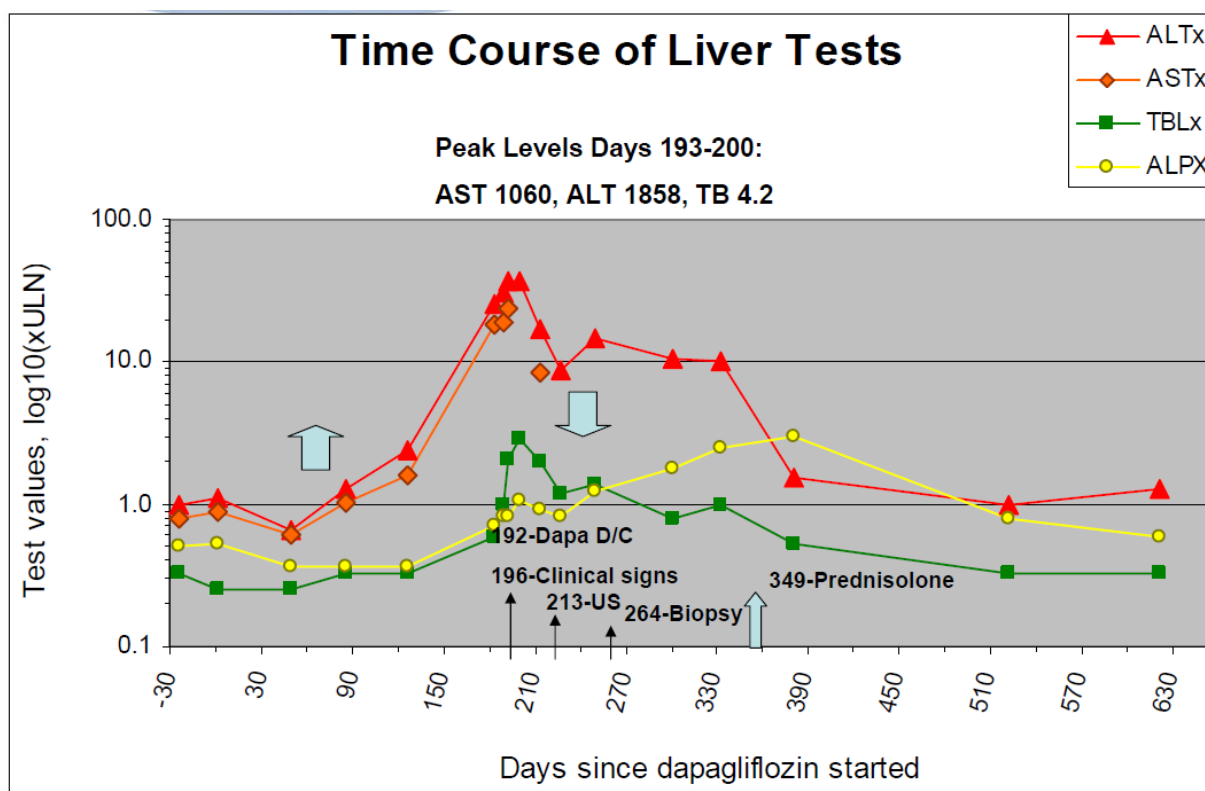
	<b>Dapagliflozin</b>	<b>Comparator</b>
<i>Original dataset including 4MSU</i>		
<i>N</i>	4287	1941
<i>AST &gt; 5x ULN</i>	0.3%	0.4%
<i>AST &gt; 10x ULN</i>	0.1%	0.2%
<i>ALT &gt; 5x ULN</i>	0.4%	0.5%
<i>ALT &gt; 10x ULN</i>	< 0.1%	0.1%
<i>Updated dataset</i>		
<i>N</i>	5501	3184
<i>AST &gt; 5x ULN</i>	0.2%	0.3%
<i>AST &gt; 10x ULN</i>	0.1%	0.1%

ALT > 5x ULN	0.3%	0.4%
ALT > 10x ULN	0.1%	0.1%
ALT > 20x ULN	<0.1%	<0.1%

However, there is a case that fulfills Hy's Law criteria as outlined below from Dr. Parks' review (page 10, 11).

*The case is of D1690C00004-4402-6, a 78-year old man from India whose concomitant medications included atorvastatin, cromolyn, lecanlidipine, atenolol, parendopril, naproxen, acetylsalicylic acid and a couple of herbal products. The patient was diagnosed as a compound heterozygote for hemochromatosis.*

**Figure 8.1 Time Course of Lab and Clinical Findings in Hy's Law Case (Source: Dr. Dunn's FDA presentation at AC meeting)**



If this case is indeed a DILI as a result of dapagliflozin exposure, from the FDA's Guidance (Drug-induced Liver Injury: Premarketing Clinical Evaluation<sup>1</sup>), one would expect to have 1 in 25,000 to 1/44,000 cases of serious DILI due to dapagliflozin, depending upon whether the

<sup>1</sup> 1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

exposure for the original submission or the total exposure including the exposure data from the extension is considered.

We have had a great deal of experience with medications that cause DILI and for the most part, there have not been preclinical signals, but there usually are transaminitis shifts noted from the clinical data in conjunction with case/s fulfilling Hy's Law criteria. If this case of hepatotoxicity is due to dapagliflozin, this would be a rare situation where transaminitis did not manifest in the overall database in conjunction with a case fulfilling Hy's Law criteria. Perhaps this case is not caused from dapagliflozin and the timing has just been bad luck. One can try to construct various scenarios where dapagliflozin use is not the culprit and there is some other cause such as one of the herbal products that the subject was taking. However, this is speculation and from a regulatory standpoint, and the timing of resolution of abnormal labs in conjunction with stopping dapagliflozin exposure, we should assume that the case of probable DILI is due to exposure to dapagliflozin until some other suspect is proven, or more exposure data is generated demonstrating that the rates of potential DILI listed above are incorrect (or greatly overestimated).

## **Cancer**

Preclinical evaluation determined that dapagliflozin was neither genotoxic nor clastogenic and animal carcinogenicity studies were negative at doses experienced in human study with adequate safety margins. However, during the clinical review numerical imbalances were noted for bladder cancer (in men only) and breast cancer (in women) for subjects taking dapagliflozin.

### Bladder Cancer

The original database had nine cases of bladder cancer in the dapagliflozin group versus one in the comparator, all in male subjects with a rate ratio of 4.0 (95% CI, 0.5-31.4). With the updated exposure database, there were not any new cases of bladder cancer, but there was a greater percentage of comparator exposure such that the updated rate ratio increased to 5.4 (95% CI, 0.84-122.2). Exposure times for those cases of bladder cancer ranged from 43 days to 727 days. As pointed out by Dr. Parks, if we consider only those cases with more than one year of exposure, we still have an imbalance of 5 cases of bladder cancer in the dapagliflozin group compared to none for comparator between 393-727 days of exposure.

The reviewers for the Office of Surveillance and Epidemiology (OSE) performed a very elegant evaluation of the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute for bladder cancer (and breast as well) to try to get a reference point as to what rate one might expect to see in the population compared to what occurred within the NDA database. I will not mention the SEER data further, as though I find it interesting, there are limitations for its use as discussed by the OSE team, and I believe that we should focus our deliberations on the data comparing cancer rates between dapagliflozin and comparator within the NDA database as these reflect controlled comparisons that should limited possible confounding.

Since use of dapagliflozin is associated with increased urinary tract infections, an extensive evaluation of potential detection bias accounting for the imbalance was undertaken. Neither the review team nor the sponsor were able to discover any type of detection biased that may have accounted for increased surveillance in the dapagliflozin group compared to the control group.

### Breast Cancer

Nine cases of breast cancer were observed in the dapagliflozin treatment groups versus none in the comparator groups with the original database, therefore a rate ratio could not be calculated using only the NDA application data. The update exposure data included additional cases of breast cancer such that there were 10 cases in the dapagliflozin treatment group and three cases in the comparator group. This provided a rate ratio of 1.9 (95% CI, 0.5-8.9). The OSE review does make further adjustments based upon whether the cases of breast cancer are *in situ* or not, where exclusion of a placebo case changes the rate ratio to 2.8. This rather dramatic change in the rate ratio based on one case demonstrates the fragility of trying to make decisions based upon only a few events. All 10 cases of breast cancer in the dapagliflozin exposure subjects were detected less than one year after exposure.

### Cancer Findings Summary

It is always difficult to know what to conclude when confronted with a safety signal based on only a few events, particularly when there are not any preclinical concerns. For cancer safety signals, one can factor in the length of exposure prior to diagnosis and confidence interval surrounding the point estimate of the rate ratio in determining the likelihood that the signal may be real. Time of exposure is important as the position could be adopted that it may be difficult to consider a drug that does not have pre-clinical indicators as a carcinogen, to be a cancer inducer with the limited time exposure that is available in the NDA database. This consideration may be different however if the drug is a tumor promoting agent. The magnitude of the rate ratio point estimate is important as the higher the ratio the greater the magnitude of harm should it be a true finding and not random error and must be considered in any risk:benefit calculation.

If it is unclear the likelihood that the signal may be real using the existing data, the benefit of the drug and the disease being treated must be considered in any determination regarding whether further data should be obtained pre- or post-approval. Consideration must always be given regarding the impact on patients should the signal turn out to be real vs. the impact to patients should their access to therapy be delayed while trying to sort out the issue.

I am sympathetic to those that feel most imbalances based on few events are spurious findings. It is difficult to conceptualize that exposure of less than a year to a drug that is not genotoxic or clastogenic would actually cause cancer in such a short time period (would a tumor-promoting agent be different for pre-existing tumors?). Additionally, we look at virtually hundreds of safety issues and categories and should expect that there will be imbalances in some of those evaluations, some favoring the drug and some not favoring the drug. Therefore, I do not find some imbalances, particularly those of limited magnitude, when considering

limited numbers of events, concerning in and of themselves. The bigger concern occurs if the magnitude is several-fold greater and the public health impact should the finding not be by chance. However, it is easy to still be skeptical findings that are of several-fold magnitude greater. To illustrate this, it is instructive to look at data from the RECORD trial.<sup>2</sup>

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As noted above for pancreatic cancer, there were 15 events which are similar to the number of events that we are considering in this application for breast and bladder cancer and the finding is similar, except it is favorable for rosiglitazone. Given the data above, one might conclude that those taking rosiglitazone experienced protection from developing pancreatic cancer. Yet, no one really believed that rosiglitazone was protective against pancreatic cancer and most felt this finding was spurious. Indeed, other trials did not repeat this finding. As such, one might wonder why we would consider the rosiglitazone finding (when it is favorable) a chance finding, but would have greater reservations making the same conclusions for the unfavorable cancer imbalances in this application.

I believe a convincing argument can be made that the breast cancer finding may be spurious. The rate ratio is unimpressive for a finding of limited events and there are not any preclinical concerns. Also, while the initial database seemed quite skewed that the drug may have an unfavorable profile, the addition of only about 30% more data changed that impression (rate ratio of 2). As noted above, whether one case is considered makes a large difference in the rate ratio, demonstrating the fragility of any conclusion.

The bladder cancer signal is another matter. As noted above, the rate ratio originally was quite high ( $\approx 4$ ) and increased with the addition of more data. This is still similar to the rosiglitazone example discussed above except it is not favorable for the drug. When the question arises of why we would dismiss a favorable effect, but require further evaluation of a potential safety issue, the argument can be made that a safety 'harm' issue warrants closer inspection than a potentially 'protective' finding. Usually, in this type of situation the question then becomes whether further investigation should be done before or after approval.

### Cardiovascular Safety

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<sup>2</sup> Home PD, et. al. rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. Lancet. 2009 Jun 20;373(9681):2125-35

I will consider this here, as some have used this as a consideration in the risk:benefit of dapagliflozin in their consideration of the aforementioned safety issues. Dapagliflozin does effect a mean decrease in blood pressure ( $\approx 3$  mmHg systolic,  $\approx 1.5$  mmHg diastolic) and a mean decrease in weight ( $\approx 1$ -5 kg depending upon population studied). It is therefore not unreasonable to speculate that dapagliflozin use may have cardiovascular benefit if the diuretic/blood pressure surrogate marker is transferable from existing anti-hypertensive medications that affect diuresis through a sodium excretion mechanism.

The original application compared a composite of time to first event for CV death, MI, stroke, and hospitalization for unstable angina in those taking dapagliflozin compared to all comparators. The meta-analysis comparing dapagliflozin to comparators (placebo and active control) demonstrated a hazard ratio (HR) of 0.67 (98% CI: 0.4-1.2-based on 78 events). We must be cautious to not over-interpret these results to indicate actual benefit, as the data is based on limited events (typical CV outcome trials in diabetic populations target  $>600$  events), from many trials of very different design and populations and also includes outcomes that are more subjective endpoints (hospitalization for unstable angina) than traditional MACE (CV death, MI, stroke) which in non-inferiority trials can bias toward no difference (although they may not bias actual superiority comparisons). However, the original data did not indicate any type of cardiovascular risk, and some may have felt that there was a demonstration of CV benefit which could be use in any risk:benefit assessment when considering safety signals of concern (cancer, hepatic).

With the additional data that we requested to evaluate the potential cancer signal, we again requested a CV meta-analysis be performed, to determine if additional data would support a potential for cardiovascular benefit. The additional data, when combined with what was already submitted, yielded a HR of 0.82 (CI: 0.58, 1.15-based on 145 events). Therefore, the additional data moved the HR more towards unity, where no benefit (although no harm) would be expected. This is summarized in the table below from Dr. Parks' review (page 17).

**Table 8.8. Primary Composite and MACE Analyses of Original MA and Updated MA**

	Original Meta-analysis Stratified HR (98% CI)	Updated Meta-analysis Stratified HR (95% CI)
Primary composite of CV death, NFMI, stroke, and hospitalization for UA	0.67 (0.38, 1.18)	0.82 (0.58, 1.15)
MACE (CV death, NFMI, stroke)	0.60 (0.32, 1.10)	0.79 (0.54, 1.17)

However, the additional data contained two trials (Trials 18 and 19) that warrant independent evaluation. These two trials were of similar design and in similar populations, and were specifically design for cardiovascular outcome evaluation in high-risk groups, and therefore the results may be more reliant than an evaluation of the overall database. At the very least, since Trials 18 and 19 seem discordant to the other 17 trials (at the interim evaluation) and



should spur hypothesis generation that there may not be a CV benefit from use of dapagliflozin. They contributed 60 events to the overall number of events, and therefore have enough information upon which to draw conclusions in their own regard.

These two trials were conducted in high-risk CV patients, most of whom had a history of coronary heart disease, hypertension and dyslipidemia. This population would be more representative of the group of diabetic patients that we are concerned with regarding any potential to increase cardiovascular event rates upon an already high baseline event rate. The meta-analysis of these two trials, using the primary composite endpoint is presented below in a table from Dr. Parks' review (page 19).

**Table 15: Meta-Analysis Results for All Trials Excluding High-Risk CV Trials and Pooled High-Risk CV Trials (D1690C00018 and D1690C00019)**

	<b>All Trials Excluding High-Risk CV Trials</b>		<b>High-Risk CV Trials (D1690C00018 and D1690C00019) combined</b>	
	<b>Dapagliflozin</b>	<b>All Comparator</b>	<b>Dapagliflozin</b>	<b>Standard of Care</b>
<b>Stratified Hazard Ratio (95% CI)</b>	0.66 (0.42, 1.04)		1.07 (0.64, 1.77)	
<b>Event/PY (% Incidence)</b>	51/5032 (1.01%)	34/2389 (1.42%)	31/706 (4.39%)	29/706 (4.11%)
<b>M-H Incidence Rate Difference (95% CI)</b>	-0.0050 (-0.011, 0.0007)		0.0028 (-0.018, 0.024)	

Source: Created by reviewer. Dataset: adcv2v2.xpt

These two trials do not mirror the overall result as their HR is greater than unity. In addition, if the traditional MACE definition is used, which allows only more objective endpoints, and perhaps less 'noise' that would bias the results toward unity, the following result is obtain (Dr. Parks' review, page 19).

**Summary of MACE using Cox Proportional Hazards Methods for Studies 18 and 19, combined.**

	Dapagliflozin (a)	Comparator (b)
Number of Subjects With at Least One Events	24	19
Number of Subjects in Treatment Group	939	945
Total Subject-Years at Risk	708	709
Subjects with Events/1000 Subject-Year	33.88	26.80
Hazard Ratio Versus Comparator		
Estimate	1.266	
95% CI (c)	(0.693 , 2.311)	

*Source: Table 25 from Sponsor's Supplemental CV events Meta-analysis Report*

Examination of traditional MACE not only doesn't support any cardiovascular benefit, it is more indicative of potential harm.

While it is always problematic to start parsing and carving out data, and one cannot rely too heavily on any subgroup analysis, the data above demonstrate that any cardiovascular conclusions based on this limited data are fragile at best and should not be used to conclude that there may be benefit, or as a justification to tolerate potential unresolved safety signals. As noted by Dr. Parks, there may be variability in event rates based on duration of exposure such that with longer duration a favorable benefit may be demonstrated in patients taking dapagliflozin, but it is premature to make this conclusion. The data from this application is valuable in progressing our understanding of design of outcome trials in diabetic drug evaluation and should be reviewed carefully to aid in the future design of CV outcome trials where sponsors wish to use composite endpoints that expand a traditional MACE endpoint.

The totality of the data above does not indicate a cardiovascular risk, and they also do not indicate a cardiovascular benefit. The incongruence of the total meta-analysis results to Trials 18 and 19 supports that a dedicated CV outcomes trial should be conducted. I believe the data we have to date demonstrate a neutral effect in any risk:benefit calculation.

### **Advisory Committee Meeting**

The AC meeting vote (approval: yes-6, no-9) with comments are detailed in the other clinical reviews. Panel members agreed that efficacy had been demonstrated, but were concerned about potential safety issues that the majority voted required further data, although many struggled with their final vote.

### **Conclusions and Recommendations**

There is internal agreement that dapagliflozin has demonstrated efficacy in controlling glycemic control in patients with T2DM that have normal or mild renal insufficiency and that efficacy has not been demonstrated in patients with moderate or severe renal insufficiency. There is also agreement that dapagliflozin use is associated with breast and bladder cancer imbalances and that there was a case that fulfilled criteria for Hy's Law DILI. There is internal disagreement between the clinical reviewers regarding the action that should occur with this application. Drs. Dunn and Irony believe that dapagliflozin should be approved and that further investigation of these safety risks should occur post-approval. Dr. Parks believes that dapagliflozin should not be approved this cycle and that further exposure data should be provided demonstrating that the HR for CV risk remains neutral and that there are no additional findings of cancer or liver toxicity.

I do not think that the breast cancer risk identified for dapagliflozin is at the level of magnitude that would require further pre-marketing evaluation and I found the updated safety data reassuring. If this were the only issue we faced, I would allow marketing and have post-marketing study for further reassurance. This decision is based on a relatively low risk ratio

generated by few events, which decreased with additional exposure data and experience that we have had in the past where signals of this magnitude eventually were disproven.

However, the bladder cancer risk ratio exceeding five is not something that can be ignored as an erroneous finding. While there are reasons to speculate that this may be an erroneous finding as I discussed earlier, the updated safety data actually increased the risk ratio. I did not discuss biologic plausibility earlier and will touch upon it here, as some have stated that as a reason to dismiss this signal. Sometimes much is made over whether there is a biologically plausible mechanism for the effect seen, in this case potential carcinogenesis. Too often ‘biologically plausibility’ is used as a crutch instead of acknowledging that we are always in a state of progressive ignorance awaiting enlightenment. If we look at our current state of knowledge compared to where we were at one, two or three decades ago, we realize how primitive our accumulated knowledge was in the past. In ten, or twenty or thirty years from now, we will think the same thing about our current state of knowledge. When the first observation was made that antihistamines could cause Torsade de Pointes, we also did not have a biologically plausible explanation of how that may occur, but we believed the effect and with time discovered the biologic mechanism. Therefore, I do not place too much weight on whether there is a biological explanation of a result. The data speaks for itself, and we must determine if the data is truth or represents a spurious finding and lack of biologically plausibility is not particularly enlightening.

Finally, we have the case that fulfills Hy’s Law. Whether dapagliflozin actually causes DILI is not clear as we do not have transaminitis shifts associated with use as we usually see with a drug that has hepatotoxicity capacity. However, due to the volume of material that we evaluate, it is not unusual for us to see a finding that does not follow the ‘usual’ experience and I am very cognizant that this could very well be a ‘learning experience’ case where the typical findings are not seen. Additionally, most clearly DILI drugs are culled out early in the development process, so we are seeing the tip of the ice berg and are probably not aware of the full presentation that drugs with DILI capacity may express.

After I consider the benefit and risks of Dapagliflozin, while I understand Drs. Dunn and Irony’s positions and do not think they are unreasonable, I find that I am aligned with Dr. Parks’ decision and reasoning for this application. Dapagliflozin does not clearly fill any particular niche that cannot be filled by a drug in one of the other 11 categories of anti-diabetic agents that are currently available. Dapagliflozin does not have an efficacy profile that stands out from any of the other categories of anti-diabetic drugs and has unresolved safety issues. As such, it is hard for me to see a reason to place patients at risk at this stage without any particularly unique advantage until these issues are further defined. I also acknowledge that this is a difficult decision and a reasonable person may come to a different conclusion than what I have, depending upon their own risk tolerance.

I think ultimately we will probably find that dapagliflozin is not associated with bladder or breast cancer and that this imbalance is just bad luck on their part. But my thinking that dapagliflozin probably isn’t associated with either of these cancers, doesn’t mean that I know that it isn’t, and this difference comes down to how much I am willing to risk that there isn’t a problem. Considering there doesn’t seem to be advantages to dapagliflozin use that can’t be

presently enjoyed by patients with one of the other anti-diabetic drugs, I am not willing to risk much. This is where risk tolerance acts as the fulcrum to balance uncertainties versus the potential advances in disease therapy that a drug may offer, all of which must be viewed under the prism of seriousness of the risk under consideration.

The Hy's Law case is a different issue. Perhaps there is another cause for the hepatotoxicity that neither we nor the sponsor were able to uncover. If that is the case, we should not see another case with more exposure data and the potential number of DILI cases per exposure quoted in my review will become less and less. If however, we accumulate more data and another case should occur, and the rates of potential DILI are those that I have speculated upon in my review, I think that approval of dapagliflozin would be tenuous. In any regard, further data will either decrease the rates as presented above, or another case will present and either scenario will help us to make some approval decisions.

I recommend a Complete Response action for this cycle. The sponsor will need to provide more data demonstrating that dapagliflozin does not cause bladder cancer and does not cause DILI at the rates mention in my review.

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/s/  
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CURTIS J ROSEBRAUGH  
01/17/2012

## Division Director's Memo

<b>Date</b>	December 22, 2011
<b>From</b>	Mary H. Parks, M.D.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	202293
<b>Supplement #</b>	
<b>Applicant Name</b>	Bristol-Myers Squibb
<b>Date of Submission</b>	December 27, 2010
<b>PDUFA Goal Date</b>	October 27, 2011, 3-month extension, January 27, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Dapagliflozin
<b>Dosage Forms / Strength</b>	5- and 10-mg tablets
<b>Proposed Indication(s)</b>	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
<b>Action/Recommended Action for NME:</b>	Complete Response

### 1. Introduction

Dapagliflozin is a first-in-class anti-diabetic therapy employing a novel mechanism of action that is not dependent upon insulin release or improving insulin sensitivity. Dapagliflozin is a sodium glucose cotransporter-2 (SGLT2) inhibitor developed to treat hyperglycemia in T2DM through the inhibition of glucose reabsorption in the proximal tubules of the kidneys.

Glucose crosses cell membranes via membrane-associated carrier proteins or glucose transporters. These glucose transporters include facilitative glucose transporters (GLUT) and the sodium glucose cotransporters, of which SGLT1 and SGLT2 are best characterized. SGLT1 is located predominantly in the intestine, whereas SGLT2 is predominantly expressed in the S1 segment of the renal proximal tubules, where it is responsible for the reabsorption of approximately 90% of glucose filtered through the nephron.

The control of hyperglycemia through an induced glucosuria may also result in several desired effects such as weight loss from urinary caloric loss and reduced blood pressure from the diuretic effect of the drug. However, efficacy is dependent upon the amount of glucose delivered to the nephron, hence a decline in glomerular filtration rate (GFR) from renal impairment will result in diminished efficacy, an important limitation for an anti-diabetic therapy given the prevalence of renal disease in the diabetes population.

Bristol-Myer-Squibb (BMS) and AstraZeneca have conducted a diabetes development program similar to several recently approved anti-diabetic therapies. This included evaluation of the efficacy and safety of dapagliflozin as monotherapy and combination therapy alongside several commonly prescribed anti-diabetic agents. In addition, a meta-analysis was conducted

to evaluate cardiovascular safety of dapagliflozin in accordance with the December 2008 Guidance for Industry.<sup>1</sup>

## 2. Background

The original NDA was submitted on December 27, 2010 and included full datasets for 26 clinical pharmacology studies, 3 Phase 2b and 11 Phase 3 studies. There were 7 ongoing studies at the time of NDA submission with some study reports provided at the 4-month safety update (4MSU). The original review of this NDA leading up to the July 19, 2011 advisory committee meeting focused primarily on the completed Phase 2b and Phase 3 studies for clinical efficacy and safety. Following the AC meeting, FDA requested additional data from ongoing clinical trials which resulted in a major amendment and a 3-month PDUFA clock extension.

This memo incorporates findings from the original NDA database and the updated data from the major amendment.

## 3. CMC/Device

Please see reviews by Drs. Ramaswamy and Xsern. CMC has recommended approval of this NDA with no postmarketing commitments or required studies. The commercial drug product is an immediate-release, film-coated tablet available in 5- and 10-mg strengths. At present, CMC has approved an expiry of 24 months for drug products packaged in HDPE bottles with (b) (4) and blister packages stored under conditions of 25°C (77°F) with excursion of 15-30 C (59-86°F).

Please see the biopharmaceutics review of Drs. Minerva Hughes, Angelica Dorantes, and Patrick Marroum. The disintegration testing proposed by the applicant has been accepted with caveats. Action letter should convey that in vitro dissolution will be necessary to support certain post-approval changes in accordance with existing FDA guidance documents and regulations. Additionally, ongoing registration stability studies should continue to monitor tablet dissolution and disintegration through the end of the study protocol. Please see their review dated May 26, 2011.

## 4. Nonclinical Pharmacology/Toxicology

Please see the reviews by Drs. Mukesh Summan and Todd Bourcier for details of the nonclinical pharmacology/toxicology program. Their overall recommendation is for approval of this NDA. Several key findings from their review which will need special mention in this memo are summarized below.

### Carcinogenicity

The carcinogenic potential of dapagliflozin was studied in two nonclinical lifetime rodent

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<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>

studies. In both rat and mouse studies, there were no statistically significant dose-response relationship or differences between controls and treated groups in survival. The statistical reviewer identified benign keratoacanthoma in the rat study and malignant lymphoma in the mouse study, as tumors with a statistically significant increase when compared to control. No dose-response was observed with these tumor findings and the increase was noted only in the medium-dosed treatment group. An increase in these two tumor types was not observed in the highest dose tested which corresponded to > 130-fold MRHD in the rats and > 70-fold MRHD in the mice. Overall, the two carcinogenicity studies did not identify a cancer signal of clinical significance. Concerns of carcinogenicity associated with dapagliflozin arose only from the clinical trial database in which there was an imbalance in the number of breast and bladder cancers, not favoring dapagliflozin.

The only noteworthy bladder finding from the carcinogenicity studies was increase dilatation which may be due to the increased urine volume from the pharmacologic action of the drug. In the mouse study, there was a slight increase in urinary bladder calculus in the high dose males (4) versus the two controls (0 and 1); no such observation was noted in female mice. The clinical relevance of this finding is unknown; however, it should be noted that all clinical bladder tumors were in male patients and increased formation of urinary calculi was a proposed mechanism for nonclinical bladder cancer findings associated with PPAR-agonists. However, unlike PPAR-agonists, there are no histologic findings of bladder neoplasm and the numerically higher bladder calculi occurred at 131x MRHD.

Mammary tumors were not identified as a significant finding in either of these two carcinogenicity studies.

Dapagliflozin was neither genotoxic nor clastogenic.

In summary, the nonclinical carcinogenicity evaluation did not identify this drug product to carry a serious signal of carcinogenicity. However, there remains the imbalance in bladder and breast neoplasms in the clinical development program. I concur with Dr. Bourcier that no additional nonclinical studies should be required of the company to further characterize this potential risk.

### **Reproductive and Developmental Toxicology**

Pre- and postnatal studies and exposure during lactation revealed dilatation of the renal pelvis and reduced weight or weight gain. These findings occurred at < 15x the clinical dose; hence, a 'no-effect dose' was not identified and it is presumed that the adverse nonclinical findings can occur near clinical exposure. The timing at which these renal effects were noted is thought to correspond with the 2<sup>nd</sup> and 3<sup>rd</sup> trimester of human pregnancy. Please see the discussion under Section 11 regarding the recommended pregnancy category labeling based on these findings.

## **5. Clinical Pharmacology/Biopharmaceutics**

Please see review authored by Drs. Ritesh Jain, Jayabharathi Vaidyanathan, Anshu Marathe, Christine Garnett, Hobart Rogers, and Michael Pacanowski. OCP's overall recommendation

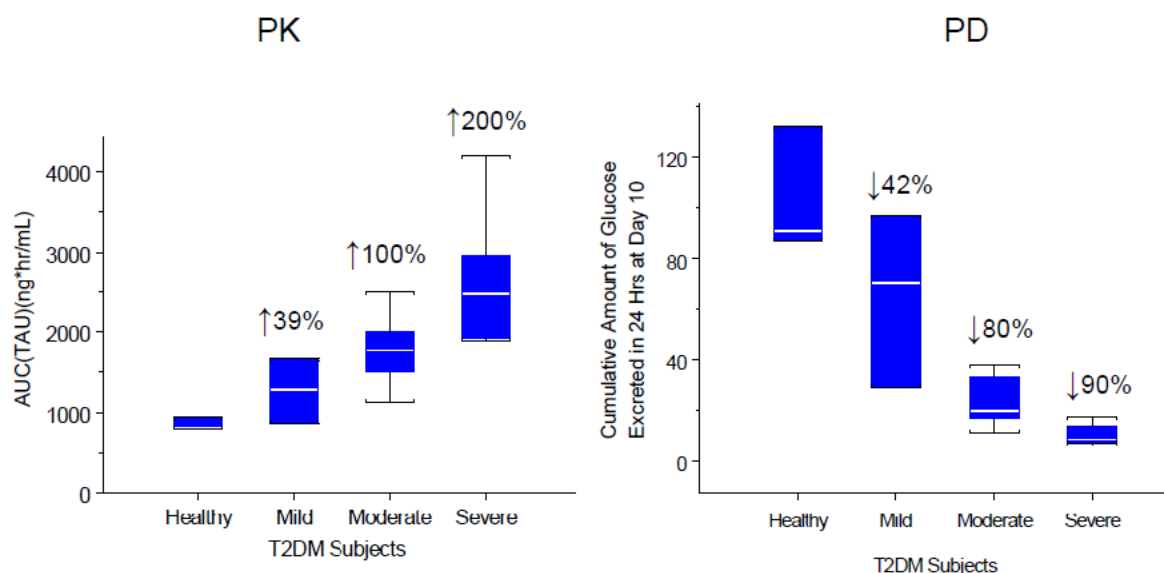


is approval of NDA 202-293.

There were a total of 26 Clinical Pharmacology studies conducted to evaluate the PK/PD of dapagliflozin, PK and limited safety in special populations (renal and hepatic impairment), drug-drug interactions, and biopharmaceutics including food effect studies. These studies support the following high-level conclusions:

- Dapagliflozin is rapidly absorbed with T<sub>max</sub> ranging between 0.5 to 2 hrs after single and multiple dose PK studies under fasting conditions. Drug half-life ranged from 11 to 17 hours. There is minimal food effect supporting a recommendation for dosing regardless of meals.
- Dapagliflozin is extensively metabolized to the primary metabolite, dapagliflozin 3-O-glucuronide by UGT1A9 with little role of CYP enzymes in its metabolism.
- In vitro and vivo DDI studies did not reveal any clinically relevant changes in dapagliflozin or co-administered drug exposures evaluated (see Table 19 from OCP review).
- Exposure-response studies support the doses selected for Phase 3 trials and proposed marketing (5 and 10 mg).
- No significant effect on the QTc interval as determined by a tQT study.
- Drug exposure increases with worsening renal impairment; however, urinary glucose excretion decreases. This relationship is illustrated in the following Figure from the OCP review:

**Figure 5.1. Effect of Renal Impairment on PK and PD (source: Dr. Jain's OCP review)**



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

This observation and the absence of evidence for significant HbA1c reduction in patients with moderate and severe renal impairment were discussed extensively at the advisory committee meeting.

In addition to the impact of decreased GFR on efficacy, a panel member inquired whether proteinuria could impact efficacy through urinary protein binding of dapagliflozin, preventing its interaction at the SGLT-2 receptor. Following the advisory committee meeting, FDA requested that the applicant provide any available clinical data correlating degree of urinary protein excretion with glycemic control. These data were submitted on as part of a major amendment. Please see section 7 below for the summary of these findings.

## 6. Clinical Microbiology

See product quality microbiology review signed by Drs. Steven Fong and John Metcalfe. No deficiencies precluding approval and no postmarketing studies are recommended.

## 7. Clinical/Statistical-Efficacy

Please see reviews of Drs. Jonathan Norton and Somya Dunn for details regarding study designs, patient demographics, disposition, and secondary efficacy results. My memo will only highlight the findings on the primary endpoint, HbA1c, including effect of drug in patients with moderate renal impairment.

### Dose Selection

Three Phase 2b studies were conducted which evaluated the efficacy and safety of a broad range of doses of dapagliflozin in T2DM. All three studies were of 12 weeks duration and have been described in detail in the reviews of Drs. Dunn and Irony.

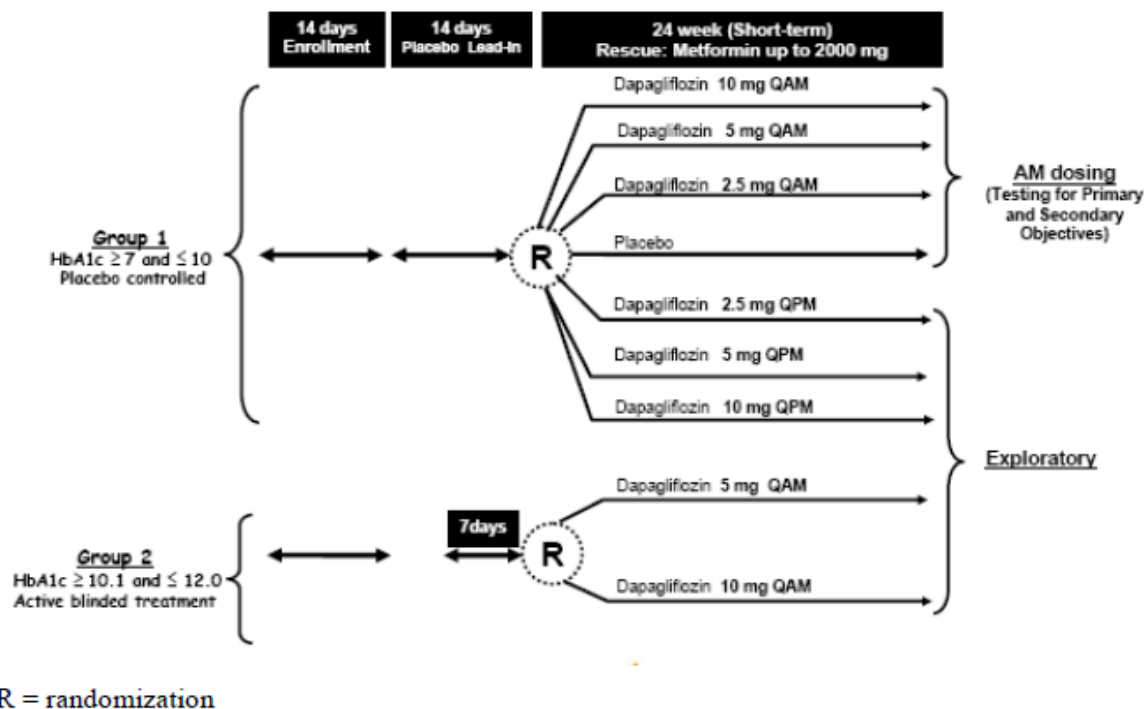
Based on the Phase 2b study findings, the applicant selected dapagliflozin 2.5, 5, and 10 mg for evaluation in its Phase 3 program. There were 11 Phase 3 trials; all had a minimum 24-week double-blind, controlled treatment period and all but three had a long-term site and subject blinded treatment period of variable duration (24 to 156 weeks). These trials differed in their assessment of dapagliflozin as a monotherapy or combination therapy and in the population studied (drug-naïve, inadequate control on prior therapies, renal impairment).

### Monotherapy

There were two Phase 3 monotherapy trials comparing dapagliflozin to placebo. Study *MB102013* investigated dapagliflozin at doses of 2.5, 5, and 10 mg versus placebo and also evaluated effects of AM or PM dosing on efficacy. The study also had a separate group of patients with poorly controlled diabetes (HbA1c > 10.1% and ≤ 12.0%) who were randomized

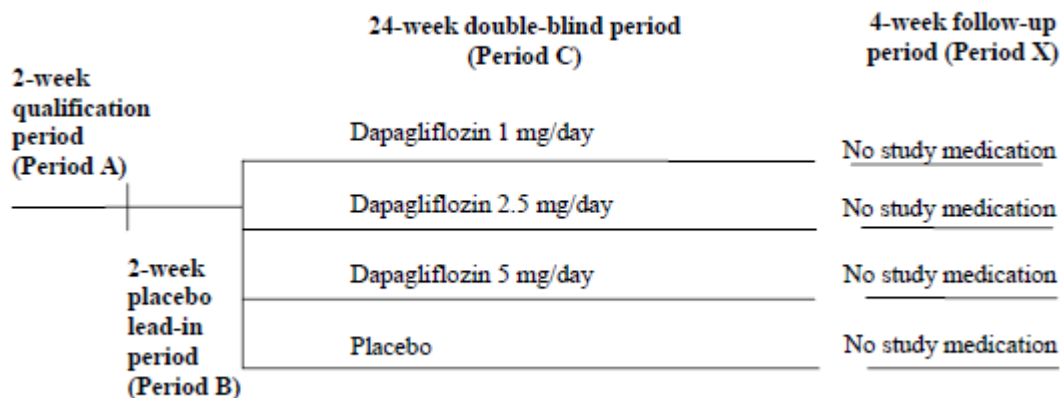
to either dapagliflozin 5 mg or 10 mg, both QAM. The following schematic illustrates the study design:

**Figure 7.1 Study MB102013 Study Design**



Study *MB102032* investigated dapagliflozin at 1, 2.5, and 5 mg doses versus placebo as illustrated in the following schematic:

**Figure 7.2 Study MB102032 Study Design**



With exception for the exploratory efficacy assessment in MB 102013 of dapagliflozin in patients with poorly controlled T2DM, both these studies had similar inclusion/exclusion criteria. They enrolled drug-naïve patients (patients who received prescription diabetes

medication for < 24 weeks since original diagnosis also allowed to enroll) and who had HbA1c  $\geq 7$  and  $\leq 10\%$  at enrollment visit. Both trials included an assessment of dapagliflozin 2.5 and 5 mg, and in both trials, these doses resulted in statistically significant reductions in HbA1c compared to placebo. The 10 mg dose in Study 2013 was also an effective dose. The following table summarizes these results based on the primary analysis using a LOCF imputation for missing data/discontinuations. Dr. Norton's review dated September 8, 2011, included three other sensitivity analyses and while the treatment effect changed somewhat across the different methodologies, dapagliflozin 2.5 and 5 mg were still shown to be statistically significantly effective at lowering HbA1c.

**Table 7.1. Efficacy of Dapagliflozin Monotherapy**

	Study 102013				Study 102032*		
	pbo	2.5mg	5mg	10mg	pbo	2.5mg	5mg
N	72	64	61	65	68	72	66
Baseline mean HbA1c	7.8	7.9	7.8	8.0	7.8	8.1	7.9
Wk 24 LOCF mean	7.6	7.3	7.1	7.1	7.8	7.3	7.1
Adj mean chg from baseline	-0.23	-0.58	-0.77	-0.89	0.02	-0.72	-0.82
difference from pbo	---	-0.35	-0.54	-0.66	---	-0.74	-0.84
p-value vs pbo		0.02	0.0005	<0.0001		<0.0001	<0.0001

source: Tables 2.5.26 for Studies 2013 and 2032 from CSR Module 5.3.5 (1/5/2011 submission)

\*Study 102032 not reviewed by FDA statistician

### Add-on Therapy

The efficacy of dapagliflozin added on to a variety of oral anti-diabetics (metformin, sulfonylureas, pioglitazone) and insulin was evaluated in five Phase 3 trials. All but one of these trials compared dapagliflozin add-on to placebo add-on. Study D1690C00004 was an active-control non-inferiority trial comparing dapagliflozin added on to metformin versus glipizide added on to metformin.

Overall, dapagliflozin added-on to metformin, SU, or a TZD achieved statistically greater HbA1c reductions than placebo. The following summarizes the range of expected efficacy across these different studies based on data provided in the individual study reports submitted by the applicant with original NDA database.

- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to metformin background therapy achieved a range of **-0.38 to -0.54** difference from placebo in HbA1c reduction (MB102014)
- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to glimepiride background therapy achieved a range of **-0.44 to -0.68** difference from placebo in HbA1c reduction (D1690C00005)
- Dapagliflozin 5 and 10 mg, added onto pioglitazone background therapy, achieved a **-0.4 to -0.55** difference from placebo in HbA1c reduction (MB102030)
- Across the doses of 2.5, 5 and 10 mg, dapagliflozin added on to insulin background therapy achieved a range of **-0.45 to -0.60** difference from placebo in HbA1c reduction (D1690C00006)

Study C00004 was different from other glycemic efficacy studies in that efficacy analysis was conducted at Week 52; this was an active-controlled trial of dapagliflozin compared to glipizide in patients on background metformin; and this trial did not include any rescue medication. The primary objective was to demonstrate non-inferiority of dapagliflozin to glipizide based on a non-inferiority margin of 0.35, which was met, as shown below from the applicant's clinical study report.

EFFICACY ENDPOINT STATISTICS	DAPA + MET (N=400)	GLIP + MET (N=401)
PRIMARY EFFICACY ENDPOINT		
HbA1c (%) AT WEEK 52 (LOCF)		
N#	400	401
BASLINE MEAN (SD)	7.69 ( 0.855)	7.74 ( 0.886)
WEEK 52 LOCF MEAN (SD)	7.19 ( 0.760)	7.21 ( 1.090)
MEAN CHANGE FROM BASELINE (SD)	-0.51 ( 0.746)	-0.53 ( 1.017)
ADJ. MEAN CHANGE FROM BSL. (SE) (a)	-0.52 ( 0.0403)	-0.52 ( 0.0402)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	( -0.60, -0.44)	( -0.60, -0.44)
DIFFERENCE FROM GLIP + MET (SE) (b)	0.00 ( 0.0569)	
95% CI FOR DIFFERENCE FROM GLIP + MET	( -0.11, 0.11)	
NON-INFERIORITY P-VALUE VS. GLIP + MET (*)	<.0001 *	

### Efficacy in Patients with Renal Impairment

Based on the mechanism of action of SGLT-2 inhibitors, it was anticipated that efficacy would be reduced with worsening renal function as the amount of filtered glucose delivered would be reduced with declining GFR. As noted under Section 5.0 of this memo, the renal PK study provided evidence that despite increasing drug levels with worsening renal function there was reduction in urinary glucose output. In the dedicated renal impairment clinical trial (Study 2029), dapagliflozin 5 and 10 mg were compared to placebo in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73m<sup>2</sup>). Neither of these doses achieved statistically significant difference in HbA1c reduction after 24 weeks compared to placebo. The applicant further analyzed the efficacy findings by subdividing the patients into two subgroups of 3A and 3B renal impairment and argued that patients with less severe moderate renal impairment (3A patients with eGFR 45-59 mL/min/1.73m<sup>2</sup>) had a greater mean HbA1c reduction from baseline than 3B patients (eGFR 30-44 mL/min/1.73m<sup>2</sup>); however, as Dr. Norton points out, the treatment difference remains nonsignificant. Even if a significant difference was demonstrated, this was an ad-hoc analysis for a trial that had failed on its pre-specified primary efficacy analysis. Please see the clinical and statistical reviews for discussion of the applicant's pooled analysis of studies to further investigate efficacy in patients with different renal impairment status. In my opinion, this analysis does not supplant the findings from a dedicated renal impairment study whose primary objective was to evaluate safety and efficacy in this special population.

The results of the two recently submitted clinical trials, Studies 18 and 19, included a larger proportion of patients with moderate renal impairment than enrolled in the original NDA. It is interesting to note that the overall glycemic efficacy of dapagliflozin 10 mg in these two trials is less than observed in previously reviewed trials. Whereas the efficacy of this dose is reported to be approximately 0.54 to 0.66, relative to placebo in a variety of clinical settings, it

was only 0.4 to 0.46 in these two trials. Dr. Dunn speculates that this may have been the result of more patients with moderate renal impairment enrolled which contributed to the overall modest results. The applicant does provide a breakdown of efficacy results by baseline eGFR in both these studies which was summarized in Dr. Norton's review. Again, it is evident that declining renal function was associated with a lower treatment effect for HbA1c reduction.

During the Advisory Committee meeting, a panel member inquired whether the reduced efficacy is also a function of proteinuria. As dapagliflozin is highly protein bound and only the unbound fraction of drug interacts with the SGLT-2 receptor, protein in the urine may further hinder drug-receptor binding contributing to the reduced efficacy. The concern raised by this panel member is that many diabetics have proteinuria without reduced GFR. To investigate this further, the applicant submitted nonclinical data and analyses from their renal PK study. As summarized in Dr. Dunn's review, both these data sources provided no evidence that HbA1c reduction was affected by urine protein concentration.

#### Conclusions on Glycemic Efficacy

The proposed doses for marketing of dapagliflozin, 5 and 10 mg, were shown to reduce HbA1c significantly relative to their comparators across different patient populations (treatment-naïve versus long-standing diabetes) and as monotherapy or in combination with other commonly prescribed anti-diabetics. In the spectrum of available therapies, the efficacy achieved with dapagliflozin is modest (range 0.4-0.7%) which is further attenuated in patients with moderate to severe renal impairment. This reduced efficacy is rather problematic for an anti-diabetic agent as the patient population to be treated with dapagliflozin is predisposed to declining renal function with prolonged duration of disease. Its use would be limited to only those with normal renal function or mild renal impairment and the patient's renal status would need to be monitored so that a different anti-diabetic would be initiated once eGFR declines to the range of moderate renal impairment. The diminished efficacy of dapagliflozin with declining renal function might limit its use to patients with early onset of disease, a population in which metformin is often considered 1<sup>st</sup> line therapy.

## **8. Safety**

The original NDA data submission and 4MSU contained cumulative exposure data from the combined short-term and long-term periods of all Phase 2b and 3 studies of 4009 patient-years (pt-yrs) in dapagliflozin versus 1682 patient-yrs in control. With the major amendment, pt-yr exposures have increased to approximately 5700 and 3100, respectively. Please see Dr. Somya Dunn's review for a more complete summary of safety findings in this NDA. Dapagliflozin treatment was associated with a higher rate of genital-urinary adverse events (e.g., urinary tract and genital infections) and volume depletion/hypotensive episodes. Preclinical findings of increased trabecular bone formation and calciuria in some animals studies also led to a careful review of fracture risk associated with dapagliflozin. Overall, these events did not result in a serious outcome or the risks could be minimized with appropriate dosing in a vulnerable population (e.g. hypotension). A consult to the Division of Reproductive and Urologic Products on fracture findings yielded a conclusion that there was no indication of a clinically significant effect of drug on bone loss or fracture. Consequently,

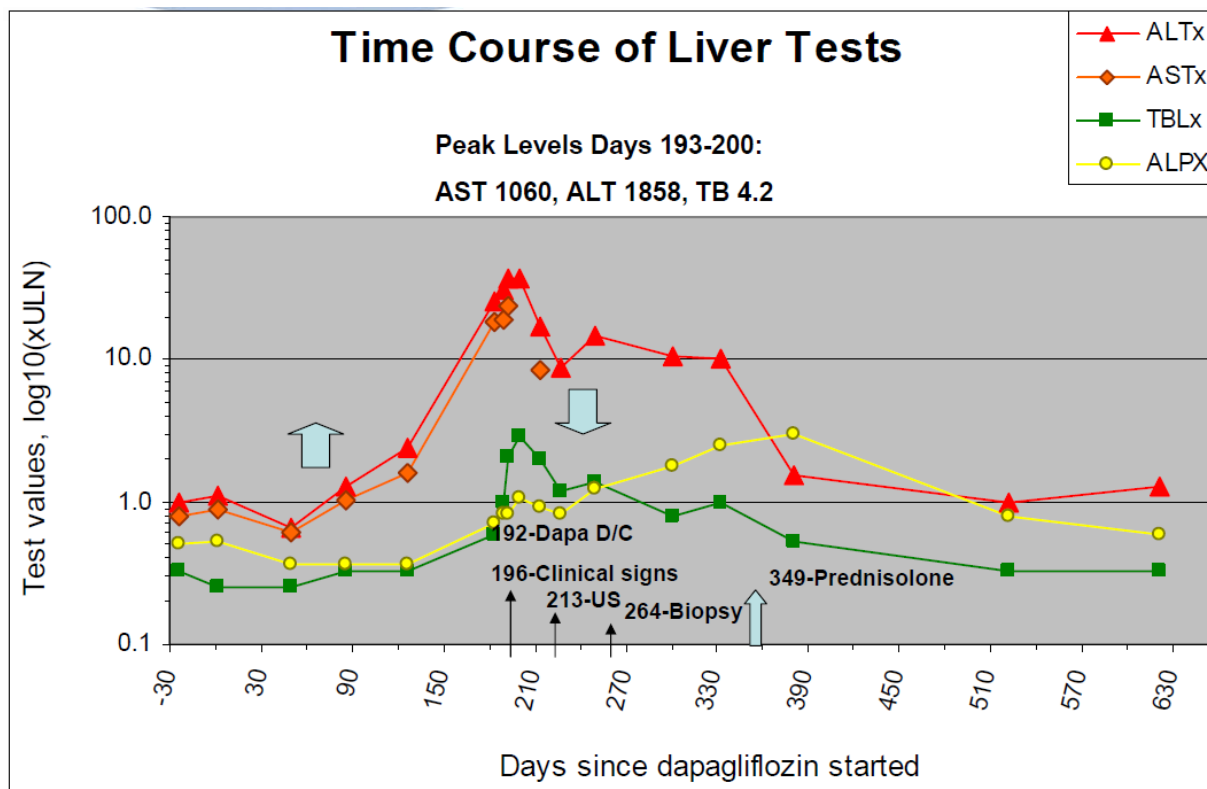
these are safety findings that can be conveyed through appropriate labeling of dapagliflozin. My memo will focus only on the safety findings that require more consideration in the benefit-risk calculus for approval of this NDA. These safety concerns relate to liver toxicity, bladder and breast cancer, and cardiovascular safety.

### Hepatic

A case of Hy's Law (ALT or AST > 3x ULN with serum total bili > 2x ULN without any causative explanation such as viral etiology, exposure to a known hepatotoxin or preexisting or acute liver disease) was identified in the Phase 2b/3 pool reviewed at the time of the AC meeting. This case was determined by FDA hepatologists to be a probable drug-induced liver injury (DILI) case. This case has also been summarized by Drs. Dunn and Irony in their reviews but for completeness, I will highlight some key features here including the timeline of hepatic enzyme values.

The case is of D1690C00004-4402-6, a 78-year old man from India whose concomitant medications included atorvastatin, cromolyn, lecanlidipine, atenolol, parendopril, naproxen, acetylsalicylic acid and a couple of herbal products. The patient was diagnosed as a compound heterozygote for hemochromatosis.

**Figure 8.1 Time Course of Lab and Clinical Findings in Hy's Law Case (Source: Dr. Dunn's FDA presentation at AC meeting)**



This patient's baseline ALT values were mildly elevated but began to increase approximately 3 months after initiating drug and peaked at approximately 6 months. Dapagliflozin was discontinued on Day 192 but clinical signs and symptoms of abdominal pain, nausea and jaundice appeared shortly thereafter prompting an ultrasound on Day 213 and later a biopsy on Day 264. The biopsy report had features suggestive of autoimmune hepatitis but other laboratory tests (anti-smooth muscle Ab, mitochondrial Ab, ANA) which would support such a diagnosis were all negative. Regardless, the patient was treated with high-dose steroids starting on Day 349, at which point, hepatic enzymes had already been declining. Serology results ruled out a viral hepatitis etiology. FDA hepatology consult dated June 21, 2011 concluded that 'based on currently available data, there is one Hy's Law case in which a causal association with dapagliflozin is "Probable"'.

An updated consult for 7 additional cases of liver injury identified up to July 15, 2011, and submitted with the 3-month extension, did not identify any additional cases of DILI. Among the 7 was a report of a 71-year old Argentinian man with HTN and history of CAD who developed nausea, vomiting, and diffuse abdominal pain approximately 9 months after initiating dapagliflozin. The case is summarized by Dr. Seeff in his review dated November 21, 2011. An external report of alcohol intake prior to the event was received from a relative. Hepatic enzymes increases initially were of concern due to the magnitude of ALT elevation (150-504) with an elevated total bilirubin of 1.7-4.3. AST values were also elevated to a greater magnitude. The clinical course of this patient was unusual for a case of DILI as there was initial improvement in transaminases after study drug discontinuation but a secondary rise occurred two weeks later, but predominantly in alkaline phosphatase and indirect bilirubin. Although an exact diagnosis for this hepatic injury could not be assigned, Dr. Seeff felt that this was unlikely due to dapagliflozin hepatotoxicity.

In the original application, the incidences of ALT and AST elevations > 3x, 5x, 10x, and 20x ULN were similar between dapagliflozin and control groups. This pattern did not change with additional pt-yr exposure provided in the 3-month extension.

**Table 8.1. Hepatic Enzyme Elevations in Phase 2b/3 Controlled Trials**

	Dapagliflozin	Comparator
Original dataset including 4MSU		
N	4287	1941
AST > 5x ULN	0.3%	0.4%
AST > 10x ULN	0.1%	0.2%
ALT > 5x ULN	0.4%	0.5%
ALT > 10x ULN	< 0.1%	0.1%
Updated dataset		
N	5501	3184
AST > 5x ULN	0.2%	0.3%
AST > 10x ULN	0.1%	0.1%
ALT > 5x ULN	0.3%	0.4%
ALT > 10x ULN	0.1%	0.1%
ALT > 20x ULN	<0.1%	<0.1%



While this is reassuring, the single case of dapagliflozin-induced liver injury remains worrisome. The crux here is how this one case translates to potential risk of dapagliflozin to cause irreversible liver failure in a broader exposure of patients so that we can weigh this risk in the overall benefit-risk calculus.

As discussed in FDA's Guidance for Industry titled, *Drug-induced Liver Injury: Premarketing Clinical Evaluation*,<sup>2</sup> "a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2x ULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases". The Guidance goes further to define Hy's Law as having the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

As noted in Table 8.1, there were no imbalances between dapagliflozin and comparators on incidence of marketed transaminase elevation (criterion 1) but Patient D1690C00004-4402-6 does meet criteria for Hy's Law. At the time of NDA submission and the 4MSU, approximately 2500 patients had received dapagliflozin for at least 6 months, a duration of exposure considered sufficient to evaluate potential signals for drug hepatotoxicity. Hence, 1/2500 patients exposed to dapagliflozin for at least 6 months developed Hy's Law, which would translate into approximately 1 in 25,000 patients exposed for 6 months at risk for serious DILI. With the 3-month extension, there have been 4394 patients exposed to dapagliflozin for at least 6 months. Without any additional cases of Hy's Law since the original NDA database, the potential risk for serious DILI due to dapagliflozin is approximately 1/44,000, an estimate to be considered in the overall benefit-risk calculus.

### **Cancer**

During the NDA review, numeric imbalances in bladder and breast cancers, not favoring dapagliflozin, were identified. To summarize, at the time of the Advisory Committee meeting there were 9 cases of bladder cancer in the dapagliflozin group versus one in comparator; all events occurred in male patients. There were nine breast cancer cases in the dapagliflozin group versus one in comparator; all events occurred in female patients. With the 3-month extension, no new cases of bladder cancer have been reported and three new cases of breast cancer in female patients were identified: one in the dapagliflozin group and 2 in comparator.

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<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Several reviews have been entered into DARRTS summarizing these cases and the risk estimates. Please refer to reviews of Drs. Dunn and Irony for a clinical description of these cases risk, time of diagnosis with respect to study drug exposure, and risk factors for these cancers in the study population. I will note that there were no apparent imbalances in the treatment groups at baseline to explain the numeric imbalance in cancer diagnosis. Specifically for bladder cancer, we could not point to evidence that the diagnoses in dapagliflozin group were due to enhanced monitoring with urinalyses as a result of urogenital adverse events to attribute the imbalance to a detection bias.

#### Bladder Cancer

From the pooled Phase 2b/3 unblinded trials with a safety cut-off date of July 15, 2011, the incidence rate ratio based on an overall stratified analysis of treated male subjects only was as follows:

**Table 8.2. Incidence Rate Ratio for Bladder Cancer- Overall Stratified Analysis of Phase 2b/3 Controlled Pool (Male subjects only)**

	Dapagliflozin N=2970	Comparator N=1825
# of events	9	1
# in treatment group	1626	1150
ttl subject-yr at risk	1979	1333
incidence rate ratio vs control (95% CI)	5.38 (0.71, 242.52)	

only trials with an event were included in analysis

Source: Sponsor submission 10/27/11

This risk estimate was similar to that obtained by Dr. Christian Hampp, FDA epidemiologist. Different methodologies were used by the applicant and FDA to calculate incidence rate differences with the applicant's yielding a wider confidence interval and overall nonsignificant finding whereas FDA's analysis yielded otherwise.

**Table 8.3 Incidence Rate Differences as Calculated by Applicant and FDA**

	Dapagliflozin N=2970	Comparator N=1825
# of events	9	1
# in treatment group	2970	1825
ttl subject-yr at risk	3166	1854
applicant's incidence rate difference	0.209%	
95% CI	(-0.305%, 0.688%)	
p-value	0.72	
FDA's incidence rate difference	0.237%	
95% CI	(0.020%, 0.455%)	
p-value	0.03	

Dr. Hampp provides an explanation for the different findings in his review. Neither methodology can be selected as superior to the other. The differences in results likely reflect the limitations in ascribing risk when the signal is derived from multiple sources based on low event numbers.

Dr. Hampp also compared the rates of bladder cancer to the background rates in the U.S. based on incidence rates extracted from the Surveillance Epidemiology and End Results (SEER) database. His review provides an excellent and detailed account of his methodology, application, and limitations of the results. I will not discuss his findings for this analysis and refer the reader to his review dated November 29, 2011. While the results are intriguing and can generate much debate, they do not allow us to dismiss the numeric imbalance of bladder cancer cases observed in the controlled clinical trials.

The applicant argues that the imbalance may have occurred by chance, citing the wide CIs of the incidence rate ratios and rate differences. In favor of the applicant's argument would be the absence of a carcinogenic or mutagenic finding from the nonclinical program. This is in contrast to the ongoing concern of bladder cancer risk with pioglitazone whose nonclinical program detected a risk in one rodent species which have since been supported by clinical trial and epidemiologic data.

The timing of diagnosis to drug exposure might also call into question a role of drug in some of these cases, as 4 out of nine were diagnosed at < 6 months of drug exposure. Such a short duration of exposure makes it unlikely that dapagliflozin *caused* the cancer. However, one would also have to exclude the comparator case which was diagnosed < 6 months of exposure. This still leaves us with a numeric imbalance of 5 dapagliflozin cases detected between Days 393-727 versus none in comparator.

#### Breast Cancer

From the pooled Phase 2b/3 unblinded trials with a safety cut-off date of July 15, 2011, the incidence rate ratio based on an overall stratified analysis of treated female subjects only was as follows:

**Table 8.4. Incidence Rate Ratio for Breast Cancer- Overall Stratified Analysis of Phase 2b/3 Controlled Pool (Female subjects only)**

	Dapagliflozin N=2531	Comparator N=1359
# of events	10	3
# in treatment group	1816	1022
ttl subject-yr at risk	2264	1153
incidence rate ratio vs control (95% CI)	1.90 (0.46, 11.23)	

Dr. Hampp pointed out that of the 3 cases in comparator group, one was classified as ductal carcinoma *in situ*. Because this histologic form has a low potential for invasion and spread, an

analysis was also performed by him wherein this case was excluded. The incidence rate ratio was higher at 2.76 but the 95% CI still included 1.0 with a corresponding two-sided p-value of 0.242. Both FDA and applicant analyses of incidence rate differences yielded non-significant findings. Similar to the summary of bladder cancer, I will not discuss analyses applying SEER data.

The applicant again argues that the numeric imbalance in breast cancer may be a chance finding. Similar to bladder cancer, no nonclinical findings of excess mammary tumors were detected in the carcinogenicity program. Unlike bladder cancer, all 10 cases of breast cancer in the dapagliflozin group were detected < 1 year after exposure to dapagliflozin with two within the first 8 weeks of treatment initiation making it highly unlikely to be due to drug exposure. Of the remaining 8 cases, four were diagnosed < 6 months and four between 6 and 12 months. I believe all these observations alongside a consistent non-significant increase risk from several analyses make for a stronger argument of a spurious finding for breast cancer.

### **Cardiovascular Safety**

In the original submission, the applicant performed a meta-analysis of 14 Phase 2 and 3 trials. The primary endpoint was a composite of time to first event of CV death, MI, stroke, and hospitalization for unstable angina. All events were adjudicated in a blinded fashion by an independent endpoints committee. The pre-specified primary analysis compared all dapagliflozin treatment groups (excluding doses below 2.5 mg) to comparators (placebo and active controls) and yielded a hazard ratio of 0.67 (98% CI: 0.38-1.18). These findings were confirmed by FDA's sensitivity analysis on the primary composite endpoint and analyses of secondary endpoints also revealed similar point estimates. Overall, the results of original meta-analysis were reassuring and met the agency's December 2008 Guidance to Industry for ruling out unacceptable CV risk in the pre-market application.

The consistently favorable point estimate in multiple analyses have led some to believe this drug might carry a protective effect such that this "benefit" could offset the uncertain safety findings of liver toxicity and cancer risk. The potential for cardioprotection could conceivably be due to favorable effects of dapagliflozin on weight reduction and blood pressure lowering, as summarized by Dr. Irony. However, subsequent to the advisory committee meeting, FDA requested that the applicant perform an updated CV meta-analysis to include additional data from trials that were ongoing at the time of the 4 month safety update. The reason for this request was to determine if additional data and more CV events from ongoing trials might further bolster the original meta-analysis findings. Clearly a continued favorable finding in the CV meta-analysis would better support an overall favorable benefit-risk conclusion.

The updated meta-analysis included 19 double-blind, controlled trials of at least 12 weeks duration. There were 8682 patients (5492 in dapa, 3184 in comparator) who contributed to the risk assessment in the updated meta-analysis. Included among these 19 trials were two new studies in high CV risk patients. These two trials were designed as 24-week, placebo-controlled trials in patients with a history of CVD (coronary heart disease, stroke, TIA or peripheral artery disease). At least 40% of randomized subjects had to be > 65 years of age. In addition, one trial required that all patients have a diagnosis of hypertension. The two trials have controlled extensions out to two years and are ongoing. The updated analysis also

included additional events from 4 trials previously reviewed but ongoing at the time of advisory committee meeting and 3 new clinical trials (two 12-week mode of action studies and an add-on to DPP4 inhibitor trial). For this memo I will only discuss the results from the primary composite endpoint of MACE plus hospitalization for unstable angina and MACE alone based on the Cox Proportional Hazards methods. Please see Dr. Abraham's review dated 11/22/11 for details of sensitivity analyses, secondary endpoints, and subgroup analyses. In general, these additional analyses were consistent with the overall primary results.

With the inclusion of the high CV risk studies, the demographics of the patient population in the updated meta-analysis differed from the original meta-analysis. The following table highlights some of these differences.

**Table 8.5. Population Characteristics of the Two Meta-analyses**

	Original Meta-Analysis		Updated Meta-Analysis	
	Dapa n=4287	Comparator n=1941	Dapa n=5498	Comparator n=3184
Mean age, yrs	55.9	56.5	57.1	58.4
Duration of T2DM, yrs	6.1	5.9	7.3	7.9
> 10 yrs, %	22.2%	21.1%	34%	35.8%
Males	50.8%	52.5%	54%	57.3%
Hx of CVD	19.6%	18.2%	33.2%	43.3%
Hx of HTN	61.5%	64.3%	67.6%	74%
Hx of Dyslipidemia	49.4%	48.8%	55.7%	60.1%
Hx of CHF	2.2%	1.7%	4.3%	5.1%

Source: Tables 5 and 4 of the sponsor's CV meta-analysis and supplementary report, respectively

While it is evident that there are more patients with CV risk factors in the updated meta-analysis, it is also noteworthy that the balance between dapagliflozin and comparator for some of these risk factors/characteristics is not maintained in the updated meta-analysis. In particular, I've highlighted in yellow the percentage of patients with a history of CVD and HTN in which there are approximately 10% more comparator patients with CVD and 7% with HTN compared to dapagliflozin. In her review, Dr. Abraham noted that this is an artifact of the pooled data and was not observed in the individual trials.

The number of events contributing to the primary composite analysis in this meta-analysis has nearly doubled from 78 in the original meta-analysis to 145. 82 events occurred in the dapagliflozin group versus 63 in the comparator group yielding a HR of 0.82 with 95% CI (0.58, 1.15). The following table summarizes the incidence of the components contributing to the overall primary endpoint results. Nonfatal MIs were the predominant first events.

**Table 8.6 Contribution of Components to the Primary Composite, Number (%)**

	Dapa N=5261	Comparator n=3021
CV death	14 (2.7%)	9 (3.0%)
NFMI	29 (5.5%)	27 (8.9%)

Stroke	19 (3.6%)	13 (4.3%)
Hospitalization for UA	20 (3.8%)	14 (4.6%)
Total	82	63

Source: Sponsor's Table 35, Section 10.3.1 from Supplemental CV events meta-analysis report

An analysis using the Cox proportional hazards model for MACE was also conducted. There were 111 MACE events: 62 in dapagliflozin and 49 in comparator, yielding a HR of 0.79 with a 95% CI (0.54, 1.17). Similar to the primary composite, the most common first event was NFMI.

**Table 8.7. Contribution of Components to the MACE analysis, Number (%)**

	Dapa N=4980	Comparator n=2882
CV death	14 (2.8%)	9 (3.1%)
NFMI	29 (5.8%)	27 (9.4%)
Stroke	19 (3.8%)	13 (4.5%)
Total	62	49

Source: Sponsor's Table 37, section 10.3.1 from Supplemental CV events meta-analysis report

While the HR for the primary composite endpoint and other endpoints in this update meta-analysis are higher, they remain below one and the upper bound of the 95% CI was less than 1.8 and 1.3. The following table summarizes the results for the primary composite and MACE from the original and this updated meta-analysis.

**Table 8.8. Primary Composite and MACE Analyses of Original MA and Updated MA**

	Original Meta-analysis Stratified HR (98% CI)	Updated Meta-analysis Stratified HR (95% CI)
Primary composite of CV death, NFMI, stroke, and hospitalization for UA	0.67 (0.38, 1.18)	0.82 (0.58, 1.15)
MACE (CV death, NFMI, stroke)	0.60 (0.32, 1.10)	0.79 (0.54, 1.17)

Although once again reassuring of CV safety, the impact of the two clinical trials enrolling high CV risk patients was evaluated further to elucidate their contribution to these overall results.

#### Studies D1690C00018 and D1690C00019 (Studies 18 and 19)

In the updated meta-analysis, only 5 additional CV primary composite events were collected from the trials that were ongoing at the time of the original meta-analysis, whereas 62 additional events were derived from the 5 new trials, the bulk of which came from Studies 18 and 19 which contributed 60 events to the primary composite endpoint. Clearly these two trials contributed a significant amount of information (~40% of events) to the overall CV risk estimates making it appropriate to perform separate CV meta-analyses for these two trials.

In addition, these two trials may be more representative of the T2DM patients in which cardiovascular safety of the anti-diabetic agent holds more clinical relevance. In Table 14 from Dr. Abraham's review she clearly highlights the differences between Studies 18 and 19, pooled, versus the other 17 trials in the meta-analysis.

**Table 14: CV Risk Factors of All Trials Excluding High-Risk CV Trials and Pooled High-Risk CV Trials (D1690C00018 and D1690C00019)**

	<b>All Trials Excluding High- Risk CV Trials  (N = 6798)</b>	<b>High-Risk CV Trials (D1690C00018 and D1690C00019) combined (N = 1884)</b>
<b>History of CVD</b>	19.1%	99.5%
<b>History of Hypertension</b>	62.7%	96.2%
<b>History of Dyslipidemia</b>	49.9%	84.2%
<b>History of Congestive Heart Failure</b>	1.9%	14.3%
<b>Renal Function</b>		
Severely Impaired	0.2%	0.1%
Moderately Impaired	10.5%	17.3%
Mildly Impaired	50.8%	59.3%
Normal	38.5%	23.3%
<b>Smoking History</b>		
Never smoked	59.4%	40.3%
Current Smoker	16.4%	14.9%
Former Smoker	24.2%	44.8%
<b>Diabetes Duration</b>		
less than 3 years	44.0%	8.4%
3 – 10 years	34.6%	34.8%
more than 10 years	21.4%	56.8%

Source: Created by reviewer. Dataset: adcv2v2.xpt

Source: Page 41 of FDA Statistical Reviewer (Dr. Anita Abraham) Findings

Dr. Abraham presented the results of the primary composite endpoint for Studies 18 and 19, pooled, compared to the remaining 17 trials in the updated meta-analysis. Although there are no statistically significant effects of CV harm or benefit in both analyses, the HR is notably different with a higher point estimated in the pooled meta-analyses of Studies 18 and 19.

**Table 15: Meta-Analysis Results for All Trials Excluding High-Risk CV Trials and Pooled High-Risk CV Trials (D1690C00018 and D1690C00019)**

	<b>All Trials Excluding High-Risk CV Trials</b>		<b>High-Risk CV Trials (D1690C00018 and D1690C0001) combined</b>	
	<b>Dapagliflozin</b>	<b>All Comparator</b>	<b>Dapagliflozin</b>	<b>Standard of Care</b>
<b>Stratified Hazard Ratio (95% CI)</b>	0.66 (0.42, 1.04)		1.07 (0.64, 1.77)	
<b>Event/PY (% Incidence)</b>	51/5032 (1.01%)	34/2389 (1.42%)	31/706 (4.39%)	29/706 (4.11%)
<b>M-H Incidence Rate Difference (95% CI)</b>	-0.0050 (-0.011, 0.0007)		0.0028 (-0.018, 0.024)	

Source: Created by reviewer. Dataset: adcv2v2.xpt

Oddly, the results on MACE were not different to the primary composite results in the updated meta-analysis of all 19 trials (see Table 8.8 above where the HR were 0.79 and 0.82, respectively, with similar 95% CI excluding 1.3) but the MACE results for Studies 18 and 19 were notably different from the primary composite results with a notably higher point estimate and upper bound of the 95% CI exceeding 1.8.

#### **Summary of MACE using Cox Proportional Hazards Methods for Studies 18 and 19, combined.**

	Dapagliflozin (a)	Comparator (b)
Number of Subjects With at Least One Events	24	19
Number of Subjects in Treatment Group	939	945
Total Subject-Years at Risk	708	709
Subjects with Events/1000 Subject-Year	33.88	26.80
Hazard Ratio Versus Comparator		
Estimate	1.266	
95% CI (c)	(0.693 , 2.311)	

Source: Table 25 from Sponsor's Supplemental CV events Meta-analysis Report

There are clearly fewer events as one starts to parse out the meta-analysis by studies and sub-populations, hence caution should be applied in making conclusions of CV safety of dapagliflozin based on the subgroup analyses of the overall meta-analysis population. But as noted earlier, these two studies contributed ~40% of the events. In fact, the total number of events from these two trials exceeded what was presented in a CV meta-analysis for the recently approved anti-diabetic, linagliptin, which had 34 events across 8 Phase 3 trials.



While we could be criticized for disregarding the overall meta-analysis of all 19 trials or to dismiss the seemingly favorable findings for the other 17 trials, I am troubled by the imbalance in baseline CV risk factors summarized in Table 8.5. Could the higher proportion of patients with CVD or HTN in the comparator group bias towards a lower CV risk estimate for dapagliflozin? When evaluating the baseline demographics of only Studies 18 and 19, there is no evidence that such imbalance is present between dapagliflozin and placebo groups, making this less of a concern with the meta-analysis for just these two studies.

**Table 8.9. Baseline CV Risk Factors in Studies 18 and 19**

	Study 18		Study 19	
	Dapa	pbo	dapa	Pbo
Hx of CVD	98.9%	99.4%	100%	99.8%
Hx of HTN	99.8%	99.8%	92.9%	92.8%
Hx of dyslipidemia	84.1%	86.4%	84.6%	81.8%
Hx of CHF	12.2%	13.4%	17.9%	13.7%
Diabetes duration > 10 yrs	55.6%	56.1%	61.9%	53.8%

Dr. Abraham applied the same inclusion criteria for Studies 18 and 19 to all data included in the overall meta-analysis. As expected, this subgroup of the meta-analysis had a higher event rate than observed in the overall analysis but rates were similar between dapagliflozin and comparators and risk estimates were comparable for the primary composite and MACE. Of note, the upper bound of the 95% CI in this subgroup analysis of the meta-analysis is < 1.8.

**Table 8.10. Further Analyses of the Overall Meta-analysis Population (19 studies)  
Limited to High CV Risk Patients Only**

	Primary Composite Endpoint		MACE Composite Endpoint	
	Dapagliflozin	All Comparator	Dapagliflozin	All Comparator
<b>Stratified Hazard Ratio (95% CI)</b>	0.88 (0.58, 1.33)		0.88 (0.54, 1.42)	
<b>Event/PY (% Incidence)</b>	53/1607 (3.30%)	43/1069 (4.02%)	40/1615 (2.48%)	32/1244 (2.57%)
<b>Subjects with Events/1000 Person-Year</b>	32.98	40.22	24.77	25.72
<b>M-H Incidence Rate Difference (95% CI)</b>	-0.0051 (-0.021, 0.0108)		-0.0029 (-0.010, 0.0042)	

Even though the above analysis is of a patient population similar to those enrolled in Studies 18 and 19 (and also included these two studies), the pooling of all these trials dilutes out a signal of concern derived from two independently-conducted studies of similar design and patient populations. For this reason, I remain reluctant to dismiss the finding of potential

excess CV risk associated with dapagliflozin in T2DM who have elevated CV risks at baseline.

The FDA statisticians also noted that the Kaplan-Meier curves for the high risk subgroup in the meta-analysis showed similar event rates until approximately year one of exposure. Thereafter, the comparator group was higher than dapagliflozin. As the analysis of Studies 18 and 19 was predominantly of patients who had only completed 6 months of the 2-year studies, it may be of interest to see if event rates crossover after a longer duration of exposure. A similar notion of changing CV risks over time was entertained in the meta-analyses of controlled clinical trials of rosiglitazone that fueled the 5-year public debate on its CV safety. The majority of the trials in the meta-analysis were of 6-month duration.

#### Conclusions on CV Safety

The overall results for the updated meta-analysis yielded slightly higher point estimates for the primary composite endpoint and MACE than what was observed in the original meta-analysis. However, the estimates are still  $< 1.0$  and the upper bound of the 95% CI exclude both 1.8 and 1.3 and therefore meet the FDA's Guidance for Industry. The CV assessment of the newly included studies that enrolled higher CV risk patients reveals a more concerning signal as risk estimates in these two similarly-designed trials are  $> 1.0$  and depending on the endpoints evaluated, no longer exclude an upper bound of 1.8.

Clearly the perception of a CV benefit can not be upheld with this updated meta-analysis. Even if we ignore the separate analyses of Studies 18 and 19, the updated meta-analysis reminds us that the risk estimates are fragile as the point estimate and accompanying confidence limits shift upward with increasing number of events and analyses of high risk patients.

Although concerning, focusing primarily on the analysis of only Studies 18 and 19 to make a conclusion of CV safety for dapagliflozin is not appropriate, as it clearly ignores the remaining 60% of events from studies that contribute far greater patient-yrs of exposure than these two studies combined. However, the inclusion of these studies now weakens the argument that dapagliflozin might carry a protective effect such that this "benefit" could offset the uncertain safety findings of liver toxicity and cancer risk

## **9. Advisory Committee Meeting**

This NDA was discussed at an advisory committee meeting on July 19, 2011. The following discussion points and voting question were posed to the panel which reflected the key concerns of FDA at the time of the meeting. I've included the minutes prepared by Mr. Paul Tran, executive secretary for the committee, and signed off by the chair of the meeting, Dr. Abraham Thomas.

### Efficacy

1. Dapagliflozin's efficacy is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment, the efficacy of the SGLT-2 inhibitor is also diminished. Please discuss the implications of this reduced efficacy in Type 2 Diabetes Mellitus (T2DM) where renal impairment can impact a sizeable proportion of patients with this disease. Please include in your discussion whether additional studies (e.g., in special populations) should be conducted to better characterize the efficacy of dapagliflozin in T2DM or whether monitoring for renal function should be performed prior to and/or during treatment with dapagliflozin.

**Committee Discussion:** *The committee expressed concerns regarding a cut-off point of 45 ml/min for the GFR as they agreed that this was an arbitrary number. Therefore, the committee suggested additional studies be performed to assess creatinine clearance and/or GFR cut-offs using measurements other than the estimated GFR formula. Based on the data provided by the sponsor, it appeared that there was no benefit in patients whose GFR is below 60 ml/min, thus a prospective trial would need to be performed in order to demonstrate efficacy in these patients. Another concern that was raised by the committee was in regards to the classification system used for kidney disease. The system, which does not exist in the U.S., separated kidney disease into two categories (3A and 3B). The committee felt that this separation might be confusing for clinicians in the U.S. In addition to their concerns, the committee suggested that the sponsor reanalyze their data for estimated GFR since different formulas were used in different countries. The committee also recommended that monitoring for renal function be done consistently during treatment with dapagliflozin in order to ensure that efficacy is still present. Additionally, scheduling of renal monitoring should be consistent with other types of monitoring in diabetes patients in order to reduce the burden on patients.*

*Please see the transcript for details of the committee's discussion.*

### Hepatic Safety

2. Five patients treated with dapagliflozin developed ALT or AST > 3x ULN with accompanying total bilirubin > 2x ULN (biochemical Hy's law). An adequate explanation for the biochemical abnormalities could be identified in all but one case. This one case was classified as a 'probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury'. Imbalances in severe hepatic transaminase elevations (> 5x and 10xULN) between dapagliflozin and comparators were not observed and no signal for hepatotoxicity was identified in the nonclinical program.

Please comment on the clinical relevance of the one case and whether sufficient evaluation has been conducted premarketing to determine if dapagliflozin is associated with a risk of hepatotoxicity.

**Committee Discussion:** *The committee was concerned with the one case of "probable dapagliflozin-induced liver injury", and commented that it was unlikely due to an autoimmune*



*disease. It was mentioned that diabetes patients who are obese may have an underlying disease pattern, such as a high rate of nonalcoholic steatohepatitis (NASH), before initiation of the medication. Also, concomitant medications, such as statins, could have clouded the true cause of liver injury/function. The committee also voiced concerns that other racial and ethnic groups were poorly represented in the trials, thus the potential differences in drug metabolism for different racial and ethnic groups should be further explored. In addition, there should be more clearly defined liver testing, frequency of testing, and criteria set forth for clinicians to identify risk factors. Also a protocol for testing and follow-up for patients who are identified to have changes in liver function while on the drug should be in place rather than leaving this up to the individual physician at the research site.*

*Please see the transcript for details of the committee's discussion.*

#### Breast and Bladder Cancer

3. Numeric imbalances in breast and bladder cancer were observed in the clinical development program. For both of these types of cancer, please discuss whether these imbalances signify a risk of carcinogenic potential associated with dapagliflozin. In addition, please comment on whether the numeric imbalances were impacted by the following:

- a. Any imbalance of baseline risk factors
- b. Any detection bias

**Committee Discussion:** *In terms of risk factor, the committee expressed uncertainty about the data that was presented as some degree of detection bias was possible in subjects who lost weight since it would have been easier to detect breast cancer or a mass via a mammogram or other methods. Dehydration, a side effect of the drug, was also mentioned as a potential detection bias for breast cancer. Similarly, there could have been detection bias for bladder cancer due to the frequent testing for urinary tract infections which could have led to the discovery of microscopic hematuria. However, the committee felt that detection bias could not explain overall risks in terms of the number of cases. Some of the members commented that there was a gender difference in the number of cases of bladder cancer in patients on the drug. Some of the imbalances in the number of cases of bladder cancer seen in the studies could have been explained by known differences in the risk for bladder cancer between genders. It was emphasized that screening should be stringent to assess the risk of breast or bladder cancer in patients prior to enrollment into future trials.*

*Please see the transcript for details of the committee's discussion.*

#### Other Safety Findings

4. Please discuss the clinical significance of the following in the T2DM population:

- a. increased genital-urinary infections associated with dapagliflozin therapy
- b. bone safety concerns
- c. any other safety issues identified in the premarketing application

**Committee Discussion:** *The committee noted that there was a clear imbalance between the placebo and treatment groups for genital-urinary infections. In addition, there appeared to be an*

*increased risk for secondary infection in the treatment group. The committee felt that longer term data was necessary to assess whether this was a true risk. Another concern that was raised was that patients treated with dapagliflozin were at an increased risk for experiencing multiple episodes of urinary infections which might lead to over-use of antibiotics, and potential antibiotic resistance in the long run. The committee did not express major concerns with bone safety, but felt that additional monitoring of bone turnover would be helpful. Other safety issues identified included dehydration, reduced creatinine clearance, and the loss of calories in the urine of subjects with nutritional imbalance. Further studies could examine nutritional balance by checking the 24- hour nitrogen or protein clearance. The committee expressed that there are many unknowns with these safety issues; however, there was less concern with the breast and bladder cancers signals.*

*Please see the transcript for details of the committee's discussion.*

Voting Question

5. Do the efficacy and safety data provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM?

(VOTING)    **Yes: 6      No: 9**

- a. If yes, do you recommend any further data be obtained post-marketing?
- b. If no, what further data should be obtained?

**Committee Discussion:** *The majority of the committee members concurred that the efficacy and safety data did not provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Some members who voted "No" indicated that they struggled with their decision and as they could have voted "Yes" since dapagliflozin proved efficacious in reducing HbA1c, but the potential signals for breast and bladder cancers in addition to the potential for liver toxicity were concerns. Thus, these panel members felt that additional safety data is necessary prior to approval. The committee further recommended that data be obtained in minority patients, the elderly, patients with hepatic insufficiency and patients with mild to moderate renal impairment. Also, longer term trials should be conducted to collect further data on patients with genital and urinary tract infections. One panel member who voted "Yes" recommended that post-marketing studies be conducted to evaluate why there is an unmasking of cancers and registries or surveillance to monitor for cancers when patients are receiving the drug.*

Dr. Irony has also provided excerpts from each member of the committee in his CDTL memo.

I believe the summary of the meeting and the votes reflect the unease many have in weighing benefit and risk of this product. While there is not a dispute that the drug provides glycemic control with some limitations, the safety concerns highlighted in this memo were not dismissed by the panel members. At the time of this meeting, FDA and the applicant agreed to not focus on the CV meta-analysis as it was felt the original meta-analysis met the FDA Guidance for pre-marketing CV risk assessment.

## 10. Pediatrics

Please see Dr. Irony's CDTL memo and the applicant's proposed pediatric development program.

## 11. Other Relevant Regulatory Issues

### Maternal Health Team

The MHT was consulted to advise on pregnancy category and recommendations to labeling regarding use during pregnancy and nursing. Please see their consult finalized on September 25, 2011.

The applicant has proposed Pregnancy Category C and advised against use during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy and while nursing due to concerns of adverse outcomes on renal development in the fetus and developing infant. MHT agreed with the applicant's pregnancy category; however, revisions were made to several sections of the label (b) (4)

(b) (4) Specifically, the applicant's proposed statement (b) (4) was removed. MHT concluded that it may be possible that the benefit of dapagliflozin use during pregnancy may be acceptable despite the potential risk of renal pelvic and tubular dilatation noted in animal studies, in line with the regulatory definition of Pregnancy Category C (21 CFR 201.57).

The review division met with MHT and the pharmacology/toxicology reviewers to discuss the nonclinical findings and whether the pregnancy category labeling should be C throughout, or if there was a basis for contraindicating the drug in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester when fetal renal development may be affected by drug exposure. A switch in pregnancy category labeling at different trimesters of pregnancy is not unprecedented (e.g., ACE-inhibitors) and it could be argued that discontinuation of dapagliflozin in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester would eliminate any potential risk to the fetus but still provide sufficient time in the first trimester for consideration of other treatment options.

After reading the proposed language put forward by MHT, I am comfortable with pregnancy category C throughout. There proposed language is informative and enables individual benefit-risk assessment by the healthcare provider and patient. In addition, I was reassured by Dr. Bourcier's comment that while the renal pelvic dilatation was likely due to drug, it did not impact the lifespan or physiology of the affected animals. For these reasons, I believe a single recommendation of C is defensible and is less confusing to the healthcare provider and patient.

## 12. Labeling

Presently, the review team has begun negotiations with the applicant on labeling pending a final decision from Dr. Rosebraugh on the approvability of this NDA.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

### Complete Response

- Risk Benefit Assessment

My recommendation for a complete response comes with some equivocation.

The safety concerns outlined under Section 8.0 were unexpected and in fact, required a modification to the AC meeting agenda and attendees to discuss the late findings of cancer imbalance. For the cancer imbalance, a plausible mechanism for carcinogenesis could not be identified. Neither the nonclinical program nor published literature on SGLT-2 receptor function and tissue localization predicted a cancer signal. The one case of drug-induced liver injury was not accompanied by imbalances in liver transaminases often observed with products later identified to be hepatotoxic. While no definitive conclusion could be made that dapagliflozin was carcinogenic or hepatotoxic, the uncertainty of risk for such serious outcomes remained that could only be tolerated if counterbalanced by a clinical benefit. With the original NDA submission, the favorable CV meta-analysis seemed like the best justification.

Since the FDA issued its Guidance to Industry requiring a prospective CV risk assessment of all new anti-diabetic therapies, dapagliflozin is the first NDA to be submitted with a pre-specified analysis plan for its meta-analysis of several controlled clinical trials which yielded a favorable point estimate with an upper 95% CI excluding both 1.8 and 1.3. There was even discussion internally on whether the applicant had fulfilled all requirements of the Guidance such that no postmarketing trial would be required. Despite the larger number of CV events from the meta-analysis than previously submitted NDAs, the Agency still felt that a dedicated CV trial would be necessary because a pooling of multiple studies of short duration and an overall low CV risk population might not adequately establish the true hazard for CV risk in the intended population. The applicant agreed that such a study would be conducted and the objectives of the study would not only be to establish CV safety and possibly benefit, but it would address the liver and cancer safety concerns identified in the NDA.

But pending such a study, we asked that the applicant submit the results of two studies prospectively designed to address CV risk. These two studies were originally planned for inclusion in the meta-analysis should an interim analysis of 14 clinical trials fail to exclude the 1.8 margin. They were designed to capture more events than is typically observed in pre-marketing diabetes programs and accordingly enrolled a high CV risk patient population. Clearly, the original favorable findings on CV risk reduction with the inclusion of these two studies could serve as a justification to allow dapagliflozin into the market pending the larger CV outcomes trial.

As summarized under Section 8.0, the updated meta-analysis did not yield the anticipated outcome of potential benefit to outweigh the potential risks. Instead, it provided the evidence that low event rates from a meta-analysis of multiple short-term trials may be adequate to



exclude 1.8 but might also result in a chance exclusion of 1.3 or a spurious finding of benefit. The updated meta-analysis also revealed a different CV risk profile of dapagliflozin in patients with long-standing diabetes and multiple CV risk factors. Instead of the consistent HR < 1.0 from the original meta-analysis, patients treated with dapagliflozin in Studies 18 and 19 had more CV events than comparator. Although this finding was only evident in 2 of the 19 studies included in the meta-analysis, these two studies alone provided more CV events than previously conducted meta-analyses of recently approved anti-diabetic therapies and their design and conduct for adjudicating the events would have met the criteria established in the FDA Guidance.

I have entertained limiting the use of dapagliflozin to a population in which the possible benefits would outweigh the potential risks. In trying to carve out a population for labeling, I also considered some of the proposals put forward by Dr. Irony in his CDTL memo. Specifically, he proposed a potential niche for dapagliflozin as an add-on to insulin secretagogues or insulin sensitizers, the elderly, or in patients who have failed other anti-diabetic therapies. But even in each of these patients, I can call on current trial data that would question dapagliflozin's efficacy or safety. For example, its use as add-on to an insulin secretagogue or insulin sensitizer or in patients who have failed currently marketed anti-diabetic drugs would likely include a population of patients who have long-standing disease and are more likely to have renal impairment where efficacy will be diminished or absent. These same populations and the elderly with normal to mild renal impairment would probably also represent a higher CV risk population in which Studies 18 and 19 raised concerns about excess risk. And finally, for every population singled out, there appears to be an available therapy from the current 11 classes of anti-diabetic agents which would effectively control glucose levels without weight gain or risks of hypoglycemia. The following table outlines some of the patient populations in which dapagliflozin could be indicated for prior to completion of the CV outcomes trial and the alternatives therapies that carry minimal risk of hypoglycemia, similar to dapagliflozin.

**Table 13.1. Potential Populations Indicated for Dapagliflozin and Alternative Approved Anti-Diabetic Agents.**

	<b>Rationale for Dapa Use</b>	<b>Metformin</b>	<b>DPP4-inhibitors</b>	<b>GLP-1 analogues</b>	<b>Pioglitazone</b>
New Onset Diabetic	Less concern of renal impairment and diminished efficacy. Evidence of efficacy established in monotherapy trials. No signal of CV risk.	Considered 1 <sup>st</sup> line therapy in this population. Extensive efficacy and safety data in this population including prevention population suggestive of CV benefit (Diabetes Prevention Program)	Efficacy established in this population for 3 currently approved in the class (sitagliptin, saxagliptin, linagliptin). Comparable efficacy to dapagliflozin.	No direct comparison of efficacy but monotherapy trials of liraglutide and exenatide strongly suggest greater glycemic efficacy. Disadvantage is route of administration (injection) and theoretical concern of medullary thyroid cancer.	Established efficacy in this population but concerns of bladder cancer and weight gain does not make this an ideal candidate.
Add-on therapy to failed therapies	Evaluated in several Phase 3	Extensive efficacy and safety data in	All three DPP4 inhibitors have	Both liraglutide and exenatide	Established efficacy in this



	<b>Rationale for Dapa Use</b>	<b>Metformin</b>	<b>DPP4-inhibitors</b>	<b>GLP-1 analogues</b>	<b>Pioglitazone</b>
	trials including Studies 18 and 19 where CV risk may be a concern. Duration of diabetes longer with these patients and renal impairment may limit its effectiveness.	this population including UKPDS. In addition, all diabetes development programs evaluate their therapies added onto metformin. May be limited if renal impairment present due to concerns of lactic acidosis.	been studied as add-on to a variety of approved anti-diabetic agents including insulin.	have been studied as add-on to a variety of approved anti-diabetic agents including insulin.	population but concerns of bladder cancer and weight gain does not make this an ideal candidate. A consideration for pioglitazone could be made given the results of PROactive trial which was a CVOT in many patients who required multiple anti-diabetic therapies and pioglitazone did not increase the risk of MACE.
Elderly patient with normal-mild renal impairment	Low risk of hypoglycemia but this patient population may also be at high CV risk. Also need to consider whether urogenital AEs and hypotension may be more problematic in this population.	If limited only to elderly with normal-mild renal impairment, would expect efficacy with low to no risk of hypoglycemia. Labeling does include restriction on use in patients > 80 yrs of age due to concerns of lactic acidosis.	Expected efficacy with similar low risk of hypoglycemia. No concern of diminished efficacy but worsening renal function associated with age may require lower dosing.	Expect greater efficacy with low risk of hypoglycemia. Liraglutide dosing does not need to be adjusted for renal impairment although both GLP-1 analogues have been reported to have nausea and vomiting which might result in dehydration and renal failure.	Established efficacy in this population but concerns of bladder cancer and weight gain does not make this an ideal candidate. A consideration for pioglitazone could be made given the results of PROactive trial which was a CVOT in many patients who required multiple anti-diabetic therapies and pioglitazone did not increase the risk of MACE. Mean age in PROactive was 62 yrs.
Expected HbA1c reduction relative to placebo*	-0.4 to -0.7%	-1.0%	-0.6 to -0.8%	-0.5 to -0.7%	-1.0 to -1.6
Effect on Weight	-1.0 to -3.0 kg	Neutral to modest wt loss ~ 1kg	Neutral to modest wt loss of ~ 1kg	-1.0 to -3.0 kg	Increase (2-5 kg)
Effect on BP	~3 mmHg reduction in SBP	neutral	neutral	Neutral	neutral

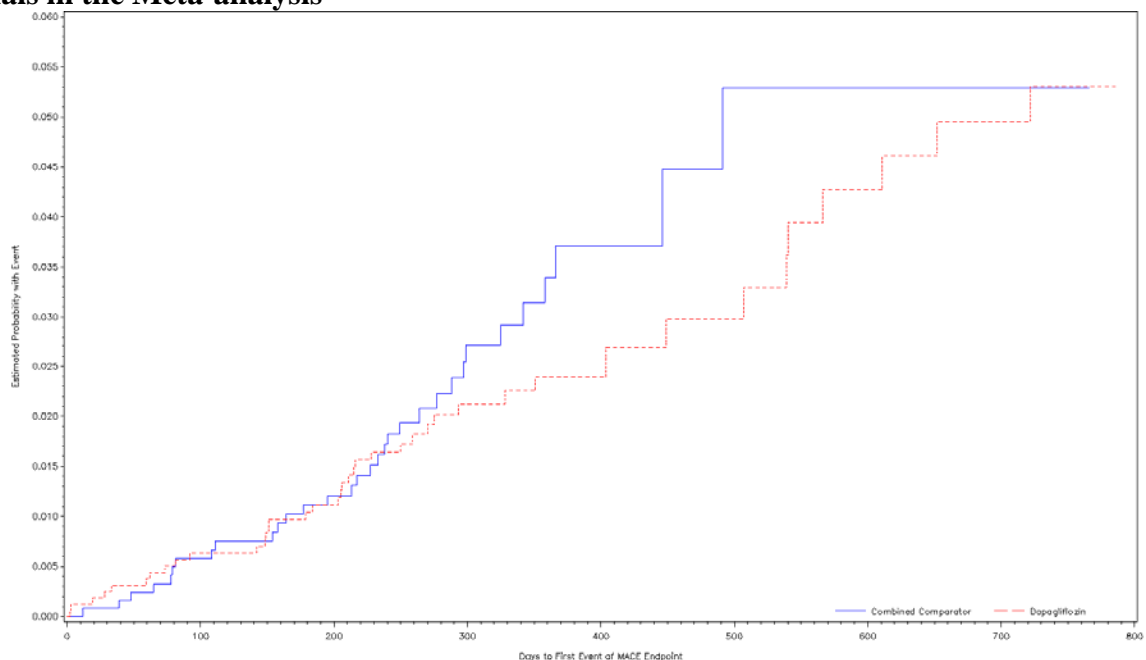
\*based on labeled data in pbo-controlled, monotherapy trials; important to note that patients had different baseline HbA1c values across these programs

The availability of multiple agents to treat type 2 diabetes has allowed physicians to tailor treatment to the individual patient's risk profile. There is no one anti-diabetic therapy that can meet the needs of all patients but the table above does attempt to show that with exception for a reduction in SBP, the benefits of dapagliflozin may be matched by other available therapies even with some of the risks they carry such as hypersensitivity reactions and pancreatitis (incretin mimetics), heart failure and bladder cancer (pioglitazone), and lactic acidosis (metformin).

In fact, it is with the knowledge that all drugs carry risks that I had some reservations in my final recommendation of a complete response because none of the risks identified for dapagliflozin was an undisputable signal of harm that would lead me to outright reject this NDA. For breast cancer, I believe the updated data from the 3-month extension are reassuring and the breast cancer diagnoses were unrelated to dapagliflozin. However, a risk ratio for bladder cancer exceeding 5.0 could not be ignored as a chance-finding and the one Hy's law case that was concluded to be a probable case of dapagliflozin-induced liver injury remains of concern. However, both of these risks, if real, will be rare events and this has been upheld with additional patient-yrs exposure from the 3-month extension in which no additional cases of bladder cancer or Hy's Law were detected. As noted above, current data reduced the risk estimate for serious liver toxicity from 1/25,000 to 1/44,000. But what tipped this equivocal benefit-risk balance was the addition of Studies 18 and 19 in which a promise of CV benefit could no longer be relied upon to dismiss the possible serious risks.

While the updated CV meta-analysis can no longer support a notion of CV benefit, I would not conclude that there is evidence of CV harm. I would also not require the applicant complete its CV outcomes trial to establish CV benefit to address my lingering concern of liver safety and bladder cancer. In Dr. Irony's memo, he alluded to the short duration of CV assessment in Studies 18 and 19 and suggested that these high-risk CV patients may have experienced a MACE event in this short duration of exposure before a favorable treatment effect of dapagliflozin could be established. FDA statisticians also observed a shift in event rates after one year that favored dapagliflozin in a K-M curve of the meta-analysis limited only to high CV risk patients.

**Figure 13.1 Survival Curve for the “high CV risk” Population Extracted from All Trials in the Meta-analysis**



Studies 18 and 19 are ongoing 2-year trials. All patients remaining in these two trials are being followed for CV events which are being prospectively adjudicated, as was done for the CV meta-analysis. Hence, there is an opportunity to further examine the event rates with longer treatment duration in these two studies. The following table was provided by the applicant in response to an FDA inquiry about the expected number of patients and pt-yrs of exposure at Year 1 and 2 of these two trials.

**Table 13.2 Subjects and Pt-Yrs in Studies 18 and 19 at Year 1 and 2**

	<b>D1690C00018</b> <b>N (n dapagliflozin / n placebo)</b>	<b>D1690C00019</b> <b>N (n dapagliflozin / n placebo)</b>
Number subjects receiving at least 1 dose of randomized treatment	922 (460/462)	965 (482/483)
Number subjects completing 24 weeks	807 (403/404)	869 (441/428)
Number of subjects completing 52 weeks	673	699
Number of subjects entering 2 <sup>nd</sup> 52 weeks extension*	231	277
Number of subjects completing 104 weeks	185	222
	<b>D1690C00018</b> <b>Patient –years on treatment</b>	<b>D1690C00019</b> <b>Patient –years on treatment</b>
Total exposure at 52 weeks	793	851
Total exposure at 104 weeks	1001	1101

\* The reason for the lower number of patients after the first year was that both trials were originally designed as 1 year trials (24 weeks plus 28 week extensions) and later extended by protocol amendments to 2 years in duration. The amendments were not approved/implemented in time in all countries resulting in a limited number of patients giving consent for the second year extension of the studies.

Data and clinical study report for Year 1 and 2 will be available for submission to FDA by July 2012 and 2013, respectively.

Because the current data presented to FDA do not allow for a conclusion of a favorable benefit-risk profile, I would recommend the applicant address this deficiency by providing FDA with additional exposure data from clinical trials to ensure that the hazard ratio for the CV risk estimate remains neutral and that there are no additional findings of cancer or liver toxicity. Although the applicant intends to initiate the CV outcomes trial in the 4<sup>th</sup> quarter of 2012, it is possible that the additional exposure data from Studies 18 and 19 summarized in Table 13.2 may also address this deficiency in advance of a planned interim analysis for the CV outcomes trial. In light of the modest efficacy, limited to a subpopulation of T2DM, the concern of liver toxicity and bladder cancer, and availability of additional data from well-designed trials that are ongoing, I do not believe this is an unreasonable expectation of the applicant to ensure that FDA's introduction to market of a first-in-class 12<sup>th</sup> member of anti-diabetic therapy is safe and effective.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
None at this time as I am recommending a complete response.

- Recommendation for other Postmarketing Requirements and Commitments  
The applicant has been informed that a CV outcomes trial will be required if this NDA is approved.

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/s/  
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MARY H PARKS  
12/22/2011

## Cross-Discipline Team Leader Review

<b>Date</b>	12/1/2011
<b>From</b>	Ilan Irony, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA</b>	202293 Original submission under 505(b)(1)
<b>Applicant</b>	Bristol Myers Squibb and Astra Zeneca
<b>Date of Submission</b>	12/28/2010
<b>PDUFA Goal Date</b>	10/28/2011 (Major amendment triggered 10/20/2011: Action letter goal 1/16/2012)
<b>Proprietary Name / Established (USAN) names</b>	Forxiga / dapagliflozin
<b>Dosage forms / Strength</b>	Oral tablets / 10 and 5 mg
<b>Proposed Indication(s)</b>	Improve glycemic control in adults with Type 2 diabetes
<b>Recommended:</b>	Approval

## 1. Introduction

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) are seeking approval for dapagliflozin for treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin is a first in class new molecular entity. Dapagliflozin is a competitive, reversible, selective small drug inhibitor of the sodium glucose co-transporter 2 (SGLT2), which is the major transporter responsible for renal tubular glucose reabsorption. This inhibitory effect results in glucosuria and in insulin-independent lowering of elevated plasma glucose in diabetics.

The basis for the therapeutic potential of inhibition of SGLT2-mediated transport as a means to facilitate glucose elimination derives from the observation that patients with rare familial renal glucosuria (FRG) have mutations in the SGLT2 gene. These patients often first present with unexplained glucosuria during routine medical assessment. Unlike patients with global renal tubular dysfunction (e.g., renal Fanconi syndrome), where tubular failure leads to excessive excretion of amino-acids, phosphate, bicarbonate and other solutes, in addition to glucose, the lack of functional SGLT2 in patients with FRG is otherwise associated with mostly benign phenotypes, with no relevant off-target effects or symptoms of chronic glycosuria. Patients with FRG generally have a good prognosis with normal life expectancy.

This review memo will provide only a brief overview of the application, the issues raised in the various disciplines and consultations, the discussion that occurred among members of the Endocrinologic and Metabolic Drugs Advisory Committee (AC) meeting, and the internal FDA discussions following that meeting. Some of the topics discussed at the AC meeting merit analyses throughout the sections of this memo, where these analyses apply, rather than confining these topics only under Section 9 of this template.

The NDA review uncovered a few important and unexpected safety issues. These risks will be described under “Section 8 - Safety” in this memo. The majority of AC members and members of the review division felt that additional clinical trial data, beyond what has originally been submitted to the NDA would be necessary to further assess the risks and the benefits associated with dapagliflozin treatment. The applicant has committed to amend the NDA with the submission of two large datasets of subjects treated with dapagliflozin in placebo-controlled trials for review prior to the Prescription Drug User Fee goal date of October 28<sup>th</sup>, 2011. The applicant submitted datasets for these trials on October 20<sup>th</sup>, which we considered a major amendment, triggering an extension of the clock in the current review cycle. The review disciplines affected by the additional data (datasets and study reports, and updated analyses) re-visited their recommendations. This CDTL memorandum provides an overview and recommendations based on the totality of the information received, including the major amendment.

## 2. Background

Dapagliflozin is the first drug in the new class of SGLT2 inhibitors to reach the milestone of NDA submission. The mechanism of action is based on the natural model of FRG. A key element in the mechanism of action of dapagliflozin is its selectivity to the renal tubular



SGLT2 (1242 – 1600-fold versus SGLT1), in contrast to non-selective inhibitors, such as its long time precursor, phlorizin. Phlorizin was not considered for development in T2DM due to its lack of selectivity and its inhibition of gut SGLT1, with impaired or delayed absorption of sugars in the gastrointestinal tract, with consequent gastrointestinal intolerance. Patients with FRG, a mutation specific to SGLT2, are usually asymptomatic and the cases reported have had normal life expectancy.

The main reasons we cannot borrow from the lifelong experience of FRG to the treatment of diabetics through drug-induced selective SGLT2 inhibition are:

- Patients with FRG are rare, in sharp contrast to the population of patients with T2DM who are the target for dapagliflozin;
- The patients described and reported to date in the Online Mendelian Inheritance in Man (OMIM) database as of May 2<sup>nd</sup> 2011<sup>1</sup> are not diabetic, and diabetes-specific risks (microvascular disease, cardiovascular and cancer) are probably not applicable;
- There are intrinsic and extrinsic factors related to any drugs, including pharmacokinetic and off target effects that are not applicable to disease models, such as FRG;
- The historical FRG cases reported are not subject to the typical scrutiny of modern clinical trials, in terms of monitoring of lab or other ancillary test abnormalities, adverse events, and analysis and reporting of these potential safety issues.

The effect of dapagliflozin is dependent on blood glucose levels and the glomerular filtration rate (GFR). Unlike most drugs approved for the treatment of T2DM, its glycemic effects are not dependent on insulin secretion or sensitivity. Importantly, efficacy wanes as GFR declines with progressive renal impairment, which is frequently observed in diabetic patients with a long history of diabetes and, less often, patients with pre-diabetes.

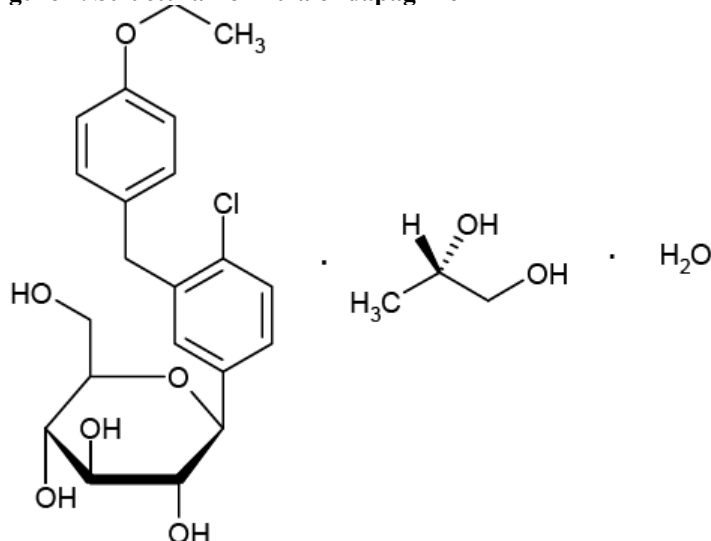
### 3. CMC/Device

The CMC team recommends approval of the NDA. Please see Dr. Ysern's review for details. The chemical name is dapagliflozin propanediol monohydrate. The chemical formula is  $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ , with a structural formula as depicted in Figure 1.

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<sup>1</sup> <http://omim.org/entry/182381>

**Figure 1. Structural formula of dapagliflozin**



Based on the stability data submitted, an expiry of 24 months for drug product packaged in either HDPE bottles (b) (4) or packaged in (b) (4) blisters is granted under the recommended storage conditions: 25 °C (77 °F) with excursions permitted to 15-30 °C (b) (4)

The establishment evaluation report was assessed as acceptable for BMS in both the Mount Vernon, IN and the Dublin, Ireland sites.

## 4. Nonclinical Pharmacology/Toxicology

The Pharmacology / Toxicology team recommends approval of the NDA. Please see Dr. Summan's review and Dr. Bourcier's supervisory memo for details.

In nonclinical models of diabetes dapagliflozin promoted glucose excretion, polyuria and lowered plasma glucose in diabetic and non-diabetic animal models under conditions of hyperglycemia (oral glucose tolerance test).

Safety pharmacology assessment of cardiovascular, neurological and pulmonary effects of dapagliflozin did not identify significant safety issues.

The following items from the Pharmacology / toxicology review will be revisited again when I discuss safety aspects of dapagliflozin, under Section 8:

- Plasma protein binding was high (91-95%) in humans and in all nonclinical species.
- Dapagliflozin was found to be excreted in the milk of lactating rats.
- Off-target effects include the increased trabecular bone and tissue mineralization, likely due to modulation of calcium homeostasis and increased urinary calcium excretion in a 2-year rat study, at 129 X clinical exposure. This finding was not confirmed in a 1-year study in dogs.

The propensity for dapagliflozin to cause off-target inhibition of SGLT1 in humans is reduced due to the lower affinity of dapagliflozin for human SGLT1 compared to the rat: dapagliflozin is 1600-fold more potent at inhibiting SGLT2 compared to SGLT1, whereas in rats it is 207-fold more potent. Dapagliflozin is a highly selective inhibitor of SGLT2, with greater than 1400-fold selectivity vs. the most closely related (> 40% protein identity) human sodium-glucose cotransporters (SGLT1, SMIT1, SGLT4, SGLT6) in vitro. Overall, target organ toxicities in adult rats occurred at high exposure multiples ( $\geq 3097\times$  MRHD) and the safety margins to the final clinical dose are high suggesting low clinical risk.

Exposure to dapagliflozin at 19-1415x MRHD in a pre- and post-natal development study in the rat had no pathological effects in the dams, yet showed renal pelvic dilatation at the high dose in the in utero and lactationally exposed pups (1415x MRHD). Due to reduced growth in the pups the NOAEL was <19x MRHD. In the dams the NOAEL was 249x MRHD due to reduced body weight gain at the high dose.

BMS/ AZ recommended against use of dapagliflozin during the second and third trimesters of pregnancy, which is compatible with a contraindication for pregnant women or women who may become pregnant, albeit with a proposed Pregnancy Category C for the label. The applicant also recommends that women not take dapagliflozin during nursing (milk to plasma ratio of 0.49X in lactating rats). Their recommendations are based on adverse findings from exposure to dapagliflozin during the peri /post-natal and juvenile periods in rats. Exposure to dapagliflozin in rats from birth to approximately 13 weeks of age, and especially from post-natal weeks 3-6, results in dilatation of the renal pelvis and tubules and a lower rate of body growth at exposure < 15x the clinical dose. A 'no-effect dose' was not identified, so it is likely that exposure causing this adverse effect in rats occurs very near clinical exposure. This susceptible period in the young rats is characterized by active morphological and functional development of the kidneys. A similar period covering morphological and functional renal development in humans would be during the second/third trimesters of gestation, with functional renal development continuing until ~2 years of age. The cause of renal pelvis and tubular dilation is not known. The FDA agrees with the applicant that dapagliflozin should not be used during pregnancy or nursing.

Treatment of juvenile rat pups until maturity replicated the renal pelvic dilatation pathology but at drug exposure that is potentially clinically relevant and also showed irreversibility in recovery animals, suggesting dapagliflozin is a renal pelvic development toxicant.

Importantly for the safety discussion, dapagliflozin was not found to be mutagenic, or clastogenic in vivo and in vitro. Dapagliflozin was found not to be carcinogenic in 2-year adequate studies in rats and mice. These studies were reviewed by the Carcinogenicity Assessment Committee, which concurred with this conclusion.

## **5. Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology team recommends NDA approval. Please refer to Dr. Jain's review.

The 27 studies that were part of the clinical pharmacology evaluation took place across a broad range of doses, ranging from 0.001 to 500 mg.

Dapagliflozin reaches maximum concentration ( $C_{max}$ ) in about two hours. The half-life is 12.5 hours. It is inactivated by UGT1A9, an enzyme present in the liver and kidney, to an inactive glucuronidated metabolite (dapagliflozin 3-O-glucuronide). There were no clinically significant drug-drug interactions.

In a thorough QTc study, dapagliflozin had no clinically meaningful effect on the QTc interval or cardiac rhythm at doses up to 150 mg once daily.

No dose-limiting toxicities were identified in studies conducted in healthy subjects administered single doses of dapagliflozin up to 500 mg, or in healthy subjects or subjects with T2DM administered daily doses of 100 mg for 2 weeks. Glucose was detectable in the urine in both healthy volunteers and subjects with T2DM for a dose-related period of time, with no events of dehydration, hypotension, or electrolyte imbalance. Mean 24-hour urine volumes increased up to an additional 400 ml per day, starting from a baseline total urine volume ranging between 2.0 to 2.4 liters/day. This additional volume amounted to an equivalent of approximately one additional void per day, on average.

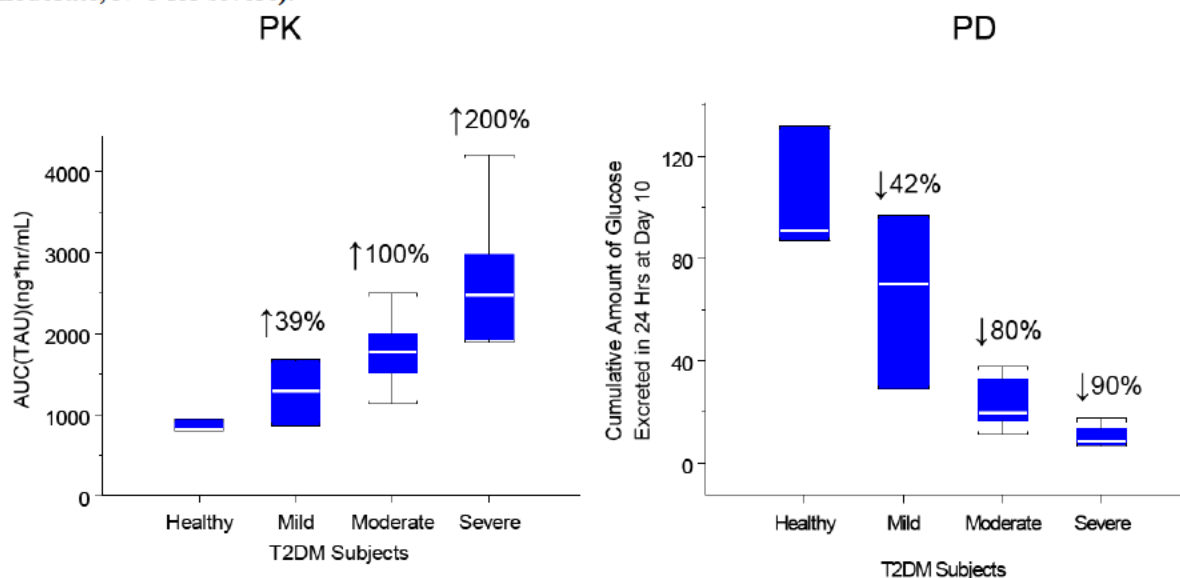
The selected dose for marketing is 10 mg, taken once daily at any time of day. There is no proposed dose adjustment for mild renal function impairment. Because dapagliflozin causes an increase in urinary volume excretion, the proposed dose for patients at risk for volume depletion (i.e., those who are on loop diuretics) is 5 mg once daily.

### Specific Populations

**Renal Impairment:** Following administration of 20 mg dapagliflozin given once daily for 7 days, subjects with T2DM with mild, moderate, or severe renal impairment had higher steady-state mean dapagliflozin  $AUC_{tau}$  as compared to subjects with T2DM and normal renal function (Figure 2). Furthermore, higher systemic exposures of dapagliflozin in subjects with moderate, and severe renal impairment did not result in higher cumulative amount of glucose excretion (Figure 2). This is consistent with dapagliflozin's GFR-dependent mechanism of action where it is not expected to provide clinically meaningful benefit in these populations.

Based on the pharmacodynamic effect seen in Figure 2, the applicant proposes that dapagliflozin should not be taken by patients with moderate or severe renal impairment. However, based on post-hoc analyses of the clinical data, the applicant established the threshold of estimated GFR (eGFR)  $> 45 \text{ mL/min/1.73 m}^2$  by the abbreviated Modification of Diet in Renal Disease study (MDRD) method or creatinine clearance (CrCl)  $> 60 \text{ mL/min}$  (estimated with the Cockcroft-Gault method) for treatment with dapagliflozin. Please refer to the discussion of this issue at the AC meeting in the Clinical Section of this memo.

**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).**



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

Source: Dr. Jain's Clinical Pharmacology review

**Hepatic Impairment:** In subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B),  $C_{max}$  and AUC of dapagliflozin were increased by 22% and 36%, respectively, compared to healthy subjects. In subjects with severe hepatic impairment (Child-Pugh Class C), dapagliflozin  $C_{max}$  and AUC were up to 40% and 67% higher than matched healthy controls, respectively. The applicant's proposal for no dose adjustment in patients with hepatic impairment is acceptable.

**Genetic Variation:** Dapagliflozin is primarily metabolized by the polymorphic enzyme uridine diphosphate glucuronosyltransferase (UGT1A9). The applicant conducted a retrospective genetic substudy of the Phase 2b trial, MB102008, to investigate the role of the UGT1A9 variants on the clearance of dapagliflozin (based on population PK parameters). No significant effects of UGT1A9 genotype on dapagliflozin clearance were identified. The results of this study coupled with the scarcity of UGT1A9 variants indicate that these variants are unlikely to play a clinically significant role in the exposure to dapagliflozin.

PK parameters are not meaningfully affected by age, T2DM, body weight, gender, race or UGT1A9 polymorphism.

During the stability studies, it was found that dapagliflozin (b) (4) for 4 weeks. To assess the impact of (b) (4) bioequivalence studies were conducted from a (b) (4) tablet formulation relative to (b) (4) tablet formulation. Geometric mean ratio and 90% CI for  $AUC_t$ ,  $AUC_{inf}$  and  $C_{max}$  were within 80% to 125% criterion limits following administration of (b) (4) and (b) (4) tablets at 2.5 mg and 10 mg dose strengths.

Dr. Hughes reviewed the biopharmaceutic aspects of the application: the dissolution method development, applicant's justification for the using disintegration testing in lieu of dissolution,

and supporting product release and stability data, and the Biopharmaceutics team recommends approval of the application.

## **6. Clinical Microbiology**

A microbiology issue was resolved with the applicant. Dr. Fong, microbiology reviewer, recommends approval of the NDA. Please refer to his review.

## **7. Clinical/Statistical- Efficacy**

The clinical reviewer, Dr. Dunn, recommended a Complete Response to the NDA based on the totality of the data reviewed in the original submission and 4-Month Safety Update. Upon review of the data included in the major amendment, she has revised her recommendation to approval. The statistical reviewer for efficacy, Dr. Norton, considers that the clinical trials provide strong evidence that dapagliflozin is effective in subjects with normal renal function or mild renal impairment. Please note that Dr. Norton's review only covered the efficacy of dapagliflozin, and therefore does not take into account the risk-benefit assessment. Dr. Abraham, from the Division of Biometrics VII, reviewed the cardiovascular risk metanalysis. I will cover the applicant's and Dr. Abraham's analyses in Part 8 - Safety of this CDTL memo.

Please refer to Dr. Dunn's original and amended reviews for details of both the efficacy and safety of the dapagliflozin clinical program, and to Dr. Norton's review for a discussion of selected statistical aspects of dapagliflozin demonstration of efficacy. The focus of Dr. Abraham's review was the metanalysis of Major Cardiovascular Adverse Events (MACE). The Division of Pharmacovigilance I was consulted to review cases of liver-associated laboratory abnormalities. Refer to Drs. Senior, Seeff and Allen's review for details. The Division of Epidemiology was consulted for the review of cancer risks potentially related to dapagliflozin and for the applicant proposed plan to continue to assess this risk in postmarketing epidemiologic studies. Refer to Drs. Ju and Hampp's reviews for details.

In this CDTL memo, I will refer to the safety and efficacy datasets as originally submitted to the NDA on 12/28/2010, unless otherwise indicated. I will specify when describing or analyzing an updated dataset, such as the 4-Month Safety Update or the July 15<sup>th</sup> 2011 cutoff date used by the applicant for the major amendment.

Following the clinical pharmacology studies, the clinical program in subjects with T2DM focused on 3 doses of dapagliflozin: 2.5, 5, and 10 mg, given once daily. One Phase 2b study in Japanese and one Phase 3 trial also assess the 1 mg dose. At the time of NDA submission, more than twice as many patients were randomized to treatment with dapagliflozin (n = 4287) as to the combined placebo or active control (n = 1941). At the time of the July 15<sup>th</sup>, 2011 Integrated Safety Update, based on data included in the major amendment, 5501 subjects had been exposed to dapagliflozin (5496 person-years) and 3184 subjects to comparator (3004 person-years).

The clinical development program for dapagliflozin is similar to that of several recently approved antidiabetic therapies. Three Phase 2b and 11 Phase 3 clinical trials investigated the efficacy and safety of dapagliflozin in drug-naïve subjects (monotherapy setting) or in subjects

whose glycemic control were inadequate with other oral agents and/or insulin (add-on to background antidiabetic therapy setting).

The primary efficacy variable for 10 of the 11 Phase 3 trials was change from baseline in HbA1c, tested with an analysis of covariance (ANCOVA) model. Measurements obtained after the start of rescue therapy were excluded from analysis. Last observation carried forward (LOCF) methodology was used when measurements were not available or when they were excluded (e.g., after initiation of glycemic rescue therapy). These methods are consistent with FDA's draft guidance on the development of new drugs for T2DM. Secondary assessments included supportive glycemic parameters (change from baseline in FPG and PPG), body weight, and the proportion of subjects achieving the ADA-recommended target response of HbA1c < 7.0%. The proportion of subjects with hypoglycemia was also a secondary endpoint in the glipizide-controlled trial.

In the active-controlled trial against glipizide, non-inferiority to glipizide would be demonstrated if the upper limit of the two-sided 95% CI for the difference in change in HbA1c from baseline to Week 52 (LOCF) between treatments was less than 0.35%. The choice of this non-inferiority margin was based on the applicant's literature review and clinical judgment. The margin had not been discussed with FDA at the time of protocol planning and power calculation, but we consider this a reasonable margin. The same non-inferiority margin was used in the factorial trial assessing the effect of dapagliflozin 10 mg, as part of an initial combination with metformin, in which a comparison between the dapagliflozin and metformin monotherapy groups was pre-specified. This was a secondary goal of the factorial trial, but it is one that I will discuss in more detail in this review. The main goal of the factorial trial was to demonstrate the glycemic superiority of coadministration of dapagliflozin and metformin against each of these drugs administered in monotherapy.

These Phase 2b and Phase 3 trials evaluated the efficacy of dapagliflozin used as monotherapy, add-on therapy to metformin, sulfonylureas, pioglitazone or insulin, and as initial combination therapy with metformin. In addition, a 52-week placebo-controlled trial was conducted in subjects with moderate renal impairment and a body composition study was conducted to investigate the effect of dapagliflozin on weight loss (Table 1 and Table 2).

Eight of these trials had long-term extension treatment periods up to 156 additional weeks in duration. The long-term periods from five trials were ongoing as of data cut-off date for the NDA submission: monotherapy (MB102013); subjects with T2DM and moderate renal impairment (MB102029), direct comparison with glipizide (D1690C00004), add-on to insulin (D1690C00006), and evaluation of body weight and composition.

**Table 1. Summary of Completed Clinical Studies with Dapagliflozin at the time of NDA submission**

<b>Study number/ Duration</b>	<b>Patient population</b>	<b>Treatment groups n per group/n treated with dapagliflozin/Total</b>
<b>Phase 2b studies</b>		
MB102008* (dose-ranging) 12 weeks	Drug-naïve patients with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Dapa 2.5, 5, 10, 20, and 50 mg, placebo and metformin XR 750/1500 mg 47-59/279/389
MB102009 (pilot add-on to insulin study) 12 weeks	Insulin-dependent patients with HbA1c $\geq 7.5\%$ and $\leq 10.0\%$	Dapa 10 or 20 mg and placebo 23-24/48/71
D1692C00005** (dose- ranging) 12 weeks	Japanese patients with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Dapa 1, 2.5, 5, and 10 mg and placebo 54-59/225/279
<b>Phase 3 studies</b>		
<b><i>Monotherapy</i></b>		
MB102013 24 plus 78 weeks	Controlled treatment, drug-naïve patients with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ (Group 1)  Controlled treatment group with HbA1c $\geq 10.1\%$ and $\leq 12.0\%$ (Group 2)	Dapa 2.5, 5, and 10 mg and placebo 64-76/410/485  Dapa 5, 10 mg 34-39/73/73
MB102032 (low-dose) 24 weeks	Drug-naïve patients with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Dapa 1, 2.5, and 5 mg and placebo 68-74/214/282
<b><i>Add-on combination therapy with metformin</i></b>		
MB102014 (add-on to metformin) 24 plus 78 weeks	Patients on metformin $\geq 1500$ mg/day with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Dapa 2.5, 5, and 10 mg and placebo 135-137/409/546
D1690C00012 (body weight & composition) 24 plus 78 weeks	Patients on metformin $\geq 1500$ mg/day with HbA1c $\geq 6.5\%$ and $\leq 8.5\%$	Dapa 10 mg and placebo 91/91/182
<b><i>Add-on combination therapy with insulin</i></b>		
D1690C00006 (add-on to insulin) 24 plus 24 plus 56 weeks	Patients on insulin $\geq 30$ IU/day $\pm$ maximum 2 OAD with HbA1c $\geq 7.5\%$ and $\leq 10.5\%$	Dapa 2.5, 5, and 10 mg and placebo 196-212/610/807
<b><i>Add-on combination therapy with pioglitazone</i></b>		
MB102030 (add-on to pioglitazone) 24 plus 24 weeks	Patients on pioglitazone with HbA1c $\geq 7.0\%$ and $\leq 10.5\%$	Dapa 5, and 10 mg and placebo 139-141/281/420



**Table 2. Summary of Completed Clinical Studies with Dapagliflozin (continued)**

Study number/ Duration	Patient population	Treatment groups n per group/n treated with dapagliflozin/Total
<b>Add-on combination therapy with glimepiride</b>		
D1690C00005 (add-on to glimepiride) 24 plus 24 weeks	Patients on glimepiride with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596
<b>Initial combination therapy with metformin</b>		
MB102021 (initial combination 5 mg) 24 weeks	Treatment- naive patients with HbA1c $\geq 7.5\%$ and $\leq 12.0\%$	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 (initial combination 10 mg) 24 weeks	Treatment- naive patients with HbA1c $\geq 7.5\%$ and $\leq 12.0\%$	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638
<b>Direct comparison with glipizide</b>		
D1690C00004 (direct comparison with glipizide) 52 plus 156 weeks	Patients on metformin $>1500$ mg/day with HbA1c $>6.5\%$ and $\leq 10.0\%$ Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814
<b>Special populations/studies</b>		
MB102029 (moderate renal impairment) 2b/3 24 plus 28 plus 52 weeks	Patients with moderate renal impairment (GFR $>30$ to $<60$ mL/min/ $1.73\text{m}^2$ on a stable anti-diabetic regimen with HbA1c $\geq 7\%$ and $\leq 11\%$	Dapa 5 and 10 mg and placebo 83-85/168/252
MB102045 <sup>†</sup> (insulin sensitivity) 2b 12 weeks	Effect on insulin sensitivity Add-on therapy to metformin $\pm$ insulin secretagogue	Dapa 5 mg or placebo 23/21/44

\* MB denotes studies sponsored by BMS

\*\*D denotes studies sponsored by AZ

<sup>†</sup> MB102045 (ST only) was completed after NDA submission as data from final databased lock for the ST + LT period of MB102013; safety assessments submitted to FDA in the 4MSU; no new safety concerns were identified from these studies.

Dapa = Dapagliflozin; GFR = glomerular filtration rate; HbA1c = Hemoglobin A1c; IU = International units; OAD = Oral anti-diabetic drug; SU = Sulfonylurea; vs = versus; XR = Extended release; ST = short-term; LT = long-term

Source: Applicant's Tables 2 in the AC Briefing Document.

It is noteworthy to also show the trials that were either ongoing or just recently concluded by the time of the applicant's document submission to the AC (Table 3).

**Table 3. Trials with Dapagliflozin as of the 12-May-2011, for inclusion in the AC background package**

Study	Study description	Treatment groups Planned n per group/n treated with dapagliflozin/total
MB102035*^ 12 weeks Phase 2b	Effects on GFR in patients with inadequate blood pressure control Add-on therapy to metformin ± SU	Dapa 10 mg, HCTZ 25 mg, and placebo 24/26/25/75
D1690C00010*^ 24 plus 24 weeks Phase 3b	Add-on combination therapy with DPP-4 inhibitor (sitagliptin)	Dapa 10 mg and placebo 225/226/451
D1690C00018^ 24 plus 28 weeks Phase 3b	Patients on usual care for diabetes with CVD and hypertension	Dapa 10 mg and placebo 470/470/940
D1690C00019^ 24 plus 28 weeks Phase 3b	Patients on usual care for diabetes with CVD	Dapa 10 mg and placebo 470/470/940
MB102073^ 12 weeks Phase 3b	Effects on blood pressure and HbA1c in patients on stable dose of OAD + inadequately controlled hypertension on stable dose of ACEI or ARB	Dapa 2.5, 5, 10 mg and placebo 276/828/1104
MB102077† 12 weeks Phase 3b	Patients with inadequately controlled hypertension treated with an ACEI or ARB and an additional antihypertensive medication	Dapa 5, 10 mg and placebo 255/510/765
MB102054^ 24 weeks Phase 3b	Monotherapy in Asian patients	Dapa 5 or 10 mg and placebo 126/254/378
MB102055^ 24 weeks Phase 3b	Add-on therapy to metformin in Asian patients	Dapa 5 or 10 mg and placebo 148/296/444

\* ST treatment recently concluded; ST treatment only for MB102035; ST + LT period for D1690C00010 ongoing.

^ Blinded safety assessments provided to FDA in the 4MSU; no new safety concerns were identified in these 2 studies.

† Started after the data cut-off date for the FDA.

ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CVD = Cardiovascular disease; Dapa = Dapagliflozin; DPP-4 = Dipeptidyl peptidase 4 inhibitor; GFR = Glomerular filtration rate; HbA1c = Hemoglobin A1c; HCTZ = Hydrochlorothiazide; IU = International units; OAD Oral anti-diabetic drug; SU = Sulfonylurea; XR = Extended release; ST = short-term; LT = long-term

From the trials listed in Table 3, the applicant committed to submission of datasets for the first 24 weeks of the large trials D1690C00018 and D1690C00019, prior to the PDUFA goal date, to provide a larger exposure database to better inform the regulatory action on the NDA during this review cycle. In addition to the 24-week data for each of these trials, the July 15<sup>th</sup> Integrated Safety Database contained data from other ongoing and recently completed dapagliflozin trials.

Dr. Dunn's clinical review followed the same pooling of trials as done by the applicant for a comprehensive analysis of effects on HbA1c, the primary efficacy endpoint, and to allow a more robust assessment within pre-specified subsets. The pooling of Phase 3 trials resulted in the following groups: monotherapy and add-on 24-week trials, initial combination with metformin trials (including a 5 mg dapagliflozin trial and a 10 mg dapagliflozin trial), a glipizide-controlled trial, and a trial in subjects with moderate renal impairment.

Key inclusion criteria were males and females between 18 and 77 years of age, with study-specific HbA1c ranges falling within the overall range of 6.5% to 12.0%. Subjects with advanced stages of T2DM, such as those with chronic complications of T2DM (retinopathy, neuropathy, and mild nephropathy), or a history of UTIs or vulvovaginitis, balanitis and related genital tract infections, were generally included in Phase 3 studies. Subjects with the following clinical characteristics were excluded from these studies: significant hepatic disease, including aminotransferase values  $> 3$  times (for most studies) the upper limit of normal (ULN) and elevated total bilirubin values; unstable cardiovascular disease, including New York Heart Association (NYHA) Class III and IV heart failure and a CV event within 6 months of enrollment; serum calcium values outside of the laboratory normal reference range; pregnant and breastfeeding women; and patients at risk for dehydration and volume depletion.

Demographic and baseline disease characteristics of subjects from all fourteen Phase 2b and 3 placebo-controlled or direct comparison studies in the NDA are presented in Table 4. Subject age ranged from 19 to 92 years, with a mean age 56 years. Most were white; black subjects comprised approximately 3.5% of the dapagliflozin and control, which is small compared to the US representation of blacks in the total diabetic population, but is comparable to clinical programs of other recently approved antidiabetic drugs. The proportion of males and females was similar. Approximately 30% of subjects were from the United States or Canada, a proportion we have recommended (as a minimum) to applicants, to allow extrapolation of the efficacy and safety data to the US population. The majority of subjects in the Phase 3 program had a BMI  $\geq 27$  kg/m<sup>2</sup> at baseline.

Relevant sub-populations included the elderly, patients with mild and moderate renal impairment, patients with long disease duration, and patients with common comorbidities such as CV disease and hypertension. As seen in Table 4, the groups are reasonably balanced for these characteristics.

**Table 4. Demographic and baseline characteristics in the All Phase 2b and Phase 3 Pool**

		<b>All Dapa N = 4287</b>	<b>All Control N = 1941</b>
Age	Mean (SD) years	55.9 (10.5)	56.5 (10.5)
	≥ 65 years, < 75 years, n (%)	764 (17.8)	402 (20.7)
	≥ 75 years, n (%)	115 (2.7)	54 (2.8)
Race	White, n (%)	3473 (81.0)	1576 (81.2)
	Non-white, n (%)	814 (19.0)	365 (18.8)
	Black, n (%)	149 (3.5)	67 (3.5)
	Asian, n (%)	557 (13.0)	242 (12.5)
	Other, n (%)	108 (2.5)	56 (2.9)
Gender	Female, n (%)	2110 (49.2)	922 (47.5)
Geography	North America, (US + Canada) n (%)	1355 (31.6)	525 (27.0)
Blood Pressure	Systolic Blood Pressure (SBP), Mean	130.4	130.9
	Diastolic Blood Pressure, Mean	79.3	79.7
	SBP < 130 mmHg, n (%)	1954 (45.6)	871 (44.9)
	SBP ≥ 130 mmHg, n (%)	2016 (47.0)	941 (48.5)
Weight	Mean (kg)	87.46	87.55
Body Mass Index	Mean (kg/m <sup>2</sup> )	31.54	31.53
Duration of T2DM	Mean, years	6.09	5.92
HbA1c	Mean, %	8.29	8.24
Baseline Renal Impairment			
Normal	≥ 90 ml/min/1.73 m <sup>2</sup> , n (%)	1612 (37.6)	753 (38.8)
Mild	≥ 60 and < 90 ml/min/1.73 m <sup>2</sup> , n (%)	2190 (51.1)	976 (50.3)
Moderate	≥ 30 and < 60 ml/min/1.73 m <sup>2</sup> , n (%)	477 (11.1)	207 (10.7)
Prior CVD*	Mean, n (%)	841 (19.6)	353 (18.2)

<sup>a</sup> Treated Patients NDA (NDA Dataset) = all patients who received at least 1 dose of double-blind study medication during short-term double-blind treatment

\* CV meta-analysis, (Table 50)

Does not include Group 2 from MB102013, Cohort 1 from MB102009, 1-mg treatment groups from MB102032 and D1692C00005.

SD = standard deviation; HbA1c = hemoglobin A1c; CVD = cardiovascular disease

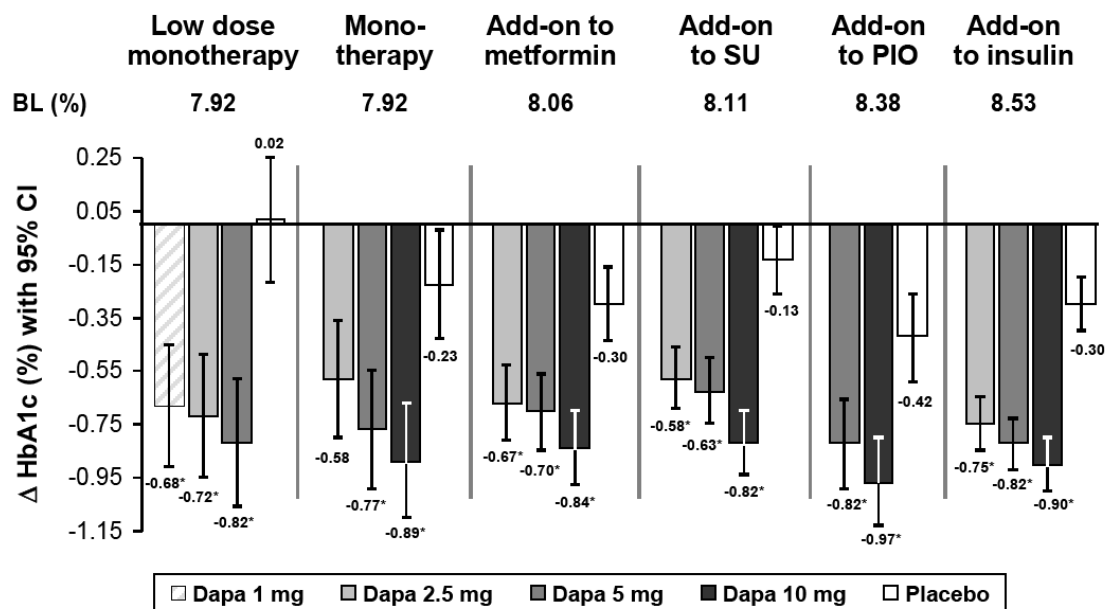
### Efficacy Results in Subjects with Normal Renal Function or Mild Renal Impairment

I will only present here summary results for HbA1c, the primary efficacy endpoint. For results of secondary endpoints, please refer to the clinical and statistical reviews.

The primary statistical methods for analysis were performed using an ANCOVA model, and imputation of missing data was done with LOCF.

Treatment with dapagliflozin 5 and 10 mg consistently resulted in statistically significant mean reductions in HbA1c compared to placebo (Figure 3). Dapagliflozin 10 mg consistently resulted in numerically greater HbA1c mean reductions compared to the 5 mg dose in each of 5 placebo-controlled Phase 3 studies that evaluated both doses (monotherapy, add-on to metformin, add-on to pioglitazone, add-on to glimepiride, and add-on to insulin).

**Figure 3. Mean Changes from Baseline to Week 24 in Phase 3 Monotherapy and Add-on Trials**



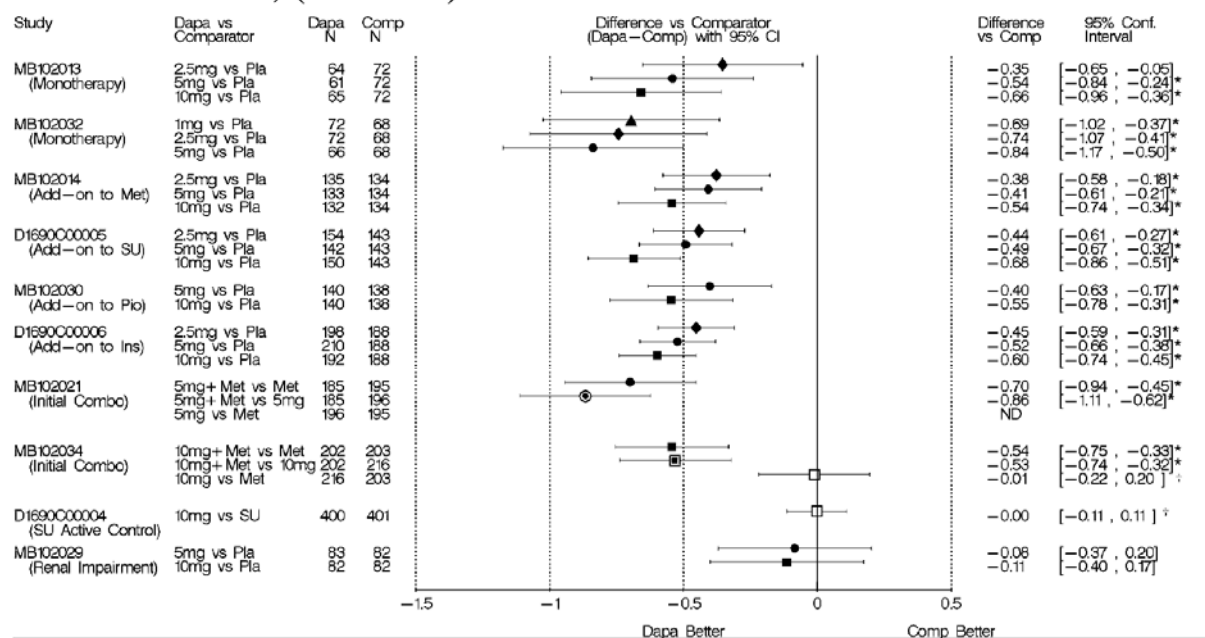
\* Statistically significant vs. placebo using Dunnett's correction

Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Randomized Patients Dataset/Full Analysis Set; BL = baseline

From the figure, we can see that the placebo-adjusted effect for the dapagliflozin 10 mg was in the range of -0.6 to -0.8%, with a dose proportional response in the effect, in the dose range from 2.5 to 10 mg daily. But also noteworthy is that the placebo group in all these trials (except for the 5 mg monotherapy) have demonstrated mean absolute HbA1c changes from baseline to week 24 in the range of -0.2 to -0.4%. Since these HbA1c means for the placebo groups exclude data post-glycemic rescue, this suggests that subjects enrolled in these trials were under effective counseling for adjunct diet and exercise. Still, the message conveyed by this figure is that dapagliflozin effected a mean HbA1c reduction of 0.6 to 0.8%, after subtracting the mean effect on the placebo group.

The forest plot in Figure 4 shows the changes in HbA1c from baseline to week 24 for all placebo- and active-comparator Phase 3 trials where HbA1c was the primary efficacy endpoint.

**Figure 4. Mean (95% CI) changes from baseline to week 24 in HbA1c in 10 Phase 3 trials**

<sup>a</sup> All evaluations based on Week 24 (LOCF) excluding data after rescue, except for D1690C00004, which is Week 52 (LOCF).

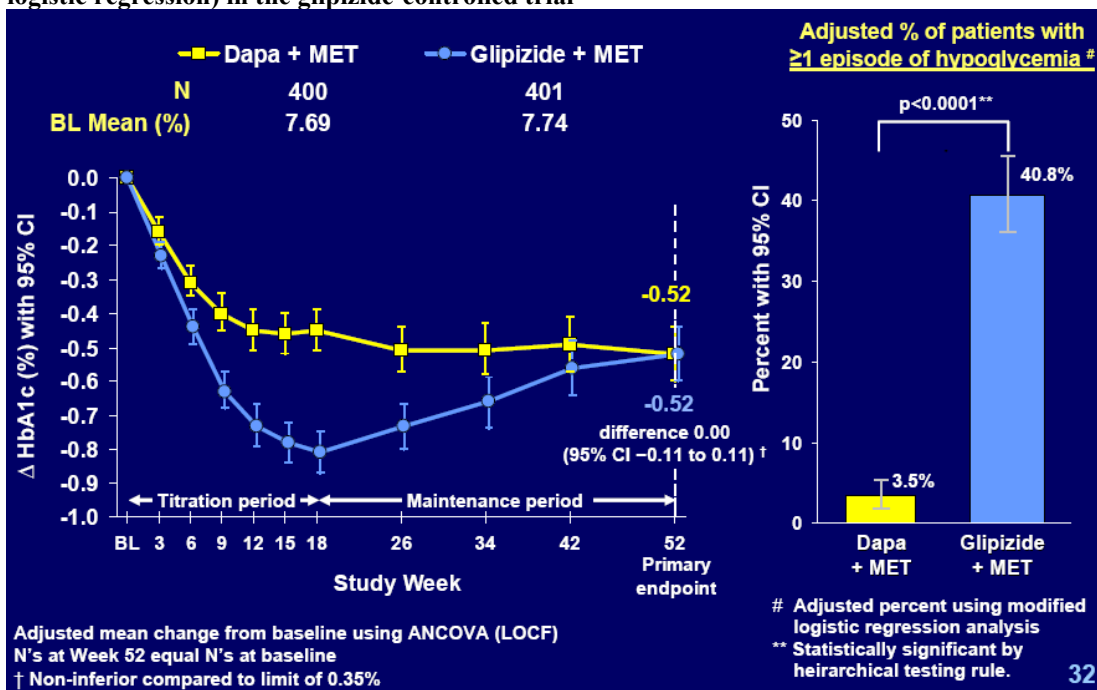
<sup>b</sup> Efficacy Analysis Data Set refers to the Randomized Patients Data Set [BMS] or Full Analysis Set [AZ].

This figure shows that dapagliflozin has placebo-adjusted glycemic efficacy (mean -0.7% for the 10 mg dose) in a range similar to that of recently approved DPP-4 inhibitors.

Importantly, the glipizide-controlled trial in subjects not controlled with metformin (mean baseline HbA1c 7.7%) shows an almost identical result of dapagliflozin 10 mg to effective doses of the sulfonylurea. And, as the applicant concludes, the improved glycemic control in this trial comes without the increased risk of hypoglycemia (Figure 5) and weight gain (Figure 6 reflects the glipizide-adjusted weight effect of dapagliflozin in the active-controlled trial. Because glipizide (and other sulfonylureas) are associated with weight gain, the effect of dapagliflozin (-4.6 kg) appears more accentuated. The mean weight effect of dapagliflozin 10 mg in the monotherapy trial was -1 kg. In the add-on to metformin trial, add-on to sulfonylurea trial, add-on to pioglitazone trial and add-on to insulin trial the placebo-adjusted mean effect of dapagliflozin was -2 kg, -1.6 kg, -1.7 kg and -1.7 kg, respectively. These mean changes are comparable to those reported in placebo-controlled trials of GLP-1 agonists.

Figure 6), adverse events usually associated with sulfonylurea treatment. It is equally important to emphasize that the latter effects (i.e., no increased risk of hypoglycemia and weight gain) were also observed in the trials of DPP-4 inhibitors and GLP-1 agonists, when compared to a sulfonylurea, so they are not unique to dapagliflozin.

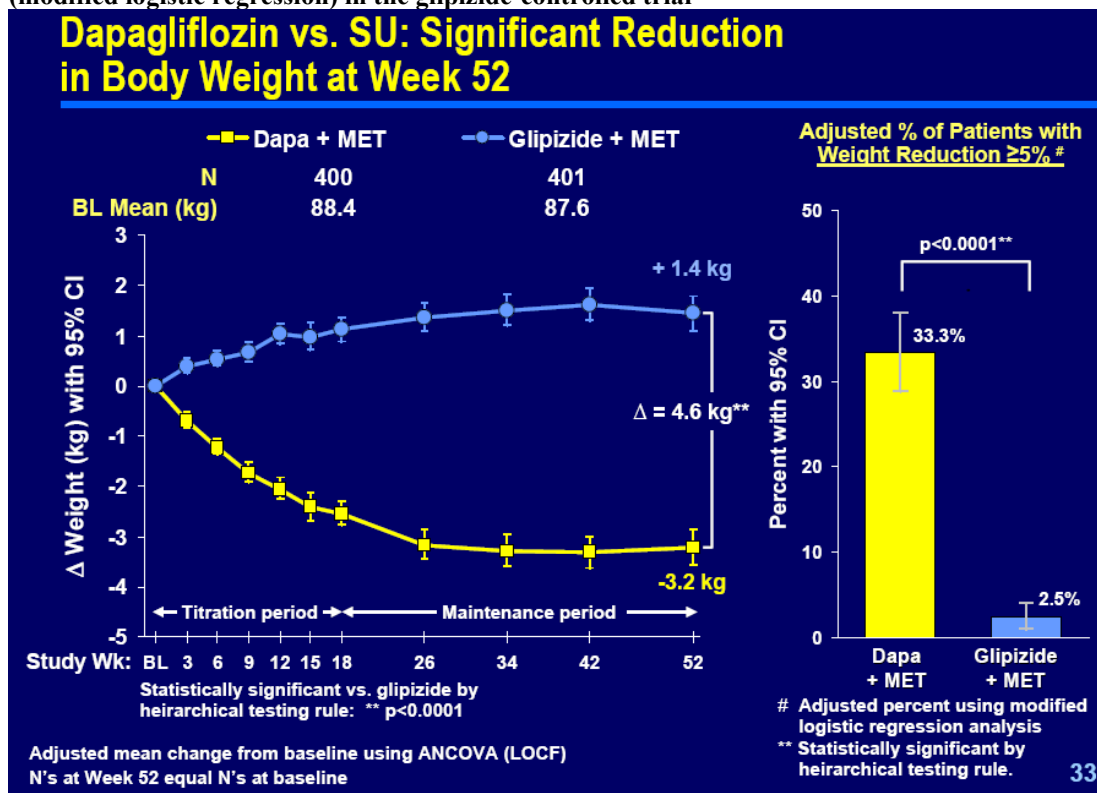
**Figure 5. Changes in HbA1c (ANCOVA –LOCF) and percent subjects with hypoglycemia (modified logistic regression) in the glipizide-controlled trial**



Source: Applicant's slide 32 presented at the AC meeting 7/19/2011; the majority of hypoglycemic events was classified as minor (symptomatic or asymptomatic episode with capillary or plasma glucose < 63 mg/dL; 3 glipizide-treated subjects had a major episode [requiring external assistance AND capillary glucose < 54 mg/dL] versus none in the dapagliflozin group)

Figure 6 reflects the glipizide-adjusted weight effect of dapagliflozin in the active-controlled trial. Because glipizide (and other sulfonylureas) are associated with weight gain, the effect of dapagliflozin (-4.6 kg) appears more accentuated. The mean weight effect of dapagliflozin 10 mg in the monotherapy trial was -1 kg. In the add-on to metformin trial, add-on to sulfonylurea trial, add-on to pioglitazone trial and add-on to insulin trial the placebo-adjusted mean effect of dapagliflozin was -2 kg, -1.6 kg, -1.7 kg and -1.7 kg, respectively. These mean changes are comparable to those reported in placebo-controlled trials of GLP-1 agonists.

**Figure 6. Changes in body weight (ANCOVA –LOCF) and percent subjects with weight loss  $\geq 5\%$  (modified logistic regression) in the glipizide-controlled trial**



Source: Applicant's slide 33 presented at the AC meeting 7/19/2011

Equally important for the assessment of efficacy, dapagliflozin 10 mg was studied as initial combination therapy with metformin (Trial MB102034); that factorial trial also had a metformin monotherapy arm and a dapagliflozin monotherapy arm. Metformin was used at effective doses. The comparison between metformin and dapagliflozin in the trial demonstrates a non-inferiority of dapagliflozin to metformin (the upper bound of the 95% CI for the between arms difference in the change of HbA1c was 0.2%).

So one must conclude that dapagliflozin, in well designed and adequately controlled trials can provide similar glycemic efficacy as the two very commonly used classes of oral drugs in the treatment of T2DM. Because the dapagliflozin mechanism of action does not overlap with metformin (insulin sensitizer) or sulfonylureas (insulin secretagogue), the combination of these drugs with dapagliflozin is also a rational choice for patients with failure to maintain glycemic control long term on these drugs.

The clinical and statistical reviews cover in detail the effect of dapagliflozin with sensitivity analyses (mixed effects model for repeated measures, or MMRM, including or excluding glycemic data post rescue), and analysis of subsets of the population based on important demographic and baseline disease characteristics. These reviews also detail the effects on secondary endpoints that support and confirm the effects on HbA1c.



Based on a recent report by the National Academy of Sciences commissioned by FDA<sup>2</sup>, Dr. Norton's review and AC presentation emphasized the flaws of the ANCOVA and MMRM analyses methods that exclude data after glycemic rescue, because this approach violates the intent-to-treat principle on which these statistical methods are based. He demonstrated the more attenuated placebo-adjusted effect of dapagliflozin in analyses that included data after rescue. Most subjects who receive glycemic rescue in placebo-controlled trials, assuming the investigational drug is effective, are those randomized to placebo. Therefore the comparison proposed by Dr. Norton is between dapagliflozin (with a small proportion of subjects rescued) against placebo (with a larger proportion of subjects rescued), and at least in part assessed the effect of rescue therapy. (b) (4)

Until we have reached a conclusion on the best statistical methodology to implement the National Academy of Science report, I believe analyses of efficacy against a placebo control which include data after rescue are useful sensitivity analyses, but in the Phase 3 diabetes trials that are commonly reviewed in our division, these methods should not be the primary analyses. Furthermore, prescribers tend to compare placebo-adjusted changes in HbA1c across different antidiabetic drugs, even if this practice is clearly not recommended. So if a label for Drug A shows a placebo-adjusted effect on HbA1c resulting from inclusion of post-rescue data and a label for Drug B shows a placebo-adjusted effect on HbA1c for another drug resulting from exclusion of post-rescue data, a prescriber may erroneously conclude that Drug B is more powerful than Drug A. Therefore, it is important that the Clinical Studies section of the Package Insert of these products carry results based on consistent analyses.

The applicant presented data to claim durability of the glycemic effect, with proportion of subjects who reached the ADA recommended HbA1c target of < 7% remaining the same virtually the same over 102 weeks, particularly for those randomized to the 10 mg dose of dapagliflozin. The applicant also presented figures at the AC that suggest sustained reduction in HbA1c in the 48 weeks of the add-on to insulin trial, and mitigation of the need to increase the dose of insulin over the same period in the add-on to insulin trial. But FDA has been reluctant to accept such claims, as the number of dropouts over time is substantial, and the population still participating after one or two years may be different than the originally randomized population.

The applicant evaluated effects of dapagliflozin on secondary glycemic endpoints: change in fasting plasma glucose (FPG) from baseline at week 24, proportion of subjects achieving HbA1c < 7% at week 24, and in one of the Phase 3 trials, change in 2-hour post-prandial glucose (PPG) from baseline at week 24 following a standard mixed meal tolerance test. The statistical analyses were similar to those performed for between group comparisons of the primary efficacy endpoint.

The mean FPG in subjects treated with 5 or 10 mg dapagliflozin decreased rapidly from week 1 to week 4, then continued to decrease until reaching a plateau between weeks 8 and 12. The effect on FPG was dose-dependent with the greatest reductions in FPG seen with the 10 mg dose (ranging from -17.5 to -26.5 mg/dL across the placebo-controlled monotherapy and add-on studies).

<sup>2</sup> Available online at [http://www.nap.edu/catalog.php?record\\_id=12955](http://www.nap.edu/catalog.php?record_id=12955)

Significant reductions in 2-hour PPG were also seen in those studies where this variable was assessed (Studies MB102032, D1690C00005 and MB102030) although there was no clear evidence of a dose relationship for the 2-hour PPG.

### Efficacy Results in Subjects with Moderate Renal Impairment

A dedicated renal impairment trial was conducted in subjects with moderate renal impairment, also known as Stage 3 according to the classification by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation. The degree of renal impairment was based on MDRD-calculated eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>. The results (noted as Study MB102029 as the last study in the forest plot in Figure 4) showed no effect against placebo, for either the 5 or the 10 mg dose of dapagliflozin (95% CI crosses the “zero” for the between-groups difference in HbA1c changes from baseline). These results were expected based on the lack of pharmacodynamic effect in this patient population (Figure 2).

The applicant further analyzed the effect on HbA1c in two subsets of Stage 3 renal impairment, defined according to British guidelines as Stage 3A, which includes subjects with eGFR between 45 and 59 mL/min/1.73 m<sup>2</sup>, and Stage 3B, which includes subjects with eGFR between 30 and 44 mL/min/1.73 m<sup>2</sup> (Figure 8) in the Moderate Renal Impairment trial as well as in the pooled subset of subjects with moderate renal impairment in the Phase 2b / Phase 3 clinical development. In the latter, the renal inclusion criterion was based on serum creatinine alone or in combination with calculated CrCl by Cockcroft-Gault (CG) formula, which resulted in the enrollment of 366 subjects with moderate renal impairment by MDRD. Of these subjects, 87% had baseline eGFR  $\geq$  45 mL/min/1.73 m<sup>2</sup>.

In the dedicated Moderate Renal Impairment trial, there was no dapagliflozin effect in either Stage 3A or Stage 3B. However, in a pooled analysis of all subjects with moderate renal impairment in the Phase 2b/ Phase 3 trials, there was a very small statistically significant (but clinically irrelevant) effect in the subset of subjects in Stage 3A (eGFR between 45 and 59) (Figure 8). The placebo-adjusted change in HbA1c in the pooled analysis had the same point estimate as that obtained in the dedicated renal trial, but with narrower confidence interval, not crossing “zero”, due to a larger number of subjects in the pooled analysis.

Based on the results of the pooled analysis, the applicant wants dapagliflozin to be indicated for subjects with eGFR greater than 45 mL/min/ 1.73 m<sup>2</sup>, despite the discrepancy with the data from the dedicated renal trial. As we will see in the safety analysis, there were numerically more fractures reported in subjects with moderate renal impairment treated with dapagliflozin than in the placebo group, and higher increases in mean serum parathyroid hormone and serum phosphorus, of unclear clinical significance, so the risk benefit (with a very questionable benefit) is not favorable. In addition, the nephrologist at the AC meeting, Dr. McBryde, stated that the uncertainty around these cutoffs based on the assays commonly used is large and does not allow precise classification within 15 mL/min differences in GFR. Dr. McBryde also stated the 45 mL/min/1.73 m<sup>2</sup> threshold would be confusing to American prescribers, who do not use the British sub-classification of Stages 3A and 3B. AC members sided with FDA, in that dapagliflozin should not be indicated to patients with moderate renal impairment (in the eGFR range between 30 and 59 mL/min/1.73m<sup>2</sup>). Realizing that the range of efficacy is part of a continuum, and the deterioration of renal function over time is gradual and variable, it is conceivable that a number of patients in the higher end of the moderate renal impairment could

individually benefit from treatment with dapagliflozin. However, the trial data do not provide sufficient evidence that the population risk benefit profile remains favorable at eGFR below 60 mL/min/1.73m<sup>2</sup>.

It is difficult to estimate the proportion of the diabetic population that would be affected by restricting the dapagliflozin indication only for those patients with eGFR > 60 mL/min/ 1.73 m<sup>2</sup> (favored by FDA) versus for those with eGFR > 45 mL/min/1.73 m<sup>2</sup> (favored by the applicant): according to the 2011 Annual Data Report from the United States Renal Data System estimates (based on NHANES 2001- 2008), the prevalence of self-reported diabetics among NHANES subjects with eGFR < 60 mL/min/1.73 m<sup>2</sup> was 21.3% by MDRD or 19.8% by CKD-EPI (Chronic Kidney Disease Epidemiology formula). There are no estimates available for prevalence of diabetics with eGFR between 45 mL/min/1.73 m<sup>2</sup> and 60 mL/min/1.73 m<sup>2</sup>. The first sets of columns in Figure 7 (“Diabetes” as the co-morbid condition) suggest the proportion of diabetics who fall in this eGFR range is approximately 18%.

**Figure 7. Proportion of diabetes in NHANES 2001-2008 participants with different degrees of eGFR estimates by MDRD or by CKD-EPI**

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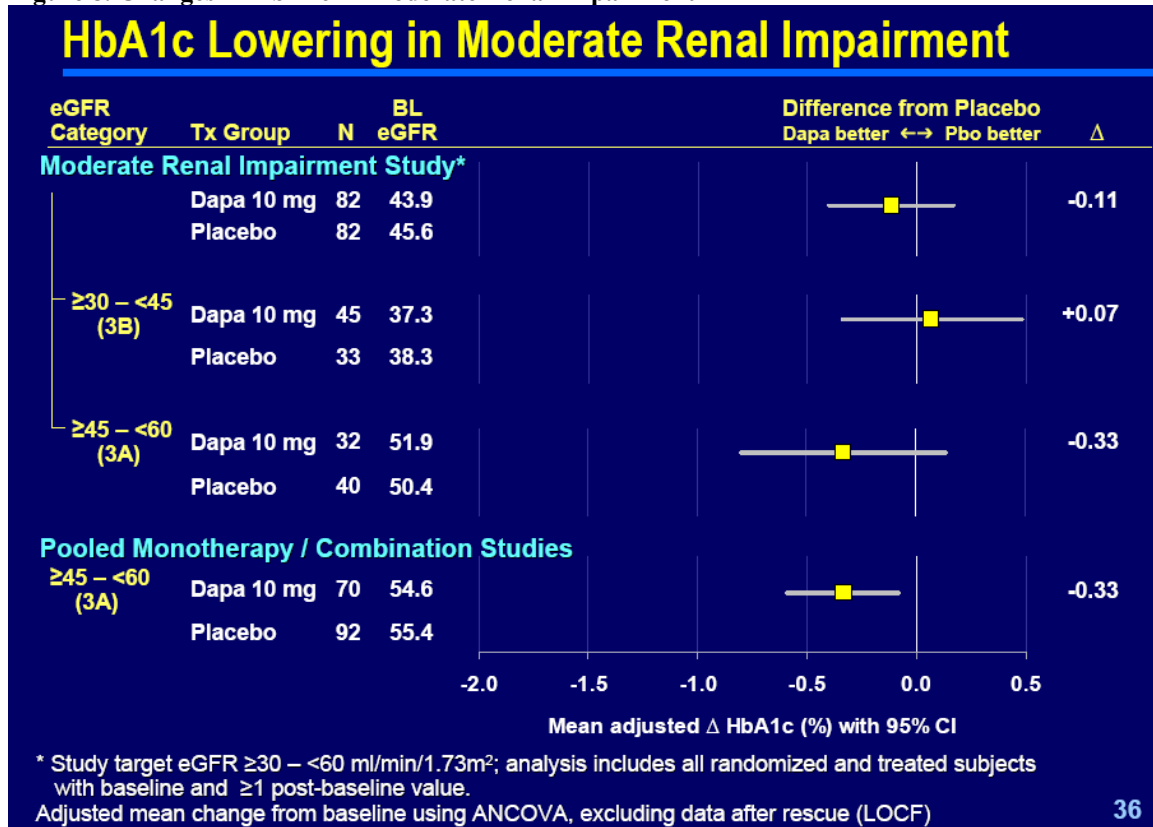


The applicant states that they can accept a limitation in the indication based on renal function similar to metformin and consistent with the criteria used for eligibility into the Phase 3 clinical trials. Such criteria could be CrCL ≥ 60 ml/min and/or serum creatinine < 1.4 mg/dl for women and < 1.5 mg/dl for men, as these accurately identified patients with eGFR values ≥

45 ml/min/1.73m<sup>2</sup> across the Phase 3 studies, with the rationale that such criteria are familiar to prescribers from other product labels, such as metformin, sitagliptin, and exenatide.

However, considering the GFR-based mechanism of action of dapagliflozin and the safety findings among subjects with eGFR between 45 and 60 ml/min/1.73m<sup>2</sup>, I cannot justify an indication for dapagliflozin in patients with eGFR < 60 ml/min/1.73m<sup>2</sup>.

**Figure 8. Changes in HbA1c in Moderate Renal Impairment**



Source: Applicant's slide 36 presented at the AC meeting 7/19/2011

### Efficacy Results in Subjects with Proteinuria

Another important efficacy point related to diabetic nephropathy: at the AC meeting, the nephrologist in the panel questioned the efficacy of dapagliflozin in patients with proteinuria. He made an analogy between dapagliflozin and furosemide: both drugs have in common their diuretic and natriuretic effect (although furosemide is a far more potent natriuretic than dapagliflozin), both are tightly bound to plasma proteins (dapagliflozin is 91% protein bound), and both act on the proximal tubule. Furosemide has a much reduced diuretic effect in patients with proteinuria. So he asked the applicant about the effect of dapagliflozin in patients with micro and macroalbuminuria, compared to patients with normoalbuminuria. The applicant conducted this analysis after the meeting, and submitted the following results to FDA:

In the 9-study monotherapy / combination therapy pool where the efficacy of dapagliflozin 10 mg was assessed<sup>3</sup>, albuminuria status at baseline appeared to have no effect on outcome of HbA1c reduction. Mean baseline HbA1c values varied by treatment group and baseline albuminuria category. Baseline HbA1c was included in the ANCOVA model as a covariate and adjusts for these differences. The p-value for interaction between treatment group and the baseline albuminuria categories (normo, micro or macroalbuminuria) was 0.92.

In the post-hoc exploratory analysis, the database was divided into subgroups by the three baseline albuminuria categories. These subgroups yielded, as expected, divergent subject numbers per subgroup and a small number of subjects with macroalbuminuria. Roughly 20% of subjects were microalbuminuric and < 3% had macroalbuminuria. The mean baseline HbA1c values were between 8.3 and 8.7% for placebo and between 8.1 and 8.6 % for the dapagliflozin arms.

The placebo-adjusted HbA1c mean changes from baseline at Week 24 (LOCF) in HbA1c by albuminuria baseline category with corresponding 95% confidence intervals for the 10 mg dapagliflozin groups were:

- Normoalbuminuria: -0.6 % (-0.7%, -0.5%)
- Microalbuminuria: -0.6 % (-0.8%, -0.5%)
- Macroalbuminuria: -0.7 % (-1.1%, -0.2%)

Based on these post-hoc analyses, dapagliflozin's glucose lowering efficacy measured as HbA1c change from baseline vs. placebo does not appear to be influenced by the presence of albumin across the overall pooled Phase 3 population, as well as within subgroups defined by baseline eGFR. The interpretation of these results is limited by the small numbers of subjects with macroalbuminuria in these analyses.

The applicant achieved similar conclusion based on analyses of dapagliflozin-induced 24-hour urinary glucose excretion plotted against baseline urinary albumin / creatinine ratio in subjects participating in Study MB102029, the renal impairment trial.

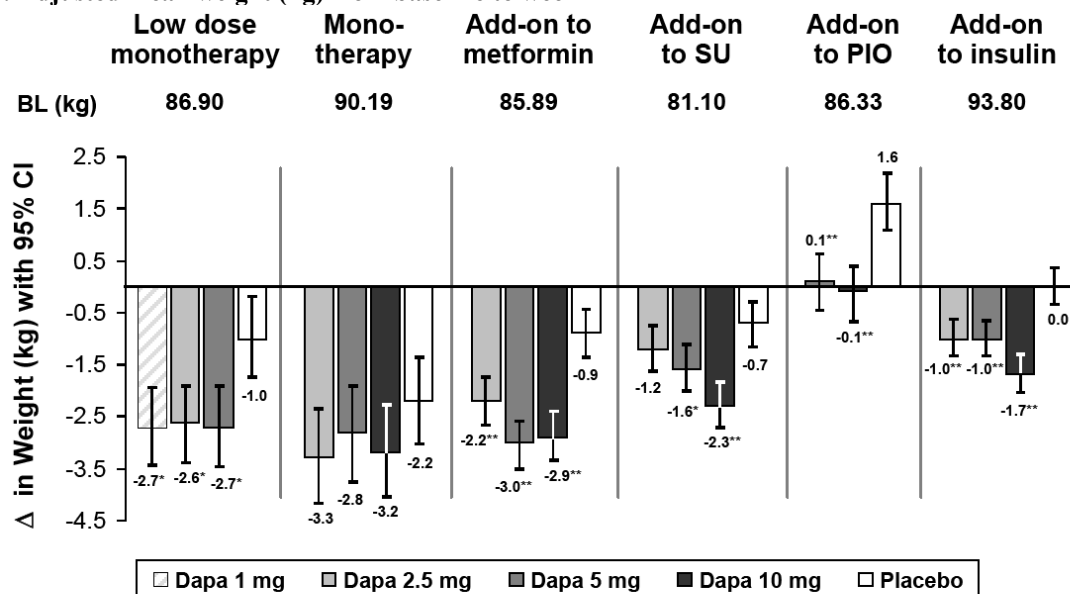
### Efficacy on Body Composition and Weight Loss

Dapagliflozin has the potential to achieve a slow and steady, although modest, weight loss with a reduction in total body fat due to its glucosuric mechanism of action, which results in persistent loss of calories in the urine.

The placebo-corrected mean weight reductions over 24 weeks ranged from -0.46 to -2.16 kg in six placebo-controlled Phase 3 trials (Figure 9). Weight loss in the placebo group in monotherapy trial MB102013 was greater than is typical for clinical trials in diabetics.

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<sup>3</sup> Includes Studies MB102013, MB102032, MB102014, D1690C00005, MB102030, D1690C00006, MB102021, MB102034 and D1690C00012.

**Figure 9. Adjusted mean weight (kg) from baseline to week 24**

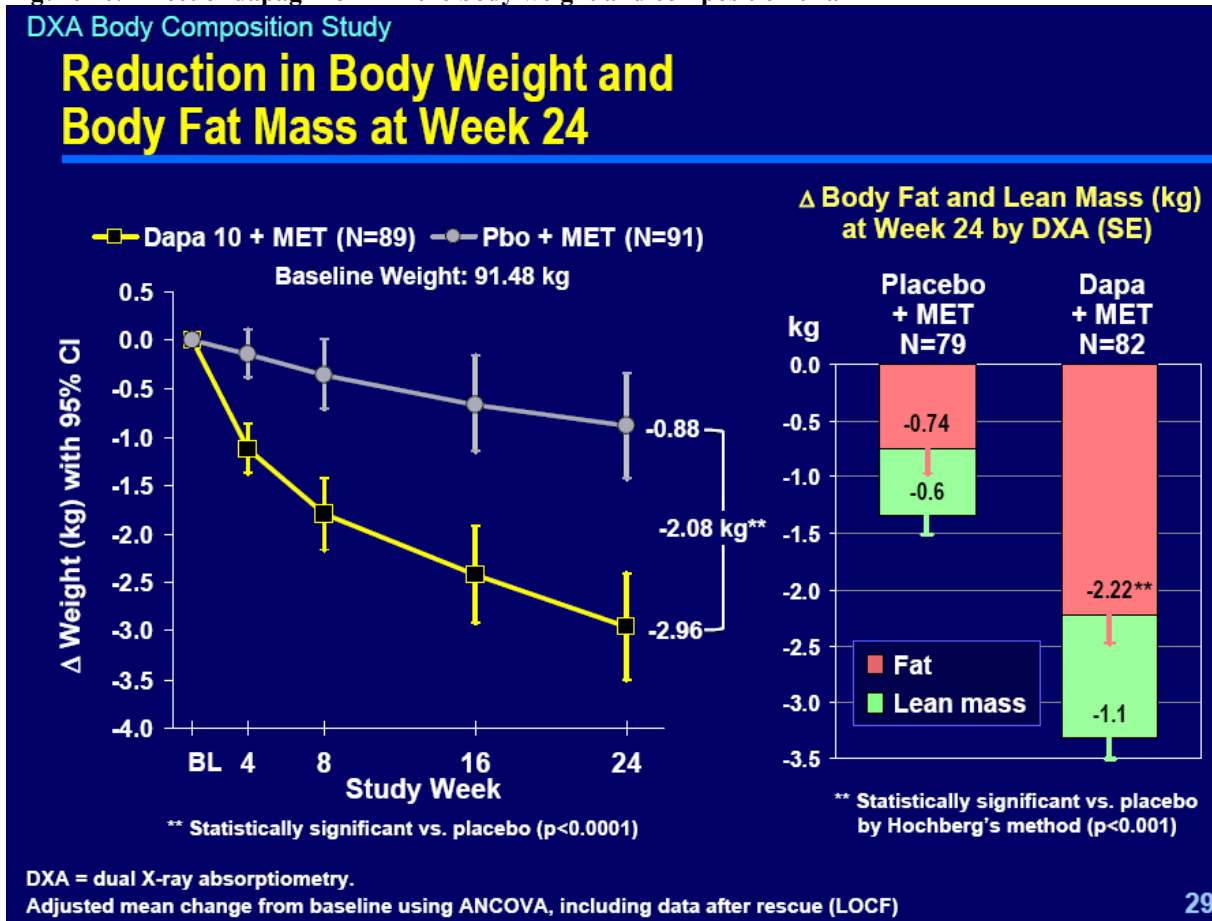
Statistically significant vs. placebo by hierarchical testing rule: \* =  $p < 0.05$ ; \*\* =  $p < 0.001$

Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Randomized Patients Dataset/Full Analysis Set; includes data after rescue (LOCF); BL = baseline

Weight loss associated with dapagliflozin treatment was further evaluated within a special trial (D1690C00012) to examine change in body weight and body composition, including adipose and lean mass changes, using dual energy X-ray absorptiometry (DXA), as well as volume of visceral adipose tissue by MRI in a subset of subjects. The primary endpoint in this study was reduction in total body weight. Subjects enrolled in this trial had previously failed to achieve glycemic control after treatment with metformin alone. The adjusted mean change in body weight for patients treated with dapagliflozin 10 mg plus metformin and placebo plus metformin was  $-2.96$  kg and  $-0.88$  kg, respectively. This difference amounted to a statistically significant, placebo-corrected mean weight change of  $-2.08$  kg ( $p < 0.0001$ ) in patients treated with dapagliflozin plus metformin. These data are consistent with the weight loss observed in the main add-on to metformin study, MB102014.

Reduction in total body fat mass accounted for two thirds of the weight loss in this study. Weight loss from reduction in lean body mass was small, indicating that the effect of treatment on weight was not due primarily to fluid loss over 24 weeks. The reduction in total body fat mass was approximately three times larger in the dapagliflozin-treated group ( $-2.22$  kg) than in the placebo group ( $-0.74$  kg) ( $p$ -value  $< 0.0001$ , for the comparison between the two treatment groups) (Figure 10). Visceral adipose tissue volume was reduced in dapagliflozin treated subjects in the exploratory sub-study. The data on body composition and on body fat distribution are considered exploratory, (b) (4)

**Figure 10. Effect of dapagliflozin in the body weight and composition trial**

Source: Applicant's slide 29 presented at the AC meeting

## 8. Safety

### Overall safety assessments

The safety of dapagliflozin in the Phase 2b and Phase 3 clinical program was evaluated at doses of 2.5, 5 and 10 mg, administered as monotherapy or in combination with other antidiabetic drugs. Its anticipated safety profile was consistent with the adverse effects related to glucosuria and diuresis resulting from the inhibition of SGLT2. Events considered as potentially related to dapagliflozin's mechanism of action at the beginning of the clinical development program, and studied in depth throughout the program were: hypoglycemia; urinary tract infections (UTIs); vulvovaginitis, balanitis and related genital infections; hemodynamic effects, such as blood pressure, volume depletion, and changes in hematocrit and hemoglobin; effects on renal function, serum sodium, potassium, and uric acid; and effects on bone, such as markers of bone formation and resorption, bone mineral density, and fractures. Safety assessments were also conducted on events of malignancy and hepatic safety, which are necessary for the complete assessment of any new molecular entity, particularly for the first treatment in a new class of antidiabetic drugs. Evaluation of CV safety included a

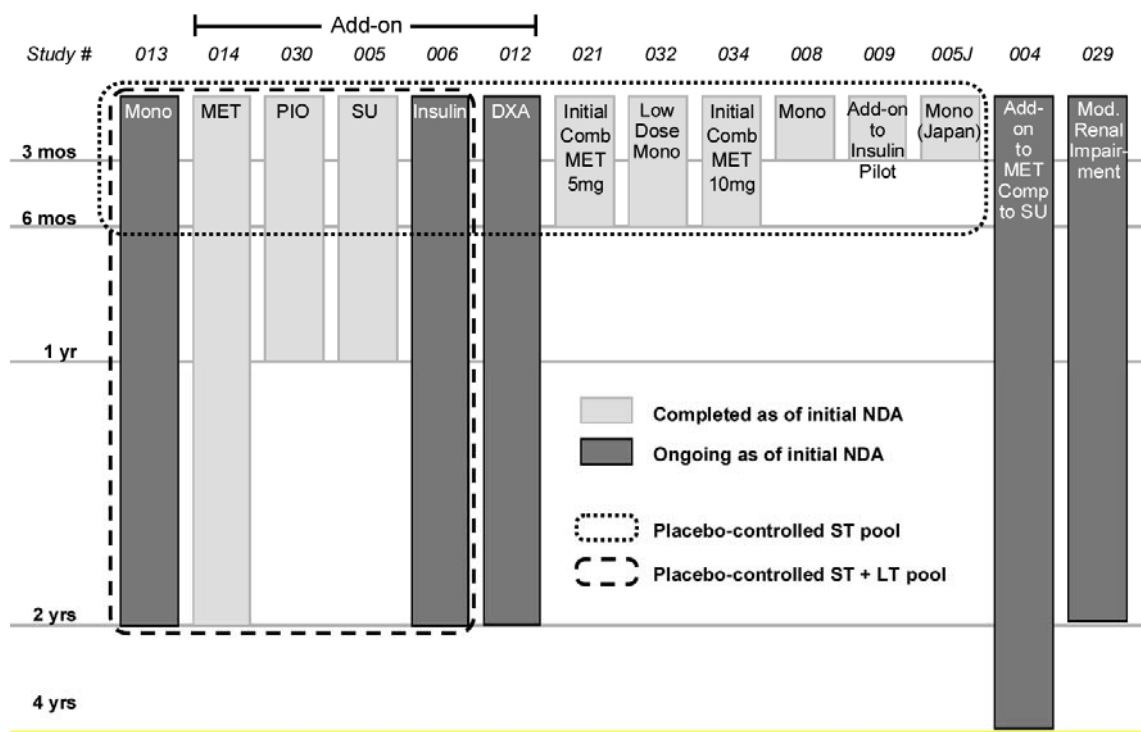
metanalysis of independently confirmed, blindly adjudicated, CV events among fourteen Phase 2b and Phase 3 trial as well as measurements of blood pressure and serum lipids, in agreement of the protocol with FDA and in accordance with FDA guidance. The applicant also assessed safety in specific populations and subsets.

Treatment with other glycemic rescue drugs was permitted based on pre-specified criteria for persistent hyperglycemia. The primary safety analyses were performed on data including treatment with rescue therapy. Select analyses were also performed on data excluding treatment with rescue therapy to assess whether results were similar, regardless of the presence of rescue. Because some glycemic rescue drugs can cause hypoglycemia, the primary analyses for hypoglycemia were performed excluding data after rescue.

#### Exposure to Dapagliflozin in the Clinical Program (excludes Clinical Pharmacology trials)

The analysis populations are illustrated in Figure 11. These were proposed by the applicant in the NDA and were also used by Dr. Dunn in her clinical review of safety.

**Figure 11. Pooling Strategy for the Short Term and Short Term plus Long Term Placebo-controlled Pool and the All Phase 2b and Phase 3 Pool**



The overall exposure to dapagliflozin at doses of 2.5 mg to 10 mg in all Phase 2b and Phase 3 trials submitted to FDA at the time of initial NDA submission is shown in Table 5.



**Table 5. Exposure to Dapagliflozin in Short Term and Long Term Treatment Periods by defined pools and individual trials in the All Phase 2b and Phase 3 trials at the time of NDA submission**

Population	Placebo/control	Dapagliflozin Dose			Total Dapa
		2.5 mg	5 mg	10 mg	
All Phase 2b and 3 Pool	1941				4287*
Placebo-controlled Pool ST	1393	814	1145	1193	3291*
Placebo-controlled Pool ST + LT	694	625	767	768	2160
Monotherapy ST	251	321	316	245	882
Monotherapy ST + LT	75	132	132	146	410
Dapagliflozin Plus Metformin ST	228			226	226
Dapagliflozin Plus Metformin ST + LT	137	137	137	135	409
Dapagliflozin Plus Insulin	197	202	212	196	610
Dapagliflozin Plus Sulfonylurea	146	154	145	151	450
Dapagliflozin Plus TZD	139		141	140	281
Initial Combination with Metformin 5 mg	201		194 (203)^		397
Initial Combination with Metformin 10 mg	208			211 (219)+	430
Dapagliflozin vs Glipizide	408				406
Moderate Renal Impairment	84		83	85	168
Moderate Renal Impairment	84		83	85	168

Dapa - dapagliflozin, LT - long-term, ST - short-term, TZD - thiazolidinedione

\*Includes DAPA 20 mg and 50 mg

^ Dapa 5 mg + Met (Dapa 5 mg)

+ Dapa 10 mg + Met (Dapa 10 mg)

The Phase 2b and Phase 3 was the largest pool to assess overall safety. The pool includes all available short-term plus long-term data from all 14 studies. Cumulative exposure to dapagliflozin in the Phase 2b and 3 studies was 4009 patient-years and 1682 patient-years to control.

As a result of the accumulation of additional study data, the 4-Month Safety Update includes approximately 9% additional patient-years than in the initial NDA. Cumulative patient-years of treatment at this update were about 2.3 times greater with dapagliflozin (4354 patient-years) than with control (1899 patient-years) (Table 6).

**Table 6. Extent of Exposure, short term and long term treatment period, including data after rescue, in the All Phase 2b and Phase 3 Pool at the 4-Month Safety Update**

	Number (%) of Patients				
	DAPA 2.5MG N = 1220	DAPA 5MG N = 1833	DAPA 10MG N = 2003	DAPA TOTAL N = 4310	ALL CONTROL N = 1962
CUMULATIVE EXPOSURE (PATIENT - YEARS)	967.1	1252.5	2103.7	4354.4	1898.9
DURATION (DAYS)					
1 - 90	544 ( 44.6)	575 ( 31.4)	254 ( 12.7)	746 ( 17.3)	356 ( 18.1)
91 - 180	115 ( 9.4)	486 ( 26.5)	470 ( 23.5)	1075 ( 24.9)	502 ( 25.6)
181 - 270	15 ( 1.2)	32 ( 1.7)	40 ( 2.0)	85 ( 2.0)	63 ( 3.2)
271 - 360	180 ( 14.8)	437 ( 23.8)	336 ( 16.8)	789 ( 18.3)	328 ( 16.7)
361 - 450	17 ( 1.4)	21 ( 1.1)	208 ( 10.4)	108 ( 2.5)	58 ( 3.0)
451 - 540	10 ( 0.8)	12 ( 0.7)	64 ( 3.2)	111 ( 2.6)	100 ( 5.1)
541 - 630	22 ( 1.8)	36 ( 2.0)	75 ( 3.8)	128 ( 3.0)	69 ( 3.5)
631 - 720	216 ( 17.7)	179 ( 9.8)	357 ( 17.8)	745 ( 17.3)	224 ( 11.4)
721 - 810	101 ( 8.3)	55 ( 3.0)	182 ( 9.1)	478 ( 11.1)	214 ( 10.9)
811 - 900	0	0	16 ( 0.8)	42 ( 1.0)	45 ( 2.3)
> 900	0	0	0	3 (<0.1)	3 ( 0.2)
Number (%) of Patients					
	DAPA 2.5MG N = 1220	DAPA 5MG N = 1833	DAPA 10MG N = 2003	DAPA TOTAL N = 4310	ALL CONTROL N = 1962
SUMMARY STATISTICS					
MEAN	289.5	249.6	383.6	369.0	353.5
MEDIAN	168.5	169.0	339.0	336.0	329.0
MIN , MAX	5, 786	1, 792	1, 859	1, 908	1, 908
STANDARD DEVIATION	282.61	219.33	243.26	257.95	255.21

This table includes all treated patients with at least one dose of dapagliflozin 2.5 mg or higher. Percentages reported are based on the total number of patients in each treatment group. The extent of exposure to study medication during the short-term plus long-term treatment period is defined as the difference between the last dose of short-term plus long-term study medication and the first dose of study medication of the short-term double-blind treatment period plus 1 day. Cumulative exposure is calculated as the sum of the exposure to study medication of all patients (in years) in a treatment group. Does not include 1 mg treatment group from Studies MB102032 and D1690C00005, as this dose was considered to be sub-therapeutic. Patients from studies D1690C00004 and D1690C00006 may be included in more than one dapagliflozin dose group due to titration. The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102045, D1690C00004, D1690C00005, D1690C00006, and D1690C00012.

At the time of the July 15<sup>th</sup>, 2011 Integrated Safety Update, based on data included in the major amendment, 5501 subjects had been exposed to dapagliflozin (5496 person-years) and 3184 subjects to comparator (3004 person-years). This exposure represents an increase of 1500 person-years in dapagliflozin exposure, compared to the exposure reported in the original NDA submission. The additional exposure derives mostly from the initial 24 weeks of Studies DC1690C00018 (Study 18) and DC1690C00019 (Study 19). These two trials can be described as multicenter, randomized, placebo-controlled, double-blind, age-stratified, with a 28-week extension after the initial efficacy assessment at week 24. Both trials are being conducted in subjects with T2DM and increased risk for CV disease (Study 18 requires presence of hypertension as a criterion for inclusion).

#### Dose selection based on balance of efficacy and safety

A 12-week dose-ranging study demonstrated that doses higher than 10 mg (20 and 50 mg) led to additional increases in hematocrit measurements, as well as vulvovaginitis, balanitis and related genital infections and UTIs, but did not provide further improvements in glycemic efficacy. The 5 mg and 10 mg doses were effective, with greater magnitude of HbA1c reduction for subjects treated with 10 mg of dapagliflozin daily. There was a trend for dose-proportional decreases in systolic blood pressure for those subjects without hypertension at baseline. There was no trend for those with BP  $\geq$  140 mmHg at baseline. In addition, events related to hypovolemia and hypotension (preferred terms such as hypotension, dehydration, syncope, blood pressure decreased, orthostatic hypotension and urine output decreased) were infrequent, but slightly more frequent in the elderly within 2 weeks of initiation of treatment. Perhaps considerations regarding the latter led the applicant to propose a starting dose of 5 mg for those patients who are at risk for volume depletion, such as users of loop diuretics. The selection of these doses is acceptable, from a risk / benefit standpoint.

### Selected aspects of dapagliflozin safety

For a more comprehensive review of safety, please refer to Dr. Dunn's clinical review and to Dr. Abraham's review for the metanalysis of major cardiovascular adverse events.

This memo will focus on selected aspects, that were discussed extensively at the AC meeting and that are being considered and debated within the review division and the various FDA consultants involved in the review.

Deaths, non-fatal SAEs and AE-related discontinuations are the top items in a safety review. These were balanced between the dapagliflozin and comparator groups. At the original NDA submission, 21 deaths (0.5%) were reported in the dapagliflozin groups, and ten deaths (0.5%) were reported in the all control group. The most common cause was cardiovascular disorders.

Non-fatal SAEs were also equally balanced between dapagliflozin and all control groups, and no dose-dependent trend was observed within the dapagliflozin groups. The two slightly more common system organ classes in which SAEs were reported were Cardiac Disorders and Infections and Infestations.

It is noteworthy that the most frequent cause of discontinuation in the dapagliflozin groups was increased blood creatinine (0.1%, 0.2% and 0.4% for dapagliflozin 2.5 mg, 5 mg and 10 mg, respectively, versus 0.1% for placebo), which may reflect both the mild transient effects on GFR (see below) and the necessary strict criterion for discontinuation of subjects on metformin background therapy or metformin control, to mitigate the risk of lactic acidosis.

The lack of any trends in deaths, non-fatal SAEs and AE-related study discontinuations, noted in the review of the original NDA submission, persisted in the review of the 4-Month Safety Update and at the July 15<sup>th</sup>, 2011 Integrated Safety Update.

With regard to common AEs, the proportion of subjects with at least one AE was higher in each of the dapagliflozin groups relative to placebo during the short-term (24 weeks) treatment period. The proportions were similar by the end of the long-term extension treatment periods. The largest contributors to this difference were events of hypoglycemia, vulvovaginitis, balanitis and related genital infections, and UTI. These events will be discussed in greater detail in this memo, as part of the selected aspects of safety.

The applicant divided these adverse events of special interest into those related to the mechanism of action and those apparently unrelated to the mechanism of action. I will start with the most contentious issues, which were unexpected and apparently unrelated to the mechanism of action of SGLT2 inhibition.

### Cancer

An analysis of the overall incidences of cancers in the Pooled All Phase 2b and Phase 3 data using the initial NDA and 4-Month Safety Update datasets as well as relevant nonclinical information did not point to any particular concern. As part of the ongoing assessment of these events, additional integrated data through May 12<sup>th</sup>, 2011 (in preparation for the AC discussion), the safety dataset has been expanded and updated. Based on the May 12<sup>th</sup>, 2011 dataset, the overall incidence rates of unspecified and malignant neoplasms are similar between dapagliflozin and control. Some individual cancer types were more common with comparator than with dapagliflozin, while others were more common for dapagliflozin than

comparator. Two types of cancer—breast and bladder cancer—will be discussed in detail in this section.

### Bladder Cancer

Dr. Hampp's November 29<sup>th</sup>, 2011 review and analyses of the incidence rates of bladder cancer are summarized here. Please also refer to his reviews of the incidence of bladder cancer of June 7<sup>th</sup>, 2011 and July 20<sup>th</sup>, 2011 for further details.

In the original NDA dataset, bladder cancer was reported in seven subjects treated with dapagliflozin and zero (0) in the control group. With the July 15<sup>th</sup>, 2011 Integrated Safety Update, two additional cases of bladder cancer were reported in the dapagliflozin group and one case in the control group.

The applicant updated age and gender exposure data for 19 Phase 2b and 3 clinical trials, including the ongoing studies 18 and 19. Because treatment assignment in the latter two studies is still masked, follow-up time by exposure was estimated by the applicant based on actual follow-up time, which was then equally assigned to the two treatment arms.

At the time of the original NDA and this updated analysis, 10 subjects were reported with bladder cancer in the phase 2b and 3 clinical trials on dapagliflozin. Nine of these cases occurred in the dapagliflozin treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76.

Table 7 summarizes the cases of bladder cancer reported in the original NDA submission, which were presented and discussed at the AC meeting.

**Table 7. List of cases of bladder cancer reported as of May 2011**

<b>Urothelial (Bladder) Cancer Cases by Study Day of Diagnosis</b>							
<b>Age/Sex</b>	<b>Dapa Dose (mg)</b>	<b>Invasive</b>	<b>Grade</b>	<b>TNM</b>	<b>Diagnosis Study Day</b>	<b>Smoking</b>	<b>Baseline Hematuria</b>
75/M	Dapa 2.5	+	Grade 2	T4 N0 M1 (lung mets)	43	Former	2+
48/M <sup>1</sup>	Dapa 10	–	Low Grade	Not avail.	74	Former	Negative
67/M	Dapa 5 + Pio	+	High Grade	T2	144	Never	Trace
55/M	Dapa 10	–	Low Grade	M0	169	Current	Trace
63/M	Dapa 5 + Ins	–	Grade 2	Ta	393 (tumor 358)	Current	Negative
67/M	Dapa 10 + Ins	Not avail.	Grade 2	Not avail.	399	Never	3+
60/M	Dapa 5 + Met	–	Low Grade	Ta N0 M0	512	Former	2+
66/M	Dapa 10 + Ins	–	Low Grade	Not avail.	581	Former	Negative
76/M	Dapa 2.5-10 + Met	+	High Grade	T1 M0	727	Former	Negative
67/M	Placebo	+	High grade	M0	136	Current	3+
All tumors were urothelial cancer (considered synonymous with transitional cell carcinoma). One tumor (in the 76 year old male) was noted to have partial squamous differentiation.							
* Includes 3 cases from 2 recently unblinded studies (D1690C00018, D1690C00019)							
<sup>1</sup> This subject had a history of hematuria since 2008.							
							<b>66</b>

Source: Applicant's slide 66 to the AC meeting

I will summarize here Dr. Hampp's November 2011 review and analysis, using the nine cases in dapagliflozin and one case in the control group, in the background of the updated exposure described in the July 15<sup>th</sup>, 2011 Integrated Safety Update.

The applicant provided trial-specific counts and follow-up durations for bladder cancer and breast cancer, separate for males and females, from the July 15th, 2011 Integrated Safety Database. Rate ratios were calculated only for trials that reported at least one case of bladder cancer, while rate differences were calculated based on all studies.

Incidence rates for bladder cancer were also compared with background rates in the general U.S. population. For this review, age- and sex-specific incidence rates were extracted from the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute. These rates were adjusted with a literature-based factor to reflect the increased risk for bladder cancer in a diabetic population. Therefore, these hazard ratios were adjusted to reflect that SEER data include diabetic patients, with the assumption that their proportion is the same as in the U.S. general population older than 20 years of age. For this review, a downward-adjusted hazard ratio of 1.40 (diabetes versus non-diabetics) was calculated for bladder cancer.

Because all cases of bladder cancer were reported in males, observed counts of bladder cancer in the dapagliflozin clinical trial program were compared with expected case counts in an age-matched male diabetic background population.

Total follow-up of male patients randomized to dapagliflozin was 3165.8 subject-years (Table 8) after cases were censored at the date of their case diagnosis. With nine cases of bladder

cancer occurring in male subjects exposed to dapagliflozin during this time, the crude incidence rate amounted to 284.3 (95% CI, 129.7 – 539.7) new cases per 100,000 subject-years. This compares to one case during 1854.4 subject-years in controls, or 53.9 (95% CI, 0.7 – 300.0) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of bladder cancer between active treatment and controls was in agreement with the applicant's calculation: 5.38 (95% CI, 0.84 – 122.2), with a two-sided p-value of 0.185. The applicant calculated the adjusted rate difference as 209 cases per 100,000 patient-years (95% CI, -305 – 688). (Note: the lower bound of this wide confidence interval is negative 305, thus including the possibility of no difference or even a protective drug effect.) The Mantel-Haenszel calculation conducted for this review yielded a rate difference of 237 cases per 100,000 patient-years (95% CI, 20.3 – 455) with a confidence interval excluding the null,  $p=0.03$ .

Based on SEER data, slightly more than three cases (3.22) of bladder cancer would be expected in the male dapagliflozin population (Table 8) at a crude rate of 101.4 new cases per 100,000 subject years. The standardized incidence ratio (SIR) of observed ( $n=9$ ) versus expected cases ( $n=3.22$ ) in males exposed to dapagliflozin was 2.80 (95% CI, 1.36 – 5.13),  $p=0.008$ . Two cases (2.08) would be expected among controls, where only one case was observed.

**Table 8. Expected cases of bladder cancer in the male clinical trial sample**

Age at diagnosis	Males			
	Observed cases, dapagliflozin	Dapagliflozin, person-time, males	Projected incidence, diabetic population, based on SEER data*	Expected bladder cancer cases in dapagliflozin patients
<25	0	1.52	0.4	0.0000
25-29	0	16.83	0.7	0.0001
30-34	0	47.98	1.5	0.0007
35-39	0	92.12	3.2	0.0029
40-44	0	183.27	7.0	0.0129
45-49	1	325.83	15.6	0.0509
50-54	0	450.45	31.8	0.1433
55-59	1	638.84	63.8	0.4077
60-64	2	591.6	111.8	0.6612
65-69	3	468.37	183.1	0.8578
70-74	2	241.81	275.3	0.6656
75-79	0	87.41	372.5	0.3256
80-84	0	19.3	455.5	0.0879
85+	0	0.46	506.9	0.0023
sum	9	3165.8	--	3.22

\* per 100000 person-years.

To summarize, the clinical trials were not powered to statistically distinguish between nine cases of bladder cancer in the active treatment arms compared to one case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population.

Dr. Hamppe points out that the limitations of these analyses preclude a conclusion of an association between dapagliflozin treatment and bladder cancer risk, but states the rate ratios unfavorable to dapagliflozin cannot be ignored, must be taken into account for a thorough assessment of the risks and benefits regarding a regulatory action and, if approved, must continue to be evaluated postmarketing.

In addition, it is noteworthy that, of the nine reported cases in the dapagliflozin group, five were diagnosed within a year of exposure, and five had baseline hematuria, ranging from trace to 3+ on urinalysis. Even if the cases diagnosed within a year were not taken into consideration, an imbalance against dapagliflozin persists. Dr. Dunn pointed out that there were no imbalances in the known risk factors for bladder cancer at the time of randomization in these trials. However, the bladder cancer incidence rate is very low, surrounded by large confidence intervals, and we cannot expect small or even moderate imbalances of risk factors to influence such an imbalance in reported cases.

## Breast Cancer

Please refer to Dr. Julia Ju's review for details on the analysis of breast cancer risk in the dapagliflozin clinical program.

Nine cases of breast cancer have been reported in the dapagliflozin treatment groups versus none in the comparator groups in dapagliflozin clinical trials at the time of NDA submission. The dataset was updated during the initial review to add one case of breast cancer to the control group (Table 9).

**Table 9. List of Confirmed Breast Cancer Cases, Short Term plus Long Term Period Up to June 13, 2011.**

Age/Sex	Dapa Dose ± Treatment	Tumor type	Grade	TNM *	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Diagnosis (Study Day)
63/F	2.5 mg + Ins	Invasive ductal carcinoma.	Grade 2	T1c, N0, M0	Highly positive, IRS 12	Highly positive, IRS 12	2+	6
53/F	5 mg	Intraductal carcinoma	Grade 3	M0	NA†	NA†	NA†	39
60/F	10 mg + Met**	Ductal carcinoma	Grade 1	T1,N0	Positive, 8/8	Positive, 8/8	Negative	193
61/F	10 mg + Ins	Invasive lobular, carcinoma	Grade 2	T2, N3a, M0	Strongly positive	Mildly positive	Negative	204
64/F	10 mg + Met	Invasive ductal carcinoma	Grade 2 – 3	T1c, N1, M0	40% – 50%	85 – 90%	NA^	211
64/F	10 mg + Met	Infiltrating adenocarcinoma	High grade	T2, N2a, MX	Negative	Negative	Negative	285
58/F	2.5 mg + Ins	Breast cancer	Grade 2	T2, N0, M0	Moderately positive (25% – 50%)	Negative	Weakly positive	292
74/F	2.5 mg	Ductal carcinoma	Grade 2	T1b, N0	Strongly positive	Strongly positive	Negative	321
69/F	10 mg + Glip	NA§	NA§	NA§	NA§	NA§	NA§	334
73/F	Placebo	Invasive, lobular	Grade 2	T3, N3a	> 80% (IRS 12)	> 80% (IRS 12)	Negative	57

Source: Applicant's Table 45 to the AC Background document

In addition to these cases listed in Table 9, one additional case of breast cancer in a 59 year old female patient was reported (study day 230), but the case remains blinded.

The epidemiologic literature was reviewed to evaluate the background incidence rate of breast cancer among type 2 diabetes patients. A study report conducted by the applicant titled "A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population" was also reviewed.

Dr. Ju used in her analysis a literature-based adjustment factor of 20% to account for increased diabetes risk to apply to the SEER database. The applicant had used age- and sex-specific incidence rates of breast cancer data from SEER to calculate the expected number of breast cancer cases in the dapagliflozin clinical trials. The SIR was calculated to evaluate the observed incidence of breast cancer for the female cohort (n=9) of the dapagliflozin clinical program compared to the expected incidence from adjusted SEER estimates (n = 7.1). SIR was 1.27 (95% CI, 0.58, 2.41) for dapagliflozin-treated subjects. But Dr. Ju also points out that the US incidence of breast cancer (between 3 and 4 per 1000 person years) is the highest reported; the Phase 2b and Phase 3 trials were conducted internationally, enrolling subjects in countries with a much lower incidence rate (e.g., Japan, with incidence rate of 0.62 per 1000 person-years). So the resulting SIR should be interpreted with caution.

In his November 29th, 2011 review, Dr. Hampp updated the calculations for breast cancer risk, using the July 15th, 2011 Integrated Safety Update. Since the breast cancer review conducted by Dr. Ju, three additional cases of breast cancer have been detected, one exposed to dapagliflozin, two exposed to placebo. Among the latter, one case was diagnosed as ductal carcinoma *in situ*.

Ten cases of breast cancer occurred in the dapagliflozin-exposed clinical trial population, and three cases occurred among controls, with one control patient diagnosed with ductal carcinoma *in situ*. All of these diagnoses were made in female subjects between the ages of 53 and 74. Total follow-up of female patients randomized to dapagliflozin was 2701.6 subject-years after cases were censored at the date of their case diagnosis. With ten cases of breast cancer occurring in female subjects exposed to dapagliflozin during this time, the crude incidence rate amounted to 370.2 (95% CI, 177.2 – 680.8) new cases per 100,000 subject-years. This compares to three cases (including the case of ductal carcinoma *in situ*) during 1361.6 subject-years in controls, or 220.3 (95% CI, 44.3 – 643.7) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of breast cancer between active treatment and controls was 1.90 (95% CI, 0.52 – 8.93), with a two-sided *p*-value of 0.374. The sponsors calculated the adjusted rate difference as 228 cases per 100,000 patient-years (95% CI, -537 – 806), with the confidence interval including the possibility of no difference. The Mantel-Haenszel calculation conducted for this review yielded a rate difference of 189 cases per 100,000 patient-years (95% CI, -128 – 506), with a confidence interval also including the null, *p*=0.244.

Excluding the case of ductal carcinoma *in situ*, the adjusted rate ratio between dapagliflozin and control was 2.76 (95% CI, 0.64 – 19.21), *p*=0.242.

Observed case counts in dapagliflozin-exposed subjects were similar to expected case counts based on SEER; however, observed counts among controls were lower than expected. When the *in situ* case was included, six cases of breast cancer were expected among controls and



only three were observed. When the *in situ* case was excluded, five cases of breast cancer were expected and only two were observed. Although these small numbers could be due to random variation, one should not discard the possibility that the clinical trials sample was at lower risk at baseline, when compared to the general U.S. diabetic population. This possibility would be consistent with a harmful drug effect in the exposed, resulting in as-expected counts.

The applicant made a valid argument discouraging an implication of causality. Similar to the time to onset of bladder cancers reported, all cases of breast cancer were diagnosed within a year of treatment with dapagliflozin.

An examination of these individual malignancy cases revealed typical clinical features. A biologic hypothesis for a potential association between dapagliflozin and either tumor type has not been identified. Both breast and bladder cancer are readily detectable in animal models of carcinogenesis, but neither were observed in the 2-year carcinogenicity studies with dapagliflozin. Dapagliflozin is not genotoxic, and rigorous 2-year carcinogenicity studies in mice and rats did not demonstrate preneoplastic or neoplastic changes. The direct pharmacologic effect of dapagliflozin, glucosuria, would not be expected to increase the risk of cancer, and no indirect effects that could increase the risk of cancer have been identified.

As discussed during the AC meeting, detection bias cannot be ruled out. Weight loss, which was more common in the dapagliflozin group overall, may have facilitated self-diagnosis of malignant and non-malignant breast tumors, and a similar between-group imbalance was detected in both malignant and non-malignant cases. The impact of potential detection biases for breast masses could not be quantified based on available clinical study data, and while it represents an uncertainty when assessing the association, it cannot be regarded as a definitive explanation for the imbalances.

Please refer to Section 13 of this memorandum, for a discussion of the postmarketing assessment of the cancer risk proposed by the applicant.

### Liver Safety

Please refer to Drs Seeff, Senior and Brinker's review of the hepatic safety data related to dapagliflozin.

Liver-related tests were monitored during the dapagliflozin development program. Investigators completed supplemental CRFs for events of increased liver tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 times upper limit of normal [ULN]). Patients with clinical liver disease and elevated hepatic parameters were excluded from the clinical studies.

Elevations of 3x, 5x, 10x and 20x in liver aminotransferases across the largest safety pool, the Phase 2b and 3 pool, display similar rates between dapagliflozin and control groups.

The applicant had a blinded adjudication process for liver abnormalities. Criteria for referral to the adjudication panel were:

- AST and/or ALT > 3X upper limit of normal (ULN) and total bilirubin (TB) > 1.5X ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT > 5X ULN

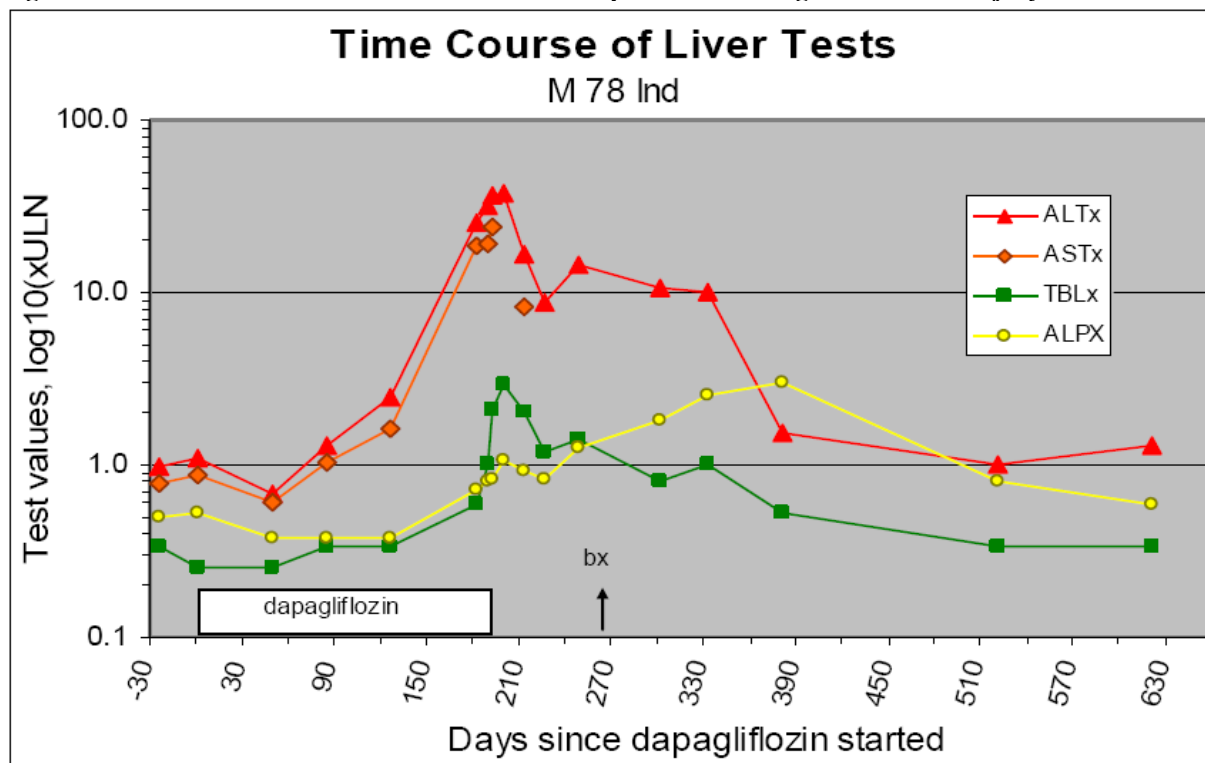
- Liver-related serious or non-serious standardized MedDRA queries (SMQ) adverse event (SAE or AE, respectively) in subjects who prematurely discontinued study treatment due to any SAE/AE
- Liver-related SMQ SAE or AE in any subjects who died

Cases for adjudication were identified through a search of all reported AEs using liver-related SMQs. Laboratory abnormalities (as listed above) were also reviewed for possible referral to adjudication. There are three hepatologists on the adjudication committee, blinded to treatment assignment, and each submits an opinion regarding probability of drug induced liver injury. The committee used the grading system developed by the NIH Drug-Induced Liver Injury Network Study Group, and categorized the cases as definite, highly likely, probable, possible, unlikely, and insufficient information to classify. This is followed by a consensus agreement if possible, on each case. The cases referred for adjudication were from the Phase 2b and Phase 3 pool. For the majority of the trials, the events were adjudicated retrospectively. Based on the above criteria, 54 cases from these trials had been referred for adjudication at the time of the 4 Month Safety Update. Of these 54 cases, 35 were treated with dapagliflozin, 17 with either placebo or a comparator drug, and 2 were from blinded ongoing studies. The proportion of subjects reported was similar between the groups, considering the differences in exposure.

There were five cases in the Phase 2b and Phase 3 Pool that met laboratory criteria for Hy's Law (AST or ALT greater than 3x ULN in addition to elevation of total bilirubin greater than 2x ULN).

- Two of these cases had clear etiology other than drug induced liver damage, and thus do not meet the definition of Hy's Law;
- A third patient had dapagliflozin discontinued due to liver enzyme elevations. Subsequently, it was restarted and the patient had no elevation of liver enzymes or other liver related complications (negative re-challenge).
- Thus the remaining two of these cases remain suspicious for drug-induced liver injury. The blinded hepatic adjudication panel established by the applicant had deemed these two cases "possible."

The single case of probable drug induced liver injury (mild to moderate), based on biochemical criteria for Hy's Law and no alternate explanation, was discussed in detail in Dr. Dunn's and Dr. Brinker's reviews (the latter also based on the unblinded readjudication by FDA's Dr. Seeff and Dr. Senior). For the reader's reference, Figure 12 provides the time course of liver laboratory test elevations, over time, plotted against the duration of dapagliflozin treatment. The applicant and the hepatic adjudication committee also considered autoimmune hepatitis as a possible alternate explanation. FDA reviewers considered autoimmune hepatitis unlikely to fit as a diagnosis based on the case narrative.

**Figure 12. Time course of liver tests elevations in one patient with drug induced liver injury**

Source: Dr. Brinker's review

As the guidance for drug induced liver<sup>4</sup> injury reminds us, Hy's Law cases identified in clinical trials or other data sources can predict severe liver injury (fatal or requiring transplantation) at a rate of roughly 1/10 of the rate of Hy's Law cases identified.

There are several examples of drugs withdrawn from the market that had pre-approval Hy's Law cases, and examples of drugs not approved because of this evidence of drug induced liver injury. But I am unaware of a precedent for a regulatory decision taken on an application on the basis of one single probable case of Hy's Law with overall balance of liver tests across groups. So in our discussions, we frequently concluded that "one case is worrisome and two is quite concerning" (Dr. Mark Avigan, from OSE, stated at the AC meeting).

The estimates of incidence rates in the clinical program are extremely variable, with a numerator of one possible case and a denominator that can vary substantially depending on the exposure being considered in the calculation (e.g., only trials with more than 6 months duration, all trials at the time of NDA filing, or the safety population at the time of the 4-Month Safety Update). Prediction of the significance of the risk for Hy's Law cases postmarketing is therefore very uncertain, and even more uncertain is the estimate of risks of drug induced liver injury (i.e., cases resulting in death or liver transplantation).

The applicant submitted an updated Hepatic Adjudication Report, with an additional seven cases referred to that committee, and which were also reviewed by our colleagues at OSE. Four of these cases were treated with dapagliflozin, while 3 were blinded to the treatment

<sup>4</sup> Guidance for Industry – Drug-Induced Liver Injury: Premarketing Evaluation. Available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM174090.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM174090.pdf)

allocation at the time of referral to the adjudication committee. None of these seven cases were considered be possible, probable, highly likely or definitely caused by treatment with dapagliflozin. The lack of new cases suspicious of drug-induced liver injury in an expanded safety database (from 4000 person-years to 5500 person-years) provides little reassurance that that single event of probable Hy's Law would be less likely to be repeated in the postmarketing setting. While additional cases of probable or likely Hy's Law would have been informative regarding a regulatory decision for dapagliflozin at this time (supporting a Complete Response action), the lack of these cases signify that continuing attention post-approval will be required to further define the risk, or lack thereof. In Section 13 of this memo I summarize my view of the risks and benefits of dapagliflozin in the treatment of patients with T2DM. Similar to the negative signal of breast and bladder cancer discussed above, this signal of potential hepatotoxicity must be considered as part of the decision on this drug. In Section 13 of this memorandum, I will also discuss the postmarketing assessment of the risk of liver injury proposed by the applicant.

### Hypoglycemia

SGLT2 inhibitors have a low intrinsic risk of hypoglycemia. Similar to other recently approved antidiabetics (GLP-1 agonists and DPP-4 inhibitors, colesevelam or bromocriptin), the risk increases when dapagliflozin is used in combination with insulin or sulfonylureas, particularly in patients with brittle glycemic control or close to the target HbA1c of < 7%. Table 10 shows the frequency of hypoglycemia or major hypoglycemia (defined in the legend of the table) in placebo-control trials of dapagliflozin.

**Table 10. Hypoglycemia in Placebo-controlled Studies Short-term Treatment Period (NDA Dataset)**

Population		DAPA 2.5 mg	DAPA 5 mg	DAPA 10 mg	PBO†
		n = 814	n = 1145	n = 1193	n = 1393
<b>Placebo-controlled Pool<sup>a</sup></b>	Total*	15.5%	10.9%	10.2%	7.0%
	Major**	0.4%	0.1%	0.1%	0.1%
		n = 321	n = 316	n = 245	n = 251
<b>Monotherapy Pool</b>	Total*	2.5%	2.2%	2.9%	2.0%
	Major**	0	0	0	0
<b>Add-on Combination Treatment</b>					
				n = 226	n = 228
<b>+ Metformin (Pool)</b>	Total*	—	—	3.1%	3.1%
	Major**	—	—	0	0
			n = 141	n = 140	n = 139
<b>+ Pioglitazone</b>	Total*	—	2.1%	0	0.7%
	Major**	—	0	0	0
		n = 154	n = 145	n = 151	n = 146
<b>+ Glimepiride</b>	Total*	7.1%	6.9%	7.3%	4.8%
	Major*	0.6%	0	0	0
		n = 202	n = 212	n = 196	n = 197
<b>+ Insulin</b>	Total*	51.5%	45.3%	42.3%	35%
	Major**	1.0%	0.5%	0.5%	0.5%

\* Total hypoglycemia included minor hypoglycemia, which was defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode.

\*\* Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.

DAPA = dapagliflozin; PBO = placebo

Rescue medication with other oral anti-diabetic drugs was permitted in most studies.

Source: Applicant's Background document for the AC Meeting

The applicant's proposed labeling (under Warnings and Precautions) is appropriate to describe the potential risk with use of dapagliflozin and insulin or insulin secretagogues.

### Urinary Tract Infection

Adverse events of UTI were reported spontaneously as well as in response to questions related to the signs and symptoms of these infections proactively posed to subjects during all study visits. A pre-specified list of events based on MedDRA PTs that indicated a diagnosis of UTI was used to identify these infections.

UTIs were reported more often among subjects treated with dapagliflozin than placebo: 4.3% and 3.7% of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-

term Placebo-controlled Pool. Most subjects responded to an initial course of standard treatment (93.1% in the dapagliflozin-treated patients overall and 85.7% in placebo) without interrupting treatment with dapagliflozin. UTIs rarely caused discontinuation from the study: 0.3% dapagliflozin 10 mg vs 0.1% placebo. UTIs were more frequently reported in females than in males. Organisms identified in subjects with UTI were those commonly associated with UTIs in the general population, such as *Escherichia coli* and *Klebsiella* species.

Subjects in the short-term Placebo-controlled Pool who had a history of recurrent UTI were more likely to have this type of event (17.6% of subjects with history of UTI treated with dapagliflozin 10 mg and 17.1% of subjects with history of UTI on placebo) during the study than those without such a history (3.7% on dapagliflozin 10 mg and 3.4% on placebo). Pyelonephritis was rare and balanced between treatment groups across the entire program (0.1% for dapagliflozin and 0.2% for control).

During long-term follow-up (the short-term plus long-term Placebo-controlled Pool), the proportions of subjects with UTIs were 7.7% (59/768) in dapagliflozin 10 mg and 6.3% (44/694) in placebo. Of the 59 subjects treated with dapagliflozin 10 mg who experienced a UTI, 74.6% had only one and 5.1% had three or more. Of the 44 subjects treated with placebo who experienced a UTI, 86.4% had only one and 6.8% had three or more.

There was no dose relationship in the frequency or intensity of UTIs between 5 mg and 10 mg. Overall, the proportion of patients with events of UTI after treatment with dapagliflozin 5 mg was similar to dapagliflozin 10 mg treatment.

The applicant described its plans for postmarketing surveillance regarding hospitalization due to severe UTIs. Briefly, the incidence and relative risk of hospitalization or emergency department visits for severe complications of UTI, including acute pyelonephritis and urosepsis, in patients with T2DM who are new users of dapagliflozin versus new users of other antidiabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated as the primary outcome in this cohort study. At minimum, a subset of potential cases will be adjudicated based on review of the medical records.

### Genital Infection

The term genital infection used by the applicant refers to vulvovaginitis, balanitis and related infections, and does not include sexually-transmitted infections. These infections were reported spontaneously as well as in response to questions related to the signs and symptoms of these infections proactively posed to subjects during all study visits. A pre-specified list of events based on MedDRA PTs that indicated a diagnosis of genital infection was used to identify these infections.

Events of non-sexually transmitted genital infections were reported more often among subjects treated with dapagliflozin than placebo. The most frequently reported types of genital infections were vulvovaginal mycotic infections and vaginal infection in females, and balanitis and fungal genital infection in males. These events were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively, in the short-term Placebo-controlled Pool. These infections did not require interruption of treatment with dapagliflozin.

Most events of vulvovaginitis, balanitis and related infections responded to an initial standard course of treatment (71.2% dapagliflozin 10 mg vs 92.3% in placebo), and rarely resulted in

discontinuation from the study (0.2% dapagliflozin 10 mg vs 0% in placebo). Additional treatment was given because of inadequate response to the initial course of treatment in a small proportion of the events: 0%, 6.5%, and 4.5% of events in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 0 events in the placebo group. Genital infections were more frequently reported in females than in males. These infections were more common in the first 6 months of dapagliflozin therapy.

Subjects in the short-term Placebo-controlled Pool who had a history of recurrent vulvovaginitis, balanitis and related infections were more likely to have a genital infection (25.0% of subjects with history of genital infection treated with dapagliflozin 10 mg and 10.0% of subjects with history of genital infection on placebo) during the study than those without such a history (5.0% on dapagliflozin 10 mg and 0.8% on placebo).

During long-term follow-up (the short-term plus long-term Placebo-controlled Pool), the proportions of subjects with vulvovaginitis, balanitis and related infections were 8.2% in dapagliflozin 10 mg and 1.3% in placebo. Of the 63 subjects treated with dapagliflozin 10 mg who experienced a genital infection, 74.6% had only one and 15.8% had three or more. Of the 20 subjects on placebo who experienced a genital infection, 80 % had only one and none had three or more.

There was no dose relationship in the frequency or intensity of vulvovaginitis, balanitis and related infections between 5 mg and 10 mg. Overall, the proportion of patients with events of genital infection after treatment with dapagliflozin 5 mg was similar to dapagliflozin 10 mg treatment.

#### Safety events related to volume depletion

In the Placebo-controlled Pool, AEs defined by the applicant as associated with volume depletion (preferred terms of hypotension / hypovolemia / dehydration) were slightly more common in the dapagliflozin dose groups versus the comparator (0.7% vs 0.4% in the short-term period), with no clear dose dependence. This was expected based on dapagliflozin's mechanism of action. Hypotension was the most common AE and there were no AEs based on preferred terms of dehydration or hypovolemia.

Modest mean reductions in systolic blood pressure in dapagliflozin-treated subjects were observed (-4.4 mmHg for both the 5 and 10 mg doses) and there was no increase in orthostatic hypotension (3.7% for both dapagliflozin 10 mg and placebo). AEs related to volume depletion were more common in subjects treated with dapagliflozin compared with placebo (0.8% vs. 0.4%, respectively, in the 24-week trials); the most common AE was hypotension (0.4% vs. 0.1% for placebo).

One subject was discontinued because of an AE of dehydration and pre-renal azotemia. This 67 year old subject was on furosemide in the dapagliflozin 10 mg plus insulin group in a pilot Phase 2b add-on to insulin study (MB102009). This was the only subject in the entire dapagliflozin clinical program discontinued due to an AE related to volume depletion. Most (20/27) of these events were mild in intensity in subjects treated with dapagliflozin. There was no pattern to the day of onset for these events, with no evidence of a first-dose effect. In general, the duration of these events varied from 1 to 6 days.

AEs related to volume depletion (hypotension / dehydration / hypovolemia) were reported for a greater proportion of patients taking loop diuretics at any time after randomization (6 of 114 subjects, or 5.3% for all dose groups of dapagliflozin) than those not taking loop diuretics at any time. Most events of volume depletion in subjects treated with concomitant loop diuretics were mild. Time to event and duration of the events were distributed across treatment groups with no pattern. A numeric imbalance in such events was also reported in users of thiazide diuretics and angiotensin receptor blockers or angiotensin converting enzyme inhibitors, but with small numbers in each category and treatment group to allow conclusions.

The AEs related to volume depletion (hypotension / dehydration / hypovolemia) were more frequent among dapagliflozin-treated subjects  $\geq 65$ -years-old dapagliflozin than for placebo-treated subjects  $\geq 65$ -years-old. Most events were mild in intensity in both age subgroups. Events of volume depletion in the elderly were infrequent but in subjects  $\geq 65$ , these events tended to occur early in treatment (4/10 within approximately 2 weeks from the first dose).

Small mean differences in hematocrit (placebo-adjusted change of up to 2.5%) and hemoglobin concentrations were reported, starting at week 1 and continuing to increase to week 16, as a lab evidence of hemoconcentration. After week 16, these differences were maintained to week 24. These differences are likely not clinically meaningful.

There were no imbalances in proportions of subjects with of deep vein thrombosis, venous thrombosis or pulmonary embolism.

### Renal Safety

Dapagliflozin was not studied in patients with severe renal impairment or kidney failure or renal replacement in large controlled studies because a treatment effect was not expected, and use in this population is not recommended.

Small mean decreases in eGFR from baseline were observed in dapagliflozin-treated subjects at Week 1 (for dapagliflozin 10 mg: mean  $-4$  mL/min/1.72 m<sup>2</sup>) in the short-term plus long-term placebo-controlled pool. Following this initial drop in eGFR, there was a gradual return to baseline over 16 -18 weeks without evidence of progressive renal dysfunction. These early decreases in renal function assessments, though small, were dose proportional. In response to a question from the advisory committee, the applicant showed data that suggest the changes are hemodynamic, not structural to the kidney.

In the dedicated study in subjects with moderate renal impairment (eGFR  $\geq 30$  and  $< 60$  mL/min/1.73 m<sup>2</sup>), mean eGFR decreased from baseline to Week 1 in the dapagliflozin 5 and 10 mg groups ( $-4.5$  and  $-5.5$  mL/min/1.73 m<sup>2</sup> respectively) then stabilized, with mean reductions from baseline at Week 52 that were maintained. Subjects treated with placebo had a progressive decline in eGFR over 52 weeks (mean decrease:  $-2.5$  mL/min/1.73 m<sup>2</sup>). The long term clinical significance of these small mean changes in patients with compromised renal function is unclear.

The applicant points out a small imbalance favoring dapagliflozin in proportion of subjects discontinued due to hyperkalemia (8% in placebo versus 5% in dapagliflozin 10 mg at week 24, and 10% in placebo versus 5% in dapagliflozin 10 mg at week 52), as well as the



proportion of subjects with marked hyperkalemia. This is likely due to the mild diuretic and natriuretic effect of dapagliflozin.

There was minimal change from baseline in mean serum creatinine ( $< 0.1$  mg/dL), and changes in blood urea nitrogen during the short-term double-blind treatment period were not clinically relevant.

The applicant proposed to continue to assess the risk of renal injury in the postmarketing setting by examining the incidence and relative risk of hospitalization for acute kidney injury in patients with T2DM who are new users of dapagliflozin vs new users of other antidiabetic medications, excluding SGLT2 inhibitors and insulin, estimated as the primary outcome in a large cohort study. As part of the secondary outcomes, death due to acute kidney injury, and composite hospitalizations for acute kidney injury and/or death due to acute kidney injury will also be estimated. At minimum, a subset of potential cases will be adjudicated based on review of the medical records.

### Bone Health

Please refer to Dr. Whitaker's consult memo for details.

The effects of dapagliflozin on markers of bone metabolism were monitored during the clinical program. The overall fracture rate in the Phase 2b/ Phase 3 pool short term plus long term studies was low (44 fractures, being 1.4% for both the dapagliflozin and control groups). There was an imbalance in fracture rate in the moderate renal dysfunction population study (MB102029) at 52 weeks (10 subjects in the two dapagliflozin groups [6%] versus zero in placebo) and at 104 weeks (12 events of fracture versus zero). But this imbalance was not reproduced when all subjects with moderate renal dysfunction in the Phase 2b and Phase 3 trials were pooled. These fracture events occurred in subjects with various risks for falls (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state) or suffered significant trauma. In addition, while a direct connection to the fracture events was not documented, rates of hypoglycemia, hypotension, dizziness, syncope, and falls were higher in this population. The 2-fold increase in fractures in patients with normal renal function over long term-exposure was associated with negligible laboratory changes suggesting that this imbalance may also not be significant. However, additional long-term data may provide further insight into this finding. In addition, there were minimal effects on mean bone mineral density (BMD) overall despite outliers with both positive and negative changes of approximately 8-12%.

Bone biomarkers showed small inconsistent changes in bone resorption and bone formation. No clinically significant changes were seen in other serum laboratory values, including calcium, 25-OH vitamin D, magnesium, phosphorus and PTH. However, among subjects with moderate renal impairment (in both the pooled analysis and in the dedicated renal study) mean increases in PTH and serum phosphorus were reported, with unclear clinical significance.

Dr. Whitaker had initially recommended continuous assessment of bone mineral density and fractures as a PMR, and caution in pediatric studies due to the theoretical risk of periarticular calcification. After the discussion at the AC meeting, and the internal discussion that followed the meeting, we have decided that a separate PMR study to assess fracture risk is unwarranted

based on the data reviewed. The applicant will continue to monitor for fractures in ongoing trials and in the dedicated CV trial.

### Cardiovascular risks

Please refer to Dr. Abraham's reviews for details.

BMS/AZ conducted a meta-analysis of the cardiovascular events that occurred in 14 trials using dapagliflozin (Table 11). The pre-specified primary composite endpoint consisted of the following adjudicated events: CV death, MI, stroke, and hospitalization for unstable angina. This composite of MACE has been accepted for recent NDA submissions of antidiabetic drugs.

Among the 6228 subjects in the database (hereby called BMS Analysis population), 78 subjects had an event that was counted in the primary composite endpoint (48 of 4287 dapagliflozin subjects and 30 of 1941 comparator subjects).

**Table 11. List of trials included in the BMS/AZ metanalysis**

Trial ID	Total Sample Size*	Dapa Dosage						Co-treatment				Control			Duration	Comments
		1	2.5	5	10	20	50	Met	Glim	Ins	Pio	Met	Placebo	Glip		
D169C00004 (Phase 3)	814	.	.	.	X <sup>2</sup>	.	.	.	.	.	.	.	.	X <sup>2</sup>	52+156 weeks	Non-inferiority
D1690C00005 (Phase 3)	596	.	X	X	X	.	.	.	X	.	.	.	X	.	24 + 24 weeks	
D1690C00006 (Phase 3)	807	.	X	X	X	.	.	.	.	X	.	.	X	.	24 + 80 weeks	
D1690C00012 (Phase 3)	182	.	.	.	X	.	.	X	.	.	.	.	X	.	24 + 78 weeks	
D1692C00005 (Phase 2b)	220	X	X	X	X	.	.	.	.	.	.	.	X	.	12 weeks	Japanese population
MB102008 (Phase 2b)	389	.	X	X	X	X	X	.	.	.	.	X	X	.	12 weeks	
MB102009 (Phase 2b)	71	.	.	.	X	X	.	.	.	X	.	.	X	.	12 weeks	
MB102013 (Phase 3)	485	.	X	X	X	.	.	.	.	.	.	.	X	.	24 + 78 weeks	
MB102014 (Phase 3)	546	.	X	X	X	.	.	X	.	.	.	.	X	.	24 + 78 weeks	
MB102021 (Phase 3)	598	.	.	X	.	.	.	X <sup>1</sup>	.	.	.	X	.	.	24 weeks	
MB102029 (Phase 2b/3)	252	.	.	X	X	.	.	.	.	.	.	.	X	.	24+28+52 weeks	Renal Impairment
MB102030 (Phase 3)	420	.	.	X	X	.	.	.	.	.	X	.	X	.	24 + 24 weeks	
MB102032 (Phase 3)	210	X	X	X	.	.	.	.	.	.	.	.	X	.	24 weeks	
MB102034 (Phase 3)	638	.	.	.	X	.	.	X <sup>1</sup>	.	.	.	X	.	.	24 weeks	

<sup>1</sup>Trials MB102021 and MB102034 Have one arm of Dapa +Met, and one arm of Dapa alone

<sup>2</sup>Trial MB102022 Has titrated doses of Dapa from 2.5 to 10mg and Glip 5 to 20mg, Dapa dose is calculated as 10mg in analyses

\*Total Sample Size indicates number of subjects included in BMS Analysis Population (excludes 1mg dose Dapagliflozin subjects)

Source: Created by reviewer. Dataset: adcv.xpt

The pre-specified primary analysis was the stratified Cox proportional hazards model including trial as the stratification factor. For the primary endpoint, the hazard ratio of dapagliflozin versus comparator was 0.67 with a 95% confidence interval of (0.42, 1.08). The 98% CI was 0.385, 1.178 (the wider interval used to account for multiple comparisons, if necessary, to meet the hazard ratio of  $\leq 1.8$  required for NDA submission). Thus, there does not

appear to be an increased risk of cardiovascular events with the use of dapagliflozin over control. The upper bound of the confidence interval for the hazard ratio is below 1.8 (and below the 1.3 threshold), which is required for approval.

A forest plot of the hazard ratios estimated from individual trials that were part of the metanalysis is shown in Figure 13 (note that two trials had zero events in both arms and were not included in the stratified Cox proportional hazards model).

The pre-specified secondary analysis was based upon Mantel-Haenszel methods for estimating the overall incident rate ratio via Breslow and Day where the estimate was calculated by stratifying for trial. Trials with no events were excluded from the analysis. In order to include trials with zero event rates, the difference of incidence rates was calculated using Mantel-Haenszel methods. Results from these two analyses are shown below.

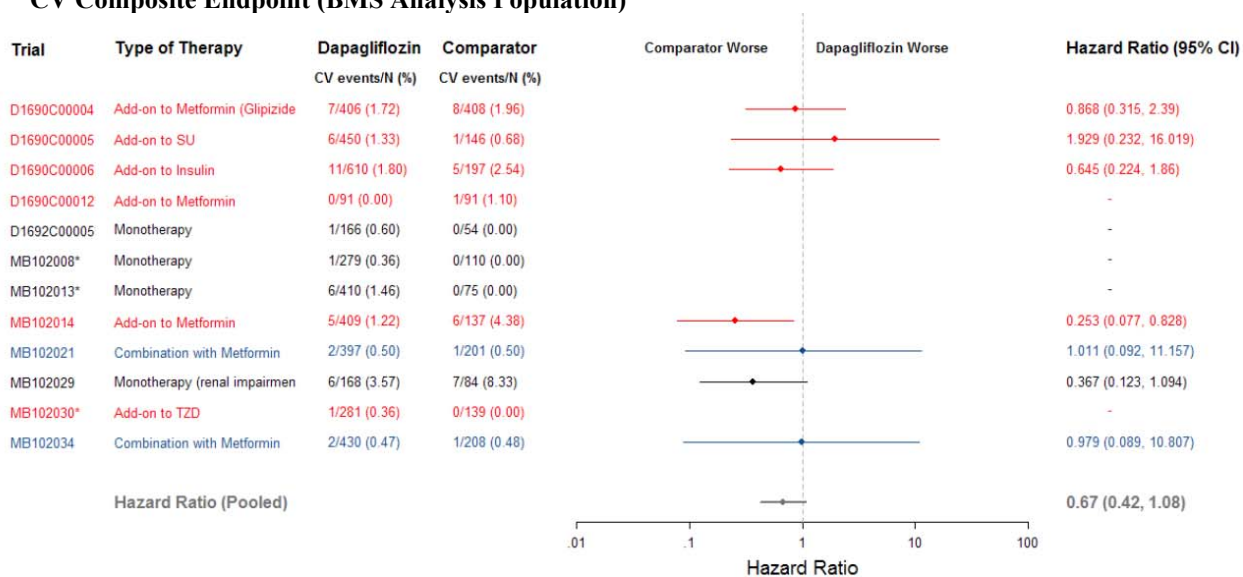
Incidence Rate Ratio: 0.672 with 95% CI (0.420, 1.076).

Difference in Incidence Rates: -0.0054 with 95% CI (-0.012, 0.0013).

Thus, as with the primary analysis, there does not appear to be an increased risk of cardiovascular events with the use of dapagliflozin over control in these secondary analyses.

To further investigate the sensitivity of the primary analysis on the primary composite endpoint, FDA conducted a sensitivity analysis excluding short-term trials (trials MB102008, MB102009, and D1692C00005) as well as the non-inferiority trial (trial D169C00004) included in the applicant's analysis. Using the same statistical method as in the primary analysis of the primary composite endpoint, this sensitivity analysis on an alternate analysis population also did not find a pattern of CV risk that was different from the primary analysis [hazard ratio = 0.60 with a 95% CI (0.35, 1.01)].

**Figure 13. Figure 1: Forest plot of Hazard Ratios and 95% CI from Cox Proportional Hazards for Primary CV Composite Endpoint (BMS Analysis Population)**



Source: Created by reviewer. Adaptation of Figure 2 from sponsor's study report using adcv.xpt

The effect was consistent among the individual components of the composite MACE. We had communicated to the applicant that a dedicated CV trial in a high risk, enriched, population would be required as a PMR. Two main reasons drove the decision to impose the required study:

1. We need more compelling evidence, from a rigorous placebo-controlled trial and based on more endpoint outcomes, that dapagliflozin is safe (i.e., HR < 1.3 post-approval). We want to be able to analyze the effect across different MACE components and different subsets of the population;
2. The trial will provide additional controlled exposure to inform on other safety issues identified in the clinical program, although it will be insufficient, in itself, to completely resolve these issues. For example, the trial will help other streams of data (both trial-derived and observational) in reducing the uncertainty around the issues of drug induced liver injury, cancer and bone health, in a more vulnerable population than the typical, healthier, phase 3 population.

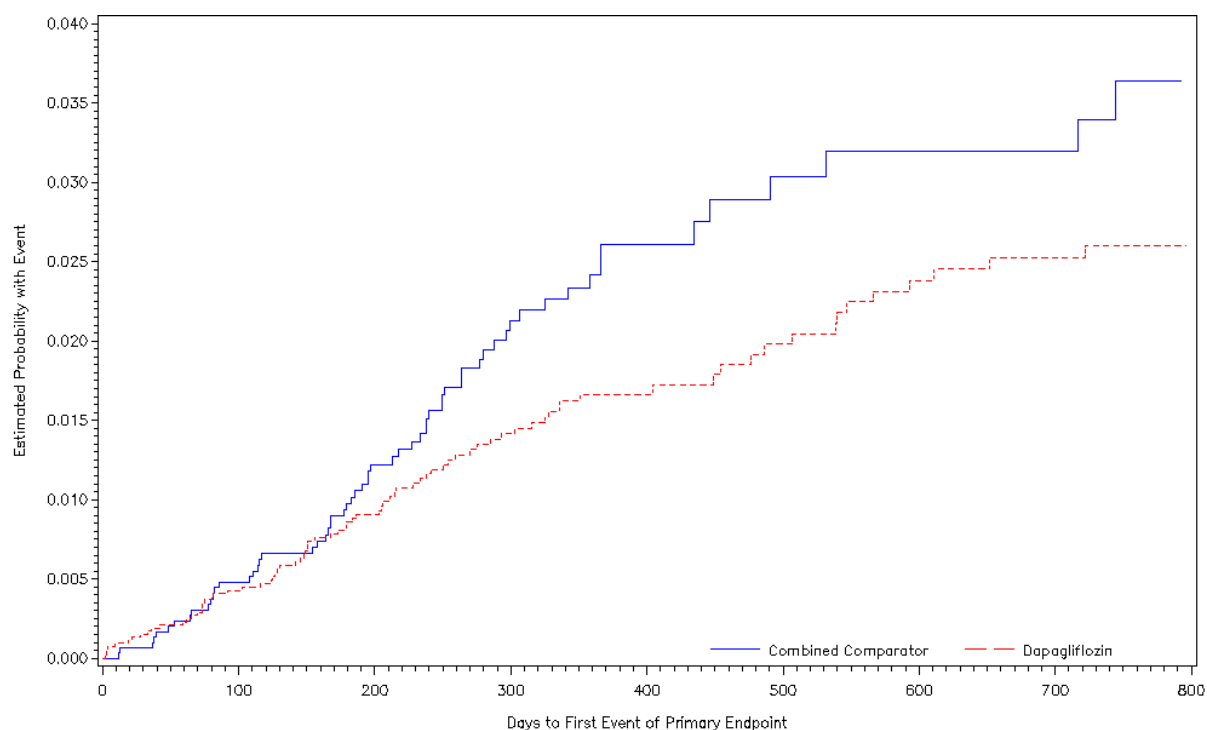
The points above are similar to ones made in the review of recently approved drugs for T2DM. With dapagliflozin, however, we see in addition to a lower point estimate and a higher number of MACE (compared to the linagliptin program, with a total number of MACE being 34), modest but favorable effects on CV risk factors, such as weight and BP reduction. For other CV risk factors, the effect was neutral: effects on lipids (a very small increase in mean LDL cholesterol accompanied by a small mean increase in HDL cholesterol, with the ratio unchanged) and effect on markers of systemic inflammation (hs-CRP, fibrinogen and PAI-1).

At our request, Dr. Abraham reanalyzed the CV risk of dapagliflozin on the basis of the additional datasets provided in the major amendment. This updated review includes additional data from four of the previously submitted trials: D1690C00004, D1690C00006, D1690C00012 and MB102029 (contributing an additional five events to the primary composite endpoint and an additional 804 person-years since the previous analysis), and data from five newly submitted trials: D1690C00010, D1690C00018, D1690C00019, MB102035 and MB102045 (an additional 2455 subjects, contributing 62 events to the primary composite endpoint in 1836 person-years).

Among the 8682 subjects in the BMS Analysis population (composed of the safety population of all 19 trials combined), 145 subjects had an event that was counted in the primary composite endpoint: 82 of 5498 dapagliflozin subjects (1.49%) and 63 of 3184 comparator subjects (1.98%). The pre-specified primary analysis of the stratified Cox proportional hazards model yielded a hazard ratio of dapagliflozin versus comparator of 0.82 (95% CI: 0.58, 1.15). To incorporate zero event trials in the meta-analysis, the incidence rate difference was considered as a secondary analysis method. Using this method, the incidence rate difference was found to be -0.0036 (95% CI: -0.0097, 0.0026). Random effects analysis was performed as two of the trials (D1690C00018 and D1690C00019) were from a higher cardiovascular risk patient population than the other trials in the metanalysis. The results of this analysis provided a slightly lower estimate of the incident rate ratio for the primary composite endpoint with a wider confidence interval: 0.75 (95% CI: 0.47, 1.18). With the variability of these trials accounted for in the random effects analysis, the addition of these trials did not change the overall conclusion of the metanalysis.

Based on the Kaplan Meyer method used in the BMS Analysis population, the cumulative probability of developing a CV-related event as measured by the primary composite endpoint is shown in Figure 14. In the combined comparator group, events of the composite CV safety endpoint occurred earlier than in the dapagliflozin group, with the survival curves separating at about 160 days. Based on the stratified log-rank test stratified by trial, the onset time of event was not statistically significantly different at the one-sided  $\alpha=0.025$  level between the dapagliflozin group and the comparator group ( $p = 0.25$ ).

**Figure 14. Time to event analysis of MACE (primary composite CV endpoint) in the BMS Analysis Population**



Reproduced from Dr. Abraham's review

A secondary composite endpoint was also evaluated which was comprised of the same CV components as the primary endpoint plus two additional CV components (unplanned coronary revascularization, and hospitalization for heart failure). No additional estimated risk of CV events in the dapagliflozin group versus the comparator group (hazard ratio (95% CI): 0.73 (0.54, 0.99)).

For the updated metanalysis, the applicant evaluated a third composite endpoint, as an exploratory analysis, based only on the three components of the strict MACE: CV death, MI and stroke. The analysis of this exploratory composite endpoint also found no additional risk of CV events in the dapagliflozin group compared to the comparator group (hazard ratio (95% CI): 0.79 (0.54, 1.17)).

Dr. Abraham also analyzed separately the CV risk estimated from Studies 18 and 19, which were conducted in the CV risk factors-enriched population. Comparing demographic factors

between the combined Studies 18 and 19 (High CV Risk Trials) and the BMS analysis population excluding these CV trials (All Trials Excluding High CV Risk Trials), the high CV risk trials had a somewhat higher proportion of males (67% versus 52%) and subjects in older age (mean 63 years versus 60 years). But CV risk factors other than demographics were, by design, strikingly different (Table 12):

**Table 12. CV risk factors in the All Trials Excluding High Risk CV Trials versus the pooled high risk CV trials 18 and 19**

	<b>All Trials Excluding High- Risk CV Trials</b>	<b>High-Risk CV Trials (D1690C00018 and D1690C0001) combined</b>
	<i>(N = 6798)</i>	<i>(N = 1884)</i>
<b>History of CVD</b>	19.1%	99.5%
<b>History of Hypertension</b>	62.7%	96.2%
<b>History of Dyslipidemia</b>	49.9%	84.2%
<b>History of Congestive Heart Failure</b>	1.9%	14.3%
<b>Renal Function</b>		
Severely Impaired	0.2%	0.1%
Moderately Impaired	10.5%	17.3%
Mildly Impaired	50.8%	59.3%
Normal	38.5%	23.3%
<b>Smoking History</b>		
Never smoked	59.4%	40.3%
Current Smoker	16.4%	14.9%
Former Smoker	24.2%	44.8%
<b>Diabetes Duration</b>		
less than 3 years	44.0%	8.4%
3 – 10 years	34.6%	34.8%
more than 10 years	21.4%	56.8%

From Dr. Abraham's updated review.

The comparison between the estimates of hazard ratios for the All Trials Excluding High CV Risk Trials and in the pooled Studies 18 and 19 are shown in Table 13. While the hazard ratio estimated for the All Trials Excluding High CV Risk Trials is low, with an upper bound of the 95% CI being 1.04, the hazard ratio from the pooled Trials 18 and 19 was higher (1.07) with an upper bound of the 95% CI reaching 1.77.

An explanation for the difference in estimated hazard ratios between the All Trials Excluding High CV Risk Trials and the pooled Trials 18 and 19 is not readily apparent. A possible explanation is that younger patients with less advanced atherosclerotic disease (part of the All Trials Excluding High CV Risk Trials) may reap more benefits from the glycemic control, blood pressure and weight reduction, than older patients already at high CV risk (part of the

pooled Trials 18 and 19), particularly in a short treatment period of 24 weeks, which has been the exposure in trials 18 and 19.

On the other hand, one would anticipate that the subject population in trials such as add-on to insulin (Study D1690C00006) and the dedicated trial in subjects with moderate renal impairment are also at high CV risk. In these trials, although contributing much less endpoint events to the metanalysis than the High CV Risk Trials, the point estimates of the hazard ratios were quite low (0.54 and 0.33, respectively).

In PROactive, a large placebo-controlled trial of pioglitazone in diabetics, the favorable effect of pioglitazone on the secondary composite endpoint of all-cause death, MI and stroke only started to become distinguishable from placebo at 12 months from randomization, in the time-to-event analysis.

My hypothesis is that the discrepancy between the hazard ratios of the All Trials Excluding High Risk CV Trials and that of the High-Risk CV Trials can be explained by higher “noise” in the latter (a number of MACE events occurring in high CV risk subjects before a favorable dapagliflozin treatment effect can plausibly be observed). This hypothesis can be tested in the dedicated CV trial, where a large population of high CV risk subjects, exposed to treatment with dapagliflozin or placebo for a longitudinal period of 3 to 6 years, will be studied (similar, in that sense, to PROactive).

**Table 13. Meta-Analysis Results for All Trials Excluding High-Risk CV Trials and Pooled High-Risk CV Trials (trials 18 and 19)**

	<b>All Trials Excluding High-Risk CV Trials</b>		<b>High-Risk CV Trials (D1690C00018 and D1690C0001) combined</b>	
	<b>Dapagliflozin</b>	<b>All Comparator</b>	<b>Dapagliflozin</b>	<b>Comparator</b>
<b>Stratified Hazard Ratio (95% CI)</b>	0.66 (0.42, 1.04)		1.07 (0.64, 1.77)	
<b>Event/PY (% Incidence)</b>	51/5032 (1.01%)	34/2389 (1.42%)	31/706 (4.39%)	29/706 (4.11%)
<b>M-H Incidence Rate Difference (95% CI)</b>	-0.0050 (-0.011, 0.0007)		0.0028 (-0.018, 0.024)	

#### Effect on lipids

Small mean increases in LDL, HDL, and total cholesterol were reported in the dapagliflozin treatment groups, around 2 to 3 % for each, placebo adjusted. Triglycerides and free fatty acids showed small changes that were inconsistent across trials. These changes were smaller in magnitude compared to the mean comparator-adjusted lipid changes seen in the rosiglitazone trials. The clinical significance of these changes is unclear.

## 9. Advisory Committee Meeting

### Discussion of selected issues by panel members

The oncologist in the panel, Dr. Piantadosi, asked about the method used in the calculation of the risk differences and ratios (for trials with zero events of cancer). The applicant replied that because many of the trials had zero events, they could not be included in the calculation of risk ratios, but they could still be included in the estimates of the risk difference, with confidence intervals that were narrower around the point estimate of cancer risk.

The nephrologist, Dr. McBryde, was concerned about the cases of acute renal failure: the applicant provided additional information stating that the number of reports (four for dapagliflozin and four for placebo) were balanced. For the dapagliflozin cases: one of the cases was not a SAE, but rather a miscalculated creatinine clearance; another was a seriously ill patient with CHF and pneumonia, the third was a case of obstructive uropathy and the fourth was a patient with moderate renal impairment in the dedicated trial who progressed to renal insufficiency. After the AC meeting, the applicant provided additional analyses of renal function over time in subjects with normal baseline renal function, as well as in subjects with baseline moderate renal impairment. They conclude that in general, early increases in serum creatinine in subjects treated with dapagliflozin were small, transient, did not lead to discontinuation or interruption of study drug, and did not indicate further deterioration of renal function, even in subjects with outlying high values. In subjects with higher serum creatinine at baseline (eGFR between 45 and 60 mL/min/1.73 m<sup>2</sup>) in the short term and long term treatment period, out of 63 placebo-treated subjects, none met the threshold of  $> 1.5 \times$  baseline creatinine or a creatinine  $\geq 2.5$  mg/dL; among subjects treated with dapagliflozin (all doses combined) out of 199 subjects, 8 (4%) had serum creatinine  $\geq 1.5 \times$  baseline creatinine and 1 (0.5%) had a serum creatinine  $\geq 2.5$  mg/dL.

The panel members also ask about dapagliflozin effects on albumin excretion: this was covered under the renal safety portion of this review. Based on the moderate renal impairment trial, where more subjects had abnormal protein excretion at baseline, more subjects on dapagliflozin than placebo experienced a shift toward improvement, but the results are inconclusive due to the very few events observed.

Some panel members expressed concern about the adequacy of efficacy assessments in the elderly and the magnitude of effect of HbA1c. The applicant showed data on those subjects older than 65 years of age (about 20% of the development program) and the efficacy of dapagliflozin in this subset was similar to the overall treated group. In analyzing the interaction between renal function and age, the applicant demonstrated that only the elderly group with moderate impairment of renal function had diminished efficacy; thus, there was no or low interaction between age and renal function, with regard to efficacy. The safety in the elderly (including rates of hypoglycemia) was also similar to the overall dapagliflozin group.

The AC members also discussed extensively the bladder and breast cancer cases, as to whether there was evidence of disease prior to enrollment, and possible detection bias, due to unmasking of some cases by frequent urine monitoring (related to UTIs) and changes in breast parenchyma imaging due to water loss and weight loss. After the meeting, the applicant submitted a discussion of factors that could lead to detection biases for these cancer cases. The applicant concluded that there were subtle indications of an increased level of medical



attention for the dapagliflozin group, e.g., a higher proportion of patients had an AE suggestive of urinary tract infection. Weight loss, which was more common in the dapagliflozin group overall, may have facilitated self-diagnosis of malignant and non-malignant breast tumors, and a similar imbalance was detected in malignant and non-malignant cases. The impact of potential detection biases for breast and bladder cancers could not be quantified based on available clinical study data, and while it represents an uncertainty when assessing the association, it cannot be regarded as a definitive explanation for the imbalances.

In the discussion about the efficacy question posed to the AC members, the issue of adequacy of monitoring during treatment was discussed. One suggestion (Dr. Seely) was to evaluate eGFR along with albumin excretion once a year. Dr. McBryde proposed that, in the absence of data, patients with proteinuria should not be prescribed dapagliflozin. However, as summarized in this review, the applicant submitted data after the AC meeting suggesting (with the relatively small numbers of patients with proteinuria in the clinical program) that dapagliflozin is effective in such subjects.

Dr. Piantadosi, the oncologist, asked the other members not to ignore the cancer signals, just like they should not ignore the efficacy data from the same population, but to focus the discussion on how to best address these concerns while allowing a promising therapy in an area of unmet medical needs while trying to reduce the magnitude of uncertainty around the cancer risk.

Dr. Kaul estimated that, looking at an incident cancer rate of about 1 percent per year, to rule out a 50% increase in risk, a trial of almost 30,000, if not greater would be needed to avoid confounding by indication (in the range of 100,000 subjects). This may not be achieved by a randomized trial. But Dr. Kaul questioned the robustness of observational studies.

The committee also expressed concern about the other safety issues that required longer term data, such as consequences of frequent UTI and genital infections (recurrence rates and serious infections), additional data on bone and lean body mass changes (not only by DEXA, but assessed by other means (quantitative MRI, serum markers of nutrition, and other anthropometric measurements)).

### The AC vote and rationale

The AC members voted 9 to 6 against dapagliflozin in the question regarding substantial safety and efficacy data to support approval as indicated. As usual, FDA looks at the reasons behind the vote as much or more than the vote itself. So it is worth summarizing each member's rationale for their vote:

Dr. Seely, an endocrinologist, voted Yes, citing the unmet need in diabetes and the weight neutral effect, but with some concern for cancer and for the population with moderate or severe renal impairment. Dr. Seely wants to see some observational studies and some controlled studies, particularly better defining effects on albuminuria and renal impairment.

Dr. Savage, an endocrinologist, voted No. But he demonstrated hesitation in his vote ("it was not a clear cut thing, where I felt absolutely certain that the only possible answer is no") and concluded that additional data would be helpful. His words: "I mean, if the word gets out there that there's a drug that has shown an effect in terms of lower risk of cardiovascular disease,

and that it can prevent elderly people from having to take insulin and so forth, it could become a very popular and widely-used drug.”.

Dr. Fellner, a pediatrician, voted No. But again showing some hesitation (“I actually like this drug...”.) but he believes a large pre-approval study is feasible, particularly to address the cancer risk.

Dr. Capuzzi, an endocrinologist, voted No. But with hesitation (“I came in here on the fence, and I was leaning towards yes until I did not hear enough to be convincing about this”). But the list of issues that he believes were not addressed, for the most part were addressed in the development program.

Dr. Brittain, the statistician, voted No. But “it was the closest of calls. I changed my mind four times in the last 10 seconds”).

Dr. Thomas, endocrinologist and AC chair, voted Yes. He was impressed by the mechanism of action, and believes that a trial of 30,000 to 100,000 subjects pre-marketing to define liver-related risks and cancer risks is not feasible. He wants the large databases currently in use (the cited Kaiser database for the assessment of pioglitazone risk for bladder cancer) to be used post-marketing for continued assessment of safety of dapagliflozin.

Dr. Gregg, an epidemiologist, voted No. He was negatively impressed by the cancer risk ratios of 4 and 5 fold. He believes additional data from ongoing trials plus a new medium size trial may be sufficient to reduce the uncertainty on cancer risk to acceptable levels.

Dr. Spruill, diabetes nurse educator, voted No. But the reason for her vote was the 27% of US participation in the overall Phase 2b and Phase 3 program, and the low participation of African Americans and the elderly. As I mentioned in this review, the proportion of elderly subjects and minorities participating in the clinical development program was in par with those seen in the clinical programs of recently approved antidiabetic drugs. Furthermore, the proportion of elderly taking into account Studies 18 and 19 is larger than most other recent programs.

Dr. Piantadosi, oncologist, voted Yes. He is impressed by the efficacy, and stated that a large pre-marketing study is not feasible: (“For example, the detection of a twofold risk requires 90 events. And if the background frequency is 0.3 percent, there's your 30,000 subjects right there. That's not going to be done pre-marketing.”).

Dr. McBryde, nephrologist, voted No. He wants more data in patients with hypoproteinemia and proteinuria before approval. He was not clear about the diabetic subpopulation being targeted by the drug, if those with even mild proteinuria were to be excluded; he questioned a limited indication for use in monotherapy or in combination therapy only in newly diagnosed diabetics.

Dr. Strader, a hepatologist, voted No. Her vote was swayed by the lack of pharmacokinetic data (ADME, drug-drug interaction, effect of proteinuria, etc), as well as by the contribution of the uncertainty regarding liver and cancer risks.

Ms. McIntyre, the patient representative, voted No. She believes the applicant can and should obtain more safety data pre-approval.

Dr. Kaul, a cardiologist, voted Yes. He commented about the inherent asymmetry between assessments for efficacy and safety. He agreed with Dr. Piantadosi that it is not feasible to address the risks discussed at the meeting pre-approval. He eloquently enlisted the risk benefit

assessment, and his expectations for labeling and for a population enriched in CV risk factors for the dedicated CV trial.

Dr. Smith, an internist, voted Yes. He also mentioned the risk benefit assessment, and the unmet needs for the treatment of T2DM, while manifesting concern regarding the unknowns: long term renal safety, safety in the elderly, etc.

Dr. Hendricks, a specialist in weight management, voted Yes. While impressed with the insulin-independent glycemic effect and overall benefits (e.g., weight loss), he believes that the safety risks can be defined in post-marketing observational studies.

## 10. Pediatrics

### Pregnancy and nursing

Please refer to the nonclinical findings from Dr. Summan's review summarized in Section 4 of this memo. We consulted the Maternal Health Team of the Pediatric and Maternal Health Staff, regarding the pregnancy category and recommendations for labeling. Please refer to Ms. Howard and Dr. Feibus consultation memo for details. The team has recommended a Pregnancy Category C, with warning regarding the potential risk of renal pelvic and tubular dilatation to the fetus and nursing infant, and a detailed description of the nonclinical findings and exposures.

### PeRC review and PREA related post marketing pediatric studies

The pediatric investigational plan has been approved by the European Pediatric Committee. Consistent with recently approved antidiabetic drugs for adults with T2DM, the Division recommended and PeRC agreed to waive studies in children in the age range 0 – 9 years, and deferred studies in the age range 10 – 17 years until approval. The pediatric plan proposed by the applicant consists of evaluation of the children's ability to swallow dapagliflozin tablets, PK/PD assessments of three different doses of dapagliflozin with blood sampling over a 48-hour period, and a safety and efficacy study (randomized, double-blind, placebo controlled on metformin background [REDACTED] (b) (4)). The latter will also include an open label, non-randomized study of diabetic children who are treatment naïve (monotherapy setting).

## 11. Other Relevant Regulatory Issues

A summary of the DSI audit findings and recommendations is shown in Table 14. DSI concludes, based on these findings and classification, that the data are considered reliable in support of the application.

**Table 14. Inspection summary findings at clinical sites or applicant sites and classification**

<b>Name of Clinical Investigator (CI), or Sponsor &amp; Location</b>	<b>Protocol #/ # Subjects Randomized</b>	<b>Inspection Date</b>	<b>Final Classification</b>
CI: Rubin H. Saavedra, M.D. Nevada Alliance Against Diabetes 1440 N. Eastern Ave Las Vegas, NV 89101	MB 102013/14S MB 102014/12S	April 26 to May 19, 2011	VAI
CI: Rafael Montoro, M.D. Clinical Therapeutics Corporation 470 Biltmore Way Suite 102 Coral Gables, FL 33134	MB 102030/14S MB 102034/24S	May 12 to June 2, 2011	VAI
CI: Jerry Ray Mitchell, M.D. Texas Ctr. For Drug Development 6550 Mapleridge Ste. 201 Houston, TX 77081	MB 102034/18S	May 19 to May 25, 2011	VAI
CI: Laura Maffei, M.D. Consultorios Asociados de Endocrinología Cervino 3365/75, Piso 1, Office 2 Buenos Aires, Argentina	MB102014/12S D1690C00004/30S	June 13 to 17, 2011	NAI
CI: Maria Rosa Ulla Centro Privado de Endocrinología Osteología y Metabolismo Damaso Larranaga 94, Córdoba X5000BNB, Argentina	MB102030/16S D1690C00004/21S	June 6 to 10, 2011	NAI
CI: Ronald Goldenberg LMC Endo. Centres (Thornhill) Ltd. 531 Atkinson Ave. Ste. 17 Thornhill, ON L4J 8L7 Canada	MB102013/11S D1690C00006/18S	June 13 to 17, 2011	NAI
CI: Guy Tellier Omnispec Clin. Res. Inc. 13714 Du Cure-Labelle, Ste. 101 Mirabel, QC J7J 2K8, Canada	MB102014/5S D1690C00006/ 9S	June 20 to 23, 2011	NAI
Sponsor: Bristol-Myers Squibb Route 206 & Providence Line Princeton, NJ 08543	MB 102013/25S MB 102014/29S MB 102030/30S MB 102034/42S	July 19 to 27, 2011	Pending (Preliminary classification VAI)
Sponsor: AstraZeneca GmbH Tinsdaler Weg 183, 22880 Wedel, Germany	D1690C00004/ 41S D1690C00006/ 27S	June 27 to 30, 2011	NAI

**Key to Classifications**

NAI = No deviation from regulations; VAI = Deviation(s) from regulations; OAI = Significant deviations from regulations.  
 Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

Source: Dr. Liebehaut's Clinical Inspection Summary

## 12. Labeling

The proprietary name Forxiga, has been acceptable. At the time of this writing, we are engaged in internal discussions about the label. The most relevant issues in labeling have been discussed throughout this document:

- A change in the indicated population to include only patients with T2DM with normal renal function or mild dysfunction, determined by an MDRD-estimated eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>, for whom the benefit risk assessment is favorable;
- Pregnancy Category C, with appropriate description of the renal pelvic and tubular dilatations findings in rat studies; in addition, under Specific Populations, a description of these findings in rats under “Pediatric Use”, because the effects on renal functional maturation seen in pups and young rats correspond to children up to 2 years of age.
- Elevating the risk of bladder and breast cancer (b) (4) to Warnings and Precautions (under internal discussion)

## 13. Recommendations/Risk Benefit Assessment

I recommend approval of dapagliflozin. I have discussed my assessment of the risk benefit throughout this memo, but will summarize the important considerations as follows:

### Benefits:

The unique benefit of dapagliflozin (and perhaps other members of this new class, under development) is the glycemic effect that is independent of the insulin; except for alpha glucosidase inhibitors, all oral antidiabetic drugs on the market and under development effect glycemia either by secretion of insulin or by increasing insulin sensitivity.

The magnitude of the glycemic effect appears to be similar to drugs in wide use and recommended in the treatment of diabetics: metformin and sulfonylureas, tested in head to head trials where the comparator (metformin or glipizide) was used at effective doses. There are no data comparing the glycemic effect of dapagliflozin to DPP-4 inhibitors or to GLP-1 receptor analogs, although one might suspect that exenatide and liraglutide have more potent glycemic effects.

Based on this insulin-independent, glucosuric mechanism of action, it may be useful when added to an insulin secretagogue and / or an insulin sensitizer. In addition, dapagliflozin has little risk of hypoglycemia, addressing an important risk in public health particularly in elderly patients who have normal renal function or mild renal impairment. A report of emergency hospitalizations due to unintended drug overdose among the elderly listed four drugs or drug

classes as the main culprit: of these, insulins and oral hypoglycemic agents were implicated in 14% and 11%, respectively<sup>5</sup>.

Other benefits are a neutral effect on body weight (or even potentially some modest weight loss, primarily related to fat, rather than lean body mass), accompanied by a modest decrease in blood pressure. The effect on lipids and inflammatory biomarkers associated with high CV risk is neutral. These effects add support to the preliminary findings of CV risk neutrality or even a CV benefit, although CV benefit is questionable, when considering the new hazard ratios from the pooled CV risk trials 18 and 19. But this has yet to be confirmed in a dedicated CV trial adequately powered and with long on treatment follow up.

The unmet need in diabetes mentioned by the AC meeting participants and throughout this memo relates in large extent to the secondary failure of currently marketed antidiabetic drugs and the limitations that each of these (or their classes) has in particular subsets of the diabetic population. Even patients who tolerate well an initial treatment with a drug or a combination of drugs will, over time, require additional drugs to continue to maintain adequate glycemic control, given the progressive nature of beta cell failure in T2DM.

### Risks

The risks identified early in clinical development and confirmed during the NDA review are related to glucosuria and osmotic diuresis: urinary tract infections (number needed to harm: 125) and genital infections (number needed to harm: 24) and effects related to volume depletion (number needed to harm: 400). These adverse events are usually mild, and in the setting of clinical trials, rarely led to serious events (such as pyelonephritis or urosepsis) or discontinuations.

In addition, also based on the mechanism of action, dapagliflozin depends on glomerular filtration rate to exert its glucosuric effect and improved glycemic control. As diabetics suffer deterioration of renal function, dapagliflozin treatment becomes ineffective, so monitoring of renal function is imperative at regular intervals and whenever glycemic control is worsened for some sustained period. With other antidiabetic drugs, a patient who experiences a secondary failure may have a new antidiabetic drug added to reestablish adequate glycemic control. In the case of dapagliflozin, if the secondary failure relates to moderate renal impairment, the treatment with dapagliflozin must be stopped, as there is no expectation that dapagliflozin will continue to have beneficial effects, and the risks (increased fracture risk, worsened renal function) may outweigh any residual benefit.

Importantly, unexpected risks were identified late in the clinical development of dapagliflozin. An imbalance in bladder cancer and breast cancer could not be clearly attributed to causes other than treatment with dapagliflozin, or to detection biases due to increased frequency of urinalysis assessments due to UTI symptoms (for bladder cancer) or weight loss / interstitial fluid loss (for breast cancer). The imbalance is based on few cases, most diagnosed within one year of dapagliflozin treatment, without any pattern different than the disease manifested in patients not treated with dapagliflozin, and without any evidence of carcinogenicity in animal studies. Still, this evidence cannot be ignored. Health care providers must be informed of these

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<sup>5</sup> Budnitz DS, Lovegrove MC, Shehab N et al. Emergency hospitalizations for Adverse Drug Events in Older Americans. NEJM 365 (21): 2002, 2011.

risks, and need to inform patients. The risk of these cancers must be continuously assessed by the applicant through clinical trial monitoring and large observational studies.

A single probable case of Hy's Law, despite the absence of nonclinical hepatic signal and mean effects on liver-related laboratory values similar to the control group, is concerning, and requires continued assessment to define further the veracity or magnitude of the risk.

Finally, we need to consider the risk of dapagliflozin use during pregnancy and nursing, with regard to renal pelvic and tubular dilatation in the fetus or infant. It is not known if the risk applies to humans, the magnitude of the risk, whether the findings are functional and transient or anatomic and permanent, and whether these findings have long term consequences on the renal function of the child.

- Postmarketing Risk Evaluation and Management Strategies

Drs. Vega and Karwoski, from the Division of Risk Management, Office of Medication Error Prevention and Risk Management / OSE, considered in their review the initial information submitted with the original NDA as well as the new data from the July 15<sup>th</sup>, 2011 Integrated Safety Update. They recommend that the risks identified with dapagliflozin in this review be managed through appropriate labeling and a Medication Guide, as well as the postmarketing required studies. REMS such as a Communication Plan and / or elements to assure safe use are not warranted. I agree with DRISK's recommendations.

- Recommendation for Postmarketing Requirements and Commitments

1. Prospective observational cohort study for cancer, consisting of three sub studies, which are defined by their primary outcome: 1) female breast cancer, 2) bladder cancer, and 3) cancer overall (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, pancreas, kidney/renal, pelvis, rectal cancer, and malignant melanoma). The goal of the study is to assess the risk of bladder cancer, female breast cancer, and cancer overall in new users of dapagliflozin compared to new users of other antidiabetic drugs. This is a 5-year prospective observational cohort study, consisting of three sub studies, which are defined by their primary outcome: 1) female breast cancer, 2) bladder cancer, and 3) cancer overall (prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, pancreas, kidney/renal, pelvis, rectal cancer, and malignant melanoma). Patients will be eligible if they are older than 40 years of age, were enrolled in the respective health plan for at least 12 months prior to the index date with a diagnosis of T2DM but without a diagnosis of cancer during the 12 months preceding the index date, and received a new prescription of dapagliflozin or an antidiabetic drug other than SGLT2 inhibitors or insulin. For female breast cancer, the incidence rate from SEER is 29 per 10,000 and for bladder cancer the incidence rate is 4.4 per 10,000. Using these rates as the presumed background rate for the study and assuming a 1-sided alpha of 0.025, power of 80%, and a 1:4 dapagliflozin to comparator ratio, approximately 5,292 and 34,817 dapagliflozin patient-years would be needed to detect 102 events of each cancer (20 on dapagliflozin) and a HR of 2.0 for breast cancer and bladder cancer, respectively.
2. A randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events in patients with T2DM. Secondary

objectives must include an assessment of the long-term effects of dapagliflozin on hepatic toxicity, breast cancer, bladder cancer, urinary tract infection and genital infections. These will also be considered adverse events of special interest. The primary objective of the trial in patients with increased cardiovascular risk trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE observed with dapagliflozin to that observed in the control group is less than 1.3. Secondary objectives and adverse events of interest will include an assessment of the long-term effects of dapagliflozin on hepatic toxicity, breast cancer, bladder cancer, urinary tract infection and genital infections. All cardiovascular events, cancer events, and liver events will be adjudicated.

3. Deferred pediatric study required under PREA in pediatric patients ages 10 to 17 years with type 2 diabetes. The pediatric plan includes an evaluation of the children's ability to swallow dapagliflozin tablets, PK/PD assessments of three different doses of dapagliflozin with blood sampling over a 48-hour period, and a safety and efficacy study (randomized, double-blind, placebo controlled on metformin background (b) (4)). The latter will also include an open label, non-randomized study of diabetic children who are treatment naïve (monotherapy setting).
4. Epidemiology study to characterize hospitalizations for acute liver failure. The objective is to compare the incidence of hospitalization for acute liver failure, including hospitalizations for liver injury and acute idiopathic hepatitis, among patients with T2DM who are new users of dapagliflozin to those who are new users of other antidiabetic drugs in classes other than SGLT2 inhibitors and insulin. The primary outcome will be hospital admission with acute liver failure, acute idiopathic hepatitis and other acute liver injury. The study will be powered to detect a relative risk of 2.0 (with 80% power). This is a prospective cohort study over 3-5 years in patients with Type 2 Diabetes (duration will depend on the actual market uptake of dapagliflozin). The data will be analyzed initially 12 months after dapagliflozin has been on the market and periodically thereafter (12-18 months). A complete case validation of that outcome via medical record should be undertaken for all identified cases.
5. A longitudinal population-based prospective cohort study using several longitudinal databases will compare the incidence of hospitalization for acute kidney injury among patients with T2DM who are new users of dapagliflozin to those who are new users of antidiabetic drugs other than SGLT2 inhibitors. Patients eligible to enroll in this study will include T2DM patients who are newly prescribed dapagliflozin or an antidiabetic drug other than SGLT2 inhibitors or insulin. This study will use longitudinal databases (at least one in Europe and one in the U.S.) that capture inpatient and outpatient diagnoses and procedures, prescription information, and allow for case adjudication. The estimated study duration is 3 to 5 years depending on the market uptake of dapagliflozin.
6. Pharmacoepidemiology program for characterization of emergency room visits or hospitalizations due to severe complications of urinary infections. Comparison of the risk of severe complications of urinary tract infections between patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic treatments. The primary objective of the proposed study is to compare the sex-specific incidence of severe complications of UTIs resulting in emergency room visits or hospitalizations among patients with T2DM who are new users of dapagliflozin and those who are new users of antidiabetic drugs other



than SGLT2 inhibitors and insulin. This study will be a longitudinal population-based prospective cohort study using several longitudinal healthcare claims or electronic medical record databases (at least one in Europe and one in the U.S.). The estimated study duration is 3 to 5 years depending on the actual market uptake of dapagliflozin. Incidence rates for severe complications of UTI will be calculated for each cohort.

In discussion with the applicant, FDA expressed reservation regarding the proposed pharmacoepidemiologic studies, particularly the one to address the potential for acute liver injury, and the expected power to rule out the specified relative risks within the 3 - 5 years. The predictions are highly dependent on the market uptake, the specific observational databases to be used and the ability to validate cases through review of medical records in those databases. But the sample sizes required are very large, and not feasible to accomplish through the dedicated CV trial or even through metaanalyses of all past and ongoing trials.

- Recommended Comments to Applicant

We will discuss with the applicant all PMRs identified and seek agreement on these. After internal review of the PI and Medication Guide, we will discuss our proposed revisions, as described in this CDTL memo.

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/s/  
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ILAN IRONY  
12/05/2011

MARY H PARKS  
12/06/2011  
Please see Division Director's memo

## CLINICAL REVIEW NDA Major Amendment

Application Type	NDA Major Amendment
Application Number(s)	202293
Submit Date(s)	10/20/2011
Received Date(s)	12/28/2010
PDUFA Goal Date	1/28/2012
Division	Office Division of Metabolism and Endocrinology Products/Office of New Drugs II
Reviewer Name(s)	Somya V. Dunn
Review Completion Date	November 22, 2011
Established Name	Dapagliflozin
Proposed Trade Name	Forxiga

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## ***Recommendation/Updated Risk Benefit Assessment***

In my initial review of the dapagliflozin NDA, I recommended a Complete Response for the original NDA Action Goal Date. The modest efficacy in light of the possible drug induced liver injury case and other potential cancer signals guided this decision.

The data submitted in the major amendment offer an additional 1500 patient years of exposure to the drug, beyond what was submitted with the original NDA. This additional exposure increases confidence in the risk ratio estimates for both bladder and breast cancer (in the case of breast cancer new cases in the control group are in favor of dapagliflozin's safety profile). In addition, no convincing evidence of any additional drug induced liver injury cases have surfaced, and liver enzymes continue to not display marked elevation imbalances in a larger clinical database. The major amendment data overall did not strengthen any of the safety signals that were raised in the NDA review.

Data from dapagliflozin therapy in high risk cardiovascular patients were added to the cardiovascular meta-analysis. Treatment associated with dapagliflozin is not associated with increased cardiovascular risk and this was confirmed with the updated meta-analysis. Furthermore, the new studies reviewed also add some favorable efficacy data. Glycemic control in the high risk cardiovascular study is modest; however, cardiovascular endpoints in high risk patients contribute to the development of a more favorable risk/benefit profile for dapagliflozin. T2DM patients often suffer from cardiovascular disease and experience related morbidity and mortality. Dapagliflozin has an effect on blood pressure and weight loss that could positively impact T2DM patients in addition to improving glycemic control.

In order to properly evaluate dapagliflozin and potential association with liver injury or cancer, both the outcome trial and epidemiology studies proposed by the applicant are necessary. However, I recommend that these be conducted post marketing and that dapagliflozin be approved for marketing.

## ***Background***

Data were submitted by the applicant and triggered a major amendment to the Dapagliflozin NDA. The primary submission that triggered the amendment consists of 24-week datasets from two studies that were ongoing during the NDA review cycle. These studies were:

**D1690C00018:** A 24-week, multicenter, randomized, double-blind, age-stratified, placebo-controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care

**D1690C00019:** A 24-week, multicenter, randomized, double-blind, age-stratified, placebo controlled phase III study with a 28-week extension period to evaluate the

efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycemic control on usual care

New data cutoffs incorporated data from these two studies. These studies are briefly described below under the ***Efficacy*** section. Other items reviewed and discussed to different degrees in this document are:

1. Study Reports for D1690C00018 and D1690C00019 submitted 11/2/11
2. Updated Risk Management Plan submitted 9/7/11
3. Information request response: HbA1c and albuminuria 9/9/11
4. Updated Cardiovascular Meta-analysis, Liver Response and Cancer Response submitted 10/27/11
5. Ad hoc analyses for D1690C00018 and D1690C00019 submitted 11/8/11
6. Updated Labeling proposal submitted 11/8/11
7. Teleconference meeting minutes submitted 10/18/11
8. Advisory Committee Responses submitted 9/11

## ***Efficacy***

Studies will be referred to as study 18 and study 19 throughout this review.

### **D1690C00018**

#### **Objectives and Endpoints**

##### *Primary Objectives*

There were two independent primary objectives:

- To assess the glycemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with cardiovascular disease (CVD) and hypertension, measured as the mean change in HbA1c from baseline to week 24, in the overall population and in two predefined age subgroups (<65 years, ≥65 years)
- To assess the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with CVD and hypertension at week 24, measured as the proportion of responders for a three item endpoint of clinical benefit, defined as:
  - an absolute drop of 0.5% or more from baseline HbA1c, and
  - a relative drop of 3% or more from baseline for total body weight, and
  - an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure (SBP)

##### *Endpoints*

- Change in HbA1c from baseline to week 24

- Proportion of subjects achieving:
  - an absolute reduction in HbA1c of  $\geq 0.5\%$  from baseline to week 24, and
  - a relative reduction in total body weight of  $\geq 3\%$  from baseline to week 24, and
  - an absolute reduction in seated SBP of  $\geq 3$  mmHg from baseline to week 24

#### *Reviewer's Comments*

**While the composite endpoint above, would theoretically contribute to an improved clinical picture, it is difficult for me to qualify the benefit to the patient. The *Guidance for Industry Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims* does not indicate any numerical decrease in blood pressure for antihypertensive medications.**

#### *Secondary Objectives*

- To compare the mean change in seated SBP from baseline to week 8 between dapagliflozin 10 mg versus placebo
- To compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo
- To compare the mean change in seated SBP from baseline to week 24 between dapagliflozin 10 mg versus placebo
- To compare the proportion of subjects with baseline body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24

#### **Eligibility and Stratification**

The study entry criteria specified enrollment of male subjects  $\geq 45$  years of age and female subjects  $\geq 50$  years of age diagnosed with T2DM, CVD, and hypertension. Subjects were eligible to enter the study if they received monotherapy or dual combination therapy with oral antidiabetic drugs (OADs), insulin therapy in combination with OADs, or insulin monotherapy on a daily basis for 8 weeks and stable for at least four weeks before enrollment and showed inadequate glycemic control ( $7.2\% \leq \text{HbA1c} \leq 10.5\%$ ). Subjects on anti-hypertensive treatment should have used this treatment uninterrupted on a daily basis the last four weeks before enrollment.

CVD was defined as:

- Prior documented coronary heart disease
- History of myocardial infarction, or
- History of revascularization, or coronary artery stenosis  $>50\%$ , confirmed with angiography, or
- Abnormal imaging at stress test, compatible with ischemia or prior myocardial infarction, or
- Prior documented stroke or transient ischemic attack (TIA), or prior documented peripheral artery disease treated with revascularization (amputation was not accepted)

Subjects eligible for the study were stratified according to age (<65 years or ≥65 years), insulin use, and time from most recent qualifying CV event (>1 year or ≤1 year before enrollment). A total of eight strata were formed by combination of the three factors, and within each stratum randomization was 1:1.

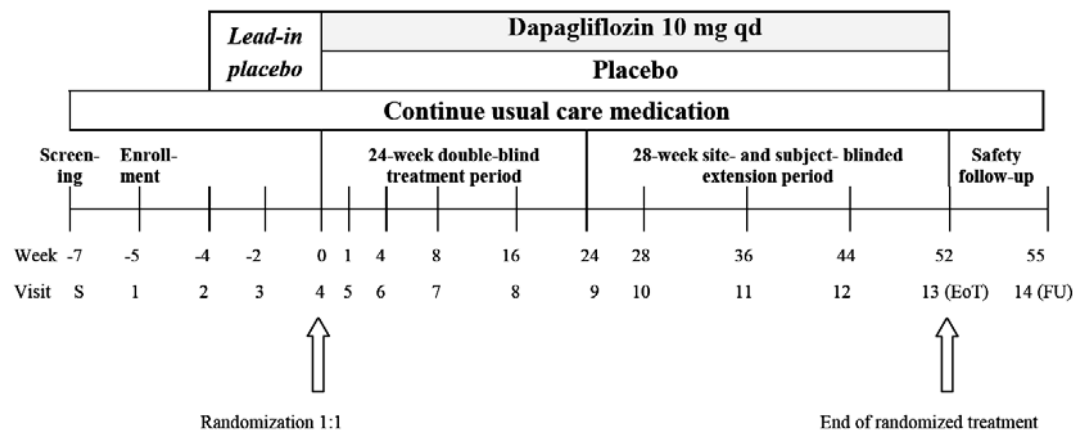
### Study Design

This was a randomized, double-blinded study. The objectives of the study included measurements at 24 and 52 weeks.

In subjects treated with insulin, the average daily insulin dose was reduced by 25% beginning at breakfast or any first occurrence of insulin administration at the beginning of the treatment period. Subjects in each stratum received pre-existing anti-hypertensive, anti-platelet, and lipid lowering treatment. During the 28-week extension period, subjects were to continue study treatment as during the 24-week short-term treatment period.

Figure 1 shows the design of the study and the sequence of treatment periods.

Figure 1 Study Design



Source CSR Figure 1

### Subject Demographics and Disposition

Demographic and baseline characteristics were balanced between groups. On average, subjects were around 63 years of age ranging from 45 to 86 years (SD 7.7) and 68% of subjects were male in both treatment groups. Mean duration of T2DM was 12.4 years, and around 56% of the subjects had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%. Most subjects reported coronary heart disease (75.2%) or stroke/TIA



(20.7%). All subjects also had hypertension according to the inclusion criteria. At baseline, the renal function for the patients is depicted in Table 1.

**Table 1 Baseline Renal Function in Study 18**

MEASURE OF BASELINE RENAL FUNCTION	PLA N = 459	DAPA 10MG N = 455	Total N = 914
eGFR (ML/MIN/1.73 M**2)			
NUMBER (PERCENT)			
< 30	1 (0.2)	1 (0.2)	2 (0.2)
>= 30 AND < 60	89 (19.4)	88 (19.3)	177 (19.4)
>= 60 AND < 90	268 (58.4)	258 (56.7)	526 (57.5)
>= 90	100 (21.8)	108 (23.7)	208 (22.8)

Source CSR Table 16

In total, 1429 subjects were enrolled out of which 922 were randomized. Approximately 88% of the randomized subjects completed the 24-week short-term treatment period and around 86% continued into the 28-week extension period. Two subjects in the dapagliflozin and one subject in the placebo group died during the 24-week short-term treatment period. Another death occurred more than 30 days after the last dose of study; this patient had been on placebo.

The safety analysis set was used to describe disposition, see Table 2.

**Table 2 Disposition at End of 24-week Short-term Treatment Period Study 18 (safety analysis set)**

	PLA	DAPA 10MG	Total
SUBJECTS	462	460	922
SUBJECTS COMPLETING THE ST PERIOD (%)	404 (87.4)	403 (87.6)	807 (87.5)
SUBJECTS NOT COMPLETING THE ST PERIOD (%)	58 (12.6)	57 (12.4)	115 (12.5)
REASON FOR NOT COMPLETING THE ST PERIOD (%)			
INCORRECT ENROLMENT	2 (0.4)	1 (0.2)	3 (0.3)
ADVERSE EVENT	3 (0.6)	8 (1.7)	11 (1.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	17 (3.7)	26 (5.7)	43 (4.7)
SUBJECT WITHDREW CONSENT	16 (3.5)	12 (2.6)	28 (3.0)
LOST TO FOLLOW-UP	10 (2.2)	2 (0.4)	12 (1.3)
POOR/NON-COMPLIANCE	6 (1.3)	5 (1.1)	11 (1.2)
SAFETY	0	1 (0.2)	1 (0.1)
DEATH	1 (0.2)	2 (0.4)	3 (0.3)
ADMINISTRATIVE REASON BY SPONSOR	1 (0.2)	0	1 (0.1)
OTHER	2 (0.4)	0	2 (0.2)
SUBJECTS CONTINUING IN THE STUDY (%)	396 (85.7)	401 (87.2)	797 (86.4)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	66 (14.3)	59 (12.8)	125 (13.6)
REASON FOR NOT CONTINUING IN THE STUDY (%)			
INCORRECT ENROLMENT	2 (0.4)	1 (0.2)	3 (0.3)
ADVERSE EVENT	4 (0.9)	9 (2.0)	13 (1.4)
SUBJECT NO LONGER MEETS STUDY CRITERIA	18 (3.9)	26 (5.7)	44 (4.8)
SUBJECT WITHDREW CONSENT	19 (4.1)	13 (2.8)	32 (3.5)
LOST TO FOLLOW-UP	10 (2.2)	2 (0.4)	12 (1.3)
POOR/NON-COMPLIANCE	6 (1.3)	5 (1.1)	11 (1.2)
SAFETY	0	1 (0.2)	1 (0.1)
DEATH	1 (0.2)	2 (0.4)	3 (0.3)
ADMINISTRATIVE REASON BY SPONSOR	1 (0.2)	0	1 (0.1)
OTHER	2 (0.4)	0	2 (0.2)
NOT REPORTED	3 (0.6)	0	3 (0.3)

Source CSR Table 8

### **Statistical Methods**

A hierarchical testing procedure was used to control the type I error rate across the two primary and four key secondary endpoints, both in the overall population as well as within individual age groups. Testing of the key secondary variables was performed in a fixed order sequence and applied separately for the overall population and for each of the two age strata.

If both primary variables were statistically significant, the alpha level of 0.05 (two-sided) was used; if only one of the primary variables was statistically significant, testing was done at a significance level of 0.025 (two-sided). If none of the primary variables was statistically significant, no further testing was done.

For the overall evaluation of the first primary efficacy variable and the continuous secondary efficacy variables, an analysis of covariance (ANCOVA) model was used.

### **Efficacy Results**

Please refer to Dr. Jonathan Norton's review for further efficacy discussion.

The full analysis set included 914 of the 922 randomized subjects (526 of 530 randomized subjects in age stratum <65 years and 388 of 392 randomized subjects in age stratum ≥65 years). The full analysis set was used to calculate and present efficacy results.

There was a statistically significant mean reduction in HbA1c from baseline to week 24 and the proportion of subjects with a clinical benefit based on response for a three-item endpoint of clinical benefit at week 24 was significantly larger in the dapagliflozin group compared to placebo in all subjects of the full analysis set.

Table 3 summarizes main efficacy results.

**Table 3 Efficacy Results for Primary and Secondary Key Endpoints Study 18 (full analysis set)**

	<b>PLA N = 459</b>	<b>DAPA 10 MG N = 455</b>
<b>Primary endpoints</b>		
HbA1c (%) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	0.08 (0.0400), 451	-0.38 (0.0403), 448
p-value vs. PLA		<0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent, N#	0.9%, 451	11.7%, 444
p-value vs. PLA		<0.0001 *
<b>Key secondary endpoints</b>		
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N#	-0.99 (0.6651), 459	-2.96 (0.6755), 451
p-value vs. PLA		0.0126 *
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N#	-0.30 (0.1645), 459	-2.56 (0.1630), 455
p-value vs. PLA		<0.0001 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	-1.03 (0.6908), 459	-2.99 (0.7016), 451
p-value vs. PLA		0.0174 *
Subjects with total body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI $\geq 27$ kg/m <sup>2</sup>		
Percent adjusted (SE), N#	4.0% (0.986), 397	16.5% (1.884), 388
p-value vs. PLA		<0.0001 *

N: number of subjects in the full analysis set.

N#: number of subjects in the full analysis set with non-missing baseline and week t (LOCF) values.

BMI: body mass index; HbA1c: glycosylated hemoglobin; PLA: placebo; DAPA: dapagliflozin; LOCF: last observation carried forward; SBP: systolic blood pressure; SE: standard error.

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

Source CSR Table S2

### ***Reviewer's Comments***

**The placebo adjusted changes for HbA1c in the NDA for a 10 mg dose of dapagliflozin ranged from -0.54 to -0.68%. The change seen here is even more modest. One contributing factor could be that the rate of moderately renal impaired patients was more than two times higher in this study than the short term treated subjects in the NDA (19.3% here vs. 8.4% in the NDA).**

The analysis in completers showed a similar mean reduction in HbA1c compared to the primary analysis using last observation carried forward (LOCF) methodology in the dapagliflozin group (-0.39%) and no mean change instead of a slight increase in the placebo group (-0.00%).

The applicant conducted an ad hoc analysis for the percent of patients able to achieve at least a 3% decrease in weight. See Table 4. This analysis, along with the one described below for blood pressure, is (b) (4) part of the composite endpoint results, without statistical significance calculations.

**Table 4 Percent of Patients Achieving At Least 3% Weight Loss at 24 Weeks Study 18**

	PLA (N=459)	DAPA 10MG (N=455)
AT LEAST 3% DECREASE FROM BASELINE AT WEEK 24 (LOCF)		
MEAN BASELINE BODY WEIGHT (KG)	93.59	92.63
X/N#	64/459	182/455
PERCENT	13.9%	40.0%
PERCENT ADJUSTED (SE)	13.9% ( 1.620)	40.0% ( 2.302)
95% CI FOR PERCENT ADJUSTED	( 10.8, 17.1)	( 35.5, 44.5)
DIFFERENCE VS. PLA, PERCENT (SE)		26.1% ( 2.809)
95% CI FOR DIFFERENCE VS. PLA		( 20.6, 31.6)
P-VALUE VS. PLA		<.0001

Source Ad Hoc analysis study 18 11/8/11 Table 1

Another ad hoc analysis was performed to evaluate the percent of patients achieving reduction in systolic blood pressure of 3 mmHg or more, see Table 5.

**Table 5 Percent of Patients Achieving At Least 3mmHG SBP Reduction at 24 Weeks Study 18**

	PLA (N=459)	DAPA 10MG (N=455)
ABSOLUTE REDUCTION IN SBP OF 3 MMHG OR MORE AT WEEK 24 (LOCF)		
MEAN BASELINE SBP (MMHG)	133.0	133.4
X/N#	190/459	223/451
PERCENT	41.4%	49.4%
PERCENT ADJUSTED (SE)	41.6% ( 2.190)	49.1% ( 2.256)
95% CI FOR PERCENT ADJUSTED	( 37.3, 45.9)	( 44.7, 53.6)
DIFFERENCE VS. PLA, PERCENT (SE)		7.5% ( 3.294)
95% CI FOR DIFFERENCE VS. PLA		( 1.1, 14.0)
P-VALUE VS. PLA		0.0227

Source Ad Hoc analysis study 18 11/8/11 Table 3

Both primary endpoints had statistically significant results over placebo in both age strata. The secondary endpoints were statistically significant, except for the seated SBP at week 8 and week 24 endpoints in the older age stratum.

**Table 6 Primary and Key Secondary Endpoints for Age Strata Study 18**

Endpoint	Dapagliflozin <65	Placebo <65	Dapagliflozin ≥65	Placebo ≥65
N	263	263	196	192
HbA1c (%) ADJUSTED MEAN CHANGE FROM BASELINE (SE)	- 0.4 ( 0.0)	0.0 ( 0.1)	-0.4 (0.8)	0.2 (0.8)
P value vs. placebo	<.0001		<.0001	
% RESPONDERS OF A 3-ITEM ENDPOINT OF CLINICAL BENEFIT AT WEEK 24	11.2%	0.4%	12.4%	1.6%
P value vs. placebo	<.0001		<.0001	

<b>ADJUSTED SEATED SBP (MMHG) CHANGE AT WEEK 8</b> <b>P value vs. placebo</b>	-3.1 ( 0.9) 0.0033	0.0 ( 0.9)	-2.8 ( 1.1) 0.6888	-2.3 ( 1.0)
<b>ADJUSTED TOTAL BODY WEIGHT (KG) CHANGE AT WEEK 24</b> <b>P value vs. placebo</b>	-2.40 ( 0.2) <.0001	-0.11 ( 0.2)	-2.73 ( 0.3) <.0001	-0.49 (0.3)
<b>ADJUSTED SEATED SBP (MMHG) CHANGE AT WEEK 24</b> <b>P value vs. placebo</b>	-2.94 ( 0.8) 0.0033	0.05 ( 0.8)	-3.03 ( 1.2) 0.6376	-2.38 ( 1.2)
<b>% SUBJECTS WITH TOTAL BODY WEIGHT DECREASE <math>\geq</math> 5% AT WEEK 24 IN SUBJECTS WITH BASELINE BMI <math>\geq</math>27 KG/M<sup>2</sup></b> <b>P value vs. placebo</b>	16.1% (2.5) <.0001	3.6 % ( 1.3)	17.0% ( 2.9) 0.0002	4.5% ( 1.6)

### ***Reviewer's Comments***

**My comments regarding this study and labeling follow the next study.**

### **D1690C00019**

This study was very similar in design, objectives and endpoints to study D1690C00018. The major difference between the studies was that this study did not include hypertension as eligibility criterion. There was one additional key secondary objective:

- To compare the mean change in seated SBP in subjects with baseline seated SBP  $\geq$ 130 mmHg achieved with dapagliflozin versus placebo from baseline to week 8

### **Subject Demographics and Disposition**

Treatment groups were balanced in demographic and baseline characteristics. Subjects were around 64 years ranging from 47 to 84 (SD 7) of age with around 47% aged  $\geq$ 65 years. There were about 67% male subjects in both treatment groups. Mean duration of T2DM was 13.2 years with around 58% of the subjects have had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%. Most subjects reported coronary heart disease (76.5%) or stroke/TIA (19.6%) as their qualifying CVD. Almost 93% of subjects had hypertension. Baseline renal function is seen in Table 7.

**Table 7 Baseline Renal Function Study 19**

MEASURE OF BASELINE RENAL FUNCTION	PLA N = 482	DAPA 10MG N = 480	Total N = 962
eGFR (ML/MIN/1.73 M**2)			
NUMBER (PERCENT)			
< 30	0	0	0
≥ 30 AND < 60	68 (14.1)	77 (16.0)	145 (15.1)
≥ 60 AND < 90	296 (61.4)	294 (61.3)	590 (61.3)
≥ 90	118 (24.5)	109 (22.7)	227 (23.6)

Source CSR Table 16

In total, 1489 subjects were enrolled out of which 964 were randomized. Two subjects in the dapagliflozin group and one subject in the placebo group died during the 24-week short-term treatment period.

**Table 8 Disposition at End of 24-week Short-term Treatment Period Study 19 (safety analysis set)**

	PLA	DAPA 10MG	Total
SUBJECTS	483	482	965
SUBJECTS COMPLETING THE ST PERIOD (%)	428 (88.6)	441 (91.5)	869 (90.1)
SUBJECTS NOT COMPLETING THE ST PERIOD (%)	55 (11.4)	41 ( 8.5)	96 ( 9.9)
REASON FOR NOT COMPLETING THE ST PERIOD (%)			
INCORRECT ENROLMENT	4 ( 0.8)	6 ( 1.2)	10 ( 1.0)
ADVERSE EVENT	12 ( 2.5)	4 ( 0.8)	16 ( 1.7)
SUBJECT NO LONGER MEETS STUDY CRITERIA	13 ( 2.7)	15 ( 3.1)	28 ( 2.9)
SUBJECT WITHDREW CONSENT	16 ( 3.3)	8 ( 1.7)	24 ( 2.5)
LOST TO FOLLOW-UP	2 ( 0.4)	0	2 ( 0.2)
POOR/NON-COMPLIANCE	4 ( 0.8)	3 ( 0.6)	7 ( 0.7)
SAFETY	2 ( 0.4)	0	2 ( 0.2)
DEATH	1 ( 0.2)	2 ( 0.4)	3 ( 0.3)
ADMINISTRATIVE REASON BY SPONSOR	1 ( 0.2)	0	1 ( 0.1)
OTHER	0	3 ( 0.6)	3 ( 0.3)
SUBJECTS CONTINUING IN THE STUDY (%)	421 (87.2)	432 (89.6)	853 (88.4)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	62 (12.8)	50 (10.4)	112 (11.6)
REASON FOR NOT CONTINUING IN THE STUDY (%)			
INCORRECT ENROLMENT	4 ( 0.8)	6 ( 1.2)	10 ( 1.0)
ADVERSE EVENT	13 ( 2.7)	5 ( 1.0)	18 ( 1.9)
SUBJECT NO LONGER MEETS STUDY CRITERIA	14 ( 2.9)	16 ( 3.3)	30 ( 3.1)
SUBJECT WITHDREW CONSENT	19 ( 3.9)	10 ( 2.1)	29 ( 3.0)
LOST TO FOLLOW-UP	2 ( 0.4)	0	2 ( 0.2)
POOR/NON-COMPLIANCE	5 ( 1.0)	6 ( 1.2)	11 ( 1.1)
SAFETY	2 ( 0.4)	1 ( 0.2)	3 ( 0.3)
DEATH	1 ( 0.2)	2 ( 0.4)	3 ( 0.3)
ADMINISTRATIVE REASON BY SPONSOR	1 ( 0.2)	0	1 ( 0.1)
OTHER	0	3 ( 0.6)	3 ( 0.3)
NOT REPORTED	1 ( 0.2)	1 ( 0.2)	2 ( 0.2)

Source CSR Table 8

## Efficacy Results

The full analysis set included 962 subjects, 511 subjects in age stratum <65 years and 451 in age stratum ≥65 years.

**Table 9 Efficacy Results for Primary and Secondary Key Endpoints Study 19 (full analysis set)**

	PLA N=482	DAPA 10 MG N=480
<b>Primary endpoints</b>		
HbA1c (%) at week 24 last observation carried forward (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.07 ( 0.0435), 471	-0.33 ( 0.0434), 474 <0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent p-value vs. PLA	1.9%, 469	10.0%, 468 <0.0001 *
<b>Key secondary endpoints</b>		
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N# p-value vs. PLA	-0.61 ( 0.1770), 481	-2.53 ( 0.1736), 480 <0.0001 *
Subjects with body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI $\geq 27$ kg/m <sup>2</sup>		
Percent adjusted (SE), N# p-value vs. PLA	4.8% ( 1.051), 415	18.4% ( 1.876), 428 <0.0001 *
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.86 ( 0.7105), 479	-1.85 ( 0.7135), 473 0.0007 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.32 ( 0.7109), 479	-2.70 ( 0.7140), 473 0.0002 *
Seated SBP (mmHg) at week 8 (LOCF) in subjects with baseline SBP $\geq 130$ mmHg		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	-1.89 ( 0.8612), 309	-5.33 ( 0.8612), 300 0.0004 *

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

Source CSR Table S2

### ***Reviewer's Comments***

**Again, the efficacy is less than what was seen in the NDA. However, the rate of moderate renal impairment patients is higher than the NDA (15.1% vs. 8.4%). This could contribute the cause.**

The ad hoc analyses for weight loss  $\geq 3\%$  and reduction of SBP was also done for this study, see Tables 10 and 11.

**Table 10 Percent of Patients Achieving At Least 3% Weight Loss at 24 Weeks Study 19**

	PLA (N=482)	DAPA 10MG (N=480)
AT LEAST 3% DECREASE FROM BASELINE AT WEEK 24 (LOCF)		
MEAN BASELINE BODY WEIGHT (KG)	93.22	94.53
X/N#	74/481	198/480
PERCENT	15.4%	41.3%
PERCENT ADJUSTED (SE)	15.4% ( 1.645)	41.2% ( 2.248)
95% CI FOR PERCENT ADJUSTED	( 12.1, 18.6)	( 36.8, 45.7)
DIFFERENCE VS. PLA, PERCENT (SE)		25.9% ( 2.786)
95% CI FOR DIFFERENCE VS. PLA		( 20.4, 31.3)
P-VALUE VS. PLA		<.0001

Source Ad Hoc analysis study 19 11/8/11 Table 1

**Table 11 Percent of Patients Achieving At Least 3mmHG SBP Reduction at 24 Weeks Study 19**

	PLA (N=482)	DAPA 10MG (N=480)
ABSOLUTE REDUCTION IN SBP OF 3 MMHG OR MORE AT WEEK 24 (LOCF)		
MEAN BASELINE SBP (MMHG)	134.6	134.7
X/N#	195/479	219/473
PERCENT	40.7%	46.3%
PERCENT ADJUSTED (SE)	40.9% ( 2.189)	46.2% ( 2.188)
95% CI FOR PERCENT ADJUSTED	( 36.6, 45.2)	( 41.9, 50.4)
DIFFERENCE VS. PLA, PERCENT (SE)		5.3% ( 3.225)
95% CI FOR DIFFERENCE VS. PLA		( -1.0, 11.6)
P-VALUE VS. PLA		0.1013

Source Ad Hoc analysis study 19 11/8/11 Table 3

The analysis of change from baseline in HbA1c including completers showed a similar adjusted mean reduction in HbA1c compared to the primary analysis in the dapagliflozin group (-0.3%) and no change in the placebo group (0.0%).

**Table 12 Primary and Key Secondary Endpoints for Age Strata Study 19**

Endpoint	Dapagliflozin <65	Placebo <65	Dapagliflozin ≥65	Placebo ≥65
N	253	258	227	224
HbA1c (%) ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.4 ( 0.06)	0.06 ( 0.06)	-0.27 ( 0.06)	0.07 ( 0.06)
P value vs. placebo	<.0001		<.0001	
% RESPONDERS OF A 3-ITEM ENDPOINT OF CLINICAL BENEFIT AT WEEK 24	10.9%	1.6%	9.1%	2.3%
P value vs. placebo	<.0001		0.0023	
ADJUSTED SEATED SBP (MMHG) CHANGE AT WEEK 8	-2.4 ( 0.97)	0.63 ( 0.96)	-1.36 ( 1.0)	0.99 ( 1.1)
P value vs. placebo	0.0061		0.0429	
ADJUSTED TOTAL BODY WEIGHT (KG) CHANGE AT WEEK 24	-2.46 ( 0.2)	-0.53 ( 0.2)	-2.59 ( 0.2)	-0.70 ( 0.2)
P value vs. placebo	<.0001		<.0001	
SEATED SBP (MMHG) AT CHANGE WEEK 24	-2.28 ( 0.95)	2.06 ( 0.9)	-3.09 ( 1.1)	-1.57 ( 1.1)
P value vs. placebo	<.0001		0.1988	



<b>% SUBJECTS WITH TOTAL BODY WEIGHT DECREASE ≥ 5% AT WEEK 24 IN SUBJECTS WITH BASELINE BMI ≥ 27 KG/M<sup>2</sup></b> <b>P value vs. placebo</b>	19.4% (2.6)  <.0001	4.9% (1.5)	17.4% (2.7)  <.0001	4.7% (1.5)
<b>ADJUSTED SEATED SBP (MMHG) AT WEEK 8 IN SUBJECTS WITH BASELINE SEATED SBP ≥ 130 MMHG</b>	-5.88 (1.3)  0.0130	-2.42 ( 1.2)	-4.81 ( 1.2)  0.0142	-1.43 (1.3)

### ***Reviewer's Comments***

The endpoints for cardiovascular risk in this high risk population show favorable results; however, as mentioned earlier, the overall benefit on cardiovascular health is unclear. The long term CV outcomes trial will be helpful to follow the dapagliflozin CV effects in a high risk population and to see if this ultimately leads to less CV-related death or major cardiovascular events.

Any data from these studies in labeling could imply an indication or be used for promotional purposes. I recommend the efficacy data from these studies be limited to Section 8 *Use in Specific Populations* and Section 14 *Clinical Studies*. Discussion of blood pressure effect in these studies in the (b) (4) section is unnecessary. The numbers of patients over 65 in these studies adds useful data to the overall picture as data in these patients was limited in the original NDA submission.

### ***Safety***

Two databases are discussed in this portion of my review. One is the July 15, 2011 applicant database cutoff; this included the following studies:

**Table 13 Studies in the July 15 Safety Database Cutoff**

Study Description/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment	Primary Efficacy Assessment
<b>MONOTHERAPY POPULATION</b>						
<b>MB102008</b> Phase 2b Monotherapy vs placebo/ Completed	Drug naive subjects with HbA1c $\geq 7.0\%$ - $\leq 10.0\%$	47 – 59/279/389	12 weeks	7 groups: dapagliflozin 2.5, 5, 10, 20 or 50 mg vs placebo Additional group: metformin XR 750/1500 mg	None	Superiority: Change in HbA1c at 12 weeks vs. placebo
<b>MB102013</b> Phase 3 Monotherapy vs placebo/ST Completed, ST + LT Completed	Group 1: drug-naive subjects with baseline HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ . Group 2: drug-naive subjects with baseline HbA1c $\geq 10.1\%$ and $\leq 12.0\%$	64 – 76/410/485 (ST)  34 -39/73/73 (ST)	24 weeks + 78 weeks  24 weeks + 78 weeks	Group 1: dapagliflozin 2.5, 5 or 10 mg, QAM or QPM, vs placebo  Group 2: dapagliflozin 5 or 10 mg, QAM  Background therapy: None	Metformin	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>MB102032</b> Phase 3 Low-dose monotherapy vs placebo/ Completed	Drug-naive subjects with HbA1c $\geq 7.0\%$ - $\leq 10.0\%$	68 – 74/214/282	24 weeks	4 groups: dapagliflozin 1, 2.5, or 5 mg, or placebo. Background therapy: None	Metformin	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>D1692C00005</b> Phase 2b Monotherapy vs placebo/Completed	Japanese subjects with inadequate glycemic control with HbA1c $\geq 7.0\%$ - $\leq 10.0\%$	54/225/279	12 weeks	4 groups: dapagliflozin 1, 2.5, 5, or 10 mg or placebo	None	Superiority: Change in HbA1c at 12 weeks vs. placebo
<b>DAPAGLIFLOZIN PLUS METFORMIN POPULATION</b>						
<b>MB102014</b> Phase 3 Add-on to metformin vs. placebo/ST Completed, ST + LT Completed	Subjects on metformin $\geq 1500$ mg/day with HbA1c $\geq 7.0\%$ - $\leq 10.0\%$	135 – 137/409/546 (ST)	24 weeks + 78 weeks	4 groups: dapagliflozin 2.5, 5, 10 mg, or placebo Background therapy: metformin $\geq 1500$ mg/day	Pioglitazone (or acarbose)	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>D1690C00012</b> Phase 3 Add-on to metformin vs. placebo/ ST + LT 50 weeks Completed/ LT Ongoing	Subjects on metformin $\geq 1500$ mg/day with HbA1c with $\geq 6.5\%$ - $\leq 8.5\%$	91/91/182	24 weeks + 78 weeks	2 groups: dapagliflozin 10 mg or placebo Background therapy: metformin $>1500$ mg	Sitagliptin	Superiority: change in total body weight at 24 weeks vs. placebo
<b>DAPAGLIFLOZIN PLUS INSULIN POPULATION</b>						
<b>MB102009</b> Phase 2b Add-on to insulin vs. placebo Completed	Subjects on insulin sensitizer (metformin and/or TZD) and insulin with HbA1c $\geq 7.5\%$ - $\leq 10.0\%$	Cohort 1: single blind, unrandomized 4/4/4  Cohort 2: double-blind: 23-24/48/71	12 weeks	dapagliflozin 20 mg (to determine insulin dose level for Cohort 2)  3 groups: dapagliflozin 10 or 20 mg in morning vs placebo Background therapy: 50% original insulin dose + metformin or TZD	Insulin up-titration	Superiority: Change in HbA1c at 12 weeks vs. placebo
<b>D1690C00006<sup>a</sup></b> Phase 3 Add-on to insulin vs. placebo ST Completed/ ST + LT Completed	Subjects on insulin $\geq 30$ IU/day $\pm$ maximum 2 OAD with HbA1c $\geq 7.5\%$ - $\leq 10.5\%$	196 – 212/610/807 (ST)	24 weeks + + 80 weeks	4 groups: dapagliflozin 2.5, 5 <sup>b</sup> , or 10 mg or placebo Background therapy: insulin $\geq 30$ IU/day $\pm$ maximum 2 OAD After 48 weeks, forced titration of dapagliflozin 5 mg to 10 mg	Insulin up-titration	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>DAPAGLIFLOZIN PLUS THIAZOLIDINEDIONE (TZD) POPULATION</b>						
<b>MB102030</b> Phase 3 Add-on to TZD vs. placebo/ST Completed/ ST + LT Completed	Subjects on pioglitazone with HbA1c $\geq 7.0\%$ - $\leq 10.5\%$	139 – 141/281/420 (ST)	24 weeks + 24 weeks	3 groups: dapagliflozin 5 or 10 mg or placebo Background therapy: pioglitazone $\geq 30$ mg	Metformin or sulfonylurea	Superiority: change in HbA1c at 24 weeks vs. placebo

<b>D1690C00012</b> Phase 3 Add-on to metformin vs. placebo/ ST + LT 50 weeks Completed/ LT Ongoing	Subjects on metformin $\geq 1500$ mg/day with HbA1c with $\geq 6.5\%$ – $\leq 8.5\%$	91/91/182	24 weeks + 78 weeks	2 groups: dapagliflozin 10 mg or placebo Background therapy: metformin $>1500$ mg	Sitagliptin	Superiority: change in total body weight at 24 weeks vs. placebo
<b>DAPAGLIFLOZIN PLUS INSULIN POPULATION</b>						
<b>MB102009</b> Phase 2b Add-on to insulin vs. placebo Completed	Subjects on insulin sensitizer (metformin and/or TZD) and insulin with HbA1c $\geq 7.5\%$ – $\leq 10.0\%$	Cohort 1: single blind, unrandomized 4/4/4  Cohort 2: double-blind: 23-24/48/71	12 weeks	dapagliflozin 20 mg (to determine insulin dose level for Cohort 2)  3 groups: dapagliflozin 10 or 20 mg in morning vs placebo Background therapy: 50% original insulin dose + metformin or TZD	Insulin up-titration	Superiority: Change in HbA1c at 12 weeks vs. placebo
<b>D1690C00006<sup>a</sup></b> Phase 3 Add-on to insulin vs. placebo ST Completed/ ST + LT Completed	Subjects on insulin $\geq 30$ IU/day $\pm$ maximum 2 OAD with HbA1c $\geq 7.5\%$ – $\leq 10.5\%$	196 – 212/610/807 (ST)	24 weeks + 80 weeks	4 groups: dapagliflozin 2.5, 5 <sup>b</sup> , or 10 mg or placebo Background therapy: insulin $\geq 30$ IU/day $\pm$ maximum 2 OAD After 48 weeks, forced titration of dapagliflozin 5 mg to 10 mg	Insulin up-titration	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>DAPAGLIFLOZIN PLUS THIAZOLIDINEDIONE (TZD) POPULATION</b>						
<b>MB102030</b> Phase 3 Add-on to TZD vs. placebo/ST Completed/ ST + LT Completed	Subjects on pioglitazone with HbA1c $\geq 7.0\%$ – $\leq 10.5\%$	139 – 141/281/420 (ST)	24 weeks + 24 weeks	3 groups: dapagliflozin 5 or 10 mg or placebo Background therapy: pioglitazone $\geq 30$ mg	Metformin or sulfonylurea	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>D1690C00004<sup>c</sup></b> Phase 3 Add-on to metformin vs. active comparator/ ST Completed/ LT 104 weeks completed/ LT Ongoing	Subjects on metformin $\geq 1500$ mg/day with HbA1c $> 6.5\%$ – $\leq 10.0\%$	406 – 408/406/814 (ST)	52 weeks + 156 weeks	2 groups: dapagliflozin titrated dose of 2.5, 5, or 10 mg or glipizide titrated dose of 5, 10, or 20 mg Background therapy: metformin $> 1500$ mg	None for the first 104 weeks. Allowed after 104 weeks.	Non-inferiority: change in HbA1c at 52 weeks vs. glipizide
<b>MODERATE RENAL IMPAIRMENT POPULATION</b>						
<b>MB102029</b> Phase 2b and 3 Diabetes and moderate renal impairment, monotherapy vs. placebo/ ST, ST+LT + $\geq 53$ weeks Completed, ST+LT + $\geq 104$ weeks Concluding	Subjects on a stable anti-diabetic regimen with HbA1c $\geq 7\%$ – $\geq 11\%$	83 - 85/168/252	24 weeks + 28 weeks + 52 weeks	3 groups: dapagliflozin 5 or 10 mg, vs. placebo. Background therapy: Any except metformin	Any approved therapy per investigator except metformin	Superiority: change in HbA1c at 24 weeks vs. placebo
<b>HIGH CV RISK POPULATION</b>						
<b>D1690C00018</b> Phase 3 Dapagliflozin vs. placebo added to usual care in patients with a history of CV disease and hypertension ST completed/LT ongoing	Subjects on usual care ( $\leq 2$ OADs or insulin + oral anti-hyperglycemic therapy or insulin monotherapy) with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	459-462/459/921	24 weeks + 80 weeks	2 groups: dapagliflozin 10 mg or placebo  Background therapy: ( $\leq 2$ OADs or insulin + oral anti-hyperglycemic therapy or insulin monotherapy)	Any approved therapy per investigator except rosiglitazone	Superiority: 1) Change from baseline in HbA1c. Dapagliflozin vs. placebo in overall population + in $< 65$ years + in $\geq 65$ years 2) clinical benefit vs. placebo in overall population + in $< 65$ years + in $\geq 65$ years

<b>D1690C00019</b> Phase 3 Dapagliflozin vs. placebo added to usual care in patients with a history of CV disease ST completed/LT ongoing	Subjects on usual care ( $\leq 2$ OADs or insulin + oral anti-hyperglycemic therapy or insulin monotherapy) with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	480-483/480/963	24 weeks + 80 weeks	2 groups: dapagliflozin 10 mg or placebo  Background therapy: ( $\leq 2$ OADs or insulin + oral anti-hyperglycemic therapy or insulin monotherapy)	Any approved therapy per investigator except rosiglitazone	Superiority: 1) Change from baseline in HbA1c. Dapagliflozin vs. placebo in overall population + in $< 65$ years + in $\geq 65$ years 2) clinical benefit vs. placebo in overall population + in $< 65$ years + in $\geq 65$ years
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#### ADDITIONAL PHASE 2 'MODE OF ACTION' STUDIES

<b>MB102035</b> Phase 2b Add-on to Metformin/SU vs. placebo and HCTZ Completed	Subjects on metformin and/or SU $\pm$ ACEI/ARB with HbA1c $\geq 6.6\%$ to $\leq 9.5\%$	25/24/26/75	12 weeks	3 groups: dapagliflozin 10 mg or HCTZ 25 mg or placebo	Up-titration of metformin and/or SU, or the initiation of metformin or SU	Change in GFR at 12 weeks vs placebo and HCTZ
<b>MB102045</b> Phase 2b Insulin sensitivity Add-on to metformin $\pm$ an insulin secretagogue vs. placebo, Completed	Subjects on metformin $\pm$ an insulin secretagogue (SU, DDP-IV, or glinide) with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	22/22/44	12 weeks	2 groups: dapagliflozin 5 mg or placebo  Background therapy: metformin $\pm$ insulin secretagogue	None	Change in insulin sensitivity at 12 weeks

CV=cardiovascular, DPP=dipeptidyl peptidase, HbA1c=glycosylated hemoglobin A1c, HCTZ=hydrochlorothiazide, LT=long-term, OAD=oral anti-diabetic drug, QAM=every morning, QP=every evening, ST=short-term, SU=sulfonylurea, TZD=thiazolidinedione, XR=extended release

a D1690C00006 was amended to add a second long-term period of 56 weeks after the originally planned extension of 24 weeks. When entering this second extension, subjects in the dapagliflozin 5 mg group were switched to treatment with dapagliflozin 10 mg.

b After the dose switch (see footnote a), exposure and any events will be counted to the 10 mg dose.

c Subjects randomized in this study will be assessed in the dapagliflozin 10 mg group

Source Updated CV Meta-analysis 10/27/11 Table 1

The applicant submitted updated cancer and liver data pulled from this database. Exposure is described in the following table, which also shows comparative exposures at other database cutoffs that were discussed in my initial NDA review.

**Table 14 Overall Exposure Short-term Plus Long-term Treatment NDA Review Cycle Cutoffs**

	Initial NDA		4MSU		12-May ICS		15-July ISD	
	Dapagliflozin	Control	Dapagliflozin	Control	Dapagliflozin	Control	Dapagliflozin	Control
Total Number of Patients	4287	1941	4310	1962	4559	2239	5501	3184
Overall Exposure (patient-years)	4009	1682	4354	1899	Not calculated <sup>a</sup>	Not calculated <sup>a</sup>	5496	3004
Follow-up time for malignancies (patient-years) <sup>b</sup>	Not calculated <sup>c</sup>	Not calculated <sup>c</sup>	4621	2024	4977	2348	Not calculated	Not calculated

4MSU = 4-month safety update; ICS = Integrated cancer summary (for malignant and unspecified tumors); ISD = Integrated safety database

<sup>a</sup> Not calculated because no other analyses were performed with the 12-May ICS.

<sup>b</sup> Includes 30 days of follow-up after the end of treatment. Follow-up time after an event is not included in the total.

<sup>c</sup> Not calculated for initial NDA

Source Response to Inquiry, Liver 10/27/11, Q1.7

In addition, the safety data from both studies D1690C00018 and D1690C00019 (studies 18 and 19) will be discussed. In these two studies, raw datasets were used to search for events. I conducted searches for adverse events (AE) by reported verbatim term and also the MedDRA preferred term (PT) equivalent in the databases. Some of these search results are reported here in tabular form. Some tables presented here and along with safety sets discussed are reported by the applicant with the clinical study reports.

In total for both studies 18 and 19, there were 941 patients on placebo and 935 patients treated with dapagliflozin 10 mg for 24 weeks.

## **Liver Safety**

Table 15 depicts the updated proportions of liver enzyme elevations at the time of the July cutoff. Overall, rates remained balanced in the updated analysis. There are no new cases of very high elevations in dapagliflozin treated patients (>10 or >20x upper limit of normal (ULN)).

**Table 15 Major Liver Enzyme Elevations at the July 15 Cutoff**

	X/N# (Percent)	
	DAPA TOTAL N = 5501	ALL CONTROL N = 3184
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS	242/5466 ( 4.4)	133/3161 ( 4.2)
AST ELEVATION		
> 3X ULN	40/5466 ( 0.7)	30/3160 ( 0.9)
> 5X ULN	12/5466 ( 0.2)	11/3160 ( 0.3)
> 10X ULN	5/5466 ( 0.1)	3/3160 ( 0.1)
> 20X ULN	4/5466 ( 0.1)	0/3160
ALT ELEVATION		
> 3X ULN	72/5466 ( 1.3)	47/3161 ( 1.5)
> 5X ULN	18/5466 ( 0.3)	13/3161 ( 0.4)
> 10X ULN	4/5466 ( 0.1)	4/3161 ( 0.1)
> 20X ULN	2/5466 (<0.1)	1/3161 (<0.1)
AST OR ALT ELEVATION		
> 3X ULN	84/5466 ( 1.5)	57/3161 ( 1.8)
> 5X ULN	20/5466 ( 0.4)	17/3161 ( 0.5)
> 10X ULN	5/5466 ( 0.1)	6/3161 ( 0.2)
> 20X ULN	4/5466 ( 0.1)	1/3161 (<0.1)
TOTAL BILIRUBIN ELEVATION		
> 1.5X ULN	63/5465 ( 1.2)	27/3160 ( 0.9)
> 2X ULN	20/5465 ( 0.4)	7/3160 ( 0.2)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION (AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	8/5465 ( 0.1)	4/3160 ( 0.1)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	5/5465 ( 0.1)	3/3160 ( 0.1)

Source Response to Inquiry, Liver 10/27/11, Table 1

## ***Reviewer's Comments***

While a Hy's Law case is described by the *Guidance for Industry Drug-Induced Liver Injury (DILI)* as the most specific predictor of drug induced liver injury, significant imbalances in proportion of subjects with these marked elevations are also thought to have high specificity, be important hepatic signals and are referred to as major indicators of DILI. The overall lack of imbalance seen with these elevations is somewhat reassuring; however, the one probable case of Hy's Law reviewed at the time of the original NDA review cycle remains concerning.

Liver related adverse events remained balanced among the treatment groups (75 events—1.4% of the dapagliflozin treated patients and 54 events—1.7% of control patients).

There were no notable differences on the preferred term level. These were described as *Adverse Events of Hepatic Disorder* in the updated submission and included enzyme elevations, cholestasis, steatosis and other liver related morbidities.

Liver related Serious Adverse Events (SAEs) occurred more frequently in patients treated with dapagliflozin but no imbalance in any preferred term was noted, see Table 16.

**Table 16 Liver Related SAEs at July 15 Cutoff**

Preferred Term (%)	DAPA 2.5MG N = 1220	DAPA 5MG N = 1454	DAPA 10MG N = 2688	DAPA TOTAL N = 5501	ALL CONTROL N = 3184
TOTAL SUBJECTS WITH AN EVENT	2 ( 0.2)	0	4 ( 0.1)	6 ( 0.1)	1 ( <0.1)
HEPATIC ENZYME INCREASED	0	0	2 ( <0.1)	2 ( <0.1)	0
HEPATIC CIRRHOSIS	1 ( <0.1)	0	0	1 ( <0.1)	0
HEPATIC NEOPLASM MALIGNANT	0	0	1 ( <0.1)	1 ( <0.1)	1 ( <0.1)
LIVER ABSCESS	1 ( <0.1)	0	0	1 ( <0.1)	0
OESOPHAGEAL VARICES HAEMORRHAGE	0	0	1 ( <0.1)	1 ( <0.1)	0

Source Response to Inquiry, Liver 10/27/11, Attachment Q1.2

Liver related AEs that led to discontinuation did occur more often in dapagliflozin treated patients 11 events/0.2% in dapagliflozin treated patients and 3 events/0.1% in controls. However, there was no PT that had more than a 0.1% difference between groups.

### Hepatic Adjudication Report Update

Findings from the Four Month Safety Update (4MSU) were detailed in the NDA review. The following criteria were used to identify potential liver-injury cases for adjudication:

- AST and/or ALT > 3×upper limit of normal (ULN) and TBL > 1.5×ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT > 5×ULN
- Hepatic disorders standardized MedDRA query (SMQ) AEs/SAEs in subjects who prematurely discontinued study treatment due to any AE/SAE
- Hepatic disorders SMQ AEs/SAEs in any subjects who died

The recent addendum to the hepatic adjudication report submitted and reviewed here stated that nine new cases met criteria for adjudication since the report was submitted with the 4MSU. Of these nine cases, seven were up to the 15-Jul-2011 cutoff, one was a case that occurred on (b) (6) (Subject MB102077-88-70220), and one case that occurred on (b) (6) and has not yet been sent for adjudication (Subject D1690C00018-201-8).

The cases, their adjudication result and designated treatment are listed in Table 17.

**Table 17 New Hepatic Adjudication Report Cases**

Patient ID	Final Adjudication Assessment	Treatment
MB102029-4-276	Excluded	Dapagliflozin
MB102054-24-498	Possible	Blinded
MB102077-88-70220	Unlikely	Blinded
D1690C00004-4601-5	Unlikely	Placebo
D1690C00010-1003-24	Unlikely	Dapagliflozin—no narrative
D1690C00019-5719-6	Excluded	Dapagliflozin
D1690C00019-1007-2	Excluded	Placebo
D1691C00003-3306-11	Possible	Blinded
D1690C00018-201-8	Not yet adjudicated	Dapagliflozin

Patient D1690C00010-1003-24 did not have an available narrative; however, the bilirubin levels remained within normal limits during treatment (patient did not meet biochemical Hy's Law) and liver enzyme elevations resolved.

There are three new patients either blinded or on dapagliflozin that met adjudication criteria that also met the biochemical criteria for Hy's Law. They are briefly described here:

**D1690C00018-201-8**

The patient is a 70-year-old Hispanic male who was hospitalized on Day 289 of treatment due to abdominal pain and vomiting. At that time, laboratory results revealed increased alkaline phosphatase, ALT, AST and TBL. Abdominal ultrasound revealed no signs of obstruction or dilation, but the quality of the study was described as suboptimal as patient had trouble cooperating due to discomfort. **Study medication was stopped on Day 289; peak levels were on day 290.** On Day 293, the subject had no fever and liver tests had decreased. A repeated abdominal ultrasound revealed steatosis and a pancreas with a pattern of fatty infiltration, there was no biliary obstruction or dilation. Subsequent liver tests indicated liver enzymes returning toward near normal ranges and the event was reported resolved on Day 297. Day 314, 25 days after study medication was discontinued, asymptomatic transient elevations in liver tests were reported. On Days 328 to 332, the subject was hospitalized due to urinary tract infection. Symptoms included abdominal pain and vomiting. No laboratory results are currently available for the hospitalization. On Day 342, laboratory results showed increased ALT, AST, ALP, and TBL (53 days after last dose of study medication). The applicant plans further work-up of the patient; they have not submitted the case for adjudication yet.

The patient had a history of coronary artery disease, hypertension and a cardiac pacemaker insertion. Concomitant medications for the patient included aspirin, metformin, losartan, atenolol and carvedilol.

The patient's list of enzyme elevations were as follows:

Day	alk	phos	alt	ast	bili
-39	180	19	18	0,8	
1	164	13	18	0,4	
9	141	14	16	0,7	
30	146	16	17	0,8	
57	126	18	22	1,2	
114	134	15	18	0,8	
177	115	11	14	0,5	
198	137	11	18	0,9	
261	152	11	17	0,5	
289*	547*	150*	262*	1,7*	
290	607*	504*	613*	4,33*	
291	515*	287*	179*	5,15*	
293	547*	133*	43*	1,39*	
295	577*	101*	57*	0,96*	
300	290	66	40	0,7	
314	433	189	61	1,9	
316	897*	115*	36*	1,2*	
321	338	48	22	1,3	

Reference values:

Alkaline phosphatase Range 45-145U/L

ALT Range 6-48 u/L

AST Range 10-45 U/L

Bilirubin Range 0.2-1.2 U/L

On Day 342, he visited the site and results are not included here above. Laboratory results revealed ALP 721 U/L, ALT 233 U/L, AST 97 U/L, and Total Bilirubin 2.8 mg/dL.

#### **MB102029-4-276**

This was an 83 year old white male with an eventual diagnosis of presumed cholangiocarcinoma, multiple small stones that were visualized on Endoscopic Retrograde Cholangiopancreatography and also developed cholangitis.

#### **MB102054-24-498**

This was a 63 year old Chinese male past medical history of cholecystitis without cholecystectomy. On study day 28, he experienced fever and anorexia, but no abdominal pain. No treatment was required and no action was taken with regard to the study medication. The subject's liver function tests were monitored and improved spontaneously. Viral hepatitis, autoimmune hepatitis and hemochromatosis were ruled out.

#### ***Reviewer's Comments***

These cases are currently being reviewed by hepatic experts at OSE and additional information of the applicant has been requested. Final recommendations to date are available in a separate OSE review. However, only case D1690C00018-201-8 does not have a clear explanation for biochemical Hy's Law making it a candidate for a Hy's Law case. This patient begins to have resolution when study drug is discontinued but then again experiences unexplained elevations off the study drug. In addition, alkaline phosphatase was slightly elevated at baseline and increased tremendously at the peak of other enzymes. Typically, per *Guidance for Industry*



***Drug-Induced Liver Injury* this is not substantially elevated. This case is unlikely to be a DILI case. OSE agrees with this classification.**

### **Cancer Update**

Please see Dr. Christian Hampp's review for a full discussion of bladder and breast cancer.

Overall in the full July cutoff database, there was no difference in the overall rate of all cancers, see the first row of Table 18. PTs that occurred at a higher rate in dapagliflozin treated patients by at least 0.1% are also displayed here. Bladder cancer is not included here because the PTs varied by cancer classification.

**Table 18 Cancer Rate at the July Cutoff**

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 5501					ALL CONTROL N = 3184				
	Subjects with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Subjects with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
SUBJECTS WITH EVENTS	81 (1.47)	(1.17, 1.83)	5837.95	1.39	(1.10, 1.72)	43 (1.35)	(0.98, 1.81)	3197.57	1.34	(0.97, 1.81)
BREAST CANCER	10 (0.40)					2 (0.15)				
PROSTATE CANCER	8 (0.27)					3 (0.16)				

Source Modified from Response to Inquiry, Cancer 10/27/11, Attachment Q2&3.1.3

My own search for cancer PTs in the database from studies 18 and 19 did not reveal any new cancer signals or imbalances, with the exception of more cases in the dapagliflozin treated patients of lung cancer. See Table 19.

**Table 19 Neoplasms and Cancers in Studies 18 and 19 Database**

Neoplasm	Dapagliflozin # events (%)	Placebo # events (%)
N	935	941
Benign salivary gland neoplasm	1(0.1)	0
Bladder cancer	0	1(0.1)
Breast cancer	1(0.1)	2 (0.2)
Colon cancer	0	1(0.1)
Colon neoplasm	0	1(0.1)
Hepatic neoplasm malignant	0	1(0.1)
Lung neoplasm malignant	3(0.3)	0
Neoplasm skin	1(0.1)	1(0.1)
Prostate cancer	1(0.1)	1(0.1)
Renal neoplasm	1(0.1)	0
Thyroid neoplasm	1(0.1)	1(0.1)

The cancer update submitted in October reveals the following lung neoplasms at the time of July cutoff. See Table 20.

**Table 20 Lung Neoplasms at the July Cutoff**

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 5501					ALL CONTROL N = 3184				
	Subjects with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Subjects with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
LUNG NEOPLASM MALIGNANT	5 (0.09)					1 (0.03)				
LUNG NEOPLASM	2 (0.04)					3 (0.09)				

Source Modified from Response to Inquiry, Cancer 10/27/11, Attachment Q2&3.1.3

## Bladder Cancer

All bladder cancer cases discussed in the updated cancer data from the applicant was discussed in my initial NDA review, including the one case noted in Table 19. There have been no additional cases not discussed.

With updated exposure, Dr. Hampp calculated exposure in male patients randomized to dapagliflozin at 3165.8 subject-years. The number of cases can be extrapolated to 284.3 (95% CI, 129.7 – 539.7) new cases per 100,000 subject-years. This compares to one case during 1854.4 subject-years in controls, or 53.9 (95% CI, 0.7 – 300.0) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of bladder cancer between active treatment and controls was: 5.38 (95% CI, 0.84 – 122.2), with a two-sided *p*-value of 0.185.

## Breast Cancer

There were three cases not discussed in my initial NDA review that were submitted with the cancer update in October 2011. These three cases are described in Table 21. Only one of these cases was a dapagliflozin treated patient. These cases are similar to that described in the initial review as all occurred within the first year of treatment and all were in women that were over the age of 50.

**Table 21 New Breast Cancer Patients at the July Cutoff**

Study and Subject ID/ Age at randomization/ Sex/Race	Treatment	Preferred Term	Diagnosis Study Day	Histology	BMI	Weight change	Risk factors and relevant medical history
12 D1690C00018-7841-5 60/Female/Asian	Comparator	Breast cancer	252	Histological type: Infiltrating ductal breast cancer TNM classification: PT1c, pN0, M0 Grade 1-2 ER status: positive, 100%, PR status: positive, 70%, HER2/neu status: negative Second / Secondary: N/A	39.9	-2.5	Overweight, postmenopausal

6	D1690C00018-7894-1 59/Female/White	Dapa 10 mg + insulin + metformin	Breast cancer	231	Histological type: Invasive, ductal carcinoma TNM classification: T2 pN3 MX Grade: 2 ER status: positive, PR status: positive, HER2/neu status: negative Second / Secondary: N/A	39.2	-1.9	Overweight, postmenopausal
13	D1690C00019-7833-2 61/Female/Not Available	Comparator	Breast cancer	347	Histological type: Ductal carcinoma in situ TNM classification: N/A (Tis) Grade: 1 ER status: positive, PR status: positive, HER2/neu status: N/A Second / Secondary: N/A	48.5	-3.1	Overweight, postmenopausal and breast biopsy in the past

Source Modified from Response to Inquiry, Cancer 10/27/11, Table 2

In my original NDA review, Dr. Ju, epidemiologist from OSE had calculated that in the dapagliflozin arm the exposure of 2416 subject-years in female patients could be extrapolated to 372 cases per 100,000 subject-years (95% CI, 170-707). Exposure in the control was 1085 subject-years for females. This was extrapolated to 92 cases per 100,000 subject-years (95% CI, 23-5138). In total, with these additional cases, breast cancer was reported in 13 female subjects (10 of 2531 total female dapagliflozin-treated subjects and 3 of 1359 total female control subjects). The proportion of female dapagliflozin-treated subjects with breast cancer versus control is 0.40% and 0.22%, respectively. The incidence rate is 370 events per 100,000 female subject-years for dapagliflozin-treated subjects and 220 events per 100,000 female subject-years for control, based on a cumulative follow-up time of 2702 female subject-years for dapagliflozin and 1362 female subject-years for control. Since the number of cases in control has increased, the incidence rate has become closer between the two treatment groups. Dr. Hampp calculated an adjusted rate ratio comparing the incidence of breast cancer between active treatment and controls at 1.90 (95% CI, 0.52 – 8.93), with a two-sided *p*-value of 0.374.

Case D1690C00019-7322-2 in the control group has ductal carcinoma in situ. This is a questionable diagnosis in terms of malignancy. Therefore, Dr. Hampp conducted calculations excluding this case. If this case is excluded, this reduces cases in controls to two cases during 1361.6 subject-years of exposure, or 146.9 (95% CI, 16.5 – 530.3) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of breast cancer between active treatment and controls was 2.76 (95% CI, 0.64 – 19.21), with a two-sided *p*-value of 0.242.

#### ***Reviewer's Comments***

**The predicted incidence of breast cancer has essentially remained the same for dapagliflozin treated patients with this data. However, the predicted incidence has increase from 92 cases per 100,000 female subject years to 220 in controls if we count the in situ case.**

**Overall, the updated cancer data remains the same or changed slightly in favor of dapagliflozin.**

## **Lipids**

### **Study 18**

Compared to placebo, subjects in the dapagliflozin group showed a slight mean percent increase to 24 weeks (dapagliflozin vs. placebo):

- total cholesterol (5.0% vs. 1.2%)
- low-density lipoprotein cholesterol (4.6% vs. -2.0%)
- high-density lipoprotein cholesterol (5.2% vs. 2.9%)
- fasting free fatty acids (9.7% vs. 3.0%)

The nominal p-value for the difference between treatment groups was <0.05 for the four lipids.

### **Study 19**

Similar results were seen in study 19, with a smaller difference with LDL.

- total cholesterol (3.6% vs. 2.4%)
- low-density lipoprotein cholesterol (3.4% vs. 3.7%)
- high-density lipoprotein cholesterol (6.8% vs. 4.7%)
- fasting free fatty acids (11.5% vs. -0.3%)

The nominal p-value for the difference between treatment groups was <0.05 for the difference regarding high-density lipoprotein and free fatty acids.

While these changes in cholesterol are small and clinical relevance is questionable, they were also seen in the larger NDA data submitted at the beginning of the review cycle.

### **Lipid Changes From the NDA Safety Summary with original submission:**

During the short-term period, the mean percent change from baseline at a range of dapagliflozin doses to week 24:

- HDL-C: 3.8 to 6.5% in the dapagliflozin groups and 3.8% in the placebo group
- LDL-C: 0.6% to 2.7% in the dapagliflozin groups and -1.9% in the placebo group
- Total cholesterol: 1.0% to 1.4% for the dapagliflozin groups and -0.4% in the placebo group
- Triglycerides: -3.2% to -5.4% for the dapagliflozin groups and -0.7% in the placebo group

- Free fatty acids (fasting): -0.5% to 1.2% in the dapagliflozin groups and -5.7% in placebo

During short-term plus long-term treatment, the mean percent change from baseline to Week 102:

- HDL-C: 9.1% to 9.9% in the dapagliflozin groups and 7.0% in the placebo group
- LDL-C: 1.5% to 5.3% in the dapagliflozin groups and -1.1% in the placebo group
- Total cholesterol: 2.7% to 3.2% for the dapagliflozin groups and -1.0% in the placebo group
- Triglycerides: -3.3% to -8.3% for the dapagliflozin groups -10.0% in the placebo group
- Free fatty acids (fasting): -10.7% to -14.7% in the dapagliflozin groups and -17.5% in the placebo group

These changes are small and have a questionable clinical significance; however, they remain consistent through the long term treatment and are again reported with studies 18 and 19 in patients with elevated cardiovascular risk at baseline. As elevated cholesterol is a known cardiovascular risk, these changes are worth noting. Similar changes are seen with other drugs that could contribute increase cardiovascular risk, although these changes are higher and therefore presumably more clinically significant. For example, rosiglitazone lipid changes reported in labeling are as follows:

**Table 22 Lipid Changes in Rosiglitazone**

	Placebo-Controlled Trials Week 26			Glyburide-Controlled Trial Week 26 and Week 52			
	Placebo	AVANDIA		Glyburide Titration		AVANDIA 8 mg	
		4 mg daily <sup>a</sup>	8 mg daily <sup>a</sup>	Wk 26	Wk 52	Wk 26	Wk 52
<b>Free fatty acids</b>							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
<b>LDL</b>							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
<b>HDL</b>							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

Source Avandia Approved Label

### ***Reviewer's Comments***

**I recommend lipid changes are closely followed and reported throughout the long term studies that are proposed by the applicant. With time, the clinical significance of these changes will become clearer. Changes in lipids are reported in proposed labeling.**

### **Other Adverse Events Discussed in the NDA**

Additional AEs of special interest to the NDA are discussed here.

### **Events of Hypovolemia**

Events of hypovolemia remain higher in the dapagliflozin treated patients. This is expected. The rates in this update are higher than those seen in the NDA (overall subjects with an event was 0.8% for dapagliflozin and 0.4% for control), see Table 23 and 24. The patients in these trials are at higher CV risk and most have hypertension and thus are more likely to be on antihypertensive treatment. However, only two of the 10 subjects in the dapagliflozin group and one of the two subjects in the placebo group were taking loop diuretics in study 18. One of the five subjects in the dapagliflozin group and two of the nine in the placebo group were taking loop diuretics in study 19.

**Table 23 Hypovolemia Related AEs Study 18**

Preferred Term (%)	PLA N = 462	DAPA 10MG N = 460
TOTAL SUBJECTS WITH AN EVENT	2 ( 0.4)	10 ( 2.2)
HYPOTENSION	1 ( 0.2)	7 ( 1.5)
DEHYDRATION	0	1 ( 0.2)
ORTHOSTATIC HYPOTENSION	1 ( 0.2)	1 ( 0.2)
SYNCOPE	0	1 ( 0.2)

Source CSR Table 33

**Table 24 Hypovolemia Related AEs Study 19**

Preferred Term (%)	PLA N = 483	DAPA 10MG N = 482
TOTAL SUBJECTS WITH AN EVENT	9 ( 1.9)	5 ( 1.0)
SYNCOPE	2 ( 0.4)	3 ( 0.6)
BLOOD PRESSURE DECREASED	0	1 ( 0.2)
HYPOTENSION	2 ( 0.4)	1 ( 0.2)
CIRCULATORY COLLAPSE	1 ( 0.2)	0
ORTHOSTATIC HYPOTENSION	4 ( 0.8)	0

Source CSR Table 32

Of note, in my search of the databases for studies 18 and 19, I also found a higher rate of dizziness in the dapagliflozin treated patients:

**Table 25 Dizziness in Studies 18 and 19**

Event	Dapagliflozin Events (%)	Placebo Events (%)
N	935	941
Dizziness	59 (6.3)	29 (3.1)

The PT dizziness could be due to several causes; hypovolemia is only one potential cause.

The applicant performed an analysis of patients with events related to volume depletion in the subgroups of patients on loop diuretics, ≥65 years of age, and patients with renal impairment. They show that the rates were similar in studies 18 and 19 as opposed to those seen in the NDA database, see Table 26.

**Table 26 AEs of Volume Depletion in NDA and Studies 18 and 19 in subsets of Patients on Loop Diuretics and ≥65 Years of Age**

	<u>Original NDA submission</u>			<u>Studies 18 and 19</u>	
	<u>TRADENAME 5 mg</u>	<u>TRADENAME 10 mg</u>	<u>Placebo</u>	<u>TRADENAME 10 mg</u>	<u>Placebo</u>
<u>Patient Subgroup n (%)</u>					
<u>Patients on loop diuretics</u>	<u>N=40*</u> <u>0</u>	<u>N=31*</u> <u>3 (9.7)</u>	<u>N=55*</u> <u>1 (1.8)</u>	<u>N=182</u> <u>3 (1.6%)</u>	<u>N=182</u> <u>3 (1.6%)</u>
<u>Patients ≥65 years of age</u>	<u>N=216*</u> <u>1 (0.5)</u>	<u>N=204*</u> <u>3 (1.5)</u>	<u>N=276*</u> <u>1 (0.4)</u>	<u>N=423</u> <u>6 (1.4%)</u>	<u>N=423</u> <u>5 (1.2%)</u>
<u>Patients with moderate renal impairment with eGFR ≥45 to &lt;60 mL/min/1.73 m<sup>2</sup></u>	<u>N=128<sup>†</sup></u> <u>3 (2.3%)</u>	<u>N=107<sup>†</sup></u> <u>5 (4.7%)</u>	<u>N=138<sup>†</sup></u> <u>2 (1.4%)</u>		

\* Placebo-controlled pool (Total pool: N=1145, TRADENAME 5 mg, N=1193, TRADENAME 10 mg, and N=1393, placebo).

† Placebo-controlled pool plus the dedicated study of patients with moderate renal impairment (≥45 to <60 mL/min/1.73 m<sup>2</sup>).

(b) (6)

### Reviewer's Comments

Hypovolemic event rates are higher in studies 18 and 19 than in the entire initial NDA database; however, the rates are also higher in placebo than had been seen in the NDA. The overall rate in study 19 is higher in the placebo group.

(b) (4)

The table is a clear, succinct way to display the important findings in the specific populations. However, the overall rate of events discussed from the NDA database is more important than the findings from these two studies. Clearly, dapagliflozin has a mechanistic reason for these events.

## Hematology and Hemoconcentration AEs

For both studies, subjects in the dapagliflozin group showed a slight increase in mean values of hemoglobin and hematocrit as expected to week 16. After this, values leveled off.

Study 18: mean change from baseline to week 24 in hemoglobin: 0.70 g/dL, hematocrit: 2.46%

Study 19: mean change from baseline to week 24 in hemoglobin: 0.66 g/dL, hematocrit: 2.44%

In the placebo groups, mean values of hemoglobin and hematocrit did not show a meaningful change during the 24-week short-term double-blind treatment period.

The rate of AEs related to hemoconcentration did not show an appreciable difference between groups of patients see Table 27.

**Table 27 Hemoconcentration Related AEs**

<b>Event</b>	<b>Dapagliflozin # Events (%)</b>	<b>Placebo # Events (%)</b>
N	935	941
Total	6 (0.6)	5 (0.5)
Deep venous thrombosis	2 (0.2)	1 (0.1)
Pulmonary embolism	1 (0.1)	2 (0.2)
Renal vein thrombosis	1 (0.1)	0
Thrombocytosis	1 (0.1)	0
Thrombosis	0	1 (0.1)
Retinal Vascular/Vein Thrombosis	1 (0.1)	1 (0.1)

## Urinary Tract Infection (UTI)

Pyelonephritis remained a rare event with one case in each treatment group. UTI, as a PT, remained higher in the dapagliflozin treated patients as seen in study 19:

Study 18: dapagliflozin group 12 patients (2.6%) and placebo 12 patients (2.6%)

Study 19: dapagliflozin group 27 patients (5.6%) and placebo 18 patients (3.7%)

Original NDA data had a rate of 4% in dapagliflozin treated patients and 2.7% in control.

## Genital Infections

The rate of genital infection in studies 18 and 19 in dapagliflozin treated patients was very similar to that seen in the original NDA (6.8% vs. 2.1% in control).



**Table 28 Events of Genital Infection Study 18**

Preferred Term (%)	PLA N = 462	DAPA 10MG N = 460
TOTAL SUBJECTS WITH AN EVENT	5 ( 1.1)	30 ( 6.5)

Source Modified from CSR Table 28

**Table 29 Events of Genital Infections Study 19**

Preferred Term (%)	PLA N = 483	DAPA 10MG N = 482
TOTAL SUBJECTS WITH AN EVENT	2 ( 0.4)	33 ( 6.8)

Source Modified from CSR Table 28

## Hypoglycemia

The rates of hypoglycemia are higher in these studies than in the NDA. In the short term placebo controlled pool this was 11.8% in dapagliflozin treated patients and 7% in controls. However, insulin and sulfonylureas were allowed in this study. The add on insulin study in the NDA had a very high rate of hypoglycemia at 42.3% in dapagliflozin treated patients (35% in control). Furthermore, the rates between the two treatment groups for these new studies were comparable:

Study 18      19.3% in dapagliflozin treated patients vs. 18.2% in control  
Study 19      21% vs. 17.4%.

## Cardiovascular Meta-analysis Update

Please refer to Dr. Anita Abraham's amendment review for more details.

The meta-analysis study population included 8682 subjects: 5498 in the dapagliflozin group and 3184 in the comparator group. The total years of exposure for the composite endpoint of CV death, MI and stroke (MACE) was 5749 in the dapagliflozin group and 3100 in the comparator group.

The added exposure in ongoing studies in the applicant's update of the CV events meta-analysis compared to the 4MSU exposure is listed in Table 30. Studies MB102035, D1690C00010, D1690C00018 and D1690C00019 are all new to the updated analysis.

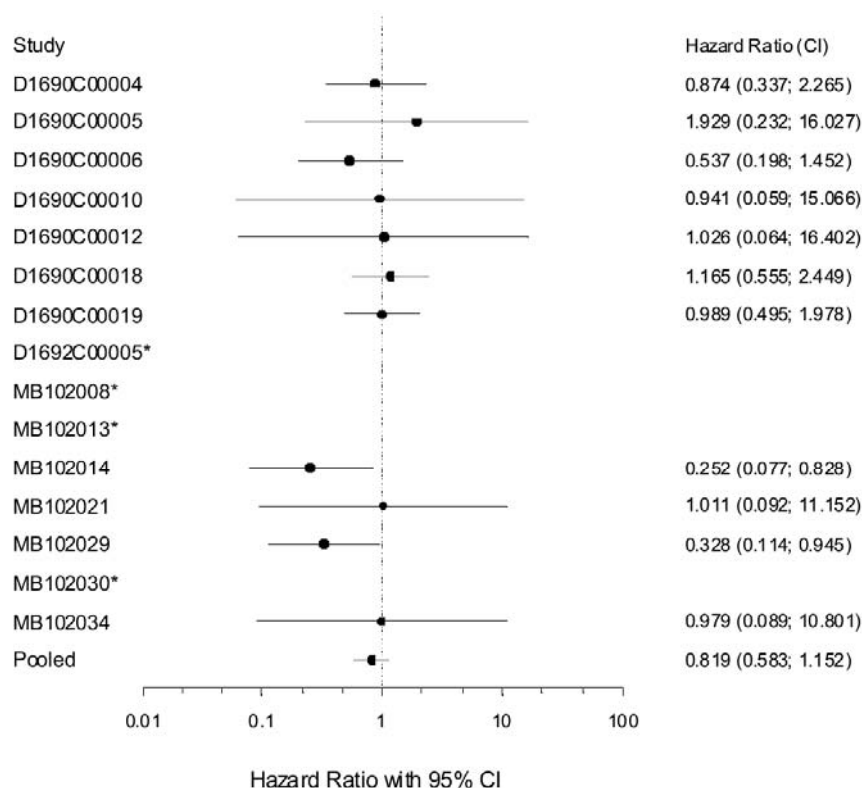
**Table 30 Ongoing Studies Added Exposure**

Study ID	Added exposure for the updated CV events meta-analysis report compared to the 4MSU report (subject years)	
	Dapagliflozin	Comparator
D1690C00004	152	139
D1690C00006	58	17
D1690C00012	53	54
MB102029	36	15

\* Exposure presented with respect to the primary endpoint.

With the updated exposure and studies, the hazard ratio versus comparator was 0.819 (95% CI: 0.583, **1.152** and 98% CI (0.547, 1.228)). The event rate (subjects with events/1000 subject years) was 14.6 in the dapagliflozin group and 20.8 in the comparator group. A forest plot depicting the hazard ratio for the individual studies and the overall stratified analysis is depicted in Figure 2.

**Figure 2 Forest Plot of HR and CI from Cox Proportional Hazards Models - Primary CV composite Endpoint**



PH = Proportional Hazards, CV = Cardiovascular, ST = Short -Term, LT = Long -Term, CI = Confidence Interval

\* - Studies with events in only one arm and estimated values out of range.

Studies MB102009, MB102032, MB102035 and MB102045 do not have at least one positively adjudicated event, hence excluded from analysis.

Source Updated CV Meta-analysis report Figure 2

The upper bound of the 98% CI is higher here than what was calculated in my NDA review (1.178). This analysis includes studies 18 and 19 which were conducted in high risk CV patients. The analysis from these studies alone, see Table 31, shows that the incidence rates are quite similar in both studies. This accounts for the higher upper bound CI in the updated analysis.

**Table 31 Summary of Primary CV composite Endpoint using Cox Proportional Overall Stratified Analysis D1690C00018 and D1690C00019 only**

	Dapagliflozin (a)	Comparator (b)
Number of Subjects With at Least One Events	31	29
Number of Subjects in Treatment Group	939	945
Total Subject-Years at Risk	706	706
Subjects with Events/1000 Subject-Year	43.89	41.06
Hazard Ratio Versus Comparator		
Estimate	1.068	
95% CI (c)	(0.643 , 1.772)	

Source Updated CV Meta-analysis report Table 19

#### ***Reviewer's Comments***

**The dedicated cardiovascular study is still being planned and will be required, if dapagliflozin is approved. Interestingly, while rates of events looked better in the original submission in dapagliflozin treated patients, the rate of events between treatment groups is similar in the new high risk CV studies, 18 and 19. The results of the dedicated CV outcomes trial will show if this trend continues into long term treatment.**

#### **Safety in Patients ≥65 years**

There were few patients in this age group in the initial NDA submission and this point was brought up at the advisory committee meeting (AC). However, efficacy regarding this population is addressed in the new studies discussed above, 18 and 19. The applicant also submitted an analysis regarding safety in this population shortly after the AC. Table 32 summarizes AE findings in patients in this subgroup. These results were similar to those seen in the overall population in the short term Placebo- controlled Pool. There, the number of patients with at least one AE was 56.9% in the placebo group and 60.6%, 61.9%, and 61.5% in the dapagliflozin 2.5, 5 and 10 mg groups, respectively.

**Table 32 AEs in Patients ≥65 Years of Age from the Initial NDA Safety Database**

CATEGORIES	PLA N = 276	DAPA 2.5MG N = 193	DAPA 5MG N = 216	DAPA 10MG N = 204	DAPA TOTAL N = 631
AT LEAST ONE ADVERSE EVENT	154 (55.8)	118 (61.1)	138 (63.9)	123 (60.3)	392 (62.1)
AT LEAST ONE HYPOGLYCEMIA	29 (10.5)	37 (19.2)	28 (13.0)	30 (14.7)	96 (15.2)
AT LEAST ONE AE OR HYPOGLYCEMIA	160 (58.0)	129 (66.8)	145 (67.1)	131 (64.2)	418 (66.2)
AT LEAST ONE RELATED ADVERSE EVENT	33 (12.0)	40 (20.7)	35 (16.2)	38 (18.6)	116 (18.4)
DEATHS	1 (0.4)	0	0	1 (0.5)	1 (0.2)
AT LEAST ONE SAE	15 (5.4)	17 (8.8)	16 (7.4)	16 (7.8)	50 (7.9)
AT LEAST ONE RELATED SAE	1 (0.4)	0	1 (0.5)	1 (0.5)	2 (0.3)
SAE LEADING TO DISC. OF STUDY MED.	5 (1.8)	4 (2.1)	4 (1.9)	1 (0.5)	9 (1.4)
AE LEADING TO DISC. OF STUDY MED.	8 (2.9)	8 (4.1)	11 (5.1)	11 (5.4)	30 (4.8)
HYPOGLYCEMIA LEADING TO DISC. OF STUDY MED.	0	0	0	0	0

Source AC Responses Sept 6 Item 10 Table 2

Newly submitted studies 18 and 19 had more patients in ≥65 Years of Age category with almost half of the subjects in this age category, compared to the proportion of subjects in this age range in the original NDA. AE rates are similar between study groups and controls, see Tables 33 and 34. For study 18, related AEs and AEs leading to discontinuation were higher in dapagliflozin treated patients. For study 19, related AEs rates were again quite different. However, evaluating AEs on the PT level did not reveal clinically significant differences. Events occurring at a notably higher rate in dapagliflozin treated patients were (control vs. dapagliflozin):

**Study 18**

Creatinine Renal Clearance Decreased	6 (3.0) vs. 10 (5.2)
Dizziness	4 (2.0) vs. 12 (6.2)
Pollakuria	2 (1.0) vs. 9 (4.6)
Hyperhidrosis	1 (0.5) vs. 5 (2.6)

None were noted in study 19.

**Table 33 Summary of AEs in Subjects ≥65 Years of Age Study 18**

STRATUM: AGE ≥ 65 YEARS	Number (Percent) of Subjects		
	PLA N = 198	DAPA 10MG N = 194	Total N = 392
AT LEAST ONE ADVERSE EVENT	117 (59.1)	116 (59.8)	233 (59.4)
AT LEAST ONE HYPOGLYCEMIA	45 (22.7)	39 (20.1)	84 (21.4)
AT LEAST ONE AE OR HYPOGLYCEMIA	131 (66.2)	128 (66.0)	259 (66.1)
AT LEAST ONE RELATED ADVERSE EVENT	22 (11.1)	46 (23.7)	68 (17.3)
DEATHS	0	1 (0.5)	1 (0.3)
AT LEAST ONE SAE	10 (5.1)	9 (4.6)	19 (4.8)
AT LEAST ONE RELATED SAE	1 (0.5)	0	1 (0.3)
SAE LEADING TO DISC. OF STUDY MED.	2 (1.0)	0	2 (0.5)
AE LEADING TO DISC. OF STUDY MED.	11 (5.6)	20 (10.3)	31 (7.9)
HYPOGLYCEMIA LEADING TO DISC. OF STUDY MED.	0	0	0

Source CSR Modified from Table 11.3.2.1.2

**Table 34 Summary of AEs in Subjects ≥65 Years of Age Study 19**

STRATUM: AGE < 65 YEARS	Number (Percent) of Subjects		
	PIA N = 258	DAPA 10MG N = 253	Total N = 511
AT LEAST ONE ADVERSE EVENT	138 (53.5)	144 (56.9)	282 (55.2)
AT LEAST ONE HYPOGLYCEMIA	55 (21.3)	60 (23.7)	115 (22.5)
AT LEAST ONE AE OR HYPOGLYCEMIA	157 (60.9)	169 (66.8)	326 (63.8)
AT LEAST ONE RELATED ADVERSE EVENT	19 (7.4)	43 (17.0)	62 (12.1)
DEATHS	1 (0.4)	1 (0.4)	2 (0.4)
AT LEAST ONE SAE	17 (6.6)	18 (7.1)	35 (6.8)
AT LEAST ONE RELATED SAE	0	0	0
SAE LEADING TO DISC. OF STUDY MED.	3 (1.2)	0	3 (0.6)
AE LEADING TO DISC. OF STUDY MED.	6 (2.3)	6 (2.4)	12 (2.3)
HYPOGLYCEMIA LEADING TO DISC. OF STUDY MED.	0	0	0

Source CSR Modified from Table 11.3.2.1.2

### ***Reviewer's Comments***

**These AE data in older patients provide some reassurance of dapagliflozin safety in this age group. However, there were only 6.5% of patients in age group over 75 years of age in study 18 and only 7.7% in study 19. Subjects in this age group are limited likely due to the nature of T2DM and renal disease/renal impairment exclusionary criterion. The low rate of patients in this age group is comparable to that seen in other antidiabetic NDAs. The long term CV outcomes study will enable a larger database of elderly patients for safety analyses.**

### ***Efficacy and Albuminuria***

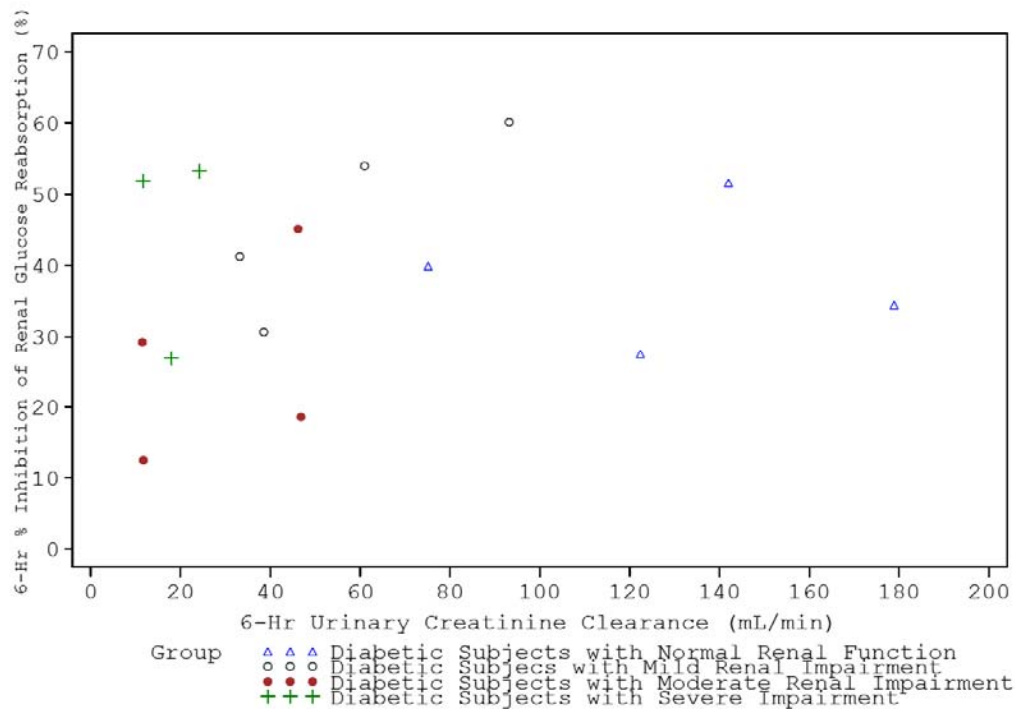
#### **Proteinuria and Dapagliflozin**

At the Advisory Committee Meeting, Dr. Kevin McBryde (Pediatric Nephrologist) questioned the potential effect of proteinuria on dapagliflozin's pharmacologic effect since dapagliflozin is largely protein bound and has a renal mechanism of action. A related question was raised as to whether dapagliflozin was evaluated for efficacy in proteinuric rats. The applicant was asked to provide an analysis addressing these issues.

In the rat data submitted by the applicant (mean total urinary protein up to 201 mg/day in males and up to 48 mg/day in females in the 6-month study) dapagliflozin still induced glucosuria. In this same 6-month rat toxicity study, dapagliflozin produced increases in total urinary glucose in rats at all doses (5, 25, and 150 mg/kg). Dapagliflozin has higher protein binding in rats compared to humans; this suggests that protein binding most likely does not influence dapagliflozin's inhibition of renal glucose reabsorption.

The applicant also presented data from study MB102007, a clinical pharmacology study in patients with renal impairment. The percent inhibition of glucose reabsorption by dapagliflozin takes into account the filtered load (glomerular filtration rate [GFR]  $\times$  plasma glucose concentration) and the amount of glucose excreted into the urine. The relationship between the 0 to 6 hour post-dose % inhibition of glucose reabsorption by dapagliflozin and urinary protein amount in patients with proteinuria is shown in Figure 3 (one outlier is removed for clarity). As seen in the figure, the amount of protein in urine had no relationship to the effect of dapagliflozin on renal glucose clearance as measured by the endpoint of % inhibition of glucose reabsorption on patients with chronic kidney disease (CKD) and T2DM.

**Figure 3 Plot of Individual 6-Hour % Inhibition of Renal Glucose Reabsorption versus 6-Hour Urinary Protein Amount by Group (Day 10) in Study MB102007 (For Clarity, Only Observations with 6-Hour Urinary Protein Amount < 1000 mg are Shown)**



Source Response to Inquiry 8/5/11 Figure 1.2.2c

### **HbA1c by Baseline Albuminuria Status**

The applicant was asked to provide HbA1c results by baseline albuminuria status. In the post-hoc exploratory analysis, the database was divided into subgroups by the three baseline albuminuria categories. Approximately 20% of subjects were microalbuminuric

and < 3% had macroalbuminuria. The mean baseline HbA1c values were between 8.3 and 8.7% for placebo and between 8.1 and 8.6 % for the dapagliflozin arms.

The placebo-subtracted adjusted HbA1c mean changes from baseline at week 24 (LOCF) in HbA1c by albuminuria baseline category with corresponding 95% confidence intervals for the 10 mg dapagliflozin groups were (Table 35):

- Normoalbuminuria: -0.6 % (-0.7%, -0.5%)
- Microalbuminuria: -0.6 % (-0.8%, -0.5%)
- Macroalbuminuria: -0.7 % (-1.1%, -0.2%)

**Table 35 HbA1c (%) Adjusted Mean Change from Baseline at Week 24 (LOCF) by Urine Albumin to Creatinine Ratio Pooled Monotherapy/Combination Therapy Group Randomized Subjects Full Analysis Set**

SUBGROUP STATISTIC	POOLED PLACEBO N=1257	POOLED DAPA 2.5 MG N=699	POOLED DAPA 5 MG N=1025	POOLED DAPA 10 MG N=1066
P-VALUE (*): 0.9182				
Urine Albumin /Creatinine Ratio < 30 mg/g				
N#	936	522	754	801
BASELINE MEAN (SD)	8.33 ( 1.126)	8.14 ( 0.880)	8.36 ( 1.106)	8.26 ( 1.068)
WEEK 24 MEAN (SD)	7.72 ( 1.297)	7.43 ( 0.939)	7.33 ( 0.999)	7.20 ( 0.915)
MEAN CHANGE FROM BASELINE (SD)	-0.61 ( 1.195)	-0.71 ( 0.841)	-1.03 ( 1.156)	-1.06 ( 0.996)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.50 ( 0.0352)	-0.95 ( 0.0458)	-1.03 ( 0.0391)	-1.08 ( 0.0379)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[ -0.57, -0.43]	[ -1.04, -0.86]	[ -1.10, -0.95]	[ -1.15, -1.00]
DIFFERENCE VS PLACEBO (SE)		-0.45 ( 0.0517)	-0.52 ( 0.0451)	-0.57 ( 0.0441)
95% CI OF DIFFERENCE VS PLACEBO		[ -0.55, -0.35]	[ -0.61, -0.43]	[ -0.66, -0.49]
Urine Albumin /Creatinine Ratio >= 30 AND < 300 mg/g				
N#	261	149	206	215
BASELINE MEAN (SD)	8.66 ( 1.264)	8.21 ( 0.893)	8.62 ( 1.106)	8.48 ( 1.122)
WEEK 24 MEAN (SD)	8.01 ( 1.314)	7.58 ( 1.038)	7.57 ( 1.010)	7.42 ( 1.077)
MEAN CHANGE FROM BASELINE (SD)	-0.65 ( 1.271)	-0.63 ( 0.866)	-1.05 ( 1.144)	-1.06 ( 1.092)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.42 ( 0.0590)	-0.87 ( 0.0771)	-0.98 ( 0.0662)	-1.03 ( 0.0647)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[ -0.53, -0.30]	[ -1.02, -0.71]	[ -1.11, -0.85]	[ -1.16, -0.91]
DIFFERENCE VS PLACEBO (SE)		-0.45 ( 0.0931)	-0.57 ( 0.0839)	-0.62 ( 0.0829)
95% CI OF DIFFERENCE VS PLACEBO		[ -0.63, -0.27]	[ -0.73, -0.40]	[ -0.78, -0.46]
Urine Albumin /Creatinine Ratio >= 300 mg/g				
N#	35	14	39	25
BASELINE MEAN (SD)	8.40 ( 1.296)	8.19 ( 0.779)	8.46 ( 0.835)	8.26 ( 0.957)
WEEK 24 MEAN (SD)	8.20 ( 1.206)	7.85 ( 1.085)	7.89 ( 1.156)	7.56 ( 0.918)
MEAN CHANGE FROM BASELINE (SD)	-0.20 ( 0.992)	-0.34 ( 1.094)	-0.56 ( 0.950)	-0.70 ( 0.964)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.14 ( 0.1528)	-0.59 ( 0.2403)	-0.54 ( 0.1448)	-0.80 ( 0.1806)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[ -0.44, 0.16]	[ -1.06, -0.12]	[ -0.83, -0.26]	[ -1.16, -0.45]
DIFFERENCE VS PLACEBO (SE)		-0.45 ( 0.2829)	-0.40 ( 0.2082)	-0.66 ( 0.2340)
95% CI OF DIFFERENCE VS PLACEBO		[ -1.00, 0.11]	[ -0.81, 0.01]	[ -1.12, -0.20]

Source Response to Inquiry 8/5/11 Table 1.3.3.2

The applicant also did an HbA1c analysis with by categories of normal, mildly and moderately impaired renal function and then by the three baseline albuminuria categories with the results seen in Table 36.

Renal Impairment categories were as follows:

- Normal: eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>
- Mildly impaired: eGFR  $\geq 60$  to  $< 90$  mL/min/1.73 m<sup>2</sup>
- Moderate: eGFR  $\geq 30$  to  $< 60$  mL/min/1.73 m<sup>2</sup>

Albuminuria categories were as follows:

- Normoalbuminuria 0 to  $< 30$  mg/g
- Microalbuminuria 30 to  $< 300$  mg/g
- Macroalbuminuria  $\geq 300$  mg/g

**Table 36 Placebo Adjusted HbA1c Results by Albuminuria in Patients Treated with 10 mg Dapagliflozin**

<b>Renal Impairment Category</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>
<b>Normoalbuminuria</b>	N=304 -0.64% (-0.79%, -0.50%)	N=442 -0.57% (-0.68%, -0.45%)	N=55 -0.28 % (-0.57%, 0.01%)
<b>Microalbuminuria</b>	N=86 -0.75% (-1.02%, -0.48%)	N=106 -0.47% (-0.70%, -0.24%)	N=23 -0.63 % (-1.08%, -0.17%)

Macroalbuminuria results are as follows:

#### *Normal Renal Function*

Macroalbuminuria: This category included only 14 placebo subjects and 5 dapagliflozin 10 mg subjects; therefore, only mean changes from baseline are provided for each treatment group (dapagliflozin -0.76 % vs. placebo +0.18%).

#### *Mild Renal Impairment*

Macroalbuminuria: This category included only 17 placebo subjects and 14 dapagliflozin 10 mg subjects; therefore, only mean changes from baseline are provided for each treatment group (dapagliflozin -0.99% vs. placebo -0.64%).

#### *Moderate Renal Impairment*

Macroalbuminuria: This category included only 4 placebo subjects and 6 dapagliflozin 10 mg subjects; therefore, only mean changes from baseline are provided for each treatment group (dapagliflozin 10 mg 0.02% vs. placebo 0.35%).



Group sizes for the moderate category are very small with wide CI, therefore conclusions are difficult to reach. However, overall, there is no evidence of differing dapagliflozin effect on albuminuria status in the renal impairment categories.

### *Moderate Renal Impairment Study*

Subgroups sizes and mean changes can be seen in Table 37.

**Table 37 HbA1c by Albuminuria in the Renal Impairment Study**

SUBGROUP STATISTICS	PLACEBO N=84	DAPA 5MG N=83	DAPA 10MG N=85
ALBUMINURIA SUBGROUP:    NORMOALBUMINURIA (0-<30 MG/G)			
N#	26	30	28
BASELINE MEAN (SD)	8.36 ( 1.260)	8.34 ( 1.107)	8.08 ( 0.875)
WEEK 24 MEAN (SD)	8.07 ( 1.285)	7.90 ( 1.189)	7.79 ( 0.854)
MEAN CHANGE FROM BASELINE (SD)	-0.30 ( 0.999)	-0.44 ( 0.994)	-0.29 ( 0.689)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.37 ( 0.2320)	-0.51 ( 0.2236)	-0.50 ( 0.2294)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[ -0.83,    0.09]	[ -0.95, -0.07]	[ -0.95, -0.04]
DIFFERENCE VS PLA (SE)		-0.14 ( 0.2505)	-0.13 ( 0.2547)
95% CI OF DIFFERENCE VS PLA		[ -0.63,    0.35]	[ -0.63,    0.37]
ALBUMINURIA SUBGROUP:    MICROALBUMINURIA (30-<300 MG/G)			
N#	33	23	34
BASELINE MEAN (SD)	8.49 ( 1.188)	8.10 ( 1.046)	8.13 ( 0.899)
WEEK 24 MEAN (SD)	8.22 ( 1.117)	7.97 ( 0.855)	7.98 ( 0.887)
MEAN CHANGE FROM BASELINE (SD)	-0.27 ( 0.990)	-0.13 ( 0.864)	-0.15 ( 0.747)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.28 ( 0.2104)	-0.30 ( 0.2429)	-0.30 ( 0.2059)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[ -0.70,    0.13]	[ -0.78,    0.18]	[ -0.70,    0.11]
DIFFERENCE VS PLA (SE)		-0.01 ( 0.2563)	-0.01 ( 0.2305)
95% CI OF DIFFERENCE VS PLA		[ -0.52,    0.49]	[ -0.47,    0.44]
ALBUMINURIA SUBGROUP:    MACROALBUMINURIA (>=300 MG/G)			
N#	23	30	20
BASELINE MEAN (SD)	8.79 ( 1.457)	8.40 ( 0.979)	8.56 ( 1.174)
WEEK 24 MEAN (SD)	8.26 ( 1.273)	8.04 ( 1.327)	7.91 ( 1.120)
MEAN CHANGE FROM BASELINE (SD)	-0.53 ( 1.800)	-0.36 ( 1.101)	-0.66 ( 1.143)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-0.38 ( 0.2413)	-0.43 ( 0.2139)	-0.65 ( 0.2552)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE			
DIFFERENCE VS PLA (SE)	[ -0.86,    0.09]	[ -0.85, -0.01]	[ -1.15, -0.14]
95% CI OF DIFFERENCE VS PLA		[ -0.04 ( 0.2631)	-0.26 ( 0.2872)
		[ -0.56,    0.47]	[ -0.83,    0.30]

Source Response to Inquiry 8/5/11 Table 1.3.3.2

Again, there is no evidence of differing dapagliflozin effect based on albuminuria status in the renal impairment categories.

### **Applicant Post Marketing Proposals**

Updated post marketing proposals were discussed in my initial NDA review. Further discussion has taken place regarding these proposals between the applicant and our agency. The applicant clarified that they plan to further assess liver injury, bladder cancer, breast cancer, and cancer risk overall among users of dapagliflozin by combining data from four sources.

- Data from ongoing clinical studies over the next 2 years for approximately 2700 additional patient-years of exposure and more than 900 patients with 2 or more years of treatment under controlled conditions
- Large, randomized CV outcomes study that will examine the risk of liver injury, cancers overall, breast cancer, and bladder cancer. A Data Monitoring Committee (DMC) will provide regular review of safety events throughout the study, which is planned for six years. Prospective independent blinded adjudication is planned for events of potential liver injury, potential breast cancer and potential bladder cancer.
- Spontaneously reported adverse events. For each case of liver injury, bladder cancer and breast cancer.
- Two large observational pharmacoepidemiology studies that will examine:
  - 1. The incidence and risk of acute liver failure; and
  - 2. Incidence and risk of cancer overall (currently defined as defined as prostate, female breast, lung/bronchus, endometrial, colon, non-Hodgkin lymphoma, pancreas, kidney/renal pelvis, rectal, and malignant melanoma), bladder cancer and breast cancer in patients who are new initiators of dapagliflozin versus new initiators of other anti-diabetic regimens.
  - The applicant proposes that these studies will assess the safety of dapagliflozin with existing healthcare databases in the United States and Europe. (b) (4)

The duration of these studies will be at least 5 years.

These plans were discussed at an October 2011 conference . FDA pointed out that market uptake is uncertain if dapagliflozin were to be approved. As a result, there are major concerns about the observational study's power, sample size, and study duration. The applicant agreed to involve FDA during the execution of the study to determine an appropriate minimum detectable hazard ratio based on the use of dapagliflozin post approval.

The duration of the pharmacoepidemiology cancer study was mutually understood to be dependent upon market uptake and the epidemiology study could take longer than the CV outcomes trial.

Changes proposed to the original risk management plan were further updated in detail and a new plan was submitted. Important changes and clarifications to the risk management plan proposed by the applicant include:

- Volume depletion analysis from ongoing clinical trials
- Increased hematocrit to be investigated in the CV outcomes study along with renal impairment, bone fracture and congestive heart failure
- There will be targeted questionnaires for ongoing studies for both breast and bladder cancer

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/s/  
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SOMYA VERMA  
11/21/2011

ILAN IRONY  
11/21/2011


I concur with Dr. Dunn's review and recommendation. Refer to the CDTL memo.

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 202293  
Priority or Standard Standard

Submit Date(s) 12/28/2010  
Received Date(s) 12/28/2010  
PDUFA Goal Date 10/28/2011  
Division / Office Division of Metabolism and  
Endocrinology Products/Office  
of New Drugs II

Reviewer Name(s) Somya V. Dunn  
Review Completion Date September 2, 2011

Established Name Dapagliflozin  
(Proposed) Trade Name  (b) (4)  
Therapeutic Class Sodium Glucose Transport  
(SGLT2) Inhibitor  
Applicant Bristol-Myers Squibb/Astra  
Zeneca

Formulation(s) Oral Tablet  
Dosing Regimen 5 mg 10 mg Tablets  
Indication(s) Treatment of Type 2 Diabetes  
Mellitus

Intended Population(s) Adults

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

Dapagliflozin is a sodium glucose co-transporter 2 inhibitor developed by Bristol-Myers Squibb and AstraZeneca. The applicant seeks the indication for dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed dose is 10 mg oral dose once daily with a 5 mg dose for patients at risk for volume depletion.

### 1.1 Recommendation on Regulatory Action

At this time, I cannot recommend approval for dapagliflozin for the proposed indication and therefore recommend a Complete Response action (if an action must be taken by the original NDA Prescription Drug User Fee (PDUFA) date). This is discussed below under section *1.2 Risk Benefit Assessment*. The applicant has decided to send additional information to be reviewed with the NDA. Once submitted, if this is considered a major amendment, this will extend the review cycle. This additional information may offer further insight into the risk benefit profile and could potentially change my recommendation to that of approval.

### 1.2 Risk Benefit Assessment

Dapagliflozin displayed modest efficacy in reducing HbA1c. There is evidence of weight loss with treatment and which is not a common finding in T2DM treatments. In addition, the cardiovascular safety meta-analysis showed that dapagliflozin does not cause increased risk of cardiovascular events in the general T2DM population. The applicant plans to pursue a study that shows benefit in a high cardiovascular risk population; however, there is no evidence of this at this time. They also plan to explore the effect on blood pressure; however, again this was not assessed as a primary endpoint in this NDA. When determining my recommendation for or against approval, I weighed the efficacy and potential benefits of dapagliflozin against the safety risks. A numeric imbalance in both breast and bladder cancer were found in the clinical program; not in favor of dapagliflozin. There was also a case of biochemical Hy's law that could be predictive of drug induced liver injury.

Dapagliflozin was studied in a large clinical program in a variety of settings in T2DM patients. It was studied as add-on to various approved T2DM therapies as well as in an active comparator setting with glipizide. The placebo-corrected efficacy for the 10 mg dose ranges from 0.5 to 0.6% decrease in HbA1c at 6 months. In the active comparator study as well as the initial combination studies (where dapagliflozin or metformin alone was compared to dapagliflozin plus metformin), efficacy was comparable to the active control. Dapagliflozin did not display efficacy in patients with moderate renal impairment, likely due to the renally dependent mechanism of action. Patients with severe renal impairment were not studied for this reason. The clinical program showed improvement in placebo-corrected fasting plasma glucose; this was studied as a



secondary endpoint in phase 3 studies, and mean decreases were around -25 mg/dL. As a novel therapy that induces glucosuria and subsequent loss of calories, dapagliflozin was found to cause weight loss. In 24-week studies, the placebo-corrected weight adjustment was around -1 to -2 kilograms. The body weight and composition study, D1690C00012, designed with weight loss as a primary endpoint, showed similar results at 24 weeks (placebo adjusted weight loss of 2.1 kg). Fifty-week data for this study were submitted too late in the review cycle to be evaluated in detail, but the weight loss appears sustained (2.3 kg). In addition, dapagliflozin exerts a diuretic effect and blood pressure effects were noted, although no study in the NDA was designed to evaluate this as a primary endpoint. The overall decrease in systolic pressure with the 10 mg dose was -4.4 mmHg and decrease in diastolic was -2.1 mmHg. The applicant is exploring these and other effects in more detail in their ongoing studies:

*D1690C00018: A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care*

*D1690C00019: A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycemic control on usual care.*

There are two independent primary objectives of equal weight in these studies:

- To assess the glycemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with CVD and hypertension, measured as the mean change in glycosylated hemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)
- To assess the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with CVD and hypertension at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as:
  - an absolute drop of 0.5% or more from baseline HbA1c, and
  - a relative drop of 3% or more from baseline for total body weight, and
  - an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure (SBP)

in the overall population and in the two predefined age subgroups

Data from these two studies were not submitted with the NDA but are forthcoming and may potentially extend the NDA review timeline as a major amendment if submitted before the PDUFA goal date.

The efficacy data and potential benefits of dapagliflozin must be considered in the context of the risks. The rate ratio for breast cancer was 4, and for bladder cancer it was 5. In other words, the risk is four fold for dapagliflozin treated female patients to be diagnosed with breast cancer, and five fold for male patients and bladder cancer. Dapagliflozin did not have preclinical signals for cancer and is not a carcinogenic; in addition, there is no clear mechanism for cause. However, the imbalance exists despite similar risk factors between the groups at baseline. Many of the cancer cases were diagnosed early in treatment. This was especially the case in the breast cancer cases, where all were diagnosed within a year of treatment initiation. This makes it even more difficult to form an association between treatment and cancer. However, until the risk is redefined with more data, this remains a concern. In addition, there is an increased chance of having urinary tract infection and candidal genital infections with dapagliflozin. These infections are likely linked to the increased glucose concentration in the genital region. They are not persistent in patients taking dapagliflozin. In addition, the urinary tract infections do not appear correlated with higher rates of pyelonephritis or other SAEs. Proper labeling and patient awareness of these infections would be adequate. Of particular concern when considering approval, however, is the one case of Hy's Law that was found in a dapagliflozin treated patient. If this is indeed liver toxicity due to dapagliflozin, many patients in the post market setting may suffer from this effect.

Dapagliflozin offers only modest efficacy in glycemic improvement. At this time, this is the only primary endpoint data that have been reviewed and submitted by the applicant in detail. While there may be benefit with blood pressure and weight loss, this remains a review issue in the future with additional data submission. Against this modest efficacy data are the risk signals detected. Most importantly, a potential for drug induced liver injury and increased risk of breast or bladder cancer. In light of the many other drugs that offer similar efficacy for T2DM treatment and the lack of solid support of significant supportive efficacy findings (weight loss, blood pressure effect or cardiovascular protection), I cannot recommend approval at this time.

The applicant has proposed to submit six month data from reports for D1690C000018 and D1690C000019. In addition to new efficacy information that involves cardiovascular benefit in a high risk group, they plan to send updated safety summary for the safety events of most concern (hepatic safety, overall cancers, breast cancer, and bladder cancer). This updated information could provide additional insight to the risk benefit profile. This will add an additional 900 patient years of exposure. We will have expert epidemiologists recalculate risk ratios for breast and bladder cancer. We will also revisit the potential for liver toxicity. At that time, the reviewer will make a recommendation for or against approval.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The applicant submitted the following pharmacovigilance plan, see Table 1.

**Table 1 Applicant's NDA Pharmacovigilance Plan**

Safety Concern	Planned Actions(s)
<b>Important Identified Risks</b>	
Genital Infection	Routine PV. Supplemental CRFs in ongoing Phase 3 clinical studies. Targeted questionnaires for serious spontaneous reports.
Urinary Tract Infections	Routine PV. Supplemental CRFs in ongoing Phase 3 clinical studies. Targeted questionnaires for serious spontaneous reports. Epidemiology program for characterization of emergency room visit or hospitalization due to severe complications of UTI. D1690C000019: Screening for asymptomatic bacteriuria in the ongoing study.
<b>Important Potential Risks</b>	
Hypoglycemia	Routine PV. Supplemental CRFs in ongoing Phase 3 clinical studies.
Volume Depletion	Routine PV.

Clinical Consequences of Increased Hematocrit	Routine PV. CV blinded adjudication in Phase 2b and 3 clinical studies. MB102035: Measured change in GFR over 12 weeks is being evaluated for dapagliflozin alone and in combination with hydrochlorothiazide. A sub-study of MB102035 will evaluate measured erythropoetin and plasma volume.
Renal Impairment/ Failure	Routine PV. Long term extension periods of study MB102029 (add-on to metformin in subjects with moderate renal impairment) and D1690C00006 (add-on to insulin) including subjects with moderate renal impairment. Targeted questionnaires for spontaneous reports. Epidemiology program for characterization of hospitalization for acute renal failure. MB102035: Measured change in GFR over 12 weeks is being evaluated for dapagliflozin alone and in combination with hydrochlorothiazide. A sub-study of MB102035 will evaluate measured erythropoetin and plasma volume.
Bone Fracture	Routine PV. D1690C00012: Phase 3 study to evaluate bone density by DXA as a safety objective with planned bone density analyses at the end of Years 1 and 2 and to study biochemical markers of bone formation and bone resorption. Safety study including assessment of bone fractures (TBD).
Liver Injury	Routine PV. Supplemental CRFs in ongoing Phase 3 clinical studies. Blinded adjudication of liver cases in Phase 3 clinical studies. Targeted questionnaires for spontaneous reports. Epidemiology program for characterization of hospitalization for acute liver failure.
<b>Important Missing/Limited Information</b>	
Pediatric population	Routine PV. A PIP has been approved by EMA and was submitted to FDA.
Elderly population	Routine PV.
Pregnancy and lactation	Routine PV. Pregnancy outcome follow-up for clinical studies and spontaneous reports.
Severe renal impairment	Routine PV. Epidemiology program for characterization of hospitalization for acute renal failure.
Moderate/severe hepatic impairment	Routine PV. Epidemiology program for characterization of hospitalization for acute liver failure.

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Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III and IV	Routine PV. CV blinded adjudication in Phase 2 and 3 clinical studies. D1690C00018 and D1690C00019 include high risk CV patients, with no exclusion criteria for CHF, NYHA class III.
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#### Source Risk Management Plan Table 2.2

This plan was proposed by the applicant prior to the findings of bladder and breast cancer imbalance. In addition, many safety issues were presented at the Advisory Committee meeting in July. The discussion and voting that took place thereafter may have played a role in the applicant's new proposed pharmacovigilance plan. This plan will be discussed over the next few weeks. An outline of what the applicant plans is as follows:

- An updated risk management plan that includes breast cancer and bladder cancer as a potential risk.
- Updated package insert (USPI) which now includes cancer information in the Adverse Reaction section.
- A Medication Guide which will replace the proposed patient package insert.
- Updated cardiovascular outcome trial synopsis which is also planned to capture bone fracture, liver and cancer safety data.
- Epidemiology protocols for liver failure, renal failure, bone fractures, and urinary tract infection complications, and an epidemiology study synopsis for cancer.

If the additional data to be submitted by the applicant as a major amendment lead to approval, epidemiology studies will be required to assess liver failure and cancer, among the other safety issues. These protocols would need to be reviewed by our statisticians to ensure adequate power to reduce the current calculated risk ratios for liver failure, breast and bladder cancer. We will continue to request these adverse events reported in an expedited manner.

In their Advisory Committee Briefing document, the applicant proposed that the pharmacoepidemiology studies would enable the overall quantitative assessment of risks associated with dapagliflozin in the context of other anti-diabetic agents, and also complement the risk information from ongoing trials, spontaneous adverse event reports, and targeted questionnaires. The background rate of events of interest, and the patient-years of exposure to dapagliflozin and number of years after approval required to rule out a relative risk equal to 2 for each of the outcomes assessed in the pharmacoepidemiology program calculated by the applicant are presented in Table 2.

**Table 2 Signal Detection Timing in Pharmacoepidemiology Studies**

Event	Event Background Rate per 10,000 Patient-years	Exposure to Dapagliflozin (patient-years)	Years to Rule out a Relative Risk = 2
All Malignancy	100	3,750	1
Bladder Cancer	4	93,750	3
Breast Cancer	30	12,500	2
Acute Liver Failure	2	187,500	5
Acute Renal Failure	10	37,500	2
Acute Pyelonephritis: Females	11	34,091	3
Acute Pyelonephritis: Males	3	125,000	5

\* Assumes an equal sample size between dapagliflozin and comparator,  $\alpha = 0.05$ , power = 85%

Source Applicant's Briefing Document Table 52

As mentioned, these proposals need to be discussed and reviewed within our agency.

#### 1.4 Recommendations for Postmarket Requirements and Commitments

i. The applicant will be required to conduct a dedicated study to assess for increased cardiovascular risk in high risk patients. This is in line with all oral antidiabetic drugs under development or review at this time per FDA *Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The primary objective of this trial will be to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with dapagliflozin to that observed in the control group is less than 1.3. Adverse Events of special interest must include hepatic toxicity, breast cancer, bladder cancer, urinary tract infection, genital infections and fractures.

ii. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

While still in review, our agency will likely waive the pediatric study requirement for ages 0 to 9 years because are too few children in this age range with T2DM to practically enable an adequate study for safety and efficacy. In addition we will likely accept the deferral of studies in patients 10 to 17 because dapagliflozin has not been proven safe and effective in adults at the time of the request. If approved, we will require that the applicant complete two clinical trials in pediatrics. One will be a dose-finding study. The other study will be a randomized, double-blind, efficacy and safety study comparing dapagliflozin monotherapy to placebo and in in patients that were not well controlled on

metformin. The proposals are seen in Table 3. The European Medicines Agency (EMA) agrees with the design of the dose finding, PK/PD. However, for the clinical safety and efficacy study, the EMA accepted a substudy of dapagliflozin in monotherapy which is open label and uncontrolled. In addition they accepted a placebo-controlled main portion study for assessing the glycemic effect of dapagliflozin in pediatric subjects who are inadequately controlled on metformin.

**Table 3 Applicant Proposed Pediatric Studies**

<b>D1690C00016:</b> A randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of dapagliflozin in children, 10 to <18 years of age with T2DM receiving one of the three dose levels of dapagliflozin over the range of 2.5 to 10 mg.	Submit full protocol	3Q2011
	Planned FPFV <sup>a</sup>	4Q2011
	Planned LPLV <sup>b</sup>	By Sep-2012
	Submit Final Clinical Study report	By Sep-2013
<b>D1690C00017:</b> A double-blind, randomised, placebo controlled Phase III study to evaluate dapagliflozin versus placebo in pediatric subjects with T2DM who are inadequately controlled on metformin monotherapy	Submit full protocol	By Sep-2013
	Planned FPFV <sup>c</sup>	After NDA approval
	Planned LPLV <sup>d</sup>	By Sep-2017
	Submit Final Clinical Study report	By Sep-2018

<sup>a</sup> FPFV=First patient first visit

<sup>b</sup> LPLV=Last patient last visit

iii. Long-term epidemiology studies are needed to reassess the risk for drug induced liver injury, breast and bladder cancer. The applicant proposed that the pharmacoepidemiology studies. The details of these studies as post marketing requirements have not been finalized.

iv. Under discussion is also a request for a study that would assess dapagliflozin glycemic efficacy in patients with micro and macroalbuminuria which is very common in T2DM (regardless of glomerular filtration rate). This was discussed in the Advisory Committee meeting and presented as a potential concern by Dr. Kevin McBryde (Pediatric Nephrologist). Dapagliflozin is highly protein bound and exerts its effects on the renal tubule. These characteristics are shared with furosemide, which has decreased efficacy with proteinuria.<sup>1</sup>

## 2 Introduction and Regulatory Background

### 2.1 Product Information

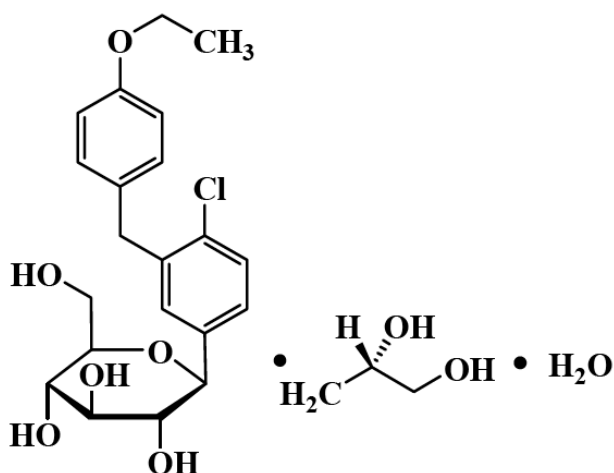
Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT2) inhibitor proposed for the treatment of type 2 diabetes mellitus. Dapagliflozin Film Coated Tablets, 5 mg and 10 mg, are the proposed commercial strengths for oral administration. The molecular formula is  $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ . The chemical names are:

CA Index Name: D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compd. with (2S)-1,2-propanediol, hydrate (1:1:1)

IUPAC Name: (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, (2S)-propane-1,2-diol (1:1) monohydrate

The chemical structure is shown in Figure 1.

Figure 1 Chemical Structure of Dapagliflozin



Source Quality Summary 2.3.S Drug Substance

### 2.2 Tables of Currently Available Treatments for Proposed Indications



**Table 4 Currently Available Treatments for Type 2 Diabetes Mellitus**

Therapy	Example	Primary mechanism of action	Adverse Effects
Sulfonylureas	Glyburide	Increases insulin secretion	Hypoglycemia
Glitinides	Repaglinide	Increases insulin secretion	Hypoglycemia
Biguanides	Metformin	Decreases hepatic glucose output	Gastrointestinal symptoms
Alpha-glucosidase inhibitors	Acarbose	Delays gastrointestinal absorption of carbohydrates	Flatulence
Thiazolidinediones	Pioglitazone	Increases insulin sensitivity	Edema
Insulin	Lispro	Increases insulin levels	Hypoglycemia, weight gain
Amylin analogues	Pramlintide	Slows gastric emptying	Gastrointestinal symptoms
GLP-1 Analogues	Exenatide	Stimulates glucose-dependent insulin release	Gastrointestinal symptoms
DPP-4 Inhibitors	Sitagliptin	Stimulates glucose-dependent insulin release	Uncommon
Bile Acid Sequestrants	Colesevelam	Binds bile acids	Gastrointestinal symptoms
Dopamine receptor agonists	Cycloset	Unknown	Gastrointestinal

*Source: Adapted from AACE Diabetes Mellitus Guidelines (2007) and Nathan D. (2002)*

## 2.3 Availability of Proposed Active Ingredient in the United States

Dapagliflozin is not currently approved for marketing in the U.S. It is only available for use under the applicant's Investigational New Drug Applications.

## 2.4 Important Safety Issues With Consideration to Related Drugs

There are no currently marketed drugs of this class in the U.S. Dapagliflozin will be a first in class medication. Since dapagliflozin causes glucosuria, safety issues pertaining to diuretics are considered in this review. For example, events of hypovolemia and hemoconcentration are considered. In addition, dapagliflozin increases trabecular bone in rats in preclinical studies. This resulted in greater bone mass, density, and strength at high exposure multiples. Similar findings in the preclinical studies of canagliflozin, another SGLT2 inhibitor in the Investigational New Drug (IND) phase have occurred. Small decreases in serum calcium were also found in the mid and high dose rat studies along with substantial increases in urine calcium with canagliflozin. In addition, there were decreases in markers of bone resorption (serum collagen type 1 carboxyl terminal

telo peptide [CTX] and urinary deoxypyridinoline [DPD]) and bone formation (serum osteocalcin [OC]). No change in bone turnover markers or in bone morphology were observed in dogs; however, a decrease in 1,25-dihydroxyvitamin D was seen. For the reasons listed above, special attention is given to bone health and fracture rate in the dapagliflozin application. The applicant was asked to have fractures adjudicated and is currently conducting a study where bone markers and dual-emission X-ray absorptiometry for bone density (DEXA) are being followed. This study, the body weight and composition D1690C00012, was completed to 50 weeks at the time of the Four Month Safety Update.

### **Other Findings with Canagliflozin**

Canagliflozin displayed an increase in liver enzymes in the 3-month and 6-month rat studies. It also increased BUN dose-dependently (up to two fold) and ALP in male and female rats and ALT and AST (less than two fold) in males in 6-month rat studies. There was a similar trend in the 13-week study (increased ALT, AST and BUN but only in males). This was not accompanied by liver pathology changes.

The preliminary results of the two year rat canagliflozin carcinogenicity study has identified increased incidence of three specific tumors. The three tumor types were renal tubular tumors (adenoma and carcinoma), leydig cell tumors and adrenal pheochromocytoma.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The End of Phase 2 meeting took place on September 11, 2007. FDA requested the inclusion of a dapagliflozin dose <2.5 mg into the clinical program and the inclusion of subjects with renal impairment in the Phase 3 program.

In response, the applicant included a 1 mg dose group in the phase 3 monotherapy study MB102032.

Study MB102029, a study in moderate renal impairment, was designed and to evaluate safety and efficacy in subjects with moderate renal impairment. Subjects with severe renal impairment (estimated GFR [eGFR]<30 mL/min/1.73m<sup>2</sup>) were not included, as meaningful efficacy was not expected in this patient group.

The FDA also requested active questioning in addition to unsolicited reporting of events of genital infections and UTIs, which the applicant subsequently added to their clinical protocols.

At the pre-NDA meeting on November 9, 2010:

The applicant was requested to analyze elevations in creatinine phosphokinase greater than 10x ULN as well as cases of rhabdomyolysis as Adverse Events of Special Interest. This was done.

The applicant was asked to provide an analysis of hepatic safety and analyze bone fractures as Adverse Events of Special Interest. The applicant also indicated they planned to send the hepatic adjudication report with the Four Month Safety Update (4MSU). Consolidated narratives were requested. The applicant complied with these requests in their NDA and 4MSU. A reviewer's guide was submitted with the NDA as requested.

## 2.6 Other Relevant Background Information

In the United States in 2010, 25.6 million or 11.3% of all people  $\geq 20$  years old had a diagnosis of diabetes. The most common form of diabetes is type 2 diabetes. Ninety to 95 percent of people with diabetes have type 2. Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States. It is the seventh leading cause of death.<sup>2</sup>

T2DM is caused by peripheral insulin resistance and impaired regulation of hepatic glucose production. This leads to increased production of glucose. There is also a decline in pancreatic  $\beta$ -cell function which leads to  $\beta$ -cell failure and thus inappropriate insulin secretion.

First line treatments for T2DM are changes to diet and an exercise. There are several medical therapies available for T2DM, see Table 4. These medications, while effective in lowering HbA1c, also exposes patients to adverse events. For example, sulfonylureas, glitinides and insulin are all associated with hypoglycemia. Metformin, a biguanide, most commonly used, is associated with gastrointestinal intolerance.

Due to the large and growing population of patients with T2DM, and limitations of current therapies, new therapies for T2DM with broader safety and/or efficacy profiles are continuously sought. In addition, a new class of medication with a novel mechanism of action may provide efficacy without some of the unfavorable side effects of current therapies. The effect of most T2DM medications is dependent on insulin. Weight gain and hypoglycemia are very common adverse events that result from current therapies. Over 85% of patients with T2DM are overweight or obese. Gaining more weight from current medical therapies can worsen insulin resistance and exacerbate T2DM comorbidities such as hypertension and dyslipidemia.

Dapagliflozin's mechanism of action is different from currently available medicines. It causes insulin-independent, elimination of glucose by the kidney. Since SGLT2 is almost exclusively expressed in the kidney, this selective nature of dapagliflozin may

minimize the possibilities of off-target adverse events. SGLT2 inhibition results in a loss of calories that may result in clinically significant weight loss. Furthermore, the inhibition of sodium and glucose transport in the proximal tubule also causes a mild diuretic effect; therefore, there is a potential for beneficial blood pressure effects.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The applicant's submission was organized well and information was easily located. The applicant responded to information requests in a timely manner for any information that was not easily found in the original submission.

Inspections of the sponsor and two Canada sites, two Argentina sites, three U.S. sites were completed. These sites enabled inspection of six of the pivotal studies for the NDA. These sites also enable inspection of more than one protocol per site. During inspections, there was a focus on the appropriateness of referrals of cardiovascular events to the Cardiovascular Clinical Event Committee.

At the time of filing of this review, there were no major protocol violations noted that would affect the integrity of the submission. However, the full Division of Scientific Investigations (DSI) review is still pending.

One minor violation was as follows:

Postural vital signs were not conducted correctly in five studies. Orthostatic blood pressure was required at day 1, weeks 1, 12, 24, 50 and 102 (for those long-term studies) but not always done in the correct sequence. For most sites the violations were sporadic and all subjects had at least one orthostatic blood pressure determined at or after week 12 except subjects from one site.

Please refer to Dr. Susan Leibenhaut's Clinical Site Inspection Review for full details.

#### **3.2 Compliance with Good Clinical Practices**

All trials were conducted according to International Conference on Harmonization Good Clinical Practice guidelines subsequent to the review and approval of the relevant ethics committees, institutional review boards, and regulatory authorities of participating sites.

The principal trials in the clinical program were randomized, double-blind, placebo-controlled, parallel-group studies to maintain trial integrity. All patients were consented for the trials and most trials included a placebo run-in phase to help ensure patient compliance with the study treatment. Appropriate patient monitoring and education were in place. Most principal trials also incorporated rescue procedures and limited patient enrollment by glycemic control (HbA1c). For the trial that did not have rescue

procedures, the active comparator study D1690C00004, patients were discontinued if they could not maintain glycemic control.

### 3.3 Financial Disclosures

The applicant submitted documentation confirming that there were no reported investigator financial disclosures that would affect data or trial integrity, with the exception of two cases. One was a principal investigator (see Table 5) and another was (b) (6) (Table 6).

**Table 5 Principal Investigator with Financial Disclosure**

(b) (6)



Source Financial Disclosures Table 3

**Table 6 (b) (6) Financial Disclosure**

(b) (6)



Source Financial Disclosures Table 5

Table 7 below lists all studies related to safety and efficacy considered “covered studies” for the purpose of 21 CFR 54.2.

**Table 7 List of Covered Studies**

<b>Study Number</b>	<b>Title</b>
MB102008 Phase 2b*	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-512148 as Monotherapy in Subjects with Type 2 Diabetes Mellitus Who Are Treatment Naive And Have Inadequate Glycemic Control on Diet and Exercise
MB102009 Phase 2b	A Pilot Study of the Efficacy and Safety of BMS512-148 on Glycemic Control in Subjects with Type 2 Diabetes Treated Aggressively but not Controlled on Combination Antihyperglycemic Therapy with Metformin and/or Thiazolidinedione (TZD) and Insulin
D1692C00005 Phase 2b	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2 Trial to Evaluate the Efficacy and Safety of Dapagliflozin as Monotherapy in Japanese Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control
MB102013 Phase 3	A Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise
MB102014 Phase 3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone

(b) (4) Dapagliflozin

MB102021 Phase 3	A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control
MB102029 Phase 2/3	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase 2/3 Trial to Evaluate the Glycemic Efficacy, Renal Safety, Pharmacokinetics, and Pharmacodynamics of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Moderate Renal Impairment Who Have Inadequate Glycemic Control
MB102030 Phase 3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone
MB102032 Phase 3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise
MB102034 Phase 3	A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control
D1690C00004 Phase 3	A 52-Week International, Multi-centre, Randomised, Parallel-group, Double-blind, Active-controlled, Phase III Study With a 156-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination With Metformin Compared With Sulphonylurea in Combination With Metformin in Adult Patients With Type 2 Diabetes Who Have Inadequate Glycaemic Control on Metformin Therapy Alone
D1690C00005 Phase 3	A 24-Week, International, Randomized, Double-blind, Parallel-group, Multi-centre, Placebo-Controlled Phase III Study With a 24-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination With Glimepiride (a Sulphonylurea) in Subjects With Type2 Diabetes Who Have Inadequate Glycaemic Control on Glimepiride Therapy Alone
D1690C00006 Phase 3	A 24-week International, Randomized, Parallel-group, Double- blind, Placebo-controlled Phase III Study With a 80-week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin Therapy When Added to the Therapy of Patients With Type 2 Diabetes With Inadequate Glycaemic Control on Insulin
D1690C00012 Phase 3	A 24-week, Multi-centre, International, Double-blind, Randomized, Parallel-group, Placebo-Controlled, Phase III Study With a 78-week Extension Period to Evaluate the Effect of Dapagliflozin in Combination With Metformin on Body Weight in Subjects With Type2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Alone

\* Studies concluded at the time of the partnership with AstraZeneca.

## Source Financial Disclosures Table 1.2

The majority of investigators, including almost all principal investigators (PIs) submitted documentation. There were some PIs and subinvestigators that did not have documentation reported, despite due diligence on part of the applicant. Most of these were subinvestigators and it was reported that they signed a form with no information to

disclose for Bristol-Myers Squibb but a form for Astra Zeneca (which was added as a partner later in the clinical program) was not done.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

See Dr. Xavier Ysern's review for full details.

Dapagliflozin has high and pH-independent aqueous solubility, high permeability in in vitro models of intestinal absorption and good absolute oral bioavailability [78%]. In addition, the dapagliflozin immediate release (IR) tablet formulations are all (b) (4) dissolved in 15 minutes).

### **4.2 Clinical Microbiology**

Not applicable. There was no clinical microbiology review for dapagliflozin.

### **4.3 Preclinical Pharmacology/Toxicology**

According to Dr. Mukesh Summan, nonclinical data supports the safe use of dapagliflozin under the proposed indication. Important points taken from his review will be briefly presented here; please refer to his review for full details.

Off-target effects in six month rat studies included increased trabecular bone and tissue mineralization likely due to modulation of calcium homeostasis and increased urinary calcium excretion. The sponsor has proposed off-target inhibition of rat SGLT1 in the intestine that results in increased calcium absorption and increased serum calcium levels. This in turn leads to increased trabecular bone and tissue mineralization as downstream events of excess calcium. The propensity for dapagliflozin to cause off-target inhibition of SGLT1 in humans is reduced due to the lower affinity of dapagliflozin for SGLT1 compared to the rat. Overall, target organ toxicities in adult rats occurred at high exposure multiples and the safety margins to the final clinical dose are high.

In the 12 month study, treated dogs were exposed to dapagliflozin at 128-3269x maximum recommended human dose (MRHD). Dose-dependent increases in weights of the kidney, adrenal and liver were observed without changes in histopathology. Increased adrenal and liver weights were irreversible. Due to renal toxicity and



moribidity at the high dose, the no observable adverse effect level (NOAEL) was the mid dose which was 516x and 619x MRHD in males and females, respectively.

Dapagliflozin was not teratogenic at up to 75 mg/kg (1141x MRHD) in the rat. Dapagliflozin was also not teratogenic in the rabbit at up to 184x MRHD.

Exposure to dapagliflozin at 19-1415x MRHD in a pre- and post-natal development study in the rat showed renal pelvic dilatation in the in utero and lactationally exposed pups at the high dose (1415x MRHD). Treatment of juvenile rat pups until maturity at identical exposures replicated the renal pelvic dilatation pathology but at a substantially lower drug exposure (1mg/kg, ~15x MRHD). A “no effect” dose was not identified so it is possible that dapagliflozin exposure causing this adverse effect occurs very near clinical exposure. The susceptible period in young rats is characterized by active morphological and functional development of the kidneys. A similar period covering morphological and functional renal development in humans would be during the second/third trimesters of gestation, with functional renal development continuing until ~2yrs of age. In addition, the renal pelvic dilatation also showed irreversibility in recovery animals, suggesting dapagliflozin is a renal pelvic development toxicant. The cause of renal pelvic and tubular dilation is not known. Consequently the sponsor has recommended against the use of dapagliflozin during the second and third trimesters of pregnancy and during nursing

Dapagliflozin was assessed for its potential to induce tumors in two-year bioassays conducted in rats and mice. The two-year bioassays are intended to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action after approximately life-time exposure to an investigational drug. Dapagliflozin did not increase the incidence of any tumor in rats and mice at drug exposures reaching 131x and 72x the clinical dose, respectively.

#### 4.4 Clinical Pharmacology

Please see Dr. Ritesh Jain’s review for full details on the clinical pharmacology of dapagliflozin. Major points from his review are discussed in this section.

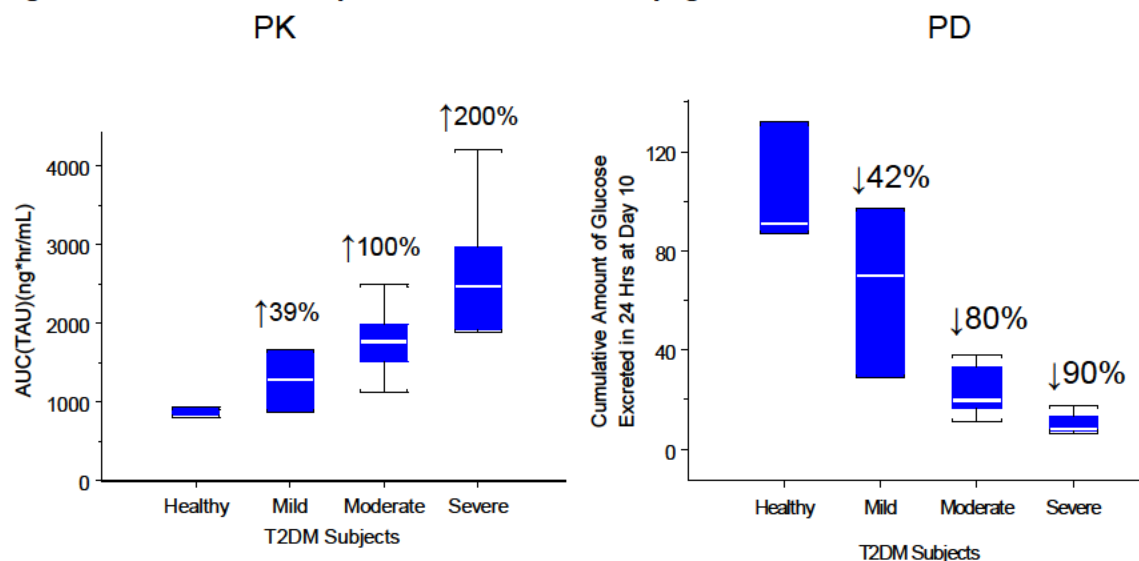
In general the dapagliflozin clinical pharmacology program consisted of single and multiple pharmacokinetic/pharmacodynamic (PK/PD) studies in healthy and T2DM subjects. These included a mass balance study, absolute oral bioavailability study, drug-drug interaction, renal impairment and hepatic impairment study, relative bioavailability study, food effect study, bioequivalence study of (b) (4) in tablets, thorough QTc study. The clinical pharmacology program also included population pharmacokinetics and exposure-response analysis from Phase 1 and Phase 2/3 studies.

## **Specific Populations**

### **Renal Impairment**

Following administration of 20-mg dapagliflozin given once daily for seven days, T2DM patients with mild, moderate, or severe renal impairment had higher steady-state mean dapagliflozin area under the curve (AUC) as compared to T2DM patients with normal renal function (Figure 2). Further, higher systemic exposures of dapagliflozin in subjects with moderate, and severe renal impairment did not result in a correspondingly higher cumulative amount of glucose excretion (Figure 2). This is consistent with dapagliflozin's glomerular filtration rate-dependent mechanism of action.

**Figure 2 Effect of Renal Impairment on PK/PD of Dapagliflozin**



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

Source Dr. Jain's Review

### **Reviewer's Comments**

**Dapagliflozin in renal impairment will be further addressed in this review. However, the PK/PD study supports my recommendation to not approve dapagliflozin for moderate renal impairment patients.**

### **Hepatic Impairment**

In subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B), C<sub>max</sub> and AUC of dapagliflozin were increased by up to 22% and 36%, respectively, compared to healthy subjects. Subjects with severe hepatic impairment (Child-Pugh

Class C), dapagliflozin C<sub>max</sub> and AUC were up to 40% and 67% higher than matched healthy controls, respectively.

#### 4.4.1 Mechanism of Action

Dapagliflozin is a stable, competitive, reversible, highly selective and orally active inhibitor of SGLT2, the major transporter responsible for the renal glucose reabsorption. Dapagliflozin inhibits human SGLT2 ( $K_i = 0.2$  nM) selectively versus human SGLT1 (3000-fold selective), the major glucose transporter responsible for the absorption of glucose in the small intestine.

Dapagliflozin results in the direct, and insulin-independent, elimination of glucose by the kidney. Urinary glucose excretion induced by dapagliflozin depends upon the amount of glucose filtered by the kidney. This filtered load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR). The action of dapagliflozin is dependent upon the patient's baseline glycemic control and renal function, and is independent of the patient's beta cell function or insulin sensitivity.

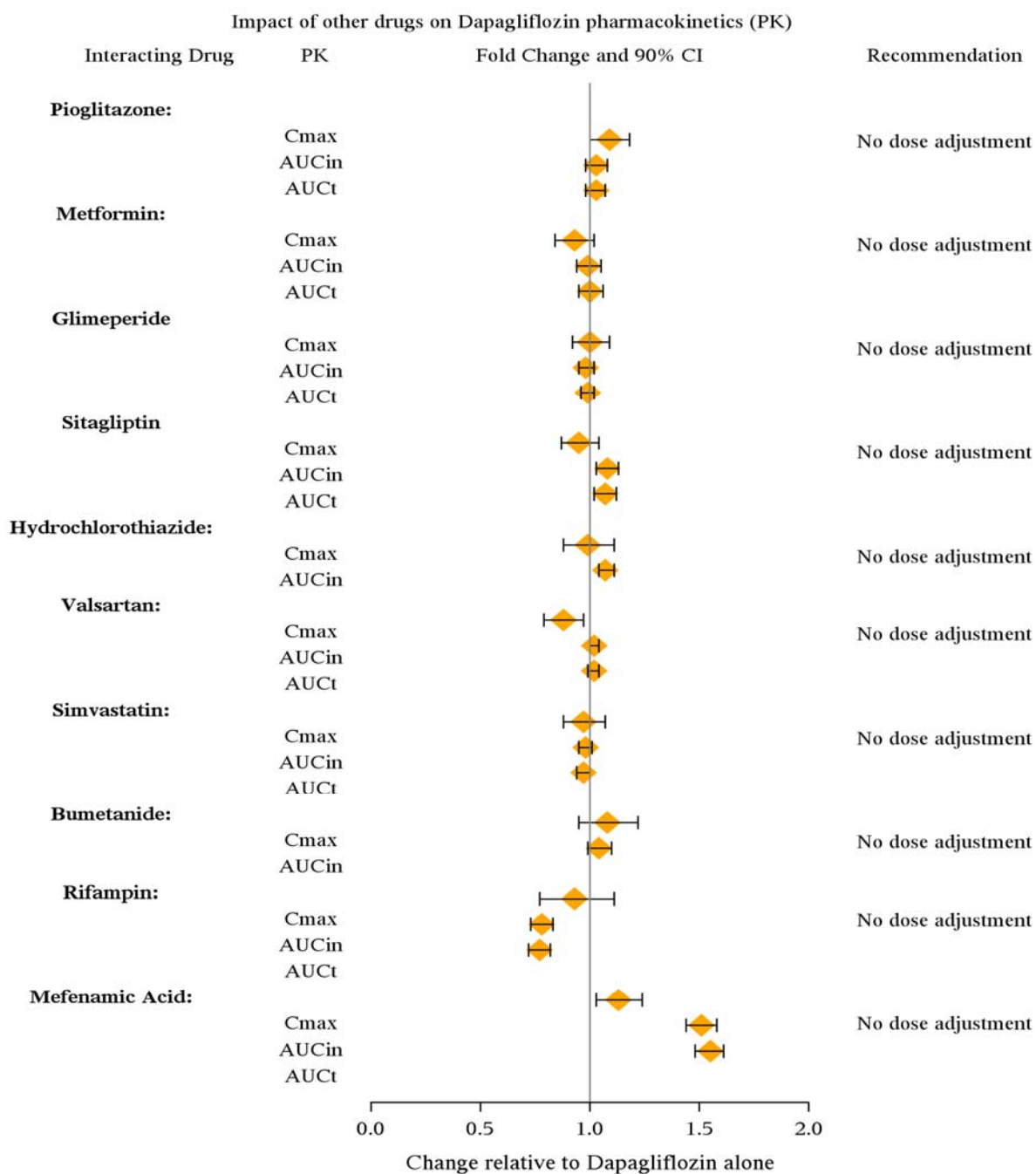
#### Pharmacodynamics

Please see the following section on pharmacokinetics for a combined discussion of pharmacodynamics and pharmacokinetics of dapagliflozin.

#### 4.4.3 Pharmacokinetics

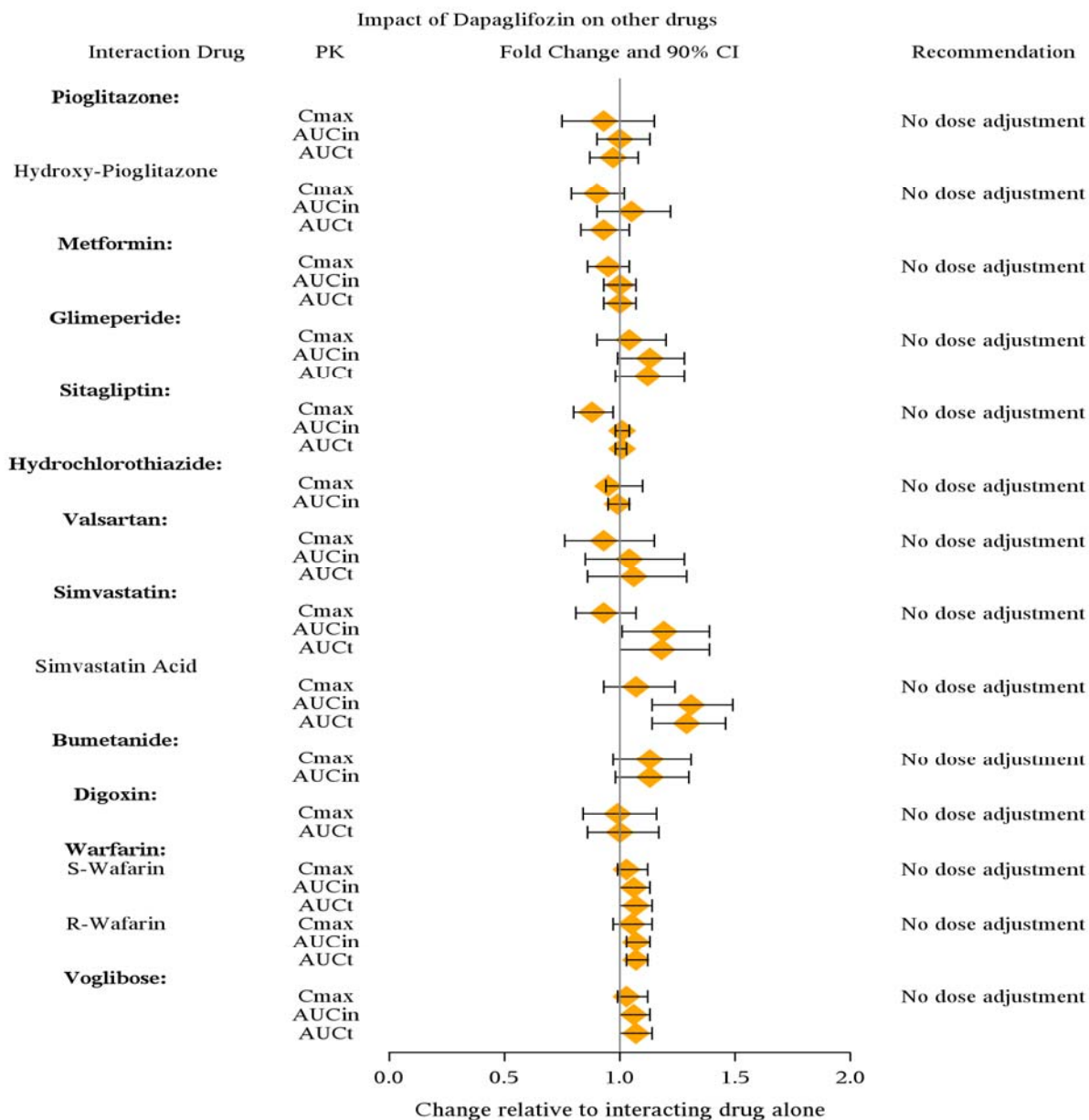
Figure 3 summarizes the effect of co-administered drugs on the pharmacokinetics of dapagliflozin. Figure 4 summarizes the impact of dapagliflozin on the pharmacokinetics of co-administered drugs. In summary, there were no clinically meaningful drug-drug interaction observed in the all the DDI studies conducted.

**Figure 3 Other Drug Impact on Dapagliflozin**



Source Dr. Jain's Review

**Figure 4 Impact of Dapagliflozin on Other Drugs**



Source Dr. Jain's Review

A summary of the main PK characteristics of dapagliflozin are seen in Table 8.

**Table 8 PK Characteristics of Dapagliflozin**

<b>PK Property</b>	<b>PK Parameter</b>	
<b>Absorption</b>	$T_{max}$ , hour	1
	$T_{1/2}$ , hour	~13
	Absolute Bioavailability (Fasted), %	78
	Food Effect	In presence of High Fat meal, No change in AUC, ~30% decrease in $C_{max}$
<b>Distribution</b>	Protein Binding, %	91
<b>Metabolism</b>	Pathways	In a mass balance study, the primary metabolite in human was dapagliflozin 3-O-glucuronide (BMS 801576) which accounted for 61% of the dapagliflozin dose. All other metabolites detected in human plasma each constituted < 5% of the radioactivity AUC. In vitro studies demonstrated that UGT1A9 is the major enzyme responsible for the formation of dapagliflozin 3-O-glucuronide.
<b>Excretion</b>		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 is because parent drug.
<b>Dose-Proportionality</b>		Exposures of dapagliflozin were slightly greater than proportionally to dose while $C_{max}$ values were less than proportionally to dose
<b>Accumulation Index following Multiple Dose in Healthy and T2DM subjects</b>		~1.3

Source Dr. Jain's Review

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The 26 pharmacology studies in the clinical program including two ongoing pharmacology studies are listed here in Table 9. The phase 2b and 3 studies are listed in Table 10.

**Table 9 Studies in the Dapagliflozin Clinical Program**

Study/ Country/	Study Design	Primary Objective(s)	Endpoints	Dose/ Route/ Duration	Subject Type/ # Dosed
MB102001 <sup>1</sup> USA	Double-blind, randomized, placebo-controlled, escalating PO single-dose study	Evaluate the safety, tolerability, PD, and PK Evaluate the effect of a high-fat meal on PK	Safety and tolerability, PK and PD	dapagliflozin 2.5-500 mg or matching placebo / PO / single dose	Healthy 64
MB102002 <sup>3</sup> USA	Double-blind, randomized, placebo-controlled, escalating PO multiple-dose study	Evaluate the safety, tolerability, PD, and PK	Safety and tolerability, PK and PD	dapagliflozin 2.5-100 mg or matching placebo / PO / 14 days	Healthy 40
MB102003 <sup>5</sup> USA	Double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study	Evaluate the safety, tolerability, PD, and PK in subjects with Type 2 Diabetes Mellitus (T2DM)	Safety and tolerability, PK and PD	dapagliflozin 5-100 mg or matching placebo / PO / 14 days with stable metformin background therapy (PO 500 mg- 2000 mg/day)	T2DM 47
MB102004 <sup>28</sup> USA	Open-label, randomized, 3-period, 3-treatment, crossover study	Evaluation of the effect of hydrochlorothiazide (HCTZ) on the PK of dapagliflozin and the effect of dapagliflozin on the PK of HCTZ	Safety, PK and PD	dapagliflozin 50 mg and HCTZ 25 mg / PO / single dose	Healthy 18
MB102005 <sup>a35</sup> USA	Open-label, randomized, 2-period, 2-treatment, crossover study	Evaluate bioavailability of 1 x 50 mg Tablet relative to 5 x 10 mg Capsules	Safety and PK	dapagliflozin 50 mg / PO / single dose	Healthy 14
MB102006 <sup>8</sup> USA	Open-label, non-randomized, single dose study	Evaluation of PK, metabolism, and elimination of dapagliflozin	Safety and PK	dapagliflozin 50 mg solution / PO / single dose	Healthy 6
MB102007 <sup>14</sup> USA	Open-label, parallel, single and multiple dose study	Assess the effect of stable renal impairment on single and multiple dose dapagliflozin PK	Safety and PK	dapagliflozin 50 mg / PO / single dose or dapagliflozin 20 mg / PO / 7 days	Healthy (8) and T2DM with renal impairment (32)
MB102010 <sup>18</sup> Japan	Double-blind, randomized, placebo-controlled, sequential, ascending, single-dose study	Evaluate the safety, tolerability, PD, and PK in healthy Japanese subjects	Safety and tolerability, PK and PD	dapagliflozin 2.5-50 mg or matching placebo / PO / single dose	Healthy 32
MB102016 <sup>42</sup> Argentina Terminated	Open-label, randomized, 3-period, 3-treatment, crossover study	Evaluate the effects of dapagliflozin on the PK of glimepiride and the effect of glimepiride on dapagliflozin PK	Safety and PK	dapagliflozin 20 mg / PO / single dose; glimepiride 4 mg / PO / single dose	Healthy 11
MB102017 <sup>20</sup> USA	Open-label, randomized, 3-period, 3-treatment, crossover study	Evaluate the effects of dapagliflozin on the PK of pioglitazone and the effect of pioglitazone on dapagliflozin PK	Safety and PK	dapagliflozin 50 mg / PO / single dose; pioglitazone 45 mg / PO / single dose	Healthy 24
MB102019 <sup>a37</sup> USA	Open-label, randomized, 2-period, 2-treatment, crossover study	Assess the effect of a high-fat meal on the PK of dapagliflozin	Safety and PK	dapagliflozin 10 mg tablet / PO / single dose	Healthy 14
MB102020 <sup>44</sup> USA Terminated	Open-label, parallel, multiple-dose study	Characterization of the kinetics of renal glucose reabsorption in response to dapagliflozin in healthy subjects and in subjects with T2DM	Safety and PK	dapagliflozin 10 mg / PO / 7 days	T2DM 1



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MB102025 <sup>19</sup> Japan	Double-blind, randomized, placebo-controlled, sequential, escalating multiple-dose study	Evaluate the safety, tolerability, PD, and PK in Japanese subjects	Safety and tolerability, PK and PD	dapagliflozin 2.5-20 mg or matching placebo / PO / 14 days	T2DM 36
MB102026 <sup>22</sup> USA	Open-label, randomized, 3-period, 3-treatment, crossover study	Evaluate the effects of dapagliflozin on the PK of metformin and the effect of metformin on dapagliflozin PK	Safety and tolerability, PK	dapagliflozin 20 mg / PO / single dose; metformin 1000 mg / PO / single dose	Healthy 18
MB102027 <sup>16</sup> Argentina Poland	Open-label, parallel-group, single-dose study	Assess the effect of stable hepatic impairment on single-dose dapagliflozin PK	Safety and PK	dapagliflozin 10 mg / PO / single dose	Healthy (6) and Hepatically-impaired (18)
MB102036 <sup>29</sup> USA	Open-label, randomized, 5-period, 5-treatment, crossover study	Evaluate the effects of dapagliflozin on the PK of simvastatin and the effect of simvastatin on dapagliflozin PK and the effect of valsartan and the effect of valsartan on dapagliflozin PK	Safety and tolerability, PK	simvastatin 40 mg or simvastatin 40 mg + dapagliflozin 20 mg or dapagliflozin 20 mg or valsartan 320 mg or dapagliflozin 20 mg + valsartan 320 mg/3 single doses of dapagliflozin and 2 single doses of simvastatin and valsartan each/tablets	Healthy 24
MB102037 <sup>24</sup> USA	Open-label, randomized, 5-period, 5-treatment, unbalanced crossover study	Evaluate the effects of dapagliflozin on the PK of glimepiride and the effect of glimepiride on dapagliflozin PK and the effect of dapagliflozin on the PK of sitagliptin and the effect of sitagliptin on dapagliflozin PK	Safety and tolerability, PK	dapagliflozin 20 mg or glimepiride 4 mg or dapagliflozin 20 mg + glimepiride 4 mg or sitagliptin 100 mg or dapagliflozin 20 mg + sitagliptin 100 mg/3 single doses of dapagliflozin and 2 single doses of glimepiride and sitagliptin each/tablets	Healthy 18
MB102057 <sup>31</sup> USA	Open-label, randomized, parallel group, multiple-dose study	Evaluate the PK and PD effects on renal parameters of bumetanide and dapagliflozin when co-administered	Safety and tolerability, PK and PD	bumetanide 1 mg / PO / 7 days; dapagliflozin 10 mg / PO / 7 days ; bumetanide 1 mg + dapagliflozin 10 mg / PO / 7 days/tablets	Healthy 42
MB102058 <sup>33</sup> USA	Open-label, randomized, 2-period, 2-treatment, crossover study	Evaluate the effect of dapagliflozin on the PK of warfarin and digoxin and evaluate the effect of dapagliflozin on the PD of warfarin	Safety and tolerability, PK and PD	dapagliflozin 20 mg loading dose + dapagliflozin 10 mg QD/7 days or warfarin 25 mg/single dose or dapagliflozin 20 mg loading dose + dapagliflozin 10 mg QD/7 days + digoxin 0.25 mg/single dose or digoxin 0.25 mg/single dose/tablets	Healthy 30
MB102059 <sup>a10</sup> USA	Open-label, single-dose study	Assess the absolute oral bioavailability of dapagliflozin	Safety and tolerability, and PK	dapagliflozin 10 mg / PO / single dose; dapagliflozin 80 µg / IV / single dose	Healthy 7
MB102062 <sup>a39</sup> USA	Open-label, randomized, 3-period, 3-treatment, crossover study	Assess the bioequivalence of dapagliflozin from a (b) (4) tablet formulation and a (b) (4) (b) (4) formulation in fed and fasted conditions	Safety and tolerability, and PK	dapagliflozin 10 mg (b) (4) (b) (4) tablet and dapagliflozin 10 mg (b) (4) (b) (4) tablet and dapagliflozin 10 mg (b) (4) tablet + food	Healthy 29
MB102066 <sup>45</sup> USA Ongoing	Open label, parallel, multiple-dose study	To examine whether there is a difference in the renal glucosuric effect of dapagliflozin as characterized by changes in the TmG of the glucose titration curve between healthy subjects and subjects with T2DM after multi dose administration of 10 mg dapagliflozin	Safety and tolerability, and PK and PD	dapagliflozin 10 mg/7 days/tablet	Healthy (10 planned) and T2DM (10 planned)
MB102074 <sup>34</sup> USA	Open-label, single-sequence study	Evaluate the effects of rifampin on the PK of dapagliflozin and assess the PD effect of rifampin and dapagliflozin when co-administered	Safety and tolerability, PK and PD	dapagliflozin 10 mg/single oral dose/tablet and rifampin 600 mg once-daily for 5 days and rifampin 600 mg (3 days) + dapagliflozin 10 mg/single dose/tablet	Healthy 14
MB102088 <sup>7</sup> USA	Randomized, open-label, parallel-group, single-dose study	Evaluate the PK and PD of low doses of dapagliflozin and dapagliflozin 3-O-glucuronide	Safety and tolerability, PK and PD	Single oral dose of dapagliflozin 0.001, 0.01, 0.1 or 0.3 mg solution 1 or 2.5 mg tablets	Healthy 35



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MB102090 <sup>a40</sup> USA	Open label, randomized, 4-period, 4-treatment, crossover study	Assess the bioequivalence of dapagliflozin from (b) (4) tablet formulation and a (b) (4) formulation in fed and fasted conditions	Safety and tolerability, and PK	dapagliflozin 2.5 mg (b) (4) tablet and dapagliflozin 2.5 mg (b) (4) tablet and dapagliflozin 2.5 mg (b) (4) tablet + food and dapagliflozin 2.5 mg (b) (4) tablet + food	Healthy 28
MB102093 <sup>46</sup> USA Ongoing	Open-label, single-sequence study	To assess the effects of mefenamic acid on the pharmacokinetics of dapagliflozin	Safety and tolerability, PK and PD	dapagliflozin 10 mg tablet single dose, washout (3 days), then mefenamic acid tablet 500 mg loading dose followed by 3 doses of mefenamic acid tablet 250 mg q6h, then dapagliflozin 10 mg single dose tablet + mefenamic acid tablet 250 mg q6h tablet for 3 days	Healthy (16 planned)
D1690C0001 <sup>11</sup> USA	Randomized, blinded, placebo-controlled, positive-controlled, 4-way crossover study	Determine the effect of dapagliflozin on the QTc interval in healthy subjects	Safety and tolerability, and PK	dapagliflozin 20 mg or 150 mg/tablets, 400 mg moxifloxacin/capsule, placebo/capsule/ single dose with each treatment	Healthy 50
D1692C00002 <sup>26</sup> Japan	Open-label, 2-period, 2-treatment crossover study	Evaluate the safety, tolerability, and PK of dapagliflozin with and without voglibose in Japanese subjects with T2DM	Safety and tolerability, and PK	dapagliflozin 10 mg/single oral dose/tablet + voglibose 0.2 mg/TID/oral tablet/3 days or dapagliflozin 10 mg single oral dose/tablet/3days	T2DM 22

QD = once daily; PO = oral; TID = three times a day; T2DM = type 2 diabetes mellitus; PD = pharmacodynamic(s); PK = pharmacokinetic(s)

Source Clinical Pharmacology Summary Table 2

**Table 10 Phase 2b and 3 Studies for Dapagliflozin**

Study Number	Study Description	Patient Population	Duration	Doses (mg)	Number of Subjects per Arm (dose—N)
<b>Phase 2b Studies</b>					
MB102008	Monotherapy vs. placebo	Drug naïve and inadequate control with diet and exercise alone	12 weeks	2.5, 5, 10, 20, 50	2.5mg-59, 5mg-58, 10mg-47, 20mg-59 / Placebo-54 / Metformin-56
D1692C00005	Monotherapy vs. placebo	Drug naïve and inadequate control with diet and exercise alone	12 weeks	1, 2.5, 5, 10	1mg-59, 2.5mg-56, 5mg-58, 10mg-53 / Placebo-54
MB102009	Add-on to insulin vs. placebo (50% insulin + metformin or TZD)	Pilot study; patients on high doses of exogenous insulin	12 weeks	10, 20	10mg-24, 20mg-24 / Placebo-23
<b>Drug Naïve/Monotherapy</b>					
MB102013	Monotherapy vs. placebo	Inadequate control with diet and exercise alone	24 weeks 78 week extension	2.5, 5, 10	AM dosing 2.5mg-65, 5mg-64, 10mg-70 / Placebo-75
MB102032	Low dose monotherapy vs. placebo	Inadequate control with diet and exercise alone	24 weeks	1, 2.5, 5	1mg-72, 2.5mg-74, 5mg-68 / Placebo-68
<b>Add-on combination studies</b>					
MB102014	Add-on to metformin IR vs. placebo (metformin $\geq$ 1500 mg)	Inadequate glycemic control on background therapy alone	24 weeks 78 week extension	2.5, 5, 10	2.5mg-137, 5mg-137, 10mg-135 / Placebo-137
D1690C00005	Add-on to SU vs. placebo (glimepiride 4 mg)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension	2.5, 5, 10	2.5mg-154, 5mg-142, 10mg-151 / Placebo-145
MB102030	Add-on to TZD vs. placebo (pioglitazone $\geq$ 30 mg)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension	5, 10	5mg-141, 10mg-140 / Placebo-139
D1690C00006	Add-on to insulin vs. placebo (Insulin $\geq$ 30 IU $\pm$ 2 OAD)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension 56 weeks—ongoing	2.5, 5, 10	2.5mg-202, 5mg-211, 10mg-194 / Placebo-193
<b>Active comparator with add on combination</b>					

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D1690C00004	Add-on to metformin IR vs. glipizide (metformin $\geq 1500$ mg)	Inadequate control on metformin	52 weeks 52 week extension—ongoing 104 week extension—ongoing	Dapagliflozin 2.5, 5, 10 / Glipizide 10 or 20 mg	Dapagliflozin-400 Glipizide-401
<b>Drug Naïve Initial Combination</b>					
MB102034	Initial combo with metformin XR vs. metformin XR or Dapagliflozin monotherapy	Baseline HbA1c $\geq 7.5$ to $\leq 12$	24 weeks	Dapagliflozin 10 mg / Metformin up to 2000 mg	Metformin 208 Dapagliflozin 10 mg-219 Metformin plus Dapagliflozin-211
MB102021	Initial combo with metformin XR vs. metformin XR or Dapagliflozin monotherapy	Baseline HbA1c $\geq 7.5$ to $\leq 12$	24 weeks	Dapagliflozin 5 mg / Metformin up to 2000 mg	Metformin 201 Dapagliflozin 10 mg-203 Metformin plus Dapagliflozin-194
<b>Moderate renal impairment</b>					
MB102029	Monotherapy vs. placebo (any AD combination except metformin)	Moderate renal impairment with inadequate glycemic control on a stable regimen	24 weeks 28 week extension 52 weeks—ongoing	5, 10	5mg-83, 10mg-85 / Placebo-84
<b>Body Weight and Composition Study</b>					
D1690C00012	Add-on to metformin vs. placebo	Baseline HbA1c $\geq 6.5$ to $\leq 8.5$ and BMI $\geq 25$ kg/m <sup>2</sup>	24 weeks 78 week extension	10	10mg-91 / Placebo-91

AD=anti-diabetic medication  
SU=sulfonylurea

## 5.2 Review Strategy

### ***Studies and Organization***

All phase 3 studies will be discussed throughout section 6 *Review of Efficacy*, with the exception of D1690C00012, what the applicant terms a “weight and body composition study.” This study will be discussed predominantly in the efficacy subsection 6.1.6 *Other Endpoints*; the primary endpoint in the latter differed from the other 10 phase 3 studies.

The phase 3 studies, when appropriate, will be divided into five categories: monotherapy, add-on combination, active comparator, initial combination/active comparator and renal impairment. The studies in each of these groupings are displayed in Table 10. There are no pooled results for these groupings. Instead, individual study results will be presented.

Long-term extension treatment periods have been completed for many of the studies. These will be discussed in section 6.1.9 *Discussion of Persistence of Efficacy and/or Tolerance Effects* as exploratory analyses.

### ***Analysis Sets***

The main dataset (referred to as the Efficacy Data Set) used in this review consists of all randomized subjects who took at least one dose of double-blind treatment with a non-missing baseline efficacy value and at least one post-baseline efficacy value. The applicant used the Last Observation Carried Forward (LOCF) as the primary method for imputation of missing data for analysis. A sensitivity analysis with observed cases (OC), not including these imputed data was performed for the individual studies. All studies were reviewed to ensure that results were consistent between the LOCF and OC analyses. I will present a few of these analyses to show this consistency. I selected the following studies that represent important components of the clinical program; the monotherapy studies, two of the add-on studies and one initial combination study.

Unless otherwise noted, the database presented in this efficacy review will be the Efficacy Data Set with LOCF methodology employed.

### ***Statistical Methods***

The applicant used an Analysis of Covariance (ANCOVA) model to analyze the primary and all secondary continuous endpoints. The model included treatment group as a fixed effect and baseline value as a continuous covariate. In studies with a pre-specified stratification factor other than site in the randomization, an additional variable for this

factor was included in the model. In most studies, the primary endpoint was evaluated by comparing the difference in the adjusted mean changes from baseline between the treatment groups and the comparator group(s), with adjustment for multiplicity by Dunnett's method. Secondary efficacy endpoint testing proceeded in a sequential manner using  $\alpha=0.05$  tests for the treatment groups found to be statistically significant in the primary efficacy analysis. The hierarchical testing strategy for the primary and secondary endpoints was designed to control the Type I error rate at the 2-sided 0.05 level within each treatment group.

The exception to the hierarchical testing method was study D1690C00012, the body composition study, where Hochberg's method rather than fixed sequential testing was chosen. This study was investigating a new area and Hochberg's method permitted testing of all key secondary endpoints.

### 5.3 Discussion of Individual Studies/Clinical Trials

Please see Table 10 for description of all the clinical trials. Section 6 *Review of Efficacy* describes all phase 3 studies in detail.

## 6 Review of Efficacy

Please refer to Dr. Jonathan Norton's statistical review of efficacy for this NDA for an additional detailed efficacy discussion.

### Efficacy Summary

#### 6.1 Indication

Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

##### 6.1.1 Methods

#### **Objectives**

The phase 3 studies were designed to demonstrate the safety and efficacy of dapagliflozin in a wide range of subjects with T2DM. The applicant selected patients with therapy backgrounds that were representative of the general population intended for treatment with dapagliflozin, including drug-naïve subjects at an early stage of disease and subjects taking oral antidiabetic agents or insulin at a later stage of the disease.

In monotherapy studies, dapagliflozin was tested in a monotherapy versus placebo setting. For studies designed with add-on combination therapy, placebo plus ongoing oral antidiabetic therapy (OADs) were administered compared to dapagliflozin plus ongoing OADs. In study D1690C00004, the active comparator study, dapagliflozin was compared to glipizide, on a background of metformin therapy. The initial combination studies were designed to evaluate initial combination treatment with dapagliflozin and metformin extended release (XR) in subjects with inadequate glycemic control.

One study (MB102029) evaluated the safety and efficacy of dapagliflozin in the subpopulation of subjects with T2DM and moderate renal impairment on a variety of background therapies.

### ***Endpoints***

The primary endpoint for nine of the phase three studies discussed in this section was HbA1c change from baseline at 24 weeks of treatment with dapagliflozin. For D1690C00004 the active comparator study, the primary efficacy endpoint was change from baseline in HbA1c to week 52.

### ***Doses of Dapagliflozin Studied***

Doses used for the studies were 1, 2.5, 5 and 10 mg. Of note, the monotherapy study, MB102013 had both AM and PM dosing regimens, in all other studies dapagliflozin was dosed in the AM. The doses for each study are given in Table 10.

### ***Study Design***

Please refer to Table 10 for a brief description of the differing study designs. The phase three studies included a qualification/enrollment phase of up to three weeks. During this time, laboratory samples were collected and eligibility criteria were determined. The end of this period was the first day of the placebo lead-in period. A lead-in period was included in all of the studies with the exception of the combination with insulin study (D1690C00006). In this study, patients had to be on a stable insulin regimen with a mean insulin dose of  $\geq 30$  IU injectable insulin for at least 8 weeks prior to enrollment. For the other studies, during the placebo lead-in period, patients were given diet and lifestyle instruction. In addition, compliance with placebo was assessed. For studies with background medication, doses of background medications were added or stabilized. The phase three studies included a short-term double-blind treatment period of 24 weeks, with the exception of study D1690C00004 (active comparator), which had a short-term period of 52 weeks. The primary endpoint was analyzed at the end of the short-term period. In seven of the 10 studies, the short-term treatment period was followed by a long-term extension treatment period of at least 24 weeks duration. Placebo-treated patients entering the long-term extension treatment period continued treatment with placebo, except for those in the monotherapy study with a 78 week extension, MB102013. In this study, placebo-treated patients who completed week 24

without rescue were treated with blinded metformin 500 mg daily during the long-term extension.

The long-term extension treatment periods were site- and subject-blinded, with the exception of study MB102029, the renal impairment study, where the long-term extension treatment period (28 weeks) was double blinded.

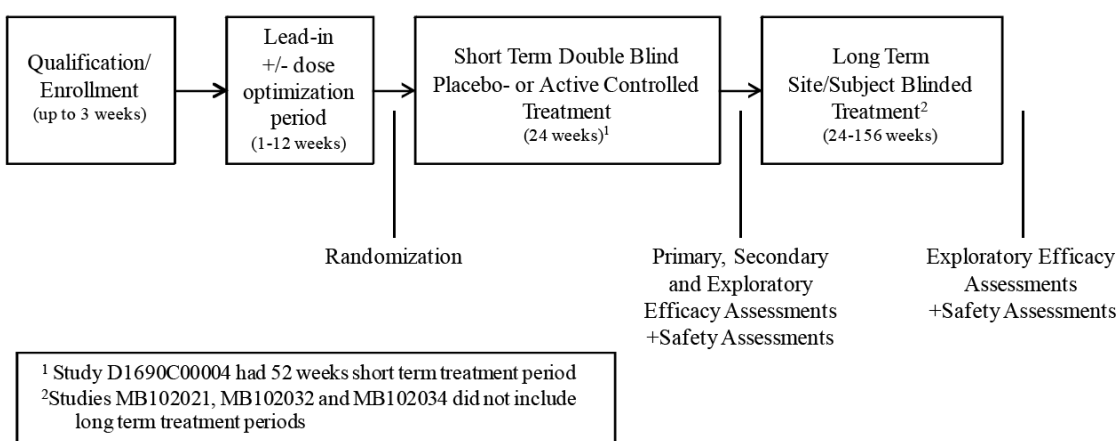
One of the monotherapy studies (MB102032) and the initial combination therapy studies (MB102021 and MB102034) did not include an extension.

Patients in all treatment arms were on the same regimen for the treatment period. From weeks 4 to 24, glycemic parameters were assessed to assess efficacy, and the protocols included glycemic criteria for institution of rescue medication.

### **Active Comparator Study DC1690C00004**

This study had a metformin dose stabilization period of 8 weeks prior to the two week lead in period. After the lead-in, there was a period for dose titration for dapagliflozin and glipizide. Patients were randomized 1:1 to glipizide or dapagliflozin (5 mg or 2.5 mg starting dose, respectively), and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL) or to the highest dose level (up to 20 mg glipizide daily and 10 mg dapagliflozin) as tolerated. After the highest dose was established, doses were kept constant, except for down-titration in the event of hypoglycemia.

**Figure 5 Study Design for Phase 3 Studies**



Source Figure 1 SCE

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***General Inclusion and Exclusion Criteria applicable to all studies***

**Main Inclusion Criteria**

- Males and females with T2DM  $\geq 18$  years of age were eligible for the phase 3 studies. There was no upper age limit unless metformin was a background therapy in the study, in which case the upper age limit was 77 years, due to the increased risk of renal impairment in this population (per metformin label).
- At enrollment, patients had to have HbA1c  $\geq 7.0$  and  $\leq 10.0\%$ , **unless noted below**
- Women of childbearing potential (WOCBP) had to be using an adequate method of contraception.
- C-peptide  $\geq 1.0$  ng/mL (0.34 nmol/L) at enrollment visit
- BMI  $\leq 45.0$  kg/m<sup>2</sup> at the enrollment visit

**Main Exclusion Criteria**

- Urine albumin: creatinine ratio (UACR)  $> 1,800$  mg/g (203.4 mg/mmol/Cr).
- Aspartate Aminotransferase (AST)  $> 3X$  upper limit of normal (ULN).
- Alanine Aminotransferase (ALT)  $> 3X$  ULN.
- Serum total bilirubin (TB)  $> 2$  mg/dL (34.2  $\mu$ mol/L).
- Serum Creatinine (Scr)  $\geq 1.5$  mg/dL (133  $\mu$ mol/L) for male and  $\geq 1.4$  mg/dL (124  $\mu$ mol/L) for female subjects (this is not a criterion for the renal impairment study)

**Other exclusion criteria:**

Severe hypertension, recent exacerbations of cardiovascular disease (i.e. myocardial infarction within six months of enrollment), renal disease (except renal impairment study), hepatic disease, hematological disease, oncological disease, and any unstable endocrine, psychiatric or rheumatic disorders. These criteria are detailed at length in the protocols.

**Additional key inclusion and exclusion criteria particular to the studies are detailed below.**

**Monotherapy Studies—MB 102013 & MB102032**

**Inclusion Criteria:**

Patients eligible were drug naïve. This was defined as patients who had never received prescription medications for diabetes or who had received prescription medications for diabetes for  $<24$  weeks since the original diagnosis, had not received antihyperglycemic therapy for at least 14 days (consecutive or not) during the 12 weeks prior to enrollment,



and who had not received any antihyperglycemic therapy during the 4 weeks prior to the enrollment visit.

### ***MB102013***

#### **Inclusion Criteria:**

This study included a cohort with baseline HbA1c  $\geq 10.1$  to  $\leq 12.0\%$  to evaluate treatment effects in patients expected to have what the applicant describes as clinically important glucosuria; this cohort did not include a placebo control arm. There is no explanation for this in the protocol other than the applicant wanted to assess safety and tolerability of dapagliflozin in a group with this HbA1c range.

### **Add on Studies MB102014, D1690C00005, MB102030, D1690C00006**

#### ***MB102014—add-on to metformin IR***

#### **Inclusion Criteria:**

Patients were generally required to be on a stable dose of background therapy for at least 8 weeks prior to screening or enrollment.

Patients who have been receiving stable metformin therapy for at least 8 weeks prior to enrollment, at a dose  $\geq 1500$  mg per day were eligible.

#### ***MB102030—add-on to Thiazolidinedione (TZD)***

#### **Inclusion Criteria:**

All patients had central laboratory A1C  $\geq 7.0$  and  $\leq 10.5\%$  obtained at entry into lead-in visit (pre-randomization HbA1c) including patients who were drug naïve in addition to those who were on stable TZD therapy. Drug-naïve patients were defined as having no exposure to OADs for 10 weeks with HbA1c  $\geq 8.0$  and  $\leq 11.0\%$ . Pioglitazone (TZD) patients had to be on stable dose of pioglitazone (30 or 45 mg/day) for at least 12 weeks prior to enrollment

#### ***D1690C00006—add-on to insulin***

#### **Inclusion Criteria:**

The lower end of the HbA1c inclusion criterion range is 7.5% due to the increased risk of hypoglycemia in this population.

Patients had to be on a stable insulin regimen with a mean insulin dose of least 30 IU of injectable insulin per day either without any OAD or with a stable dose of OADs that has been approved in combination with insulin. In addition, daily insulin requirements over the past seven days with insulin dose documentation could not vary more than 10% on more than one occasion of the calculated mean daily insulin dose at randomization.

**Exclusion Criteria:**

Treatment with more than two additional OADs.

**Active Control Study DC1690C00004**

**Inclusion Criteria:**

Inclusion criteria at start of metformin dose-stabilization period:

- HbA1c >6.5% and ≤10.0%; patients with HbA1c >6.5% to <7% were no longer eligible when the cohort of randomized patients having HbA1c <7% was approximately 25% of the study population, and the lower bound of HbA1c for enrollment was set at HbA1c ≥7% for the remainder of the study enrollment.
- FPG ≤ 270 mg/dL (≤15 mmol/L)
- C-peptide level ≥1.0 ng/mL (≥0.375 nmol/L)

Inclusion criteria at placebo lead-in period:

- Treatment with metformin alone on a stable dose of ≥1500 mg/day for at least 8 weeks.

For patients on a stable dose of metformin monotherapy ≥1500 mg/day with no other OAD therapy in the last 8 weeks and who skipped the metformin dose-stabilization period:

- HbA1c >6.5% and ≤10.0%; patients with HbA1c >6.5% to <7% were no longer eligible when the cohort of randomized patients having HbA1c <7% was approximately 25%, and the lower bound of HbA1c for enrollment was set at HbA1c ≥7% for the remainder of the study.
- FPG ≤270 mg/dL (≤15 mmol/L)
- C-peptide level ≥1.0 ng/mL (≥0.375 nmol/L)

Inclusion criteria at randomization:

- HbA1c >6.5% and ≤10.0%; patients with HbA1c >6.5% to <7% were no longer eligible when the cohort of randomized patients having HbA1c <7% was approximately 25%, and the lower bound of HbA1c for enrollment was set at HbA1c <7% for the remainder of the study enrollment.
- FPG ≤270 mg/dL (≤15 mmol/L)

**Initial Combination Studies MB102021 and MB102034**

**Inclusion Criteria:**

Studies MB102021 and MB102034 enrolled poorly controlled patients with HbA1c ≥7.5% and ≤ 12.0%.

Eligible patients were drug naïve, defined as never receiving prescription medications for diabetes or receiving prescription medications for diabetes for < 24 weeks since the original diagnosis, not receiving antihyperglycemic therapy for at least 14 days (consecutive or not) during the 12 weeks prior to enrollment, and not receiving any antihyperglycemic therapy during the 4 weeks prior to the enrollment visit.

**Renal Impairment Study MB102029**

**Inclusion Criteria:**

- Patients with T2DM with inadequate glycemic control, defined as central laboratory HbA1c ≥ 7.0 and ≤ 11.0% obtained at the enrollment visit
- Stable anti-diabetic regimen defined as either diet and exercise therapy alone or in combination with a regimen of any approved anti-diabetic medication(s), including insulin, in which either the doses of oral anti-diabetic medications have not changed during the 6 weeks prior to enrollment; or the doses of long-acting insulin or intermediate-acting insulin have not varied by more than 20% during the 6 weeks prior to enrollment.
- Patients with moderate renal impairment defined as an eGFR (estimated glomerular filtration rate) value in the range of 30 mL/min/1.73m<sup>2</sup> to 59 mL/min/1.73m<sup>2</sup>.

**Exclusion Criteria:**

Patients with other types of renal disease (i.e. lupus) and history of hemodialysis, ultrafiltration therapy, or peritoneal dialysis within 6 months prior to enrollment were excluded.

## ***Stratification***

### **Monotherapy Studies—MB102013 and MB102032**

Patients were stratified by site.

### **Add on Studies MB102014, D1690C00006, MB102030, D1690C00005**

For study MB102014, add on to metformin IR, stratification was done by site. Stratification at randomization for background therapy was done in studies MB102030 and D1690C00006.

In MB102030, the add-on to TZD study, randomization was stratified by pre-enrollment antihyperglycemic therapy (Group 1: pioglitazone 30 or 45 mg/day; Group 2: other eligible therapies including diet and exercise). Randomization of patients from Group 2 was limited to approximately 67% of the total number of subjects.

In study D1690C00006, the add-on to insulin study, randomization was stratified into two groups: those taking OADs and those not taking OADs at baseline. Subjects taking insulin plus OAD were not to exceed 60% of the total number of subjects.

There was no designated stratification plan for study D1690C00005.

### **Active Comparator Study D1690C00004**

There was no stratification plan in for this study. The applicant explains that the randomization was balanced given the large planned total sample size (746 randomized patients) and the large expected number of subjects with low HbA1c values (25% of the total = 187).

### **Initial Combination Studies MB102021 and MB102034**

MB102014 (add-on to metformin study) and MB102021 and MB102034 (initial combination studies).

### **Renal Impairment Study MB102029**

Stratification in study MB102029 was based on the pre-enrollment therapies: insulin-based regimen, sulfonylurea (SU)-based regimen, TZD-based regimen, or other regimen.

## Rescue Criteria

Patients who did not meet pre-specified glycemic targets received rescue medication, which varied from study to study. The pre-specified targets became more stringent as time progressed in the studies. In study D1690C00006, the add-on to insulin study, insulin was titrated to higher doses for rescue and there was no oral rescue therapy. In study D1690C00004, the active comparator study, there was no rescue medication. Patients were discontinued if they could not maintain glycemic control.

Table 11 provides the rescue plan for the phase 3 studies and Table 12 provides the rescue therapies used.

**Table 11 Rescue Criteria for Phase 3 Studies**

Background	Monotherapy		Add-on combination, placebo-controlled				Add-on combination vs SU	Initial combination with Metformin XR		Weight and body composition	Moderate renal impairment
	MB102013	MB102032	Metformin MB102014	SU D1690C00005	TZD MB102030	Insulin D1690C00006	Metformin D1690C00004	MB102021	MB102034	Metformin D1690C00012	Any <sup>a</sup> MB102029
None							none				
FPG >270 mg/dL	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7			Weeks 6,7	Weeks 6,7		Weeks 4,5
FPG >240 mg/dL	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 1 to 12 <sup>b</sup>		Weeks 8 to 11	Weeks 8 to 11	Weeks 4 to 7	Weeks 6 to 11
FPG >220 mg/dL						Weeks 13 to 24 <sup>b</sup>					
FPG >200 mg/dL	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24			Weeks 12 to 20	Weeks 12 to 20	Weeks 8 to 24	Weeks 12 to 24

Source: Protocols for MB102013, MB102032, MB102014, D1690C00005, MB102030, D1690C00006, D1690C00004, MB102021, MB102034, D1690C00012, MB102029

a Except metformin

b At least 3 fasting SMBG diary measurements from the past 7 days or visit measurement

Source SCE Appendix A2.5.1.1 Table 1

**Table 12 Rescue Medications for the Phase 3 Studies**

<b>Study Number— Description</b>	<b>Rescue Therapy</b>
MB102013— monotherapy	Metformin
MB102032— monotherapy	Metformin
MB102014—add-on to metformin	Pioglitazone or acarbose
D1690C00005— add-on to SU	Metformin or TZD
MB102030—add-on to TZD	Metformin or SU
D1690C00006— add-on to insulin	Insulin up-titration
D1690C00004— active comparator	None for first 104 weeks
MB102034—initial combination	Pioglitazone, acarbose or sitagliptin
MB102021—initial combination	Pioglitazone, acarbose or sitagliptin
MB102029—renal impairment	Any therapy except metformin

### 6.1.2 Demographics

Patients in the phase 3 studies came from 33 different countries. The total number of treated patients was 5693, of which 1581 (27.8%) were North American (1104 [19.4%] in the US) and 2361 (41.5%) were in European. In total, the mean age was 56 years; 1212 (21.3%) patients were ≥65 years old and 157 (2.8%) patients were ≥75 years old. The proportion of males (50.5%) was similar to the proportion of females (49.5%). Across the phase 3 studies, 83.7% of the patients were white, 3.4% were black or African American, and 10.2% were Asian.

Overall, there was generally a balance of patients across treatment groups in the studies. Of note, there were relatively few black or African American patients (3.4%) in the entire clinical program. The applicant states that this particular population is frequently underrepresented in clinical trials due to various factors such as poor access to primary medical care and cultural barriers. Hispanic/Latino ethnicity was reported for 11.8% of the subjects, though this information was requested only from sites in the US. The applicant argues that although some regions and races were less well represented, the effects of dapagliflozin are expected to be applicable to all regional populations as

available data suggest that SGLT2 polymorphisms are rare. No reports describing polymorphisms unique to different racial or ethnic groups have been identified.

***Reviewer's Comments***

**While lack of polymorphisms is a relevant point, in general, intrinsic factors play only a limited role in racial/ ethnic variability of effects in safety and efficacy. Dietary habits and lifestyle may also play important roles. The lack of African-American subjects will be addressed both in the efficacy and safety review, but is a common problem with clinical programs for antidiabetic therapies and has been seen in other NDAs. Of note, the PK data (please refer to Dr. Jain's review) does not indicate any differences in African-American patients.**

Demographics for the monotherapy studies are summarized in

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Table 13 and Table 14. Group 2 is the higher HbA1c entry group (HbA1c  $\geq 10.1$  to  $\leq 12.0\%$ ).

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**Table 13 Baseline Characteristics in Monotherapy Studies AM Dosing**

Category	Monotherapy (MB102013 QAM Dosing)				Monotherapy (MB102032)			
	Placebo N=75	Dapa 2.5 mg N=65	Dapa 5 mg N=64	Dapa 10 mg N=70	Placebo N=68	Dapa 1 mg N=72	Dapa 2.5 mg N=74	Dapa 5 mg N=68
Mean Age (yr) (SD)	52.7 (10.26)	53.0 (11.73)	52.6 (10.89)	50.6 (9.97)	53.5 (11.08)	53.7 (9.04)	53.5 (10.61)	51.3 (11.51)
Age <65, n (%)	66 (88.0)	54 (83.1)	54 (84.4)	66 (94.3)	55 (80.9)	63 (87.5)	61 (82.4)	61 (89.7)
≥65 Age < 75, n (%)	8 (10.7)	11 (16.9)	10 (15.6)	4 (5.7)	11 (16.2)	9 (12.5)	12 (16.2)	6 (8.8)
Age ≥75, n (%)	1 (1.3)	0	0	0	2 (2.9)	0	1 (1.4)	1 (1.5)
Male, n (%)	31 (41.3)	36 (55.4)	31 (48.4)	34 (48.6)	37 (54.4)	38 (52.8)	34 (45.9)	32 (47.1)
Female, n (%)	44 (58.7)	29 (44.6)	33 (51.6)	36 (51.4)	31 (45.6)	34 (47.2)	40 (54.1)	36 (52.9)
Race, n (%): White	71 (94.7)	63 (96.9)	61 (95.3)	63 (90.0)	57 (83.8)	56 (77.8)	61 (82.4)	55 (80.9)
Black/Afr. Amer.	2 (2.7)	0	1 (1.6)	2 (2.9)	3 (4.4)	4 (5.6)	2 (2.7)	3 (4.4)
Asian	2 (2.7)	2 (3.1)	1 (1.6)	3 (4.3)	7 (10.3)	11 (15.3)	10 (13.5)	10 (14.7)
Other	0	0	1 (1.6)	2 (2.9)	1 (1.5)	1 (1.4)	1 (1.4)	0
Ethnicity, n (%): Hispanic	13 (17.3)	8 (12.3)	6 (9.4)	7 (10.0)	3 (4.4)	1 (1.4)	2 (2.7)	3 (4.4)
Non-hispanic	19 (25.3)	16 (24.6)	14 (21.9)	20 (28.6)	10 (14.7)	13 (18.1)	11 (14.9)	9 (13.2)
Not reported	43 (57.3)	41 (63.1)	44 (68.8)	43 (61.4)	55 (80.9)	58 (80.6)	61 (82.4)	56 (82.4)
Geographic region, n (%): North America	41 (54.7)	31 (47.7)	27 (42.2)	37 (52.9)	24 (35.3)	25 (34.7)	24 (32.4)	21 (30.9)
Latin America	25 (33.3)	23 (35.4)	26 (40.6)	24 (34.3)	18 (26.5)	19 (26.4)	22 (29.7)	20 (29.4)
Europe	9 (12.0)	11 (16.9)	11 (17.2)	9 (12.9)	19 (27.9)	19 (26.4)	20 (27.0)	20 (29.4)
Asia/Pacific	0	0	0	0	7 (10.3)	9 (12.5)	8 (10.8)	7 (10.3)
Mean Baseline HbA1C (%) (SD)	7.84 (0.866)	7.92 (0.895)	7.86 (0.938)	8.01 (0.957)	7.80 (1.117)	7.80 (0.984)	8.11 (1.072)	7.94 (1.029)
Mean Duration of Diabetes (yr) (SD)	2.11 (3.086)	2.14 (3.228)	0.98 (1.580)	2.28 (3.668)	1.12 (1.954)	1.58 (2.554)	1.45 (2.190)	1.37 (3.242)
Mean Baseline weight (kg) (SD)	88.77 (18.986)	90.79 (22.763)	87.58 (17.077)	94.17 (18.661)	89.96 (17.981)	88.15 (18.488)	84.27 (18.177)	85.38 (19.429)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	0	0	0	0	0	0	0	0
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	2 (2.7)	6 (9.2)	6 (9.4)	5 (7.1)	3 (4.4)	4 (5.6)	1 (1.4)	5 (7.4)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	44 (58.7)	31 (47.7)	40 (62.5)	43 (61.4)	40 (58.8)	43 (59.7)	42 (56.8)	28 (41.2)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	29 (38.7)	28 (43.1)	18 (28.1)	22 (31.4)	25 (36.8)	25 (34.7)	31 (41.9)	35 (51.5)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

**Table 14 Baseline Characteristics in Monotherapy Studies PM Dosing and Group 2**

Category	Monotherapy (MB102013 QPM Dosing)			Monotherapy (MB102013 Group 2)	
	Dapa 2.5 mg N=67	Dapa 5 mg N=68	Dapa 10 mg N=76	Dapa 5 mg N=34	Dapa 10 mg N=39
Mean Age (yr) (SD)	54.3 (11.49)	54.5 (10.98)	50.7 (9.73)	48.3 (9.25)	47.9 (12.10)
Age <65, n (%)	52 (77.6)	53 (77.9)	72 (94.7)	34 (100.0)	36 (92.3)
≥65 Age < 75, n (%)	15 (22.4)	12 (17.6)	4 (5.3)	0	2 (5.1)
Age ≥75, n (%)	0	3 (4.4)	0	0	1 (2.6)
Male, n (%)	29 (43.3):	29 (42.6):	39 (51.3):	24 (70.6):	23 (59.0):
Female, n (%)	38 (56.7)	39 (57.4)	37 (48.7)	10 (29.4)	16 (41.0)
Race, n (%): White	65 (97.0)	65 (95.6)	72 (94.7)	31 (91.2)	38 (69.4)
Black/Afr. Amer.	1 (1.5)	1 (1.5)	2 (2.6)	1 (2.9)	0
Asian	1 (1.5)	0	1 (1.3)	1 (2.9)	1 (2.6)
Other	0	2 (3.0)	1 (1.3)	1 (2.9)	0
Ethnicity, n (%): Hispanic	8 (11.9)	7 (10.3)	10 (13.2)	10 (29.4)	8 (20.5)
Non-hispanic	20 (29.9)	19 (27.9)	22 (28.9)	8 (23.5)	12 (30.8)
Not reported	39 (58.2)	42 (61.8)	44 (57.9)	16 (47.1)	19 (48.7)
Geographic region, n (%): North America	33 (49.3)	34 (50.0)	41 (53.9)	16 (47.1)	20 (51.3)
Latin America	25 (37.3)	24 (35.3)	24 (31.6)	18 (52.9)	19 (48.7)
Europe	9 (13.4)	10 (14.7)	11 (14.5)	0	0
Asia/Pacific	0	0	0	0	0
Mean Baseline HbA1C (%) (SD)	7.99 (0.986)	7.82 (0.912)	7.99 (1.048)	10.82 (0.930)	10.73 (0.852)
Mean Duration of Diabetes (yr) (SD)	1.04 (1.608)	1.87 (3.093)	1.65 (2.698)	1.85 (2.928)	2.08 (2.347)
Mean Baseline weight (kg) (SD)	88.33 (20.474)	89.23 (20.454)	92.09 (21.965)	88.70 (19.208)	87.46 (22.671)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	0	0	0	0	0
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	3 (4.5)	6 (8.8)	5 (3.9)	0	1 (2.6)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	40 (59.7)	36 (52.9)	36 (47.4)	15 (44.1)	13 (33.3)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	24 (35.8)	26 (38.2)	37 (48.7)	19 (55.9)	25 (64.1)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

Table 15 summarizes the baseline demographics for the add-on studies.

**Table 15 Baseline Characteristics in Add-on Studies**

Category	Add-on Combination (MB102014) (metformin)				Add-on Combination (D1690C00005) (SU)			
	Placebo + met N=137	Dapa 2.5 mg + met N=137	Dapa 5 mg + met N=137	Dapa 10 mg + met N=135	Placebo + Gli N=145	Dapa 2.5 mg + Gli N=154	Dapa 5 mg + Gli N=142	Dapa 10 mg + Gli N=151
Mean Age (yr) (SD)	53.7 (10.29)	55.0 (9.27)	54.3 (9.41)	52.7 (9.91)	60.3 (10.16)	59.9 (10.14)	60.2 (9.73)	58.9 (8.32)
Age <65, n (%)	114 (83.2)	116 (84.7)	119 (86.9)	118 (87.4)	92 (63.4)	100 (64.9)	93 (65.5)	114 (75.5)
≥65 Age < 75, n (%)	23 (16.8)	19 (13.9)	17 (12.4)	16 (11.9)	46 (31.7)	45 (29.2)	40 (28.2)	32 (21.2)
Age ≥75, n (%)	0	2 (1.5)	1 (0.7)	1 (0.7)	7 (4.8)	9 (5.8)	9 (6.3)	5 (3.3)
Male, n (%)	76 (55.5)	70 (51.1)	69 (50.4)	77 (57.0)	71 (49.0)	77 (50.0)	71 (50.0)	66 (43.7)
Female, n (%)	61 (44.5)	67 (48.9)	68 (49.6)	58 (43.0)	74 (51.0)	77 (50.0)	71 (50.0)	85 (56.3)
Race, n (%): White	124 (90.5)	117 (85.4)	118 (86.1)	121 (89.6)	101 (69.7)	108 (70.1)	96 (67.6)	106 (70.2)
Black/Afr. Amer.	2 (1.5)	5 (3.7)	6 (4.4)	4 (3.0)	0	0	0	0
Asian	3 (2.2)	3 (1.5)	4 (2.9)	1 (0.7)	44 (30.3)	46 (29.9)	46 (32.4)	45 (29.8)
Other	8 (5.8)	12 (8.8)	9 (6.6)	9 (6.7)	0	0	0	0
Ethnicity, n (%): Hispanic	12 (8.8)	14 (10.2)	12 (8.8)	13 (9.6)	0	0	0	0
Non-hispanic	25 (18.2)	17 (12.4)	25 (18.2)	21 (15.6)	145 (100.0)	154 (100.0)	142 (100.0)	151 (100.0)
Not reported	100 (73.0)	106 (77.4)	100 (73.0)	101 (74.8)	0	0	0	0
Geographic region, n (%): North America	48 (35.0)	47 (34.4)	53 (38.7)	50 (37.0)	0	0	0	0
Latin America	89 (65.0)	90 (65.7)	84 (61.3)	85 (63.0)	0	0	0	0
Europe	0	0	0	0	101 (69.7)	108 (70.1)	96 (67.6)	106 (70.2)
Asia/Pacific	0	0	0	0	44 (30.3)	46 (29.9)	46 (32.4)	45 (29.8)
Mean Baseline HbA1C (%) (SD)	8.13 (0.958)	7.99 (0.894)	8.16 (0.962)	7.95 (0.835)	8.15 (0.736)	8.11 (0.749)	8.12 (0.781)	8.07 (0.790)
Mean Duration of Diabetes (yr) (SD)	5.83 (5.060)	6.02 (6.204)	6.38 (5.798)	6.14 (5.398)	7.38 (5.741)	7.71 (6.006)	7.35 (5.706)	7.15 (5.459)
Mean Baseline weight (kg) (SD)	87.85 (19.215)	84.90 (17.773)	84.73 (16.265)	86.10 (17.561)	80.94 (15.773)	81.89 (19.003)	81.00 (18.635)	80.56 (17.869)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	0	0	0	0	0	0	0	0
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	12 (8.8)	15 (10.9)	19 (13.9)	12 (8.9)	24 (16.6)	17 (11.0)	11 (7.7)	11 (7.3)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	71 (51.8)	76 (55.5)	76 (55.5)	71 (52.6)	79 (54.5)	90 (58.4)	80 (56.3)	93 (61.6)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	54 (39.4)	46 (33.6)	42 (30.7)	52 (38.5)	42 (29.0)	47 (30.5)	51 (35.9)	47 (31.1)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

Category	Add-on Combination (MB102030) (TZD)			Add-on Combination (D1690C00006) (insulin)			
	Placebo + Pio N=139	Dapa 5 mg + Pio N=141	Dapa 10 mg + Pio N=140	Placebo + ins N=193	Dapa 2.5 mg + ins N=202	Dapa 5 mg + ins N=211	Dapa 10 mg + ins N=194
Mean Age (yr) (SD)	53.5 (11.38)	53.2 (10.90)	53.8 (10.35)	58.8 (8.61)	59.8 (7.64)	59.3 (7.91)	59.3 (8.75)
Age <65, n (%)	115 (82.7)	120 (85.1)	118 (84.3)	144 (74.6)	150 (74.3)	163 (77.3)	146 (75.3)
≥65 Age < 75, n (%)	21 (15.1)	16 (11.3)	20 (14.3)	45 (23.3)	48 (23.8)	42 (19.9)	40 (20.6)
Age ≥75, n (%)	3 (2.2)	5 (3.5)	2 (1.4)	4 (2.1)	4 (2.0)	6 (2.8)	8 (4.1)
Male, n (%)	71 (51.1):	78 (55.3):	59 (42.1):	95 (49.2):	100 (49.5):	100 (47.4):	87 (44.8):
Female, n (%)	68 (48.9)	63 (44.7)	81 (57.9)	98 (50.8)	102 (50.5)	111 (52.6)	107 (55.2)
Race, n (%): White	102 (73.4)	102 (72.3)	101 (72.1)	186 (96.4)	190 (94.1)	200 (94.8)	184 (94.8)
Black/Afr. Amer.	6 (4.3)	9 (6.4)	7 (5.0)	6 (3.1)	3 (1.5)	5 (2.4)	5 (2.6)
Asian	24 (17.3)	26 (18.4)	21 (15.0)	0	7 (3.5)	3 (1.4)	3 (1.5)
Other	7 (5.0)	4 (2.8)	11 (7.9)	1 (0.5)	2 (1.0)	3 (1.4)	2 (1.0)
Ethnicity, n (%): Hispanic	20 (14.4)	18 (12.8)	21 (15.0)	2 (1.0)	2 (1.0)	3 (1.4)	4 (2.1)
Non-hispanic	30 (21.6)	38 (27.0)	29 (20.7)	191 (99.0)	200 (99.0)	208 (98.6)	190 (97.9)
Not reported	89 (64.0)	85 (60.3)	90 (64.6)	0	0	0	0
Geographic region, n (%): North America	61 (43.9)	65 (46.1)	62 (43.3)	39 (20.2)	41 (20.3)	49 (23.2)	40 (20.6)
Latin America	57 (41.0)	54 (38.3)	61 (43.6)	0	0	0	0
Europe	0	0	0	154 (79.8)	161 (79.7)	162 (76.8)	154 (79.4)
Asia/Pacific	21 (15.1)	22 (15.6)	17 (12.1)	0	0	0	0
Mean Baseline HbA1C (%) (SD)	8.36 (1.011)	8.40 (1.023)	8.37 (0.963)	8.47 (0.768)	8.46 (0.780)	8.62 (0.892)	8.57 (0.820)
Mean Duration of Diabetes (yr) (SD)	5.07 (5.048)	5.64 (5.362)	5.75 (6.438)	13.54 (7.277)	13.62 (6.574)	13.13 (7.841)	14.15 (7.315)
Mean Baseline weight (kg) (SD)	86.40 (21.324)	87.76 (20.701)	84.82 (22.177)	94.48 (19.823)	92.96 (16.733)	93.32 (17.434)	94.52 (16.790)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	0	0	0	0	0	0	0
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	7 (5.0)	4 (2.8)	13 (9.3)	27 (14.0)	31 (15.3)	42 (19.9)	30 (15.5)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	79 (56.8)	79 (56.0)	60 (42.9)	108 (56.0)	116 (57.4)	123 (58.3)	104 (53.6)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	53 (38.1)	58 (41.1)	67 (47.9)	58 (30.1)	55 (27.2)	46 (21.8)	60 (30.9)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

Table 16 summarizes the demographics for the active comparator study.

**Table 16 Baseline Characteristics in Active Comparator Study**

Category	Dapa + metformin N=400	Glip + metformin N=401
Mean Age (yr) (SD)	58.1 (9.37)	58.6 (9.80)
Age <65, n (%)	300 (75.0)	281 (70.1)
≥65 Age < 75, n (%)	83 (20.8)	109 (27.2)
Age ≥75, n (%)	17 (4.3)	11 (2.7)
Male, n (%)	221 (55.3)	220 (54.9)
Female, n (%)	179 (44.8)	181 (45.1)
Race, n (%): White	327 (81.8)	323 (80.5)
Black/Afr. Amer.	26 (6.5)	24 (6.0)
Asian	27 (6.8)	34 (8.5)
Other	20 (5.0)	20 (5.0)
Ethnicity, n (%): Hispanic	101 (25.3)	102 (25.4)
Non-hispanic	299 (74.8)	299 (74.6)
Not reported	0	0
Geographic region, n (%): North America	0	0
Latin America	104 (26.0)	101 (25.2)
Europe	296 (74.0)	300 (74.8)
Asia/Pacific	0	0
Mean Baseline HbA1C (%) (SD)	7.69 (0.855)	7.74 (0.886)
Mean Duration of Diabetes (yr) (SD)	6.08 (4.611)	6.55 (5.902)
Mean Baseline weight (kg) (SD)	88.44 (16.323)	87.60 (16.970)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	1 (0.3)	1 (0.2)
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	18 (4.5)	23 (5.7)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	198 (49.5)	181 (45.1)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	183 (45.8)	196 (48.9)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

Table 17 summarizes demographics for the initial combination studies.

**Table 17 Baseline Characteristics in Initial Combination Studies**

Category	Study MB102021			Study MB102034		
	Metformin XR up to 2000 mg N=201	Dapa 5 mg N=203	Metformin XR up to 2000 mg +Dapa 5 mg N=194	Metformin XR up to 2000 mg N=208	Dapa 10 mg N=219	Metformin XR up to 2000 mg +Dapa 10 mg N=211
Mean Age (yr) (SD)	51.8 (9.80)	52.3 (10.20)	51.7 (9.31)	52.7 (10.38)	51.1 (11.53)	51.0 (10.13)
Age <65, n (%)	184 (91.5)	183 (90.1)	177 (90.2)	181 (87.0)	192 (87.7)	190 (90.0)
≥65 Age < 75, n (%)	16 (8.0)	17 (8.4)	17 (8.8)	25 (12.0)	24 (11.0)	21 (10.0)
Age ≥75, n (%)	1 (0.5)	3 (1.5)	0	2 (1.0)	3 (1.4)	0
Male, n (%)	95 (47.3)	92 (45.3)	78 (40.2)	97 (46.6)	105 (47.9)	106 (50.2)
Female, n (%)	106 (52.7)	111 (54.7)	116 (59.8)	111 (53.4)	114 (52.1)	105 (49.8)
Race, n (%): White	158 (78.6)	166 (81.8)	153 (78.9)	166 (79.8)	176 (80.4)	174 (82.5)
Black/Afr. Amer.	6 (3.0)	4 (2.0)	8 (4.1)	8 (3.8)	13 (5.9)	11 (5.2)
Asian	35 (17.4)	33 (16.3)	32 (16.5)	31 (14.9)	27 (12.3)	24 (11.4)
Other	2 (1.0)	0	1 (0.5)	3 (1.4)	3 (1.4)	2 (0.9)
Ethnicity, n (%): Hispanic	28 (13.9)	25 (12.3)	22 (11.3)	35 (16.8)	34 (15.5)	34 (16.1)
Non-hispanic	36 (17.9)	41 (20.2)	40 (20.6)	54 (26.0)	63 (28.8)	54 (25.6)
Not reported	137 (68.2)	137 (67.5)	132 (68.0)	119 (57.2)	122 (55.7)	123 (58.3)
Geographic region, n (%): North America	70 (34.8)	74 (36.5)	69 (35.6)	94 (45.2)	104 (47.5)	96 (45.5)
Latin America	44 (21.9)	44 (21.7)	48 (24.7)	25 (12.0)	27 (12.3)	28 (13.3)
Europe	54 (26.9)	54 (26.6)	46 (23.7)	66 (31.7)	64 (29.2)	64 (30.3)
Asia/Pacific	33 (16.4)	31 (15.3)	31 (16.0)	23 (11.1)	24 (11.0)	23 (10.9)
Mean Baseline HbA1C (%) (SD)	9.18 (1.340)	9.13 (1.372)	9.24 (1.322)	9.05 (1.308)	9.05 (1.279)	9.09 (1.258)
Mean Duration of Diabetes (yr) (SD)	1.64 (2.577)	1.62 (3.071)	1.56 (2.445)	1.85 (4.009)	2.05 (3.793)	2.18 (3.332)
Mean Baseline weight (kg) (SD)	85.60 (20.000)	86.20 (21.132)	84.14 (19.474)	87.24 (19.423)	88.53 (19.334)	88.43 (19.668)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	0	1 (0.49)	0	0	0	0
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	8 (3.98)	13 (6.40)	12 (6.19)	14 (6.7)	12 (5.5)	11 (5.2)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	108 (53.73)	104 (51.23)	97 (50.00)	115 (55.3)	117 (53.4)	111 (52.6)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	85 (42.29)	85 (41.87)	85 (43.81)	79 (38.0)	90 (41.1)	89 (42.2)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

Table 18 summarizes the key demographics for the moderate renal impairment study.

**Table 18 Baseline Characteristics in Renal Impairment Study**

Category	Placebo N=84	Dapa 5 mg N=83	Dapa 10 mg N=85
Mean Age (yr) (SD)	67 (8.6)	66 (8.9)	68 (7.7)
Age <65, n (%)	36 (42.9)	39 (47.0)	29 (34.1)
≥65 Age < 75, n (%)	48 (57.1)	44 (53.0)	56 (65.9)
Age ≥75, n (%)	19 (22.6)	9 (10.8)	16 (18.8)
Male, n (%)	53 (63.1)	55 (66.3)	56 (65.9)
Female, n (%)	31 (36.9)	28 (33.7)	29 (34.1)
Race, n (%): White	69 (82.1)	65 (78.3)	77 (90.6)
Black/Afr. Amer.	1 (1.1)	7 (8.4)	4 (4.7)
Asian	6 (7.1)	4 (4.8)	3 (3.5)
Other	8 (9.5)	7 (8.4)	1 (1.2)
Ethnicity, n (%): Hispanic	1 (1.2)	4 (4.8)	2 (2.4)
Non-hispanic	21 (25.0)	28 (33.7)	32 (37.6)
Not reported	62 (73.8)	51 (61.4)	51 (60.0)
Geographic region, n (%): North America	41 (48.8)	51 (61.4)	48 (56.5)
Latin America	23 (27.4)	15 (18.1)	17 (20.0)
Europe	11 (13.1)	9 (10.8)	9 (10.6)
Asia/Pacific	9 (10.7)	8 (9.6)	11 (12.9)
Mean Baseline HbA1C (%) (SD)	8.53 (1.275)	8.30 (1.040)	8.22 (0.983)
Mean Duration of Diabetes (yr) (SD)	15.67 (9.455)	16.92 (9.017)	18.21 (10.114)
Mean Baseline weight (kg) (SD)	89.61 (20.046)	95.23 (20.909)	93.25 (17.309)
Baseline eGFR <30 mL/min/1.73 m <sup>2</sup> , n (%)	4 (4.8)	4 (4.8)	2 (2.4)
Baseline eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> , n (%)	34 (40.5)	41 (49.4)	47 (55.3)
Baseline eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> , n (%)	41 (48.8)	35 (42.2)	33 (38.8)
Baseline eGFR ≥90 mL/min/1.73 m <sup>2</sup> , n (%)	5 (6.0)	3 (3.6)	3 (3.5)

N is the number of subjects in the Randomized Subjects (BMS studies) of Full Analyses Set (AZ studies). Percentages are based on the total number of subjects in each treatment group.

**\*\*Important note about this table: there is an error in the baseline eGFR categories listed. The n (%) are correct but the categories should read as follows:**

- Baseline eGFR <30 mL/min/1.73 m<sup>2</sup>
- Baseline eGFR ≥ 30 to < 45 mL/min/1.73 m<sup>2</sup>
- Baseline eGFR ≥ 45 to < 60 mL/min/1.73 m<sup>2</sup>
- Baseline eGFR ≥ 60 mL/min/1.73 m<sup>2</sup>

Source: all tables from this section were taken from Response to FDA Inquiry 3/31/11

### ***Reviewer's Comments***

**While there are few black patients in these trials and this is not indicative of the U.S. T2DM population, there are adequate numbers of Hispanic patients in the trials to assess proper efficacy (11.3% in the phase 3 studies). The applicant's argument that efficacy response would not be expected to differ will be addressed in the subpopulation analyses. Of note, the patients in the add-on to insulin study generally had higher weight than in the other studies, which is expected due to weight gain with this treatment. This was also seen in the moderate renal impairment study, where insulin was allowed. The baseline HbA1c means varied as expected by inclusion criteria.**

#### **6.1.3 Subject Disposition**

In the phase three studies, 86.5% of subjects in all treatment groups completed the short-term (ST) period treatment periods. There were more patients in the control groups that were rescued or discontinued from the study due to lack of efficacy compared to patients treated with dapagliflozin (Table 19). Study D1690C00004, the active comparator study with a 52 week short-term (ST) period, did not include rescue criteria during the ST period. This could explain why this study had a lower completion rate than the other studies. In addition, this is a longer trial than the others and a lower completion rate is expected. In Study D1690C00006, the add-on to insulin study, insulin was titrated instead of another OAD used for rescue therapy and more patients were rescued. See rescue criteria details above under *Study Design—Rescue Criteria*.



**Table 19 Disposition of Patients in Phase 3 Studies**

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy <sup>a</sup> n (%)	Rescued n (%)
<b>Phase 3 placebo-controlled studies</b>					
<b>MB102013</b>					
Group 1 QAM dosing					
	Placebo	75	63 (84.0)	1 (1.3)	9 (12.0)
	Dapa 2.5 mg	65	60 (92.3)	0 (0.0)	7 (10.8)
	Dapa 5 mg	64	52 (81.3)	0 (0.0)	1 (1.6)
	Dapa 10 mg	70	57 (81.4)	0 (0.0)	0 (0.0)
Group 1: QPM dosing					
	Dapa 2.5 mg	67	58 (86.6)	0 (0.0)	2 (3.0)
	Dapa 5 mg	68	57 (83.8)	0 (0.0)	2 (2.9)
	Dapa 10 mg	76	65 (85.5)	0 (0.0)	0 (0.0)
Group 2 QAM dosing					
	Dapa 5 mg	34	28 (82.4)	0 (0.0)	3 (8.8)
	Dapa 10 mg	39	34 (87.2)	0 (0.0)	3 (7.7)
<b>MB102032</b>					
	Placebo	68	65 (95.6)	1 (1.5)	13 (19.1)
	Dapa 1 mg	72	68 (94.4)	1 (1.4)	4 (5.6)
	Dapa 2.5 mg	74	67 (90.5)	0 (0.0)	3 (4.1)
	Dapa 5 mg	68	63 (92.6)	1 (1.5)	3 (4.4)
<b>MB102014</b>					
	Placebo	137	119 (86.9)	3 (2.2)	22 (16.1)
	Dapa 2.5 mg	137	121 (88.3)	0 (0.0)	5 (3.6)
	Dapa 5 mg	137	122 (89.1)	1 (0.7)	5 (3.6)
	Dapa 10 mg	135	121 (89.6)	0 (0.0)	5 (3.7)
<b>D1692C00005</b>					
	Placebo	146	133 (91.1)	2 (1.4)	23 (15.8)
	Dapa 2.5 mg	154	140 (90.9)	0 (0.0)	9 (5.8)
	Dapa 5 mg	145	132 (91.0)	1 (0.7)	8 (5.5)
	Dapa 10 mg	151	141 (93.4)	0 (0.0)	3 (2.0)
<b>MB102030</b>					
	Placebo	139	116 (83.5)	3 (2.2)	16 (11.5)
	Dapa 5 mg	141	125 (88.7)	0 (0.0)	2 (1.4)
	Dapa 10 mg	140	126 (90.0)	1 (0.7)	5 (3.6)

<b>D1690C00006</b>					
Placebo	197	168 (85.3)	1 (0.5)	54 (27.4)	
Dapa 2.5 mg	202	179 (88.6)	1 (0.5)	20 (9.9)	
Dapa 5 mg	212	186 (87.7)	0 (0.0)	24 (11.3)	
Dapa 10 mg	196	178 (90.8)	0 (0.0)	19 (9.7)	
<b>D1690C00012</b>					
Placebo	91	86 (94.5)	0 (0.0)	2 (2.2)	
Dapa 10 mg	91	83 (91.2)	0 (0.0)	0 (0.0)	
<b>MB102029</b>					
Placebo	84	63 (75.0)	2 (2.4)	13 (15.5)	
Dapa 5 mg	83	72 (86.7)	0 (0.0)	9 (10.8)	
Dapa 10 mg	85	69 (81.2)	0 (0.0)	2 (2.4)	
<b>Phase 3 active comparator Add-on combination Study</b>					
<b>D1690C00004<sup>b</sup></b>					
SU (titrated dosing)	408	314 (77.0)	15 (3.7)	NA	
Dapa (titrated dosing)	406	322 (79.3)	1 (0.2)	NA	
<b>Phase 3 active comparator Initial Combination Studies</b>					
<b>MB102021</b>					
Metformin XR	201	171 (85.1)	0 (0.0)	26 (12.9)	
Dapa 5 mg	203	170 (83.7)	1 (0.5)	15 (7.4)	
Dapa 5 mg + Metformin XR	194	177 (91.2)	0 (0.0)	1 (0.5)	
<b>MB102034</b>					
Metformin XR	208	181 (87.0)	1 (0.5)	27 (13.0)	
Dapa 10 mg	219	188 (85.8)	1 (0.5)	17 (7.8)	
Dapa 10 mg + Metformin XR	211	183 (86.7)	0 (0.0)	3 (1.4)	

a Discontinuation due to lack of efficacy is determined from the glycemic control page of the CRF, or study termination page for study D1690C00005

Source Table 9 SCE

### Reviewer's Comments

As expected, more patients that were randomized to placebo required rescue therapy. The numbers, however, did not appear higher in the monotherapy studies (MB102013 and MB102032) compared to the add-on studies or initial combination studies. This indicates that dapagliflozin treatment alone was often sufficient. As indicated above, the proportion of patients rescued was higher in the add-on insulin study, D1690C00006; this study had less stringent rescue criteria during the treatment period.

In several of the studies, the number of patients that discontinued on placebo was similar to that of patients randomized to dapagliflozin.

Overall, the number of patients that were reported as discontinuing due to lack of efficacy was small, in both the placebo and dapagliflozin groups. In the active comparator study, there were more patients that discontinued participation in the SU group than in the dapagliflozin group.

Overall, these disposition data are not concerning.

#### 6.1.4 Analysis of Primary Endpoint(s)

##### **Monotherapy Studies MB102013 & MB102032**

Dapagliflozin at doses of 2.5 mg, 5 mg, and 10 mg daily (administered with the morning [QAM] or evening [QPM] meals) was evaluated in study MB102013. In study MB102032, doses of 1 mg, 2.5 mg, and 5 mg were administered in the AM only. In MB102013, the applicant performed primary analysis for the QAM groups while exploratory analyses were performed for the QPM groups. MB102013 also included an exploratory cohort of subjects with baseline HbA1c  $\geq 10.1\%$  to  $\leq 12.0\%$  (Group 2); there was no placebo control for this group.

In both studies, treatment with dapagliflozin resulted in statistically significant reductions in HbA1c by week 24 versus placebo in the 5 mg and 10 mg arms (10 mg in MB102013 only) (Table 20).

In study MB102013, the results were statistically significant for the 5 mg QAM and 10 mg QAM dose groups but not the 2.5 mg QAM dose group. The QPM dosing of dapagliflozin 2.5 mg, 5 mg, and 10 mg also provided reductions in HbA1c. Comparisons between the QAM and QPM groups are not indicative of a difference between the two dose regimens based on descriptive 95% confidence intervals of differences.

Comparing both studies, HbA1c reductions were statistically significant for the 1 mg and 2.5 mg dose arms in study MB102032, but not for the 2.5 mg QAM dose arm in study MB102013. Ninety-five percent confidence intervals exhibit overlap between treatment groups, and the applicant suggests that apparent differences may be explained by natural variability alone within study populations.

**Table 20 HbA1c (%) Change from Baseline at Week 24, Monotherapy Studies**

Treatment	MB102013		MB102032
	QAM dosing <sup>a</sup>	QPM dosing <sup>b</sup>	QAM dosing
<b>Placebo</b>	(N=75)	-	(N=68)
N#	72	-	68
Baseline mean (SD)	7.79 (0.831)	-	7.80 (1.117)
Mean at Week 24 (SD)	7.60 (1.434)	-	7.84 (1.787)
Adj. mean change (SE)	-0.23 (0.1044)	-	0.02 (0.1200)
<b>Dapagliflozin 1 mg/day</b>	-	-	(N=72)
N#	-	-	72
Baseline mean (SD)	-	-	7.80 (0.984)
Mean at Week 24 (SD)	-	-	7.15 (1.115)
Adj. mean change (SE)	-	-	-0.68 (0.1166)
Difference vs PLA (95% CI)	-	-	-0.69 (-1.02,-0.37)
p-value vs PLA	-	-	<0.0001 *
<b>Dapagliflozin 2.5 mg/day</b>	(N=65)	(N=67)	(N=74)
N#	64	62	72
Baseline mean (SD)	7.91 (0.892)	7.97 (0.997)	8.07 (1.032)
Mean at Week 24 (SD)	7.32 (1.178)	7.10 (1.086)	7.30 (1.100)
Adj. mean change (SE)	-0.58 (0.1107)	-0.83 (0.1125)	-0.72 (0.1169)
Difference vs PLA (95% CI)	-0.35 (-0.65,-0.05)	-0.61 (-0.91,-0.30)	-0.74 (-1.07,-0.41)
p-value vs PLA	0.0207	NA	<0.0001 *
<b>Dapagliflozin 5 mg/day</b>	(N=64)	(N=68)	(N=68)
N#	61	63	66
Baseline mean (SD)	7.83 (0.916)	7.74 (0.835)	7.92 (1.035)
Mean at Week 24 (SD)	7.09 (0.775)	7.01 (0.907)	7.10 (0.882)
Adj. mean change (SE)	-0.77 (0.1134)	-0.79 (0.1117)	-0.82 (0.1217)
Difference vs PLA (95% CI)	-0.54 (-0.84,-0.24)	-0.56 (-0.86,-0.26)	-0.84 (-1.17,-0.50)
p-value vs PLA	0.0005 *	NA	<0.0001 *
<b>Dapagliflozin 10 mg/day</b>	(N=70)	(N=76)	-
N#	65	73	-
Baseline mean (SD)	8.01 (0.952)	8.02 (1.061)	-
Mean at Week 24 (SD)	7.08 (0.751)	7.18 (0.994)	-
Adj. mean change (SE)	-0.89 (0.1099)	-0.79 (0.1037)	-
Difference vs PLA (95% CI)	-0.66 (-0.96,-0.36)	-0.56 (-0.85,-0.27)	-
p-value vs PLA	<0.001 *	NA	-

a In Study MB102013, the primary efficacy objective was assessed using data from Group 1, AM dosing.

b In Study MB102013, data from Group 1, PM dosing group was used to assess an exploratory efficacy objective related to dosing time of day.

(\*) Significant p-value compared to placebo: the primary endpoint was tested at alpha=0.019 applying the Dunnett's adjustment. In Study MB102013, both AM and PM treatment groups were included in the same ANCOVA model.

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

NA P-value is not available because this endpoint or exploratory dose group was not included in the sequential testing procedure for this study (BMS sponsored studies only).

Source SCE Table 12

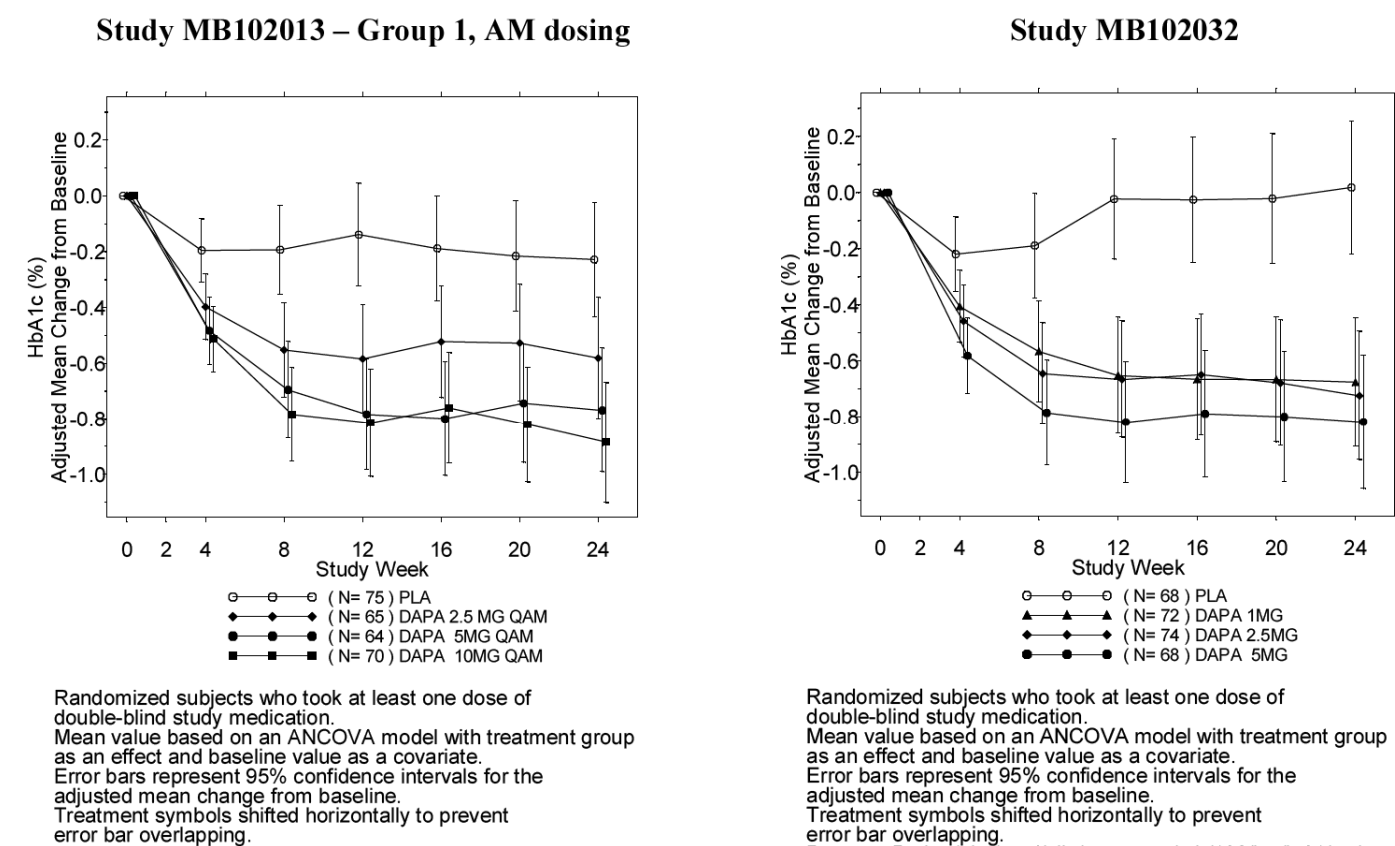
### Reviewer's Comments

**The modest efficacy seen with dapagliflozin is evident in all arms of this study. The sensitivity analyses for PM dosing show effect comparable to AM dosing.**

Interestingly, the lowest effect is seen in the AM dosing group for 2.5 mg in MB102013 as opposed to the 1 mg dosing group in MB102032.

**Error! Reference source not found.** Figure 6 shows the change in HbA1c over time for the two studies. In both studies, adjusted mean HbA1c was lower than baseline at each time point for all dapagliflozin treatment groups. Reductions were greater for each dapagliflozin arm versus placebo. The reductions are noted by week 4, the earliest time point measured. The maximum effect was generally seen by week 12, and efficacy was maintained until the end of the 24 week treatment time.

Figure 6 HbA1c Change Over Time, Monotherapy Studies—Efficacy Data Set



Source SCE Figure 5

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Treatment for Group 2, dosed with 5 mg and 10 mg (sensitivity analyses for higher baseline HbA1c 10.1-12.0% with no placebo arm), resulted in numerical HbA1c reductions from baseline of 2.88% and 2.66%, respectively, at week 24. The results did not appear to be dose dependent.

The observed cases (OC) analysis was also reviewed for both studies. This dataset does not include rescued patients or other LOCF imputed values. See Table 21 and Table 22 for results.

**Table 21 HbA1c (%) Change from Baseline at Week 24, MB102013—Observed Cases Repeated Measures Analysis**

	PIA N=75	DAPA 2.5MG QAM N=65	DAPA 5MG QAM N=64	DAPA 10MG QAM N=70	DAPA 2.5MG QPM N=67	DAPA 5MG QPM N=68	DAPA 10MG QPM N=76
WEEK: 24							
SUMMARY STATISTICS							
N#	55	53	49	55	56	55	63
BASELINE MEAN (SD)	7.70 ( 0.742)	7.81 ( 0.850)	7.76 ( 0.873)	8.06 ( 0.994)	7.84 ( 0.887)	7.72 ( 0.829)	7.96 ( 1.081)
WEEK 24 MEAN (SD)	7.16 ( 0.721)	6.99 ( 0.667)	7.00 ( 0.707)	7.08 ( 0.756)	6.98 ( 0.985)	6.93 ( 0.887)	7.05 ( 0.896)
MEAN CHANGE FROM BASELINE (SD)	-0.54 ( 0.752)	-0.82 ( 0.741)	-0.76 ( 0.826)	-0.98 ( 0.878)	-0.86 ( 0.883)	-0.79 ( 0.832)	-0.91 ( 0.983)
ADJUSTED CHANGE FROM BASELINE (a)							
MEAN (SE)	-0.62 ( 0.0944)	-0.83 ( 0.0960)	-0.80 ( 0.0999)	-0.86 ( 0.0947)	-0.86 ( 0.0934)	-0.85 ( 0.0944)	-0.84 ( 0.0882)
95% CI	[ -0.80, -0.43]	[ -1.02, -0.64]	[ -1.00, -0.61]	[ -1.05, -0.68]	[ -1.04, -0.68]	[ -1.04, -0.66]	[ -1.02, -0.67]
DIFFERENCE VS PIA (a)							
MEAN (SE)		-0.22 ( 0.1346)	-0.19 ( 0.1373)	-0.25 ( 0.1340)	-0.25 ( 0.1328)	-0.23 ( 0.1333)	-0.23 ( 0.1294)
95% CI		[ -0.48, 0.05]	[ -0.46, 0.08]	[ -0.51, 0.02]	[ -0.51, 0.02]	[ -0.50, 0.03]	[ -0.48, 0.03]

Source CTR Table S.5.2 page 341

**Table 22 HbA1c (%) Change from Baseline at Week 24, MB102032—Observed Cases Repeated Measures Analysis**

	PIA N=68	DAPA 1MG N=72	DAPA 2.5MG N=74	DAPA 5MG N=68
WEEK: 24				
SUMMARY STATISTICS				
N#	51	63	63	58
BASELINE MEAN (SD)	7.51 ( 0.796)	7.73 ( 0.890)	8.04 ( 1.038)	7.84 ( 1.002)
WEEK 24 MEAN (SD)	7.24 ( 1.074)	6.99 ( 0.833)	7.20 ( 1.003)	6.99 ( 0.778)
MEAN CHANGE FROM BASELINE (SD)	-0.28 ( 0.995)	-0.73 ( 0.849)	-0.84 ( 0.799)	-0.85 ( 0.956)
ADJUSTED CHANGE FROM BASELINE (a)				
MEAN (SE)	-0.41 ( 0.1104)	-0.76 ( 0.0985)	-0.73 ( 0.0993)	-0.83 ( 0.1026)
95% TWO-SIDED CI	[ -0.63, -0.19]	[ -0.96, -0.57]	[ -0.92, -0.53]	[ -1.03, -0.63]
DIFFERENCE VS PIA (a)				
MEAN (SE)		-0.36 ( 0.1476)	-0.32 ( 0.1499)	-0.42 ( 0.1510)
95% TWO-SIDED CI		[ -0.65, -0.06]	[ -0.61, -0.02]	[ -0.72, -0.12]

Source CTR Table S.5.2 page 536

### Reviewer's Comments

The difference in efficacy observed between the OC sensitivity analysis and the primary analysis is mostly explained by robust improvement in glycemic control observed in the placebo groups. This is especially evident in MB102013. In these OC data, the worst cases of response to treatment are censored. This censoring would have a greater effect in patients that are not receiving treatment (the placebo group) at least partially explaining the robust glycemic response seen in this group. This response in the placebo group may be further explained by other measures that were in place to assure compliance to diet and exercise recommendations.

**Add-on Studies MB102014, D1690C00005, MB102030, D1690C00006**

The add-on studies included MB102014 (add-on to metformin study), D1690C00005 (add-on to SU study), MB102030 (add-on to TZD study), and D1690C00006 (add-on to insulin  $\pm$  OAD study). The 5 mg and 10 mg dapagliflozin doses were included in all four studies. The 2.5 mg dose of dapagliflozin was included in all studies with the exception of MB102030 (add-on TZD).

In all four studies, treatment with dapagliflozin resulted in significant reductions in HbA1c at week 24 versus placebo. These reductions for this grouping appeared to be dose dependent (Table 23). The lowest reduction was seen with the 2.5 mg dose in study MB102014 (add-on to metformin study) at a placebo adjusted mean change of -0.4%. The greatest change was seen with 10 mg in D1690C00005 (add-on to SU study) with -0.7% mean reduction. For the proposed doses of 5 and 10 mg, the range of placebo adjusted mean reduction ranged from -0.4 to -0.7%.

**Table 23 HbA1c (%) Change from Baseline at Week 24, Add-on Studies**

Treatment	MB102014 Metformin	D1690C00005 SU	MB102030 TZD	D1690C00006 Insulin
<b>Placebo</b>	(N=137)	(N=145)	(N=139)	(N=193)
N#	134	143	138	188
Baseline mean (SD)	8.11 (0.959)	8.15 (0.741)	8.34 (1.003)	8.46 (0.764)
Mean at Week 24 (SD)	7.79 (1.184)	8.00 (0.928)	7.93 (1.375)	8.19 (0.972)
Adj. mean change (SE)	-0.30 (0.0718)	-0.13 (0.0625)	-0.42 (0.0834)	-0.30 (0.0521)
<b>Dapagliflozin 2.5 mg/day</b>	(N=137)	(N=154)	-	(N=202)
N#	135	154	-	198
Baseline mean (SD)	7.99 (0.897)	8.11 (0.749)	-	8.47 (0.776)
Mean at Week 24 (SD)	7.34 (0.934)	7.54 (0.871)	-	7.74 (0.815)
Adj. mean change (SE)	-0.67 (0.0715)	-0.58 (0.0602)	-	-0.75 (0.0507)
Difference vs PLA (95% CI)	-0.38 (-0.58,-0.18)	-0.44 (-0.61,-0.27)	-	-0.45 (-0.59,-0.31)
p-value vs PLA	0.0002 *	<0.0001 *	-	<0.0001 *
<b>Dapagliflozin 5 mg/day</b>	(N=137)	(N=142)	(N=141)	(N=211)
N#	133	142	140	210
Baseline mean (SD)	8.17 (0.964)	8.12 (0.781)	8.40 (1.026)	8.61 (0.893)
Mean at Week 24 (SD)	7.42 (0.937)	7.49 (0.924)	7.56 (1.068)	7.76 (0.898)
Adj. mean change (SE)	-0.70 (0.0722)	-0.63 (0.0627)	-0.82 (0.0828)	-0.82 (0.0493)
Difference vs PLA (95% CI)	-0.41 (-0.61,-0.21)	-0.49 (-0.67,-0.32)	-0.40 (-0.63, -0.17)	-0.52 (-0.66,-0.38)
p-value vs PLA	<0.0001 *	<0.0001 *	0.0007 *	<0.0001 *
<b>Dapagliflozin 10 mg/day</b>	(N=135)	(N=151)	(N=140)	(N=194)
N#	132	150	140	192
Baseline mean (SD)	7.92 (0.818)	8.07 (0.792)	8.37 (0.963)	8.58 (0.818)
Mean at Week 24 (SD)	7.13 (0.941)	7.27 (0.843)	7.40 (1.216)	7.66 (0.823)
Adj. mean change (SE)	-0.84 (0.0724)	-0.82 (0.0610)	-0.97 (0.0828)	-0.90 (0.0515)
Difference vs PLA (95% CI)	-0.54 (-0.74,-0.34)	-0.68 (-0.86,-0.51)	-0.55 (-0.78, -0.31)	-0.60 (-0.74,-0.45)
p-value vs PLA	<0.0001 *	<0.0001 *	<0.0001 *	<0.0001 *

(\*) Significant p-value compared to placebo: the primary endpoint was tested at alpha=0.019 (alpha=0.027 in study MB102030) applying Dunnett's adjustment.

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

Source SCE Table 18

### Reviewer's Comments

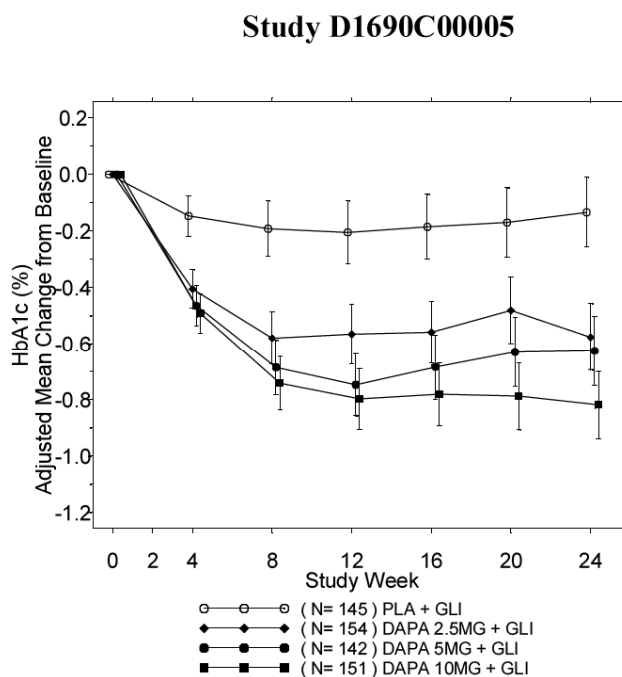
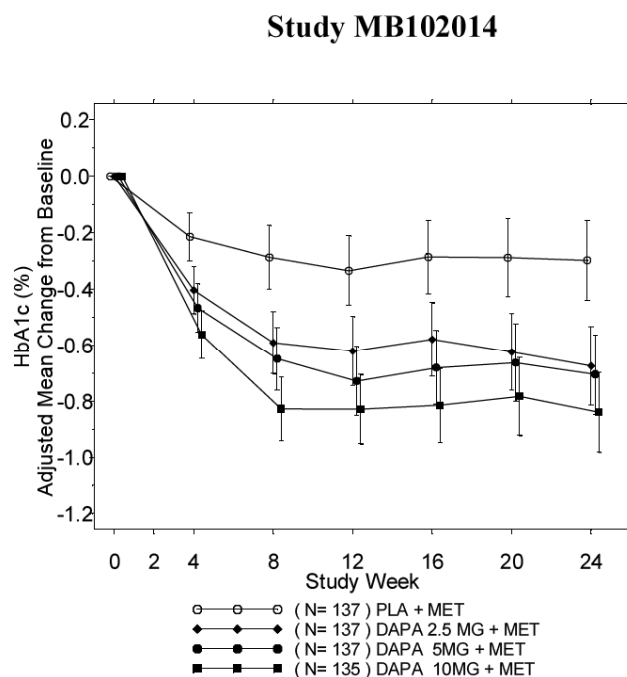
Although there is an evident dose response in this grouping, it is subtle.

HbA1c changes over time in these add-on studies are depicted in Figure 7. Error! Reference source not found.. Similar to the monotherapy studies, reductions in

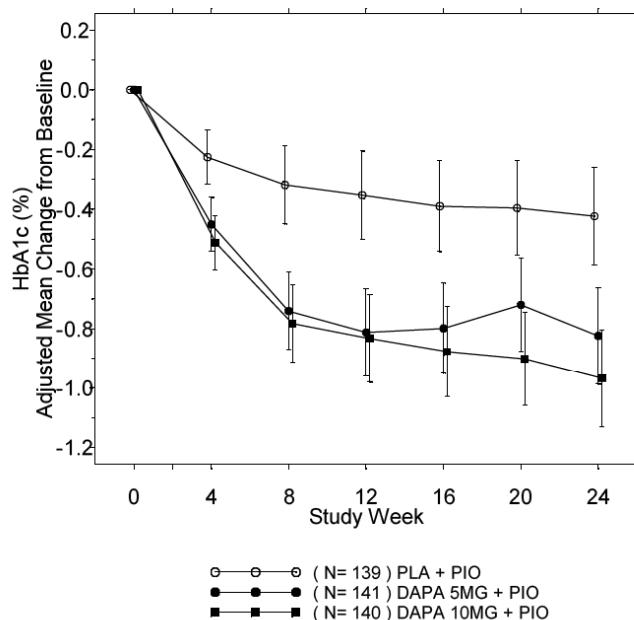


HbA1c were observed in all treatment groups relative to placebo at week 4, generally reached a plateau by week 8 to 12, and remained stable until week 24.

Figure 7 HbA1c Change Over Time, Add-on Studies—Efficacy Data Set

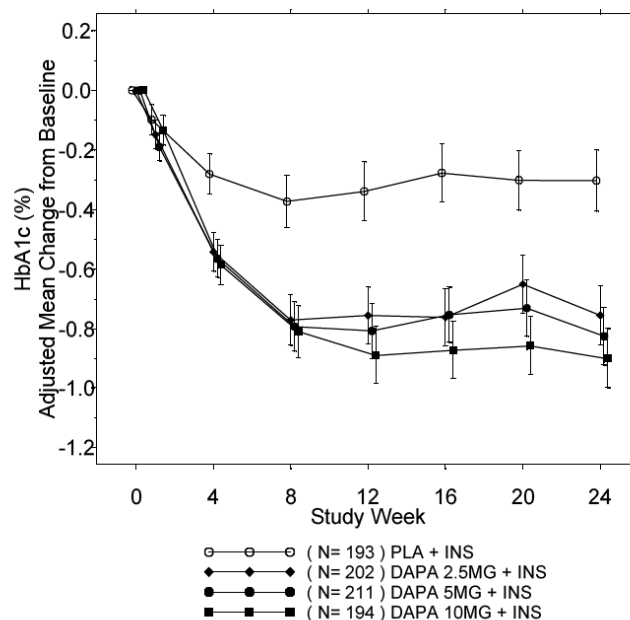


Study MB102030



Randomized subjects who took at least one dose of double-blind study medication.  
Mean value based on an ANCOVA model with treatment group as an effect, baseline value and enrollment strata as covariates.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.

Study D1690C00006



Subjects in the full analysis set  
Mean value based on an ANCOVA model with treatment group and stratum as effects and baseline value as a covariate.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.

Source SCE Figure 9

OC analysis were reviewed for all studies and presented for two of these studies below ( Table 24 and Table 25). Results were consistent with the main efficacy analysis; however, were not as robust (similar to the monotherapy studies).

Table 24 HbA1c (%) Change from Baseline at Week 24, MB102014—Observed Cases Repeated Measures Analysis

	PLA + MET N=137	DAPA 2.5MG + MET N=137	DAPA 5MG + MET N=137	DAPA 10MG + MET N=135
WEEK: 24				
SUMMARY STATISTICS				
N#	100	117	118	117
BASELINE MEAN (SD)	7.90 ( 0.826)	7.96 ( 0.898)	8.13 ( 0.941)	7.89 ( 0.769)
WEEK 24 MEAN (SD)	7.39 ( 0.938)	7.25 ( 0.850)	7.33 ( 0.863)	7.01 ( 0.781)
MEAN CHANGE FROM BASELINE (SD)	-0.51 ( 0.902)	-0.72 ( 0.899)	-0.80 ( 0.909)	-0.88 ( 0.771)
ADJUSTED CHANGE FROM BASELINE (a)				
MEAN (SE)	-0.55 ( 0.0750)	-0.72 ( 0.0693)	-0.72 ( 0.0693)	-0.92 ( 0.0694)
95% TWO-SIDED CI	[ -0.69, -0.40]	[ -0.86, -0.58]	[ -0.86, -0.59]	[ -1.06, -0.79]
DIFFERENCE VS PLA + MET (a)				
MEAN (SE)		-0.18 ( 0.1021)	-0.18 ( 0.1023)	-0.38 ( 0.1021)
95% TWO-SIDED CI		[ -0.38, 0.03]	[ -0.38, 0.02]	[ -0.58, -0.18]

Source CTR Table S.5.2 page 245

**Table 25 HbA1c (%) Change from Baseline at Week 24, MB102030—Observed Cases Repeated Measures Analysis**

	PLA + PIO N=139	DAPA 5MG + PIO N=141	DAPA 10MG + PIO N=140
WEEK: 24			
SUMMARY STATISTICS			
N#	104	122	123
BASELINE MEAN (SD)	8.22 ( 0.972)	8.36 ( 1.009)	8.32 ( 0.919)
WEEK 24 MEAN (SD)	7.68 ( 1.187)	7.45 ( 0.969)	7.23 ( 0.836)
MEAN CHANGE FROM BASELINE (SD)	-0.55 ( 0.863)	-0.92 ( 0.966)	-1.09 ( 0.976)
ADJUSTED CHANGE FROM BASELINE (a)			
MEAN (SE)	-0.58 ( 0.0823)	-0.89 ( 0.0760)	-1.08 ( 0.0757)
95% TWO-SIDED CI	[ -0.75, -0.42]	[ -1.04, -0.74]	[ -1.23, -0.93]
DIFFERENCE VS PLA + PIO (a)			
MEAN (SE)		-0.31 ( 0.1122)	-0.50 ( 0.1119)
95% TWO-SIDED CI		[ -0.53, -0.09]	[ -0.72, -0.28]

Source CTR Table S.5.2 page 671

### ***Reviewer's Comments***

**The placebo group response is quite robust. Still, the effect of dapagliflozin treatment remains consistent.**

### **Initial Combination Studies MB102021 and MB102034**

In MB102021, all arms experienced reductions in HbA1c by 24 weeks. Statistical inferential comparisons were made for the combination of dapagliflozin 5 mg plus metformin XR up to 2000 mg versus dapagliflozin alone and versus metformin alone; all were statistically significant and favorable to the dapagliflozin and metformin combinations as compared to the individual components (

Table 26).

In MB102034, the combination of dapagliflozin 10 mg plus metformin XR up to 2000 mg also resulted in statistically and clinically significant mean reductions in HbA1c as compared to both the dapagliflozin 10 mg monotherapy group and the metformin XR monotherapy group (

Table 26).

As part of the hierarchical testing strategy for study MB102034, this study included a secondary assessment of non-inferiority for change from baseline in HbA1c at Week 24 between dapagliflozin 10 mg monotherapy and metformin XR monotherapy (non-inferiority margin of 0.35%). Dapagliflozin 10 mg was found to be non-inferior to metformin XR in lowering HbA1c at week 24 (95% CI for difference -0.22 to 0.20).

**Table 26 HbA1c (%) Change from Baseline at Week 24, Initial Combination Studies**

Treatment	MB102021			MB102034		
	Metformin XR up to 2000 mg	Dapa 5 mg	Combination of Metformin XR up to 2000 mg + Dapa 5 mg	Metformin XR up to 2000 mg	Dapa 10 mg	Combination of Metformin XR up to 2000 mg + Dapa 10 mg
<b>Primary Efficacy Variable: HbA1c (%)</b>						
N	(N=201)	(N=203)	(N=194)	(N=208)	(N=219)	(N=211)
N#	195	196	185	203	216	202
Baseline mean (SD)	9.14 (1.317)	9.14 (1.374)	9.21 (1.305)	9.03 (1.295)	9.03 (1.272)	9.10 (1.276)
Mean at Week 24 (SD)	7.79 (1.530)	7.96 (1.443)	7.13 (1.201)	7.60 (1.420)	7.59 (1.232)	7.10 (1.001)
Adj. mean change (SE)	-1.35 (0.0868)	-1.19 (0.0866)	-2.05 (0.0892)	-1.44 (0.757)	-1.45 (0.0734)	-1.98 (0.0759)
Difference vs Dapa (95% CI)			-0.86 (-1.11, -0.62)			-0.53 (-0.74; -0.32)
p-value vs Dapa			<0.0001 *			<0.0001 *
Difference vs Met (95% CI)			-0.70 (-0.94, -0.45)			-0.54 (-0.75; -0.33)
p-value vs Met			<0.0001 *			<0.0001 *
Difference Dapa vs Met (95% CI)					-0.01 (-0.22, 0.20)*	
p-value for Dapa vs Met					0.9144	

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value: Secondary endpoints are tested following a sequential procedure at alpha=0.05. When combination is compared to each control, significance is claimed only if the combination is superior to both controls. In Study MB102034, a secondary objective was to compare Dapagliflozin 10 mg to Metformin, first by assessing non-inferiority using a margin of 0.35% for HbA1c (asterisk indicates non-inferiority successfully demonstrated, no p-value shown), and if successful, then by testing for superiority (p-value shown)

Source SCE Table 27

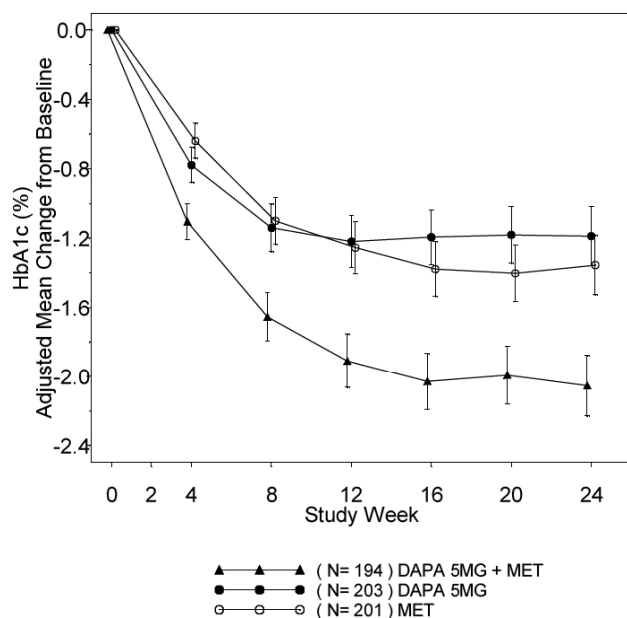
### Reviewer's Comments

This analyses provides reassurance that dapagliflozin combined with metformin provides improved glycemic control compared to dapagliflozin alone or metformin alone. There is no placebo arm here with which to compare results, however that data exist with other studies. As expected, the 10 mg dose provided in MB102034 resulted in better glycemic control than the 5 mg dose in MB102021. The non-inferiority result is proposed for inclusion in the label in both text and tabular format. Of note, these data are from a trial that has patients with worse glycemic control at baseline, where greater magnitude of improvement is expected. This should be mentioned in the label when these data are presented.

Similar to observations in other phase 3 study groups, reductions in mean HbA1c were evident by week 4. Here, the effect reaches a plateau at approximately weeks 8 to 12 for 5 mg dose and 12 to 16 weeks for 10 mg dose. The metformin XR and dapagliflozin (5 mg or 10 mg) plus metformin XR groups appear to plateau at weeks 16 to 20. The effect in all groups is still evident by week 24.

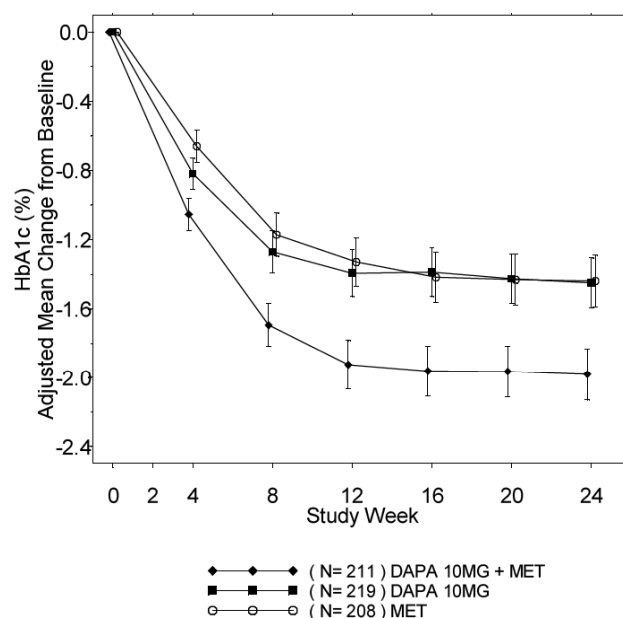
**Figure 8 HbA1c Change Over Time, Initial Combination Studies**

Study MB102021



Randomized subjects who took at least one dose of double-blind study medication.  
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.  
Report Path: \\shared\alis\programs\mb102021\figs\OC\mb102021\_OC.pdf

Study MB102034



Randomized subjects who took at least one dose of double-blind study medication.  
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.  
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Source SCE Figure 13

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OC data for MB102021 are presented in Table 27.

**Table 27 HbA1c (%) Change from Baseline at Week 24, MB102021—Observed Cases Repeated Measures Analysis**

	DAPA 5MG + MET N=194	DAPA 5MG N=203	MET N=201
WEEK: 24			
SUMMARY STATISTICS			
N#	169	159	148
BASELINE MEAN (SD)	9.19 ( 1.314)	8.99 ( 1.316)	8.94 ( 1.221)
WEEK 24 MEAN (SD)	7.13 ( 1.245)	7.69 ( 1.173)	7.35 ( 1.157)
MEAN CHANGE FROM BASELINE (SD)	-2.06 ( 1.590)	-1.30 ( 1.170)	-1.59 ( 1.293)
ADJUSTED CHANGE FROM BASELINE			
MEAN (SE)	-1.97 ( 0.0848)	-1.34 ( 0.0872)	-1.66 ( 0.0905)
95% TWO-SIDED CI	[ -2.13, -1.80]	[ -1.51, -1.16]	[ -1.84, -1.48]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS DAPA 5MG			
MEAN (SE)	-0.63 ( 0.1217)		
95% TWO-SIDED CI	[ -0.87, -0.39]		
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS MET			
MEAN (SE)	-0.30 ( 0.1242)		
95% TWO-SIDED CI	[ -0.55, -0.06]		

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 values.  
Based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.

Source CTR Table S.5.2 page 864

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### Reviewer's Comments

Though not compared to each other, the dapagliflozin plus metformin group has improved glycemic control over either group alone in this analysis which is consistent with the main efficacy data set with LOCF analysis.

### Active Control Study D1690C00004

D1690C00004 had an active control group on glipizide. This was the only phase 3 study to include a dose-titration scheme due to dosing recommendations for glipizide, see *Study Design* section. At the end of the titration period, 87% of patients in the dapagliflozin group had been titrated to the maximum dose (10 mg), versus 73% in the glipizide group (20 mg). Titration protocol was the same for patients on both arms and down-titration only occurred with recurrent hypoglycemia. Of the patients receiving dapagliflozin, 0.5% subsequently required down-titration compared to 5.1% of subjects receiving glipizide.

Treatment with either dapagliflozin or glipizide resulted in a mean reduction of 0.52% in HbA1c compared to baseline at week 52. Dapagliflozin was non-inferior to glipizide for change in HbA1c at Week 52 according to predetermined statistical criteria of a non-inferiority margin = 0.35%, with 95% confidence interval completely below margin. Table 28 displays these results.

**Table 28 Change from Baseline at Week 24, Active Comparator Study**

	<b>Dapa + metformin</b>	<b>Glip + metformin</b>
<b>Primary: HbA1c (%)</b>		
N	(N=400)	(N=401)
N#	400	401
Baseline mean (SD)	7.69 (0.855)	7.74 (0.886)
Mean at Week 52 (SD)	7.19 (0.760)	7.21 (1.090)
Adj. mean change (SE)	-0.52 (0.0403)	-0.52 (0.0402)
Difference vs glip + met (95% CI)	0.00 (-0.11, 0.11)	-
Non-inferiority p-value vs glip + metformin	<0.0001 *	-

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 52 (LOCF) values.

(\*) Significant p-value: Primary endpoint is significantly non-inferior (alpha=0.025 one-sided) if upper limit of 95% confidence interval is <0.35%.

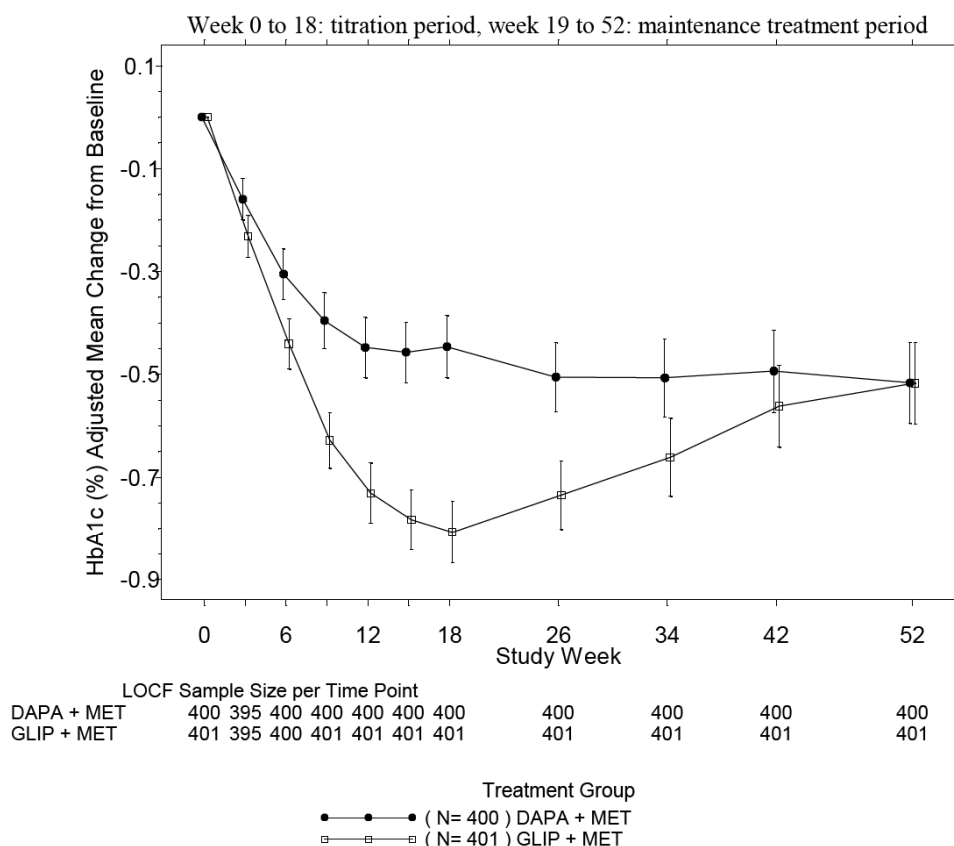
Source SCE Table 26

### ***Reviewer's Comments***

**Although we had not agreed in advance with the sponsor on the non-inferiority margin, this is reasonable and is consistent with the non-inferiority margin cited in the FDA Draft Guidance for Industry: *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.**

Figure 9 shows the change in HbA1c over time. In the dapagliflozin group, most of the HbA1c effect occurred by the twelfth week of treatment, with some further HbA1c reduction into week 52. In the glipizide group, there was a rapid decrease in HbA1c from baseline to week 18 followed by a trend of worsening glycemic control towards week 52. By week 52, the mean change from baseline in HbA1c was identical in both of the groups.

**Figure 9 HbA1c Change Over Time, Active Comparator Study**



Subjects in the full analysis set.

Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Treatment symbols shifted horizontally to prevent error bar overlapping.

## Source SCE Figure 12

The differences in adjusted mean changes from baseline in HbA1c between the dapagliflozin and the glipizide group in the OC analysis are consistent with the LOCF analysis (Table 29) at 52 weeks.



**Table 29 HbA1c (%) Change from Baseline at Week 52, D1690C00004—Observed Cases**

	DAPA + MET N=400	GLIP + MET N=401
WEEK: 52		
SUMMARY STATISTICS		
N#	321	315
BASELINE MEAN (SD)	7.71 ( 0.862)	7.72 ( 0.893)
WEEK 52 MEAN (SD)	7.14 ( 0.742)	7.13 ( 0.986)
MEAN CHANGE FROM BASELINE (SD)	-0.58 ( 0.709)	-0.59 ( 0.964)
ADJUSTED CHANGE FROM BASELINE		
MEAN (SE)	-0.58 ( 0.0412)	-0.59 ( 0.0416)
95% TWO-SIDED CI	[ -0.66, -0.50]	[ -0.67, -0.51]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS. GLIP + MET		
MEAN (SE)	0.01 ( 0.0585)	
95% TWO-SIDED CI	[ -0.10, 0.13]	

Source CSR Table 11.2.2.1.6

### **Renal Impairment Study MB102029**

In contrast to the results of the various subgroup analyses described above, the HbA1c mean changes from baseline by week 24 were small in both the dapagliflozin 5 mg and 10 mg treatment groups, and were not statistically significant (Table 30).

**Table 30 Change from Baseline at Week 24, Renal Impairment Study—Efficacy Data Set**

Treatment	Study MB102029		
	Placebo	Dapa 5 mg	Dapa 10 mg
HbA1c (%)	(N=84)	(N=83)	(N=85)
N#	82	83	82
Baseline mean (SD)	8.53 (1.285)	8.30 (1.040)	8.22 (0.973)
Mean at Week 24 (SD)	8.18 (1.204)	7.97 (1.150)	7.90 (0.930)
Adj. mean change (SE)	-0.32 (0.1701)	-0.41 (0.1701)	-0.44 (0.1708)
Difference vs PLA (95% CI)		-0.08 (-0.37, 0.20)	-0.11 (-0.40, 0.17)
p-value vs PLA		0.561	0.435

N is the number of subjects in the efficacy analysis data set (randomized subjects in BMS studies, full analysis set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

Source SCE Table 37

**Reviewer's Comments**

Dapagliflozin effect on glycemia depends on the plasma glucose concentration and the GFR. In patients with decreased GFR (such as those with moderate renal impairment), the lack of glycemic effect is expected.

**Results in Moderate Renal Impairment Study Patients—Two Groups**

The applicant subdivided moderate renal impairment into two sub-stages: 3A which defines a group with GFR 45 to 59 ml/min/1.73 m<sup>2</sup>, and 3B which defines a group with GFR 30 to 44 ml/min/1.73 m<sup>2</sup>. A sensitivity analysis was performed on these two groups.

**Table 31 HbA1c (%) Placebo Adjusted Mean Change from Baseline for Groups 3A and 3B**

Dose	Change from Baseline HbA1c (%) in 3A (SE)	Change from Baseline in HbA1c (%) in 3B (SE)
5 mg	N=35 -0.37 (0.23)	N=41 0.05 (0.21)
10 mg	N=33 -0.33 (0.24)	N=45 0.07 (0.21)

Source CSR ST and LT Appendices 38 and 39

**Reviewer's Comments**

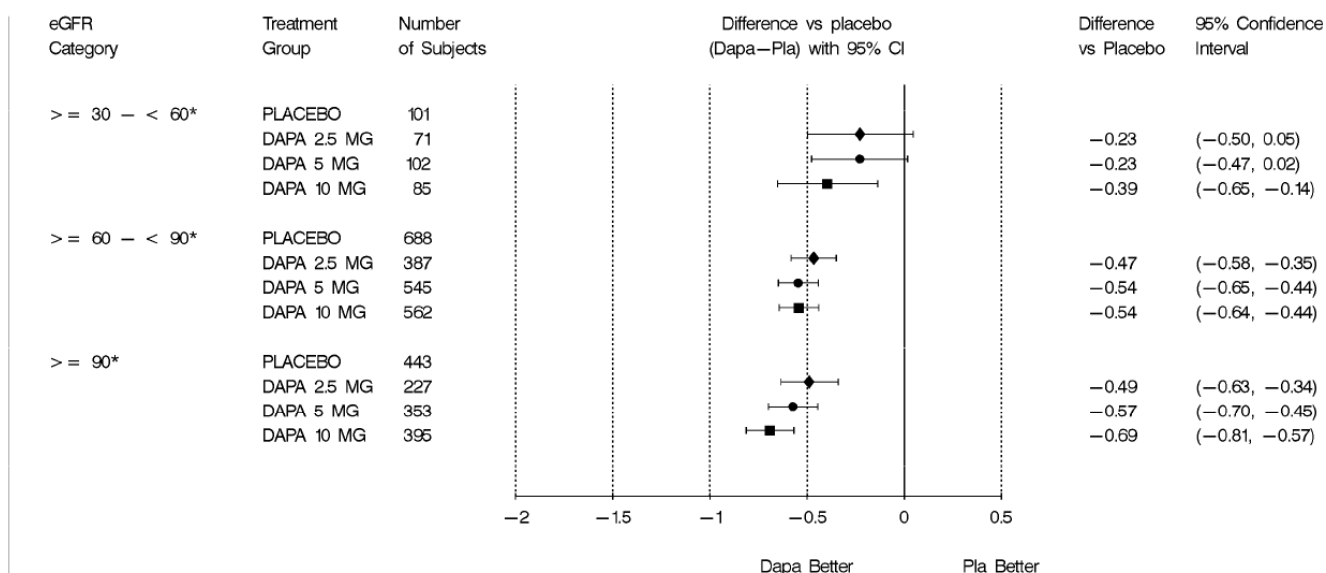
These results show a difference in placebo adjusted decrease in HbA1c between the two moderate impairment subgroups. However, this is a post-hoc analysis as the study was not designed to determine efficacy in this subgroup.

**Results in Subgroup of Subjects with Moderate Renal Impairment in the Pooled Monotherapy and Combination Studies**

The applicant performed a pooled analysis of efficacy in moderate renal impairment patients in nine placebo-controlled studies (2 monotherapy studies; four combination add-on to metformin, pioglitazone, glimepiride, and insulin studies; a body weight and composition study; and two initial combination with metformin studies).

Dapagliflozin 10 mg demonstrated a placebo-corrected mean HbA1c reduction of -0.4% for these patients, with a 95% CI excluding zero.

**Figure 10 Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 by eGFR\* Category, Monotherapy/Combination Therapy Pool\*\***



Randomized Patients/Full Analysis Set; excludes data after rescue

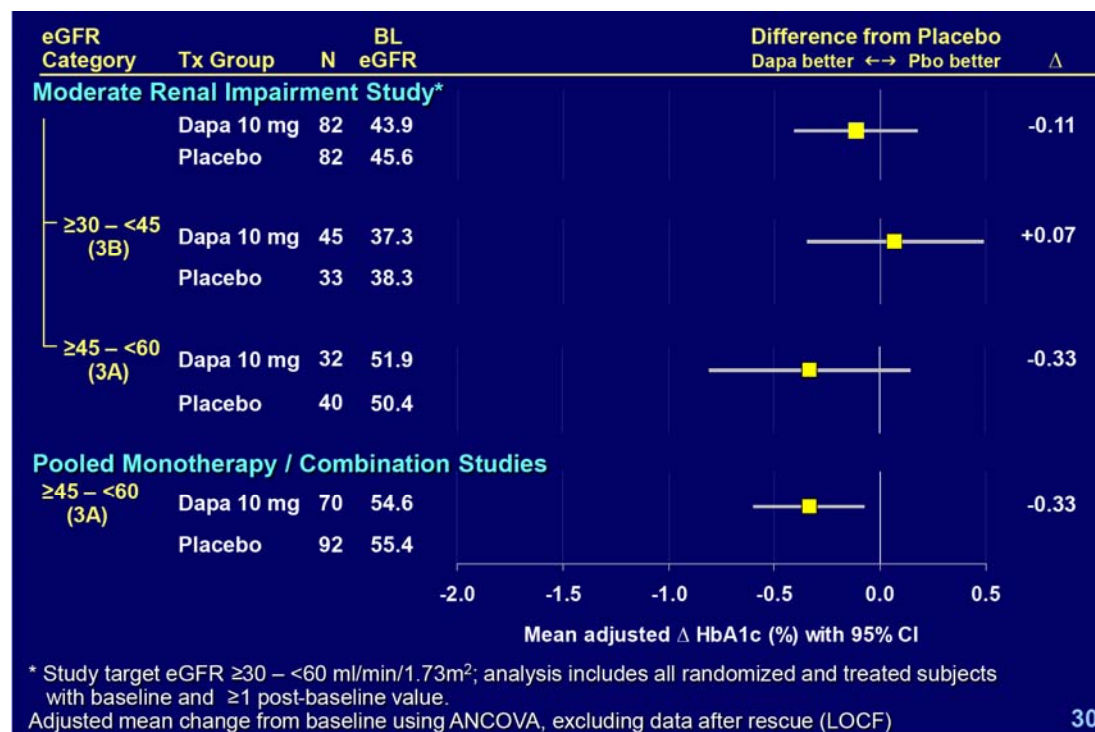
\* Units of eGFR are mL/min/1.73m<sup>2</sup>

\*\* Studies in Pooled Monotherapy/Combination Therapy Subgroup: monotherapy, low-dose monotherapy, excluding 1 mg, add-on to metformin, add-on to pioglitazone, add-on to glimepiride, add-on to insulin, body weight and composition, and initial combination with metformin (dapagliflozin 5 mg and 10 mg, excluding dapagliflozin only patients).

Source Applicant Advisory Committee Briefing Document Figure 25

The applicant also presented a slide at the advisory committee (AC) meeting that shows the efficacy of dapagliflozin 10 mg in the 3A subgroup in the monotherapy/combination studies pool as well as in the dedicated study. The mean difference from placebo was - 0.3%. See Figure 11.

Figure 11 Efficacy in Moderate Renal Impairment by Subgroup



Source Applicant's AC Slides, Slide 30

### Reviewer's Comments

(b) (4) the applicant proposes that dapagliflozin not be taken by patients with renal impairment defined as eGFR <45 mL/min/1.73 m<sup>2</sup> or CrCl <60 mL/min. The only evidence of efficacy in patients with eGFR >45 mL/min/1.73 m<sup>2</sup> < 60 mL/min/1.73 m<sup>2</sup> is that provided in the post-hoc analysis of the moderate renal impairment study and the AC data presented above. There was no dedicated study for this group. Dosing in patients with renal impairment between 45-60 mL/min/1.73 m<sup>2</sup> has not been adequately studied in the clinical program. Furthermore, separation of the moderate renal impairment category into two non-standard sub-categories may cause confusion for health care providers. I do not recommend this (b) (4) Dapagliflozin should not be used in any patient with moderate renal impairment (Stage 3).

Discussion at the AC meeting led to the question of HbA1c response by degree of macro or microalbuminuria. An inquiry was sent to the applicant. In this moderate renal impairment study, approximately one-third of the patients each had micro-, macroalbuminuria, or normoalbuminuria at baseline. An analysis of the change from baseline for urinary glucose to creatinine ratio stratified by baseline albuminuria was performed (see Table 32, Table 33 and Table 34) for this study. Results suggest that the glucosuric response with dapagliflozin is not affected by baseline albuminuria.

**Table 32 24-Hour Urinary Glucose to Creatinine Ratio (g/g) Change from Baseline Summary, 52-week Double blind Short-term Plus Long-term Treatment Period in Subjects with Baseline Urinary Albumin to Creatinine Ratio 0 to < 30 mg/g (MB102029)**

	Week	N#	Baseline Value		Value at Visit		Change From Baseline			
			Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error	Median	95% Confidence Interval
PLA (N = 27)	0	21			3.673	7.6786				
	6	20	3.849	7.8347	3.561	9.0828	-0.288	2.4182	0.000	( -5.349, 4.773)
	52	11	3.241	4.6720	1.967	2.9731	-1.274	0.8476	-0.160	( -3.162, 0.615)
DAPA 5MG (N = 30)	0	26			2.984	8.0923				
	6	25	3.102	8.2364	26.775	16.2887	23.673	3.1153	22.410	( 17.244, 30.103)
	52	14	1.379	1.9100	29.121	15.4822	27.743	4.0442	24.225	( 19.006, 36.480)
DAPA 10MG (N = 29)	0	20			3.622	6.9938				
	6	18	4.024	7.2768	29.215	15.1981	25.191	3.2391	23.965	( 18.357, 32.024)
	52	12	3.667	8.3452	26.784	20.9695	23.118	4.5473	21.210	( 13.109, 33.126)

**Table 33 24-Hour Urinary Glucose to Creatinine Ratio (g/g) Change from Baseline Summary, 52-week Double blind Short-term Plus Long-term Treatment Period in Subjects with Baseline Urinary Albumin to Creatinine Ratio ≥ 30 to <300 mg/g (MB102029)**

	Week	N#	Baseline Value		Value at Visit		Change From Baseline			
			Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error	Median	95% Confidence Interval
PLA (N = 33)	0	28			11.418	34.1305				
	6	27	10.994	34.7053	5.709	9.4769	-5.284	6.5162	0.180	(-18.679, 8.110)
	52	17	14.636	41.5769	6.295	10.2810	-8.341	8.5878	0.400	(-26.547, 9.864)
DAPA 5MG (N = 23)	0	18			3.684	7.4991				
	6	17	3.768	7.7211	34.888	34.1003	31.120	6.6008	23.610	( 17.127, 45.113)
	52	9	5.538	10.3241	30.089	23.5116	24.551	4.9492	25.740	( 13.138, 35.964)
DAPA 10MG (N = 34)	0	29			6.644	16.9668				
	6	27	7.126	17.5080	31.992	21.0766	24.866	3.9621	25.280	( 16.722, 33.011)
	52	17	9.044	21.6468	25.901	10.1620	16.857	4.9398	21.360	( 6.385, 27.329)

**Table 34 24-Hour Urinary Glucose to Creatinine Ratio (g/g) Change from Baseline Summary, 52-week Double blind Short-term Plus Long-term Treatment Period in Subjects with Baseline Urinary Albumin to Creatinine Ratio ≥ 300 mg/g (MB102029)**

	Week	N#	Baseline Value		Value at Visit		Change From Baseline			
			Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Error	Median	95% Confidence Interval
PLA (N = 24)	0	16			4.391	7.1989				
	6	16	4.391	7.1989	4.989	6.8181	0.598	2.4700	0.080	( -4.667, 5.863)
	52	6	3.520	6.2669	1.122	1.3041	-2.398	2.6465	0.075	( -9.201, 4.405)
DAPA 5MG (N = 30)	0	28			2.973	5.9454				
	6	27	3.033	6.0498	23.840	16.6723	20.807	2.6969	19.970	( 15.263, 26.350)
	52	17	3.442	6.8262	30.748	17.8059	27.306	4.0273	24.000	( 18.769, 35.844)
DAPA 10MG (N = 22)	0	18			5.529	10.2787				
	6	18	5.529	10.2787	29.753	12.5707	24.224	2.8970	20.970	( 18.112, 30.336)
	52	9	5.519	13.2398	34.658	9.7127	29.139	3.7476	30.310	( 20.497, 37.781)

Source FDA Response to Inquiry 7/29/2011

***\*\*Of note, the applicant plans to submit HbA1c analyses by baseline macro or microalbuminuria with pooled groups from the NDA in the near future.***

#### 6.1.5 Analysis of Secondary Endpoints(s)

(b) (4)

### ***Fasting Plasma Glucose***

#### **Monotherapy Studies MB 102013 & MB102032**

Significant reductions in FPG were seen with treatment with dapagliflozin by week 24 compared to placebo. This effect appeared to be dose dependent, Table 35.

In study MB102013, statistical testing was not performed for the dapagliflozin 2.5 mg group, consistent with sequential testing methods used to control type I error. In the exploratory PM dosing arms similar numerical reductions in FPG and apparent dose ordering were observed. In the exploratory analysis of Group 2 (HbA1c 10.1-12.0 % at baseline; no placebo control included) mean reductions from baseline in FPG were also observed.

In study MB102032, statistically significant decreases in FPG were observed for dapagliflozin 1 mg, 2.5 mg and 5 mg at Week 24.

**Table 35 FPG (mg/dL) Change from Baseline to Week 24, Monotherapy Studies**

Treatment	MB102013		MB102032
	AM dosing <sup>a</sup>	PM dosing <sup>b</sup>	AM dosing
<b>Placebo</b>	(N=75)	-	(N=68)
N#	75	-	68
Baseline mean (SD)	159.9 (42.08)	-	161.6 (57.46)
Mean at Week 24 (SD)	156.7 (49.81)	-	164.3 (56.02)
Adj. mean change (SE)	-4.1 (3.906)	-	4.1 (4.200)
<b>Dapagliflozin 1 mg/day</b>	-	-	(N=72)
N#	-	-	72
Baseline mean (SD)	-	-	155.6 (48.26)
Mean at Week 24 (SD)	-	-	145.8 (53.31)
Adj. mean change (SE)	-	-	-11.0 (4.082)
Difference vs PLA (95% CI)	-	-	-15.1 (-26.7, -3.6)
p-value vs PLA	-	-	0.0103 *
<b>Dapagliflozin 2.5 mg/day</b>	(N=65)	(N=67)	(N=74)
N#	65	67	74
Baseline mean (SD)	164.1 (48.01)	160.6 (45.85)	159.8 (51.47)
Mean at Week 24 (SD)	147.7 (64.95)	135.6 (33.54)	137.6 (35.17)
Adj. mean change (SE)	-15.2 (4.196)	-25.6 (4.132)	-21.6 (4.025)
Difference vs PLA (95% CI)	-11.1 (-22.4, 0.2)	-21.5 (-32.6, -10.3)	-25.7 (-37.2, -14.3)
p-value vs PLA	ND	NA	<0.0001 *
<b>Dapagliflozin 5 mg/day</b>	(N=64)	(N=68)	(N=68)
N#	62	66	67
Baseline mean (SD)	157.2(35.41)	154.8 (49.34)	157.1 (41.88)
Mean at Week 24 (SD)	135.4 (30.17)	130.9 (32.94)	129.3 ( 27.93)
Adj. mean change (SE)	-24.1 (4.298)	-27.3 (4.170)	-28.5 (4.230)
Difference vs PLA (95% CI)	-19.9 (-31.3, -8.5)	-23.2 (-34.4, -12.0)	-32.6 (-44.3, -20.8)
p-value vs PLA	0.0007 *	NA	<0.0001 *
<b>Dapagliflozin 10 mg/day</b>	(N=70)	(N=76)	-
N#	70	73	-
Baseline mean (SD)	166.6 (41.46)	167.8 (58.69)	-
Mean at Week 24 (SD)	135.4 (25.84)	135.2 (35.90)	-
Adj. mean change (SE)	-28.8 (4.046)	-29.6 (3.964)	-
Difference vs PLA (95% CI)	-24.7 (-35.7, -13.6)	-25.5 (-36.4, -14.5)	-
p-value vs PLA	<0.0001 *	NA	-

a In Study MB102013, the primary efficacy objective was assessed using data from Group 1, AM dosing.

b In Study MB102013, data from Group 1, PM dosing group was used to assess an exploratory efficacy objective related to dosing time of day.

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05. In Study MB102013, both AM and PM treatment groups were included in the same ANCOVA model.

NA P-value is not available because this endpoint or exploratory dose group was not included in the sequential testing procedure for this study (BMS sponsored studies only).

ND P-value is not calculated because a test of a previous endpoint in the sequential testing procedure was not statistically significant (defined as  $p \leq 0.05$ ) for this treatment group (BMS sponsored studies only).

Source SCE Table 13

### **Add-on Studies MB102014, D1690C00005, MB102030, D1690C00006**

Reductions in FPG from baseline to week 24 compared to placebo were observed across the add-on combination studies in the dapagliflozin treated patient groups (Table

36). These results were statistically significant with the exception of the 2.5 mg group in study D1690C00005 (add-on to SU) and the 5 mg group in study D1690C00006 (add-on to insulin) where formal statistical testing was not performed based on the hierarchical closed testing procedure; however, nominal p-values were generated. FPG reductions appeared to be generally dose dependent.

**Table 36 FPG (mg/dL) Change from Baseline to Week 24, Add-on Studies**

	MB102014	D1690C00005	MB102030	D1690C00006
Treatment	Metformin	SU	TZD	Insulin
<b>Placebo</b>	(N=137)	(N=145)	(N=139)	(N=193)
N#	136	145	139	177
Baseline mean (SD)	165.6 (46.39)	172.7 (37.31)	160.7 (46.97)	170.0 (57.30)
Mean at Week 24 (SD)	158.3 (44.61)	170.8 (44.56)	157.4 (47.70)	178.0 (61.39)
Adj. mean change (SE)	-6.0 (2.673)	-2.0 (2.528)	-5.5 (2.893)	3.3 (3.370)
<b>Dapagliflozin 2.5 mg/day</b>	(N=137)	(N=154)	-	(N=202)
N#	137	154	-	190
Baseline mean (SD)	161.5 (43.12)	172.2 (38.42)	-	180.7 (60.68)
Mean at Week 24 (SD)	144.6 (33.81)	155.7 (31.43)	-	166.3 (45.34)
Adj. mean change (SE)	-17.8 (2.663)	-16.8 (2.453)	-	-12.5 (3.247)
Difference vs PLA (95% CI)	-11.8 (-19.2, -4.4)	-14.9 (-21.8, -7.9)	-	-15.8 (-25.0, -6.6)
p-value vs PLA	0.0019*	<0.0001 <sup>nom</sup>	-	0.0008 *
<b>Dapagliflozin 5 mg/day</b>	(N=137)	(N=142)	(N=141)	(N=211)
N#	136	142	140	204
Baseline mean (SD)	169.2 (48.96)	174.5 (38.19)	168.3 (52.17)	185.1 (58.76)
Mean at Week 24 (SD)	144.6 (38.05)	152.4 (33.90)	141.3 (33.90)	161.7 (48.44)
Adj. mean change (SE)	-21.5 (2.679)	-21.2 (2.555)	-24.9 (2.884)	-18.8 (3.140)
Difference vs PLA (95% CI)	-15.5 (-22.9, -8.1)	-19.3 (-26.3, -12.2)	-19.5 (-27.5, -11.4)	-22.1 (-31.2, -13.1)
p-value vs PLA	<0.0001 *	<0.0001 *	<0.0001 *	<0.0001 <sup>nom</sup>
<b>Dapagliflozin 10 mg/day</b>	(N=135)	(N=151)	(N=140)	(N=194)
N#	132	150	140	183
Baseline mean (SD)	156.0 (38.68)	172.4 (36.82)	164.9 (46.34)	173.7 (54.88)
Mean at Week 24 (SD)	136.2 (33.93)	144.2 (31.79)	135.1 (37.67)	154.4 (43.52)
Adj. mean change (SE)	-23.5 (2.721)	-28.5 (2.485)	-29.6 (2.880)	-21.7 (3.309)
Difference vs PLA (95% CI)	-17.5 (-25.0, -10.0)	-26.5 (-33.5, -19.5)	-24.1 (-32.2, -16.1)	-25.0 (-34.3, -15.8)
p-value vs PLA	<0.0001 *	<0.0001 *	<0.0001 *	<0.0001 *

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05.

nom Nominal p-value without statistical inference performed. For AZ sponsored studies, a nominal p-value is calculated when either 1) the sequential testing procedure for this treatment group stopped because an earlier key secondary endpoint in the sequence was not statistically significant or 2) this endpoint was classified as an exploratory or 'other' secondary endpoint..

Source SCE Table 19



### **Initial Combination Studies MB102021 and MB102034**

Treatment with dapagliflozin 5 mg and 10 mg (combined with metformin XR) resulted in statistically significantly greater reductions from baseline in FPG at week 24 as compared with both of the two monotherapy treatments (Table 37).

The non-inferiority comparison of the monotherapy dapagliflozin group with the metformin monotherapy group (secondary objective in study MB102034) was statistically significant (Table 38). This comparison was performed with a non-inferiority margin of 15 mg/dL. In addition, the superiority comparison of the dapagliflozin group with the metformin group was statistically significant. In study MB102021, a comparison between dapagliflozin monotherapy versus metformin monotherapy was not statistically tested.

**Table 37 FPG (mg/dL) Change from Baseline to Week 24, Initial Combination Studies**

Treatment	MB102021			MB102034		
	Metformin XR up to 2000 mg	Dapa 5 mg	Combination of Metformin XR up to 2000 mg + Dapa 5 mg	Metformin XR up to 2000 mg	Dapa 10 mg	Combination of Metformin XR up to 2000 mg + Dapa 10 mg
<b>Secondary variable FPG (mg/dL)</b>						
N	(N=201)	(N=203)	(N=194)	(N=208)	(N=219)	(N=211)
N#	200	203	192	207	216	209
Baseline mean (SD)	196.7 (59.93)	190.8 (56.49)	193.4 (55.78)	189.9 (53.72)	197.5 (62.03)	189.6 (58.21)
Mean at Week 24 (SD)	161.3 (56.66)	150.5 (40.02)	132.5 (35.52)	156.6 (47.14)	147.8 (44.19)	131.0 (34.69)
Adj. mean change (SE)	-33.6 (2.728)	-42.0 (2.708)	-61.0 (2.783)	-34.8 (2.545)	-46.4 (2.494)	-60.4 (2.533)
Difference vs Dapa (95% CI)			-19.1 (-26.7; -11.4)			-13.9 (-20.9; -7.0)
p-value vs Dapa			<0.0001*			<0.0001*
Difference vs Met (95% CI)			-27.5 (-35.1; -19.8)			-25.5 (-32.6; -18.5)
p-value vs Met			<0.0001*			<0.0001*
Difference Dapa vs Met (95% CI)					-11.6 (-18.6, -4.6)*	
p-value for Dapa vs Met					0.0012*	

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value: Secondary endpoints are tested following a sequential procedure at alpha=0.05. When combination is compared to each control, significance is claimed only if is the combination is superior to both controls. In Study MB102034, a secondary objective was to compare Dapa 10 mg to Metformin, first by assessing non-inferiority using a margin 15 mg/dL for FPG (asterisk indicates non-inferiority successfully demonstrated, no p-value shown), and if successful, by testing then for superiority (p-value shown)

Source SCE Table 28

### **Reviewer's Comments**

The applicant's provided no rationale for the non-inferiority margin selected. However, the data show an improvement in FPG in the dapagliflozin group similar to that achieved with effective doses of metformin and its inclusion in the label is appropriate.

### **Active Comparator Study D1690C00004**

Subjects in both treatment groups showed a mean reduction in FPG from baseline to week 52 of approximately 20 mg/dL.

**Table 38 FPG (mg/dL) Change from Baseline to Week 24, Active Comparator Study**

	DAPA + MET N=400	GLIP + MET N=401
SUMMARY STATISTICS		
N#	399	394
BASELINE MEAN (SD)	162.3 ( 37.83)	164.3 ( 41.62)
WEEK 52 LOCF MEAN (SD)	140.5 ( 28.64)	144.9 ( 41.89)
MEAN CHANGE FROM BASELINE (SD)	-21.8 ( 33.43)	-19.4 ( 44.55)
ADJUSTED CHANGE FROM BASELINE		
MEAN (SE)	-22.4 ( 1.592)	-18.8 ( 1.603)
95% TWO-SIDED CI	[ -25.5, -19.2]	[ -21.9, -15.7]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS. GLIP + MET		
MEAN (SE)	-3.6 ( 2.260)	
95% TWO-SIDED CI	[ -8.0, 0.9]	
P-VALUE VS. GLIP + MET	0.1159	

Source Study Report Table 11.2.5

### **Renal Impairment Study MB102029**

Formal statistical hypothesis testing was not performed for this secondary endpoint in this study. Small reductions in FPG were seen with the 5 mg dose of dapagliflozin, but no change with the 10 mg dose.

**Table 39 FPG (mg/dL) Change from Baseline to Week 24, Renal Impairment Study**

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
SECONDARY EFFICACY ENDPOINT			
FPG (MG/DL) AT WEEK 24 (LOCF)			
N#	83	83	84
BASELINE MEAN (SD)	150.2 (48.19)	161.4 (55.88)	164.8 (66.81)
WEEK 24 LOCF MEAN (SD)	158.0 (50.01)	147.4 (54.12)	153.0 (58.38)
MEAN CHANGE FROM BASELINE (SD)	7.8 (53.80)	-14.0 (59.32)	-11.8 (83.55)
ADJ. MEAN CHANGE FROM BSL. (SE)	8.4 (9.621)	-5.2 (9.548)	-0.6 (9.524)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	( -10.5, 27.4)	( -24.0, 13.6)	( -19.3, 18.2)
DIFFERENCE FROM PLACEBO (SE)		-13.6 (8.142)	-9.0 (8.136)
95% CI FOR DIFFERENCE FROM PLACEBO		( -29.7, 2.4)	( -25.0, 7.0)

Source Study Report Table 5

## Two Hour Post Prandial Glucose

This was not a secondary endpoint in either of the initial combination studies, MB102021 and MB102034, the active comparator study D1690C00004, or the renal impairment study, MB102029.

## Monotherapy Study MB102032

This was not a secondary endpoint in MB102013.

There was a statistically significant decrease in change from baseline in 2-hour PPG after meal tolerance tests (MTT) at 24 weeks in study MB102032. This occurred in all three dapagliflozin dose groups in dose dependent manner, with the greatest reduction observed in the 5 mg group (Table 40).

**Table 40 PPG (mg/dL) Change from Baseline to Week 24, MB103032**

Treatment	Placebo (N=68)	Dapagliflozin 1 mg/day (N=72)	Dapagliflozin 2.5 mg/day (N=74)	Dapagliflozin 5 mg/day (N=68)
N#	58	67	58	58
Baseline mean (SD)	201.3 (70.214)	206.3 (69.096)	213.5 (66.475)	198.4 (70.741)
Mean at Week 24 (SD)	211.6 (84.270)	172.4 (67.390)	170.5 (50.670)	149.4 (41.315)
Adj. Mean change (SE)	8.81 (6.4925)	-33.3 (6.0390)	-39.3 (6.5025)	-51.8 (6.4973)
Difference vs PLA (95% CI)		-42.1 (-59.56, -24.61)	-48.1 (-66.27, -30.03)	-60.6 (-78.67, -42.50)
p-value vs PLA		<0.0001 *	<0.0001 *	<0.0001 *

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05.

Source SCE Table 14

## Add-on Studies D1690C00005, MB102030

Change in 2-hour PPG levels as a response to an oral glucose tolerance test (OGTT) from baseline to week 24 was a secondary variable in studies D1690C00005—add-on SU and MB102030—add-on TZD, it was not in MB102014—add-on metformin or D1690C00006—add-on insulin.

Dapagliflozin decreased 2-hour PPG levels in response to an OGTT from baseline to week 24, compared to placebo, across all dapagliflozin groups in both studies (Table 41). This effect was more pronounced in Study MB102030; however there was a much higher baseline mean PPG in this study compared to study D1690C00006. For the 2.5

mg group in study D1690C00005, formal statistical testing was not performed based on the hierarchical closed testing procedure (nominal p-value calculated). There was no clear dose relationship for the dapagliflozin effect on PPG within either study, in contrast to PPG after MTT results in MB102032, the monotherapy study reported above, where a dose-dependent effect was observed after MTT.

**Table 41 PPG (mg/dL) Change from Baseline to Week 24, Add-on Studies—Efficacy Data Set**

Treatment	Study D1690C00005	Study MB102030
	SU	TZD
<b>Placebo</b>	(N=145)	(N=139)
N#	109	112
Baseline mean (SD)	158.6 (58.75)	293.6 (81.17)
Mean at Week 24 (SD)	149.6 (68.82)	280.5 (88.12)
Adj. mean change (SE)	-6.0 (5.016)	-14.1 (6.421)
<b>Dapagliflozin 2.5 mg/day</b>	(N=154)	-
N#	126	-
Baseline mean (SD)	140.4 (68.18)	-
Mean at Week 24 (SD)	107.9 (58.37)	-
Adj. mean change (SE)	-37.5 (4.678)	-
Difference vs PLA (95% CI)	-31.5 (-45.0, -18.0)	-
p-value vs PLA	<0.0001 <sup>nom</sup>	-
<b>Dapagliflozin 5 mg/day</b>	(N=142)	(N=141)
N#	117	116
Baseline mean (SD)	151.2 (64.21)	284.8 (98.51)
Mean at Week 24 (SD)	119.4 (63.33)	225.1 (72.29)
Adj. mean change (SE)	-32.0 (4.836)	-65.1 (6.325)
Difference vs PLA (95% CI)	-26.0 (-39.7, -12.3)	-51.0 (-68.7, -33.2)
p-value vs PLA	0.0002 *	<0.0001 *
<b>Dapagliflozin 10 mg/day</b>	(N=151)	(N=140)
N#	132	115
Baseline mean (SD)	157.3 (69.03)	308.0 (92.76)
Mean at Week 24 (SD)	120.0 (65.17)	234.4 (84.66)
Adj. mean change (SE)	-34.9 (4.557)	-67.5 (6.359)
Difference vs PLA (95% CI)	-28.9 (-42.2, -15.6)	-53.3 (-71.1, -35.6)
p-value vs PLA	<0.0001 *	<0.0001 *

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05.

nom Nominal p-value without statistical inference performed. For AZ sponsored studies, a nominal p-value is calculated when either 1) the sequential testing procedure for this treatment group stopped because an earlier key secondary endpoint in the sequence was not statistically significant or 2) this endpoint was classified as an exploratory or 'other' secondary endpoint..

## ***Weight Changes***

### **Monotherapy Studies MB 102013 & MB102032**

In study MB102013, treatment with dapagliflozin 2.5 mg, 5 mg and 10 mg resulted in decreases in body weight compared to placebo, but these were not statistically significant. In study MB102032 there were statistically significant decreases in body weight in subjects treated with dapagliflozin 1 mg, 2.5 mg and 5 mg compared to placebo (Table 42). In neither of the studies was a dose response effect on weight loss noted. Weight loss was also noted in the placebo groups, though not statistically significant.

**Table 42 Weight (kg) Adjusted Mean Change from Baseline to Week 24, Monotherapy Studies—Efficacy Data Set**

Treatment	MB102013		MB102032
	AM dosinga	PM dosingb	AM dosing
<b>Placebo</b>	(N=75)	-	(N=68)
N#	75	-	68
Baseline mean (SD)	88.77 (18.99)	-	89.96 (17.981)
Mean at Week 24 (SD)	86.64 (18.63)	-	88.86 (17.770)
Adj. mean change (SE)	-2.19 (0.4297)	-	-0.96 (0.3942)
<b>Dapagliflozin 1 mg/day</b>	-	-	(N=72)
N#	-	-	72
Baseline mean (SD)	-	-	88.15 (18.488)
Mean at Week 24 (SD)	-	-	85.40 (18.488)
Adj. mean change (SE)	-	-	-2.69 (0.3820)
Difference vs PLA (95% CI)	-	-	-1.73 (-2.81, -0.65)
p-value vs PLA	-	-	0.0018 *
<b>Dapagliflozin 2.5 mg/day</b>	(N=65)	(N=67)	(N=74)
N#	65	67	74
Baseline mean (SD)	90.79 (22.76)	88.33 (20.474)	84.27 (18.177)
Mean at Week 24 (SD)	87.51 (21.95)	84.58 (19.208)	81.74 (16.978)
Adj. mean change (SE)	-3.25 (0.4615)	-3.82 (0.4548)	-2.64 (0.3776)
Difference vs PLA (95% CI)	-1.06 (-2.30, 0.18)	-1.63 (-2.86, -0.41)	-1.68 (-2.76, -0.60)
p-value vs PLA	ND	NA	0.0024 *
<b>Dapagliflozin 5 mg/day</b>	(N=64)	(N=68)	(N=68)
N#	62	66	67
Baseline mean (SD)	87.17 (16.09)	88.48 (19.987)	85.30 (19.566)
Mean at Week 24 (SD)	84.46 (16.57)	85.00 (20.002)	82.68 (18.899)
Adj. mean change (SE)	-2.83 (0.4731)	-3.55 (0.4582)	-2.69 (0.3961)
Difference vs PLA (95% CI)	-0.65 (-1.90, 0.61)	-1.36 (-2.60, -0.13)	-1.73 (-2.83, -0.63)
p-value vs PLA	0.3101	NA	0.0022 *
<b>Dapagliflozin 10 mg/day</b>	(N=70)	(N=76)	-
N#	69	74	-
Baseline mean (SD)	94.13 (18.79)	92.17 (22.242)	-
Mean at Week 24 (SD)	90.79 (18.30)	89.02 (21.328)	-
Adj. mean change (SE)	-3.16 (0.4493)	-3.05 (0.4329)	-
Difference vs PLA (95% CI)	-0.97 (-2.20, 0.25)	-0.87 (-2.06, 0.33)	-
p-value vs PLA	0.1189	NA	-

a In Study MB102013, the primary efficacy objective was assessed using data from Group 1, AM dosing.

b In Study MB102013, data from Group 1, PM dosing group was used to assess an exploratory efficacy objective related to dosing time of day.

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05. In Study MB102013, both AM and PM treatment groups were included in the same ANCOVA model.

NA P-value is not available because this endpoint or exploratory dose group was not included in the sequential testing procedure for this study (BMS sponsored studies only).

ND P-value is not calculated because a test of a previous endpoint in the sequential testing procedure was not statistically significant (defined as  $p \leq 0.05$ ) for this treatment group (BMS sponsored studies only)..

**Add-on Studies MB102014, D1690C00005, MB102030, D1690C00006**

Across the four add-on studies, treatment with dapagliflozin 2.5 mg, 5 mg, and 10 mg resulted in statistically significant reductions in body weight compared to placebo except for the 2.5 mg dose in study D1690C00005 (add-on to SU), where the reductions were not statistically significant (Table 43). A dose dependent effect was generally observed in the studies.

**Table 43 Weight (kg) Adjusted Mean Change from Baseline to Week 24, Add-on Studies**

	<b>MB102014</b>	<b>D1690C00005</b>	<b>MB102030</b>	<b>D1690C00006</b>
<b>Treatment</b>	Metformin	SU	TZD	Insulin
<b>Placebo</b>	(N=137)	(N=145)	(N=139)	(N=193)
N#	136	145	139	188
Baseline mean (SD)	87.74 (19.242)	80.94 (15.773)	86.40 (21.324)	94.21 (19.491)
Mean at Week 24 (SD)	86.81 (18.928)	80.22 (15.516)	88.05 (21.796)	94.22 (19.474)
Adj. mean change (SE)	-0.89 (0.2368)	-0.72 (0.2263)	1.64 (0.2760)	0.02 (0.1833)
<b>Dapagliflozin 2.5 mg/day</b>	(N=137)	(N=154)	-	(N=202)
N#	137	154	-	198
Baseline mean (SD)	84.90 (17.773)	81.89 (19.003)	-	93.10 (16.754)
Mean at Week 24 (SD)	82.71 (17.637)	80.69 (19.302)	-	92.13 (16.977)
Adj. mean change (SE)	-2.21 (0.2357)	-1.18 (0.2196)	-	-0.98 (0.1786)
Difference vs PLA (95% CI)	-1.32 (-1.98, -0.67)	-0.46 (-1.08, 0.15)	-	-1.00 (-1.50, -0.49)
p-value vs PLA	<0.0001 *	0.1410	-	0.0001 *
<b>Dapagliflozin 5 mg/day</b>	(N=137)	(N=142)	(N=141)	(N=211)
N#	137	142	140	210
Baseline mean (SD)	84.73 (16.265)	81.00 (18.635)	87.80 (20.769)	93.20 (17.377)
Mean at Week 24 (SD)	81.71 (16.143)	79.44 (18.363)	87.90 (21.423)	92.22 (17.201)
Adj. mean change (SE)	-3.04 (0.2358)	-1.56 (0.2286)	0.09 (0.2752)	-0.98 (0.1734)
Difference vs PLA (95% CI)	-2.16 (-2.81, -1.50)	-0.84 (-1.47, -0.21)	-1.55 (-2.32, -0.79)	-1.00 (-1.50, -0.50)
p-value vs PLA	<0.0001 *	0.0091 *	<0.0001 *	<0.0001 *
<b>Dapagliflozin 10 mg/day</b>	(N=135)	(N=151)	(N=140)	(N=194)
N#	133	151	140	192
Baseline mean (SD)	86.28 (17.527)	80.56 (17.869)	84.82 (22.177)	94.63 (16.829)
Mean at Week 24 (SD)	83.42 (17.391)	78.31 (17.804)	84.68 (22.263)	92.96 (16.665)
Adj. mean change (SE)	-2.86 (0.2392)	-2.26 (0.2217)	-0.14 (0.2753)	-1.67 (0.1814)
Difference vs PLA (95% CI)	-1.97 (-2.63, -1.31)	-1.54 (-2.17, -0.92)	-1.78 (-2.55, -1.02)	-1.68 (-2.19, -1.18)
p-value vs PLA	<0.0001 *	<0.0001 *	<0.0001 *	<0.0001 *

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05.

Source SCE Table 32

### **Initial Combination Studies MB102021 and MB102034**

The comparisons that were part of the planned sequential testing procedure differed between the two studies; in study MB102034 it was not required to calculate a p-value



for the combination versus dapagliflozin comparison in order to declare a statistically significant difference for the combination versus metformin comparison. In both studies, treatment with dapagliflozin 5 mg or 10 mg in combination with metformin resulted in a greater mean reduction in total body weight than treatment with metformin alone (Table 44). For study MB102021 the mean change in body weight in the combination treatment group was similar to the dapagliflozin 5 mg monotherapy treatment group.

**Table 44 Weight (kg) Adjusted Mean Change from Baseline to Week 24, Initial Combination Studies**

Treatment	Study MB102021			Study MB102034		
	Metformin XR up to 2000 mg	Dapa 5 mg	Combination of Metformin XR up to 2000 mg + Dapa 5 mg	Metformin XR up to 2000 mg	Dapa 10 mg	Combination of Metformin XR up to 2000 mg + Dapa 10 mg
N	(N=201)	(N=203)	(N=194)	(N=208)	(N=219)	(N=211)
N#	200	203	192	208	219	209
Baseline mean (SD)	85.75 (19.932)	86.20 (21.132)	84.24 (19.512)	87.24 (19.423)	88.53 (19.334)	88.56 (19.717)
Mean at Week 24 (SD)	84.45 (19.674)	83.57 (20.848)	81.62 (18.881)	85.92 (19.096)	85.78 (18.665)	85.21 (18.863)
Adj. mean change (SE)	-1.29 (0.2378)	-2.61 (0.2361)	-2.66 (0.2428)	-1.36 (0.2408)	-2.73 (0.2346)	-3.33 (0.2401)
Difference vs Dapa (95% CI)			-0.05 (-0.72, 0.61)			-
p-value vs Dapa mg			0.8769			-
Difference vs Met (95% CI)			-1.37 (-2.04, -0.71)		-1.37 (-2.03; -0.71)	-1.97 (-2.64; -1.30)
p-value vs Met			<0.0001		<0.0001*	<0.0001*

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

(\*) Significant p-value: Secondary endpoints are tested following a sequential procedure at alpha=0.05. When combination is compared to each control, significance is claimed only if the combination is superior to both controls.

Source SCE Table 35

### **Active Comparator Study D1690C00004**

A statistically significant mean reduction in body-weight-related variables from baseline to week 52 compared to glipizide was observed in the dapagliflozin treatment group ( Table 45).

**Table 45 Weight (kg) Adjusted Mean Change from Baseline to Week 24, Active Comparator Study**

	Dapa + metformin	Glip + metformin
Total body weight (kg)		
N	400	401
N#	400	401
Baseline mean (SD)	88.44 (16.323)	87.60 (16.970)
Mean at Week 52 (SD)	85.22 (16.191)	89.04 (17.560)
Adj. mean change <sup>a</sup> (SE)	-3.22 (0.1756)	1.44 (0.1754)
Difference vs glip + met (95% CI)	-4.65 (-5.14, -4.17)	
p-value vs glip + metformin	<0.0001 *	
Proportion of subjects with ≥5% weight loss at Week 52		
N	400	401
N#	400	401
Number of subjects with ≥5% weight loss	133	10
Proportion of subjects (95% CI)	33.3% (28.7, 37.9)	2.5% (1.0, 4.0)
Difference <sup>b</sup> vs glip + met (95% CI)	30.8% (26.0, 35.7)	
p-value vs glip + metformin	<0.0001 *	

a Proportion adjusted for baseline weight, unadjusted proportions are available in CSR source tables.

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

Significant p-value compared to placebo: secondary endpoints were tested following a sequential testing procedure at alpha=0.05.

Source SCE Table 33

### **Renal Impairment Study MB102029**

The adjusted mean change from baseline in body weight at week 24 displayed a reduction in weight in the dapagliflozin treatment groups compared with an increase in the placebo group (Table 46).

(b) (4) Dapagliflozin

**Table 46 Weight (kg) Adjusted Mean Change from Baseline to Week 24, Renal Impairment Study**

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL BODY WEIGHT (KG) AT WEEK 24 (LOCF)			
N#	84	83	85
BASELINE MEAN (SD)	89.61 (20.046)	95.23 (20.909)	93.25 (17.309)
WEEK 24 LOCF MEAN (SD)	90.04 (19.776)	93.82 (21.268)	91.51 (17.658)
MEAN CHANGE FROM BASELINE (SD)	0.43 (2.425)	-1.41 (3.010)	-1.74 (3.088)
ADJ. MEAN CHANGE FROM BSL. (SE)	0.27 (0.4872)	-1.54 (0.4815)	-1.89 (0.4693)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	( -0.69, 1.23)	( -2.48, -0.59)	( -2.81, -0.96)
DIFFERENCE FROM PLACEBO (SE)		-1.81 (0.4435)	-2.16 (0.4395)
95% CI FOR DIFFERENCE FROM PLACEBO		( -2.68, -0.94)	( -3.03, -1.29)

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: 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.

Source CTR Table 7.3.2

### Reviewer's Comments

(b) (4)

recommend that these data be presented in text form with the study discussion to minimize the promotional potential of these data. These data do not meet the criteria for weight loss in the *Guidance for Industry Developing Products for Weight Management* and therefore should not be emphasized in the label and imply an indication for the treatment of obesity. This is also consistent with our approach to other antidiabetic drugs associated with weight loss

### Percent of Patients Achieving HbA1c <7%

(b) (4)

### Monotherapy Study MB102013

By 24 weeks there were more patients that achieved the glycemic response of HbA1c < 7%, adjusted for baseline HbA1c value, in all of the dapagliflozin treatment groups compared with placebo (Table 47). The greatest proportion of subjects was in the dapagliflozin 10 mg QAM group. The results appeared to be dose dependent.

**Table 47 Glycemic Response (HbA1c < 7%) at Week 24, Monotherapy Study**

EFFICACY ENDPOINT STATISTICS	PLA (N=75)	DAPA 2.5MG QAM (N=65)	DAPA 5MG QAM (N=64)	DAPA 10MG QAM (N=70)
SUBJECTS WITH HBA1C<7.0% AT WEEK 24 (LOCF)				
X/N#	24/ 72	26/ 64	28/ 61	31/ 65
PERCENT	33.3%	40.6%	45.9%	47.7%
PERCENT ADJUSTED FOR BASELINE HBA1C	31.6%	41.3%	44.2%	50.8%
95% CI FOR PERCENT ADJ FOR BSL. HBA1C	(21.8, 41.5)	(30.4, 52.3)	(32.6, 55.8)	(39.8, 61.8)
DIFFERENCE VERSUS PLA		9.7%	12.6%	19.2%
95% CI FOR DIFFERENCE VERSUS PLA		(-5.3, 24.7)	(-2.9, 28.1)	(4.1, 34.2)

Source CTR Table 7.3.3

### **Add-on Studies D1690C00005. MB102014 and MB102030**

Dapagliflozin 5 and 10 mg treatment over 24 weeks met the key secondary objective of HbA1c <7%. Dapagliflozin 2.5 mg, compared to placebo did not reach statistical significance for weight reduction and could therefore not be formally tested for subsequent secondary endpoints such as HbA1c <7%.

**Table 48 Glycemic Response (HbA1c < 7%) at Week 24, Add-on SU Study**

EFFICACY ENDPOINT STATISTICS	PLA + GLI (N=145)	DAPA 2.5MG + GLI (N=154)	DAPA 5MG + GLI (N=142)	DAPA 10MG + GLI (N=151)
SUBJECTS WITH HBA1C < 7.0% AT WEEK 24 (LOCF)				
X/N#	18/143	41/154	43/142	49/150
PERCENT	12.6%	26.6%	30.3%	32.7%
PERCENT ADJUSTED (SE)	13.0% ( 2.742)	26.8% ( 3.331)	30.3% ( 3.499)	31.7% ( 3.574)
95% CI FOR PERCENT ADJUSTED	( 7.6, 18.4)	( 20.2, 33.3)	( 23.4, 37.1)	( 24.7, 38.7)
DIFFERENCE VS. PLA + GLI, PERCENT (SE)		13.7% ( 4.363)	17.3% ( 4.498)	18.7% ( 4.552)
95% CI FOR DIFFERENCE VS. PLA + GLI		( 5.2, 22.3)	( 8.5, 26.1)	( 9.7, 27.6)
P-VALUE VS. PLA + GLI (*)		0.0016	0.0001 *	<.0001 *

Source CTR Table 20

In study MB102014, add-on to metformin, there was a larger proportion of patients achieved a therapeutic glycemic response, defined as HbA1c < 7%, adjusted for baseline HbA1c value, in all of the dapagliflozin treatment groups compared with placebo (Table 49). Comparisons with placebo were statistically significant in the dapagliflozin 5 mg and 10 mg groups.

**Table 49 Glycemic Response (HbA1c < 7%) at Week 24, Add-on Metformin Study**

EFFICACY ENDPOINT STATISTICS	PLA + MET (N=137)	DAPA 2.5MG + MET (N=137)	DAPA 5MG + MET (N=137)	DAPA 10MG + MET (N=135)
KEY SECONDARY EFFICACY ENDPOINT				
SUBJECTS WITH HBA1C<7.0% AT WEEK 24 (LOCF)				
X/N#	33/134	46/135	47/133	58/132
PERCENT	24.6%	34.1%	35.3%	43.9%
PERCENT ADJUSTED FOR BASELINE HBA1C	25.9%	33.0%	37.5%	40.6%
95% CI FOR PERCENT ADJ FOR BSL. HBA1C	( 19.1, 32.6)	( 25.4, 40.6)	( 30.0, 45.1)	( 32.9, 48.3)
DIFFERENCE VS. PLA + MET		7.1%	11.7%	14.7%
95% CI FOR DIFFERENCE VS. PLA + MET		( -3.2, 17.5)	( 1.3, 22.1)	( 4.2, 25.3)
P-VALUE VS. PLA + MET (*)		0.1775	0.0275 *	0.0062 *

Source CTR Table 7.3.3

In study MB102030, add-on to TZD study, a statistically significantly larger proportion of subjects achieved HbA1c < 7%, in both of the dapagliflozin treatment groups compared with placebo (Table 50).

**Table 50 Glycemic Response (HbA1c < 7%) at Week 24, Add-on TZD Study**

EFFICACY ENDPOINT STATISTICS	PLA + PIO (N=139)	DAPA 5MG + PIO (N=141)	DAPA 10MG + PIO (N=140)
SUBJECTS WITH HBA1C<7.0% AT WEEK 24 (LOCF)			
X/N#	32/138	45/140	54/140
PERCENT	23.2%	32.1%	38.6%
PERCENT ADJUSTED FOR BSL. HBA1C AND STRATA (SE)	22.4% (3.276)	32.5% (3.669)	38.8% (3.835)
95% CI FOR PERCENT ADJ FOR BSL. HBA1C AND STRATA	(16.0, 28.8)	(25.3, 39.6)	(31.2, 46.3)
DIFFERENCE FROM PLA + PIO (SE)		10.1% (5.119)	16.4% (5.253)
95% CI FOR DIFFERENCE FROM PLA + PIO		(0.0, 20.1)	(6.1, 26.7)
P-VALUE VS. PLA + PIO (*)		0.0496 *	0.0018 *

Source CTR Table 7.3.4

### **Initial Combination Study MB102034**

By week 24, a statistically significantly larger proportion of subjects in the dapagliflozin plus metformin group achieved HbA1c < 7.0%, compared with both the dapagliflozin and the metformin monotherapy treatment groups (Table 51).

**Table 51 Glycemic Response (HbA1c < 7%) at Week 24, Initial Combination Study**

EFFICACY ENDPOINT STATISTICS	DAPA 10MG + MET (N=211)	DAPA 10MG (N=219)	MET (N=208)
SUBJECTS WITH HBA1C<7.0% AT WEEK 24 (LOCF)			
X/N#	92/202	69/216	72/203
PERCENT	45.5%	31.9%	35.5%
PERCENT ADJUSTED FOR BASELINE HBA1C (SE)	46.6% (3.278)	31.7% (3.053)	35.2% (3.298)
95% CI FOR PERCENT ADJ FOR BSL. HBA1C	(40.1, 53.0)	(25.7, 37.7)	(28.8, 41.7)
COMBINATION GROUP VS. DAPA 10MG			
DIFFERENCE (SE) (b)	14.9% (4.598)		
95% CI FOR DIFFERENCE	(5.9, 23.9)		
P-VALUE (*)	0.0012 *		
COMBINATION GROUP VS. MET			
DIFFERENCE (SE) (b)	11.3% (4.730)		
95% CI FOR DIFFERENCE	(2.1, 20.6)		
P-VALUE (*)	0.0165 *		

Source CTR Table 7.3.2

#### 6.1.6 Other Endpoints

All other relevant endpoints in the studies in the dapagliflozin clinical program are discussed in other sections of the efficacy review, with the exception of the endpoints from the study D1690C00012, the body composition study.

##### **Study D1690C00012**

This study involved an analysis of body fat mass as measured by dual energy X-ray absorptiometry (DEXA) and visceral adipose tissue volume as measured by magnetic resonance imaging (MRI). The change from baseline in total body weight at 24 weeks was the primary efficacy variable in this study. The study also included the following secondary endpoints:

- Change from baseline in waist circumference at 24 weeks
- Change from baseline in total body fat mass at 24 weeks
- Proportion of subjects with  $\geq 5\%$  reduction in total body weight at 24 weeks

This study had a lower HbA1c inclusion threshold (HbA1c  $\geq 6.5\%$  and  $\leq 8.5\%$ ). This population was chosen because these patients were less likely to require supplementary anti-diabetic treatment and therefore more likely to complete the long-term treatment. The applicant plans to study bone mineral density in these patients over two years (inclusive of a 78 week extension) and wants minimal use of potentially confounding rescue therapies. Other differences in inclusion criteria compared to other studies were the differential age thresholds for men and women ( $\geq 30$  and  $\leq 75$  years for men and  $\geq 55$  and  $\leq 75$  years for women) and the BMI inclusion criterion (BMI  $\geq 25$  kg/m<sup>2</sup>), however, the proportion of subjects with BMI  $\geq 27$  kg/m<sup>2</sup> (87%) was similar to other studies. This study was performed exclusively at European sites.

This study included only the 10 mg dose. This was considered the most relevant to study the effect of dapagliflozin therapy on body weight (primary efficacy variable) and safety (including bone mineral density).

In the 24-week short-term treatment period, 182 subjects were randomized and received study medication (91 placebo + metformin and 91 dapagliflozin + metformin).

Treatment with dapagliflozin as add-on therapy to metformin over 24 weeks resulted in reduced body weight compared to placebo; the mean decrease in total body weight from baseline to week 24 in the dapagliflozin 10 mg group was statistically significantly larger than in the placebo group ( $p < 0.0001$ ). See Table 52.

All key secondary endpoints were statistically significant in favor of dapagliflozin. Waist circumference and body fat mass showed mean decreases in both the dapagliflozin and

placebo groups. Approximately 30% of the subjects in the dapagliflozin group and 4% of the subjects in the placebo group showed a decrease in body weight of at least 5% by 24 weeks ( $p < 0.0001$ ). This is also shown in Table 52.

**Table 52 Primary and Secondary Endpoints at Week 24, Body Weight/Composition Study-**

	Placebo	Dapa 10 mg
<b>Primary: Weight (kg)</b>		
N	91	89
N#	91	89
Baseline mean (SD)	90.91 (13.716)	92.06 (14.128)
Mean at Week 24 (SD)	90.01 (13.711)	89.06 (13.862)
Adj. mean change (SE)	-0.88 (0.2746)	-2.96 (0.2766)
Difference vs PLA (95% CI)		-2.08 (-2.84, -1.31)
p-value vs PLA		<0.0001*
<b>Waist circumference (cm)</b>		
N	91	89
N#	91	89
Baseline mean (SD)	104.53 (12.246)	105.55 (10.115)
Mean at Week 24 (SD)	103.52 (12.347)	102.97 (10.165)
Adj. mean change (SE)	-0.99 (0.4349)	-2.51 (0.4388)
Difference vs PLA (95% CI)		-1.52 (-2.74, -0.31)
p-value vs PLA		0.0143*
<b>Total body fat mass (kg)</b>		
N	91	89
N#	79	82
Baseline mean (SD)	33.08 (9.952)	33.56 (8.431)
Mean at Week 24 (SD)	32.32 (9.772)	31.29 (8.522)
Adj. mean change (SE)	-0.74 (0.2670)	-2.22 (0.2626)
Difference vs PLA (95% CI)		-1.48 (-2.22, -0.74))
p-value vs PLA		0.0001*
<b>Proportion of subjects with <math>\geq 5\%</math> weight loss at week 24</b>		
N	91	89
N#	91	89
Number of subjects with $> 5\%$ weight loss	4	27
Proportion of subjects <sup>a</sup> (95% CI)	4.3% (0.1, 8.6)	30.5% (20.9, 40.2)
Difference vs PLA (95% CI)		26.2% (15.6, 36.7)
p-value vs PLA		<0.0001*

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).

N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

a Proportion adjusted for baseline value and enrolment strata; unadjusted proportions are available in CSR source table.

(\*) Significant p-value: primary endpoint is tested at  $\alpha = 0.05$ , if this p-value is significant, the results of the key secondary endpoints are interpreted using Hochberg's method.

Source SCE Table 34

In an exploratory MRI sub-study, magnetic resonance imaging was used to measure abdominal adipose tissue in a way that allowed for discrimination between visceral adipose tissue and subcutaneous adipose tissue. Mean visceral adipose tissue volume was reduced from baseline to week 24 by approximately 10% in the dapagliflozin group (-322.6 cm<sup>3</sup>), and no meaningful change was found in the placebo group (-8.7 cm<sup>3</sup>) (nominal p=0.0063). The mean hepatic lipid content, measured by magnetic resonance spectroscopy, was slightly reduced in both treatment groups and not found to be different.

### Reviewer's Comments

(b) (4)

This data for weight loss is only to 24 weeks and the *Guidance for Industry Developing Products for Weight Management* recommends weight loss data to one year that is ≥5%. For this reason, I do not think data from this study should be included in the label. Of note, the applicant did submit the 50 week data from this study in June of the review cycle. This could not be reviewed in detail, however, the weight loss presented appeared to improve and be sustained to 50 weeks, see Table 53.

Table 53 Weight Loss (Kg) at 50 Weeks Body Weight and Composition Study

TOTAL BODY WEIGHT (KG)		PLA + MET N=91	DAPA 10MG + MET N=89
BASELINE	N#	91	89
	MEAN (SD)	90.91 ( 13.716)	92.06 ( 14.128)
WEEK 24	N#	86	83
	MEAN (SD)	90.20 ( 13.559)	89.10 ( 13.737)
	CHANGE FROM BASELINE: MEAN (SD)	-0.93 ( 2.611)	-2.95 ( 2.731)
	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-1.40 ( 0.3942)	-3.52 ( 0.4068)
	95% CONFIDENCE INTERVAL FOR ADJUSTED MEAN	( -2.17, -0.62)	( -4.31, -2.72)
	DIFFERENCE VS. PLA + MET (SE)		-2.12 ( 0.4012)
WEEK 50	95% CONFIDENCE INTERVAL FOR DIFFERENCE		( -2.91, -1.33)
	N#	84	81
	MEAN (SD)	89.70 ( 14.513)	88.40 ( 13.822)
	CHANGE FROM BASELINE: MEAN (SD)	-1.63 ( 3.598)	-3.87 ( 3.325)
	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-2.03 ( 0.4461)	-4.39 ( 0.4663)
	95% CONFIDENCE INTERVAL FOR ADJUSTED MEAN	( -2.90, -1.15)	( -5.31, -3.48)
	DIFFERENCE VS. PLA + MET (SE)		-2.37 ( 0.5288)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE		( -3.41, -1.32)

Source 50 week CTR Table 11.2.1.1.1

### Secondary Glycemic Endpoints—Body Weight and Composition Study

#### D1690C00012

The mean HbA1c reduction from baseline to week 24 was larger in the dapagliflozin group than in the placebo group (p<0.0001). The reduction was 0.39% in the dapagliflozin group and 0.10% in the placebo group.



Dapagliflozin showed effect in lowering of mean FPG from baseline to week 24, whereas there was no meaningful change in the placebo group ( $p < 0.0001$ ). The placebo-adjusted reduction from baseline was 17.1 mg/dL.

### 6.1.7 Subpopulations

The applicant performed treatment-by-subgroup interaction testing to evaluate subgroup categories where the effect of dapagliflozin might vary from the mean overall effect, see

Table 54. This test was designed to detect differential patterns across subgroup categories by comparing the average effect of dapagliflozin to placebo across categories. This testing was performed in individual studies and the results were also pooled. The renal impairment study, MB102029 was not included in this testing, while the weight composition study D1690C000012 (which did not have HbA1c as a primary endpoint and has not been part of the main efficacy analysis in this review), was. In addition, D1690C00004, the active comparator study was also not included.

The p-values calculated represent all treatment groups in the primary analysis of each study, except for the initial combination studies, where only the combination and metformin arms are included in the test. In the pooled analyses, only the 2.5 mg, 5 mg, 10 mg and placebo groups are included. The numbers in bold indicate those treatment-by-subgroup interactions with a  $p$ -value  $< 0.1$ , indicating a potential interaction.

**Table 54 Treatment-by-subgroup Interaction p-values for HbA1c (%) change from Baseline at Week 24**

Background: Study	Monotherapy, placebo-controlled		Add-on Combination, placebo-controlled				Initial combination with metformin XR		Weight and Body Composition	Number of studies where $p < 0.10$ for inter-action test
	MB102013	MB102032	MB102014	D1690C00005	MB102030	D1690C00006	MB102021	MB102034	Metformin D1690C00012	
Baseline HbA1c <sup>a</sup>	0.1919	<b>&lt;0.0001</b>	<b>0.0681</b>	0.2546	<b>0.0001</b>	<b>0.0023</b>	<b>&lt;0.0001</b>	0.5332	0.3710	5
Baseline eGFR <sup>a</sup>	0.9355	0.7067	0.8912	<b>0.0115</b>	<b>0.0571</b>	<b>0.0819</b>	0.3080	0.5644	0.5139	3
Age	ND	ND	<b>0.0140</b>	0.9166	<b>0.0484</b>	0.8512	0.6929	0.5185	0.5322	2
Gender	0.6178	0.2881	0.5373	0.9164	0.6790	0.4030	0.7246	0.7115	<b>0.0005</b>	1
Ethnicity	ND	ND	0.8359	ND	<b>0.0374</b>	ND	0.2637	0.1950	ND	1
Female age	ND	0.5279	0.6413	ND	0.2451	0.2920	0.5167	0.6984	NA	0
Region	0.2323	0.8739	0.5624	0.4089	0.9465	0.1612	0.1218	0.7105	ND	0
Race	ND	ND	ND	0.4089	0.7998	ND	0.5028	0.8521	ND	0
Baseline BMI	ND	ND	0.9481	0.9041	0.1975	0.1234	0.3757	0.1673	0.8587	0
Duration of T2DM	ND	ND	0.7275	0.7160	0.7189	0.7530	0.9001	0.3603	0.2285	0

ND: Not done because fewer than 2 subgroups had 10 or more subjects in each treatment group.

NA: Not applicable in Study D1690C00012 due to the baseline stratification factor for sex where females were included if 55-75 years of age while males were included if 30-75 years of age

Source SCE Table 36

The bolded values indicate there may be treatment difference based on category of baseline HbA1c, baseline estimated glomerular filtration rate (eGFR) and age. These are analyzed in more detail in this review.

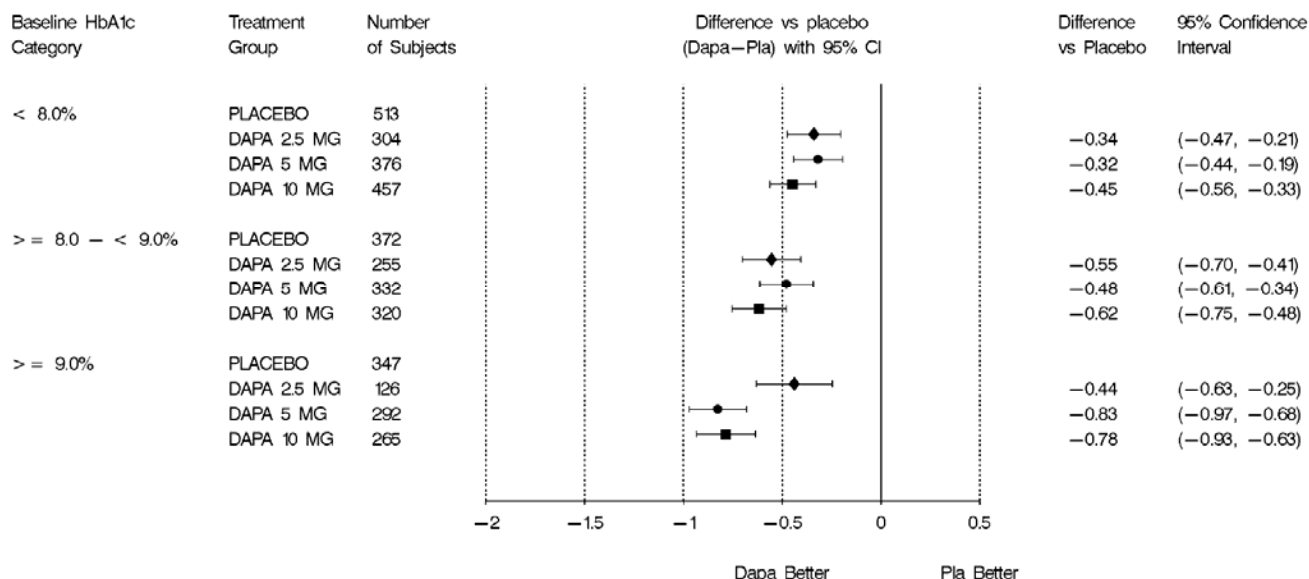
### Reviewer's Comments

While there are few African-American patients in the clinical program, there is no evidence that there would be a difference in efficacy in this racial group.

### Baseline HbA1c

Dapagliflozin treatment resulted in greater HbA1c reductions from baseline in subjects with higher baseline HbA1c, and smaller HbA1c reductions in subjects with lower baseline HbA1c (groups were <8.0%, ≥8.0% and <9.0%, and ≥9.0%). *This effect was anticipated, as similar findings are observed with other T2DM therapies (Bloomgarden et al 2006).* For the pooled studies displayed in Table 54, the 95% Confidence Interval (CI) for the placebo-subtracted adjusted mean results did not cross zero in any baseline HbA1c category for any dapagliflozin dose (Figure 12) indicating superiority over placebo.

**Figure 12 Difference Versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 by Baseline HbA1c, Pooled Monotherapy/Combination Therapy Studies**



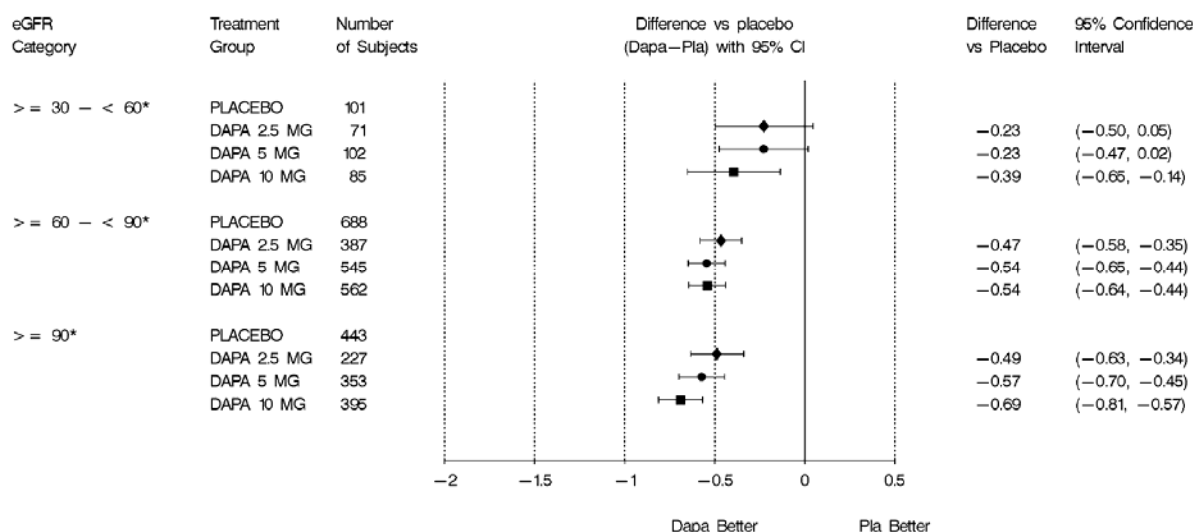
Source SCE Figure 22

### Baseline Estimated Glomerular Filtration Rate (eGFR)

HbA1c reductions were greater in subjects with higher baseline eGFR, and smaller in subjects with lower baseline eGFR. This finding was not unexpected, given the

dapagliflozin mechanism of action discussed previously in this review and results of the moderate renal impairment study. Glucose excretion induced by SGLT2 inhibition is dependent on the filtered load of glucose, and this is reduced in subjects with lower baseline eGFR. Placebo adjusted change from baseline HbA1c means in moderately impaired patients were very small see Figure 13.

**Figure 13 Difference Versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 by Renal Impairment, Pooled Monotherapy/Combination Therapy Studies**



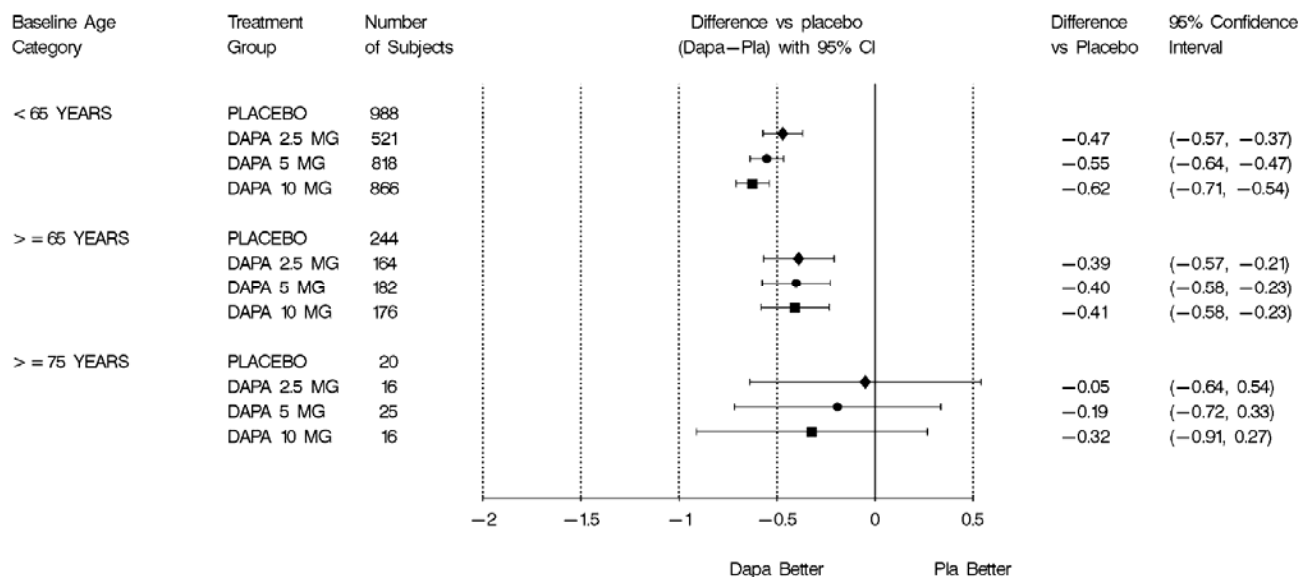
Source SCE Figure 23

## Age

Efficacy of dapagliflozin appeared to be greater in the <65 years of age category than in the ≥65 years of age category or the ≥ 75 years of age. Interpretation of findings in the ≥75 years of age subgroup was limited by the small numbers of patients of this age group (n = 15 to 25), resulting in wide 95% confidence intervals.

The pooled analysis presented above in Table 54, placebo-corrected HbA1c reductions were greater numerically in the <65 subgroup than in the ≥65 subgroup for each dapagliflozin dose. When examining the nine studies pooled, the 95% CI for the adjusted mean results did not cross zero in any dapagliflozin treatment group versus placebo (Figure 14).

**Figure 14 Difference Versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 by Age, Pooled Monotherapy/Combination Therapy Studies**



Source SCE Figure 24

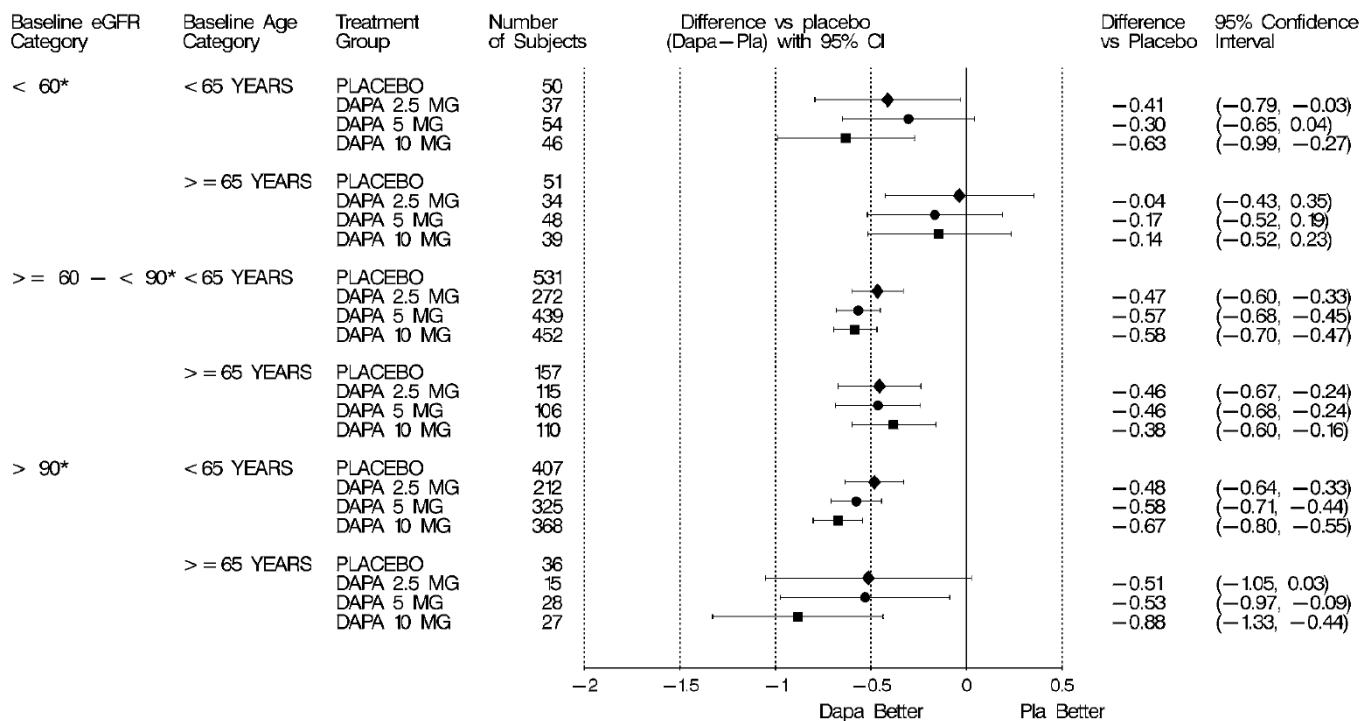
A potential treatment-by-subgroup interaction for this subgroup category was observed in two of the nine phase 3 studies that were included in the pool in Table 54: MB102014 and MB102030. In both studies, placebo-corrected HbA1c reductions were observed in the <65 subgroup. In the ≥65 subgroups, the applicant did not draw conclusions about treatment due to few patients in each of the dapagliflozin treatment arms (n=16 to 24).

Of note, study D1690C00004, the active comparator study, included large numbers of subjects in the ≥65 group (n = 100 to 120). The interaction analysis was performed for this study and the p value was 0.2178.

### ***Effect of age and estimated GFR on HbA1c***

To determine whether the treatment-by-subgroup interaction observed for the age subgroup analysis was still present after controlling for baseline eGFR in the age subgroups, a pre-specified analysis was performed. This analysis was done in the nine pooled studies.

**Figure 15 Difference Versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 by Age and Renal Impairment, Pooled Monotherapy/Combination Therapy Studies**



Source SCE Figure 25

### Reviewer's Comments

Figure 15 implies that the lower efficacy of dapagliflozin seen in subjects older than 65 years of age is accounted for by the lower eGFR which is more prevalent in the elderly. However, for labeling purposes, it is important to consider more intense monitoring of renal function among the elderly, similarly to what is done in medical practice for older patients treated with metformin. (8.5 Geriatric Use). There were few patients studied in the >75 year old age group, this should be mentioned in the label in the Geriatric Use section.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

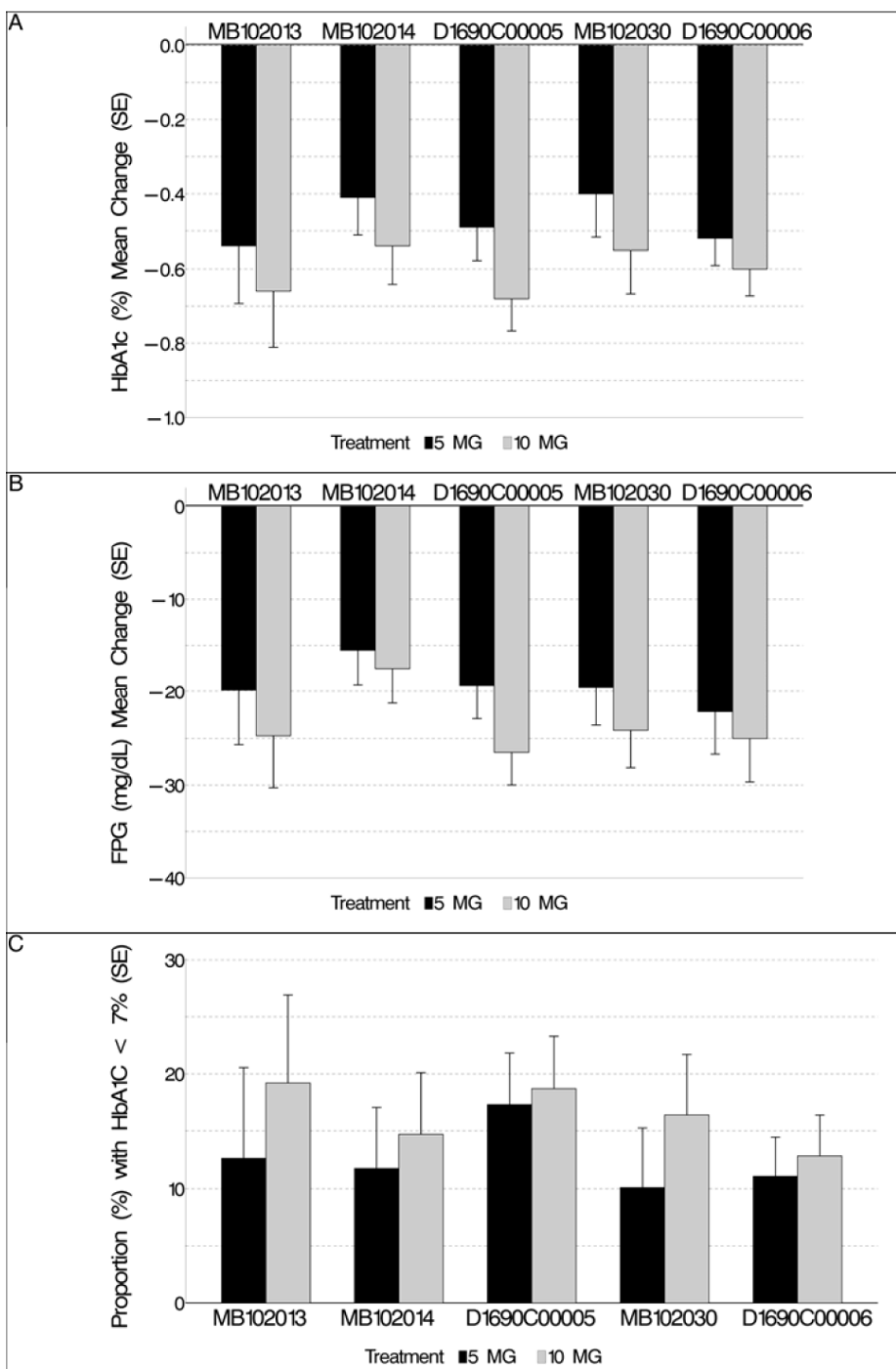
A range of doses were tested in the phase 3 studies, including 1, 2.5, 5 and 10 mg. The applicant plans to market the 5 and 10 mg doses. They recommend the 10 mg dose for most patients. The 5 mg dose is recommended for patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. This is discussed below.

Generally, there was a dose response effect observed in decrease of HbA1c. However, this was not always observed, as was the case in the monotherapy studies. It was observed across the add-on studies and mild effect was seen in the renal

impairment study, please see section 6.1.4 *Analysis of Primary Endpoint(s)*.

Dapagliflozin 10 mg demonstrated superior HbA1c reductions versus the 5 mg dose in each of the 5 placebo-controlled phase 3 studies (MB102013, MB102014, MB102030, D1690C00005 and D1690C00006) that evaluated both the 5 and 10 mg doses in the general population (Figure 16). Dapagliflozin 10 mg, but not dapagliflozin 5 mg, also consistently resulted in reductions of HbA1c of at least 0.5%. Numerically greater FPG reductions were seen with dapagliflozin 10 mg and a larger proportion of subjects treated with the 10 mg dose achieved glycemic control (HbA1c <7.0%) versus dapagliflozin 5 mg.

**Figure 16 Comparison of Dapagliflozin 5 mg and 10 mg at Week 24 in Studies Where Both Doses Were Present**



Source SCE Figure 27

## Dosing in Renal Impairment

In the pharmacodynamic study in patients with renal impairment, MB102007, T2DM patients with mild, moderate or severe renal impairment had 28%, 52% and 75% higher mean dapagliflozin AUC values, respectively, compared to subjects with normal renal function. Urinary glucose excretion was observed in all subjects (84.9 g/day, 51.8 g/day, 17.5 g/day and 10.7 g/day in subjects with normal renal function and mild, moderate, and severe renal impairment, respectively).

Data from the phase 3 renal impairment study, MB102029 indicate that dapagliflozin does not improve glycemic control in patients with moderate renal impairment. Patients with severe renal impairment were not studied as efficacy was not expected in this group.

Overall, dapagliflozin activity depends on renal function. No dose adjustment is needed for patients with mild renal impairment. Dapagliflozin has limited efficacy in patients with moderate renal impairment and this efficacy does depend on the continuum of eGFR (see discussion of moderate impairment subgroups above and Table 31). Dapagliflozin should not be used in patients with moderate or severe renal impairment.

## Dosing in Hepatic Impairment

Dapagliflozin is metabolized in the liver and kidney by the UGT1A9 pathway to an inactive glucuronide metabolite. There were no patients with severe hepatic impairment in the phase 3 program. No dosage adjustment for dapagliflozin is suggested for patients with mild, moderate, or severe hepatic impairment.

### **Reviewer's Comments**

**The proposed dose of 10 mg is acceptable based on the efficacy data. The dosing issue is also addressed in the *Review of Safety*.**

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Active Control Study D1690C00004, had a primary endpoint at 52 weeks of treatment and this was discussed under 6.1.4 *Analysis of Primary Endpoint(s)*. In addition, study 102029 in moderate renal impairment did not test change in HbA1c at the long-term extension; this was not found statistically significant at 24 weeks as discussed in 6.1.4.

At the time of NDA submission, long-term extensions in the following studies were completed: MB102030, D1690C00005, D1690C00006 (all with 48 weeks of treatment from randomization), and MB102014 (102 weeks of treatment from randomization). In addition, a statistical analysis of monotherapy study MB102013, derived from



supplemental data, is also reported (a minimum of 99 weeks of treatment from randomization for those continuing in the study, and 102 weeks of treatment from randomization for those completing the study). Rescue of patients over these long-term treatment periods will be discussed in this section along with exploratory efficacy results. Rescue criteria for the long-term extensions are described in Table 55.

**Table 55 Rescue Criteria for Long-Term Treatment**

Background	Monotherapy	Add-on combination, placebo-controlled				Add-on combination vs SU	Weight and body composition	Moderate renal impairment
	MB102013	Metformin MB102014	SU D1690C00005	TZD MB102030	Insulin D1690C00006	Metformin D1690C00004	Metformin D1690C00012	Any <sup>a</sup> MB102029
FPG >180 mg/dL					Weeks 25 to 48 <sup>b</sup>			
HbA1c >8%	Weeks 25 to 50	Weeks 25 to 50	Weeks 25 to 48	Weeks 25 to 36	Weeks 25 to 48		Weeks 25 to 50	Weeks 25 to 51
HbA1c >7.5%	Weeks 51 to 76	Weeks 51 to 76		Weeks 37 to 47	Weeks 49 to 64		Weeks 51 to 101	
HbA1c >7%	Weeks 77 to 101	Weeks 77 to 101			Weeks 65 to 104			
HbA1c ≥7.0% and <8.0%						Week 105 to 208 <sup>c</sup>		
HbA1c ≥ 8.0%						Week 105 to 208		

Source: Protocols for MB102013, MB102014, D1690C00005, MB102030, D1690C00006, D1690C00004, D1690C00012, MB102029

a Except metformin

b At least 3 fasting SMBG diary measurements from the past 7 days or visit measurement

c Rescue therapy may be initiated at the discretion of the investigator

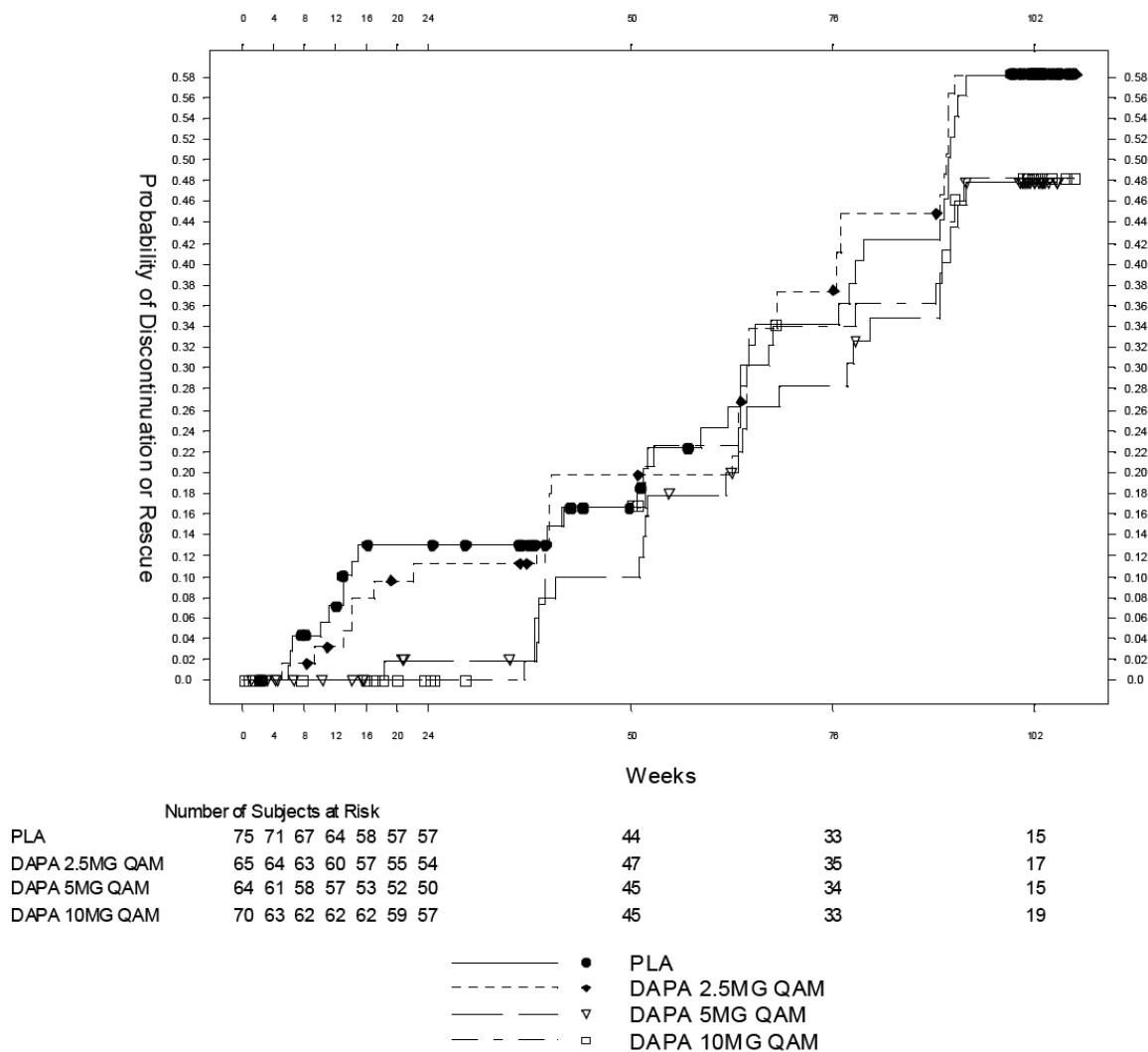
Source SCE Appendices for 2.7.3 Table 2

## **Monotherapy Study MB102013**

### ***Rescue***

The proportion of patients in the QAM groups in MB102013 who were rescued or discontinued for lack of efficacy was lower for the dapagliflozin 5 mg (36.1%) and 10 mg (33.8%) groups compared to the dapagliflozin 2.5 mg (50.6%) and placebo (44%) groups at week 102. The time to rescue for failing to achieve glycemic control or discontinuation due to lack of glycemic control, revealed that the probability of rescue or discontinuation was greater for the placebo and dapagliflozin 2.5 mg QAM groups than for the dapagliflozin 5 mg or 10 mg QAM treatment groups at most time points up to Week 102. These results are displayed in Figure 17.

**Figure 17 Time to Rescue or Discontinuation for Failing to Achieve Glycemic Targets to Week 102, Monotherapy Study**



Symbols represent censored observations

Week is not the scheduled visit week but the actual number of 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 CTR LT Supplement Figure 7.4

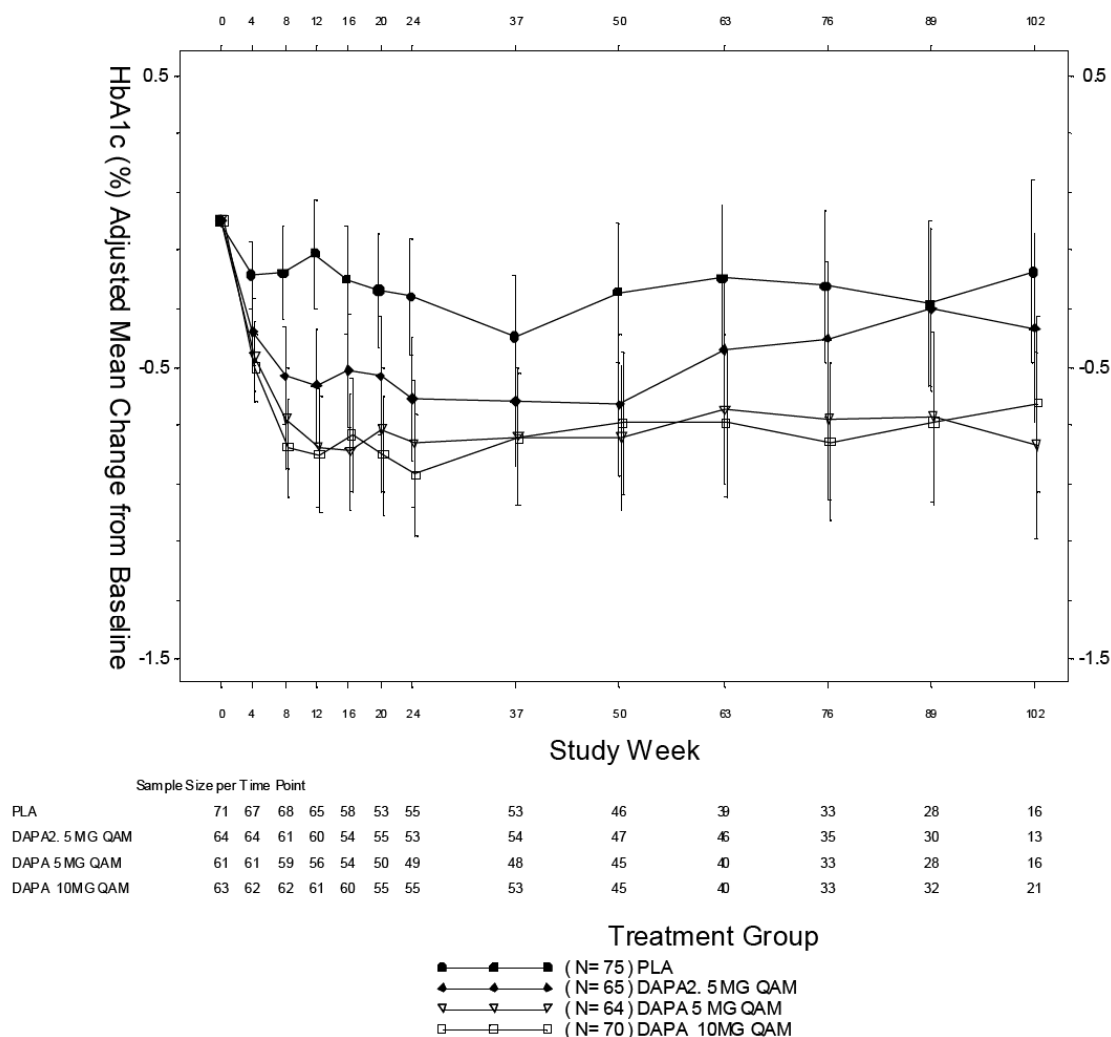
### Long-term Data

Study MB102013 is ongoing, the cut-off date for this long-term data was July 14, 2010.

In this study, all placebo-treated subjects who completed to week 24 without rescue were treated with metformin 500 mg daily during the long-term extension treatment period.

HbA1c reductions were maintained through week 102 in the dapagliflozin treatment groups in MB102013. The effect remained relatively stable up to week 102 for the dapagliflozin 5 mg QAM and 10 mg QAM groups. The effect for the dapagliflozin 2.5 mg QAM group remained relatively stable through week 50 and then diminished, see Figure 18.

**Figure 18 HbA1c (%) Adjusted Mean Change Over Time, Short-term Plus Long-term Data—MB102013**



Randomized subjects who took at least one dose of double-blind study medication  
Mean value based on a longitudinal repeated measures model with fixed categorical effects of treatment, week, and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.

Source CTR LT supplement Figure 7.2

At week 102, results depicted in Table 56 reflect these findings. Table 56 displays maintained glycemic effect of the 5 mg and 10 mg doses. The PM dose groups, including the 2.5 mg group, appear to have maintained effect.

**Table 56 HbA1c (%) Repeated Measures Analysis, Short-term Plus Long-term Data—MB102013**

		PLA N=75	DAPA 2.5MG QAM N=65	DAPA 5MG QAM N=64	DAPA 10MG QAM N=70
WEEK 102	N#	16	13	16	21
	MEAN (SD)	6.71 ( 0.654)	6.45 ( 0.595)	6.37 ( 0.687)	6.49 ( 0.452)
	MEAN CHANGE FROM BASELINE (SD)	-0.71 ( 0.674)	-0.91 ( 1.005)	-1.01 ( 1.024)	-1.15 ( 0.772)
	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-0.18 ( 0.1581)	-0.37 ( 0.1642)	-0.77 ( 0.1623)	-0.63 ( 0.1522)
	95% CONFIDENCE INTERVAL FOR ADJ. MEAN	( -0.49, 0.14)	( -0.69, -0.04)	( -1.09, -0.45)	( -0.93, -0.32)
	DIFFERENCE VS. PLA (SE)		-0.19 ( 0.2263)	-0.59 ( 0.2248)	-0.45 ( 0.2190)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE		( -0.64, 0.25)	( -1.04, -0.15)	( -0.88, -0.02)

		DAPA 2.5MG QAM N=67	DAPA 5MG QAM N=68	DAPA 10MG QAM N=76
WEEK 102	N#	19	21	19
	MEAN (SD)	6.16 ( 0.475)	6.41 ( 0.644)	6.66 ( 0.536)
	MEAN CHANGE FROM BASELINE (SD)	-1.19 ( 0.672)	-1.11 ( 0.777)	-0.96 ( 0.999)
	ADJUSTED CHANGE FROM BASELINE: MEAN (SE)	-0.58 ( 0.1581)	-0.56 ( 0.1504)	-0.58 ( 0.1465)
	95% CONFIDENCE INTERVAL FOR ADJ. MEAN	( -0.90, -0.27)	( -0.86, -0.26)	( -0.87, -0.29)
	DIFFERENCE VS. PLA (SE)	-0.41 ( 0.2218)	-0.39 ( 0.2170)	-0.40 ( 0.2151)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE	( -0.85, 0.03)	( -0.82, 0.04)	( -0.83, 0.02)

N is the number of randomized subjects who took at least one dose of double-blind study medication. Otherwise N# is the number of randomized subjects with non-missing baseline and Week t values. MIXED model: post-baseline = baseline treatment week week\*treatment week\*baseline

## Source CTR LT Supplement Table 7.2

These data are presented with the LOCF method applied. The results look similar in the analysis of the OC dataset; , however, the numbers are smaller, giving limited value to this analysis.

### Reviewer's Comments

The effect of dapagliflozin in the proposed to be marketed doses of 5 and 10 mg appears to have lasting effect to 102 weeks.

### Add-on Studies MB102014, D1690C00005, MB102030, D1690C00006

#### Rescue

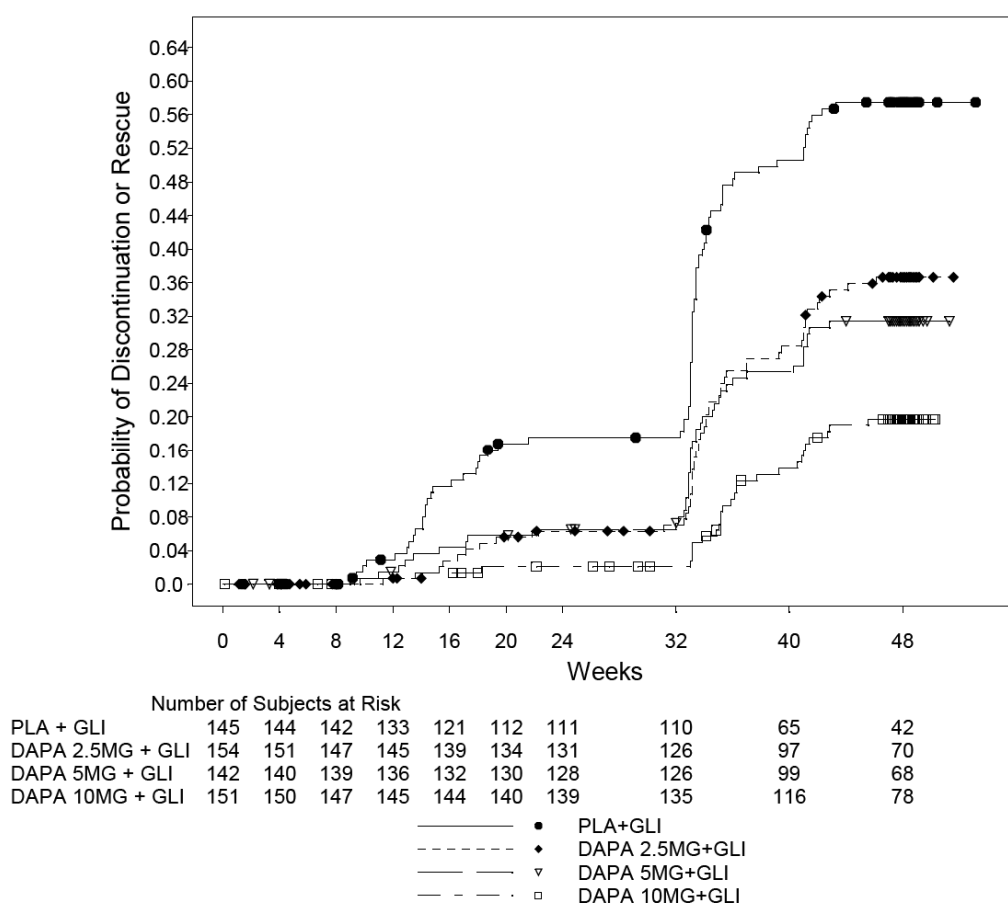
Fewer patients treated with dapagliflozin versus placebo were rescued or discontinued for lack of efficacy in studies D1690C00005 (add-on to SU), MB102030 (add-on to TZD), and D1690C00006 (add-on to insulin). This difference was seen early in the short-term treatment period, persisted through week 48 and was dose-dependent ( Figure 19). Probability of discontinuation for lack of efficacy in the dapagliflozin groups as estimated by Kaplan-Meier methodology was lower than that in the placebo groups at all time-points after week 16 in study D1690C00005, after week 4 in study MB102030, and after randomization in study D1690C00006.

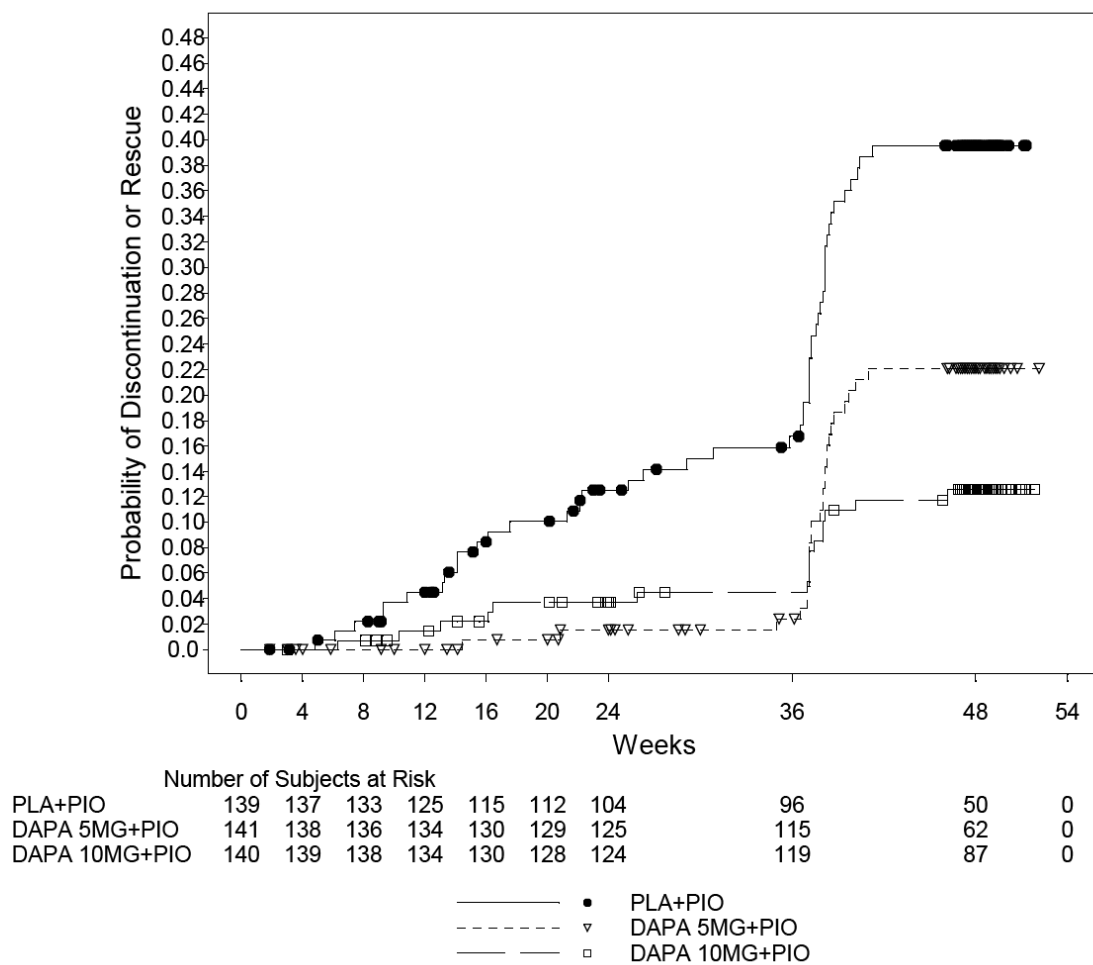
In D1690C00005 (add-on to SU), the proportion of subjects rescued or discontinued for lack of efficacy was lower in the dapagliflozin 10 mg group (18.4%) compared to the dapagliflozin 5 mg (29.1%), 2.5 mg (32.5%), and placebo (52.1%) groups at week 48.

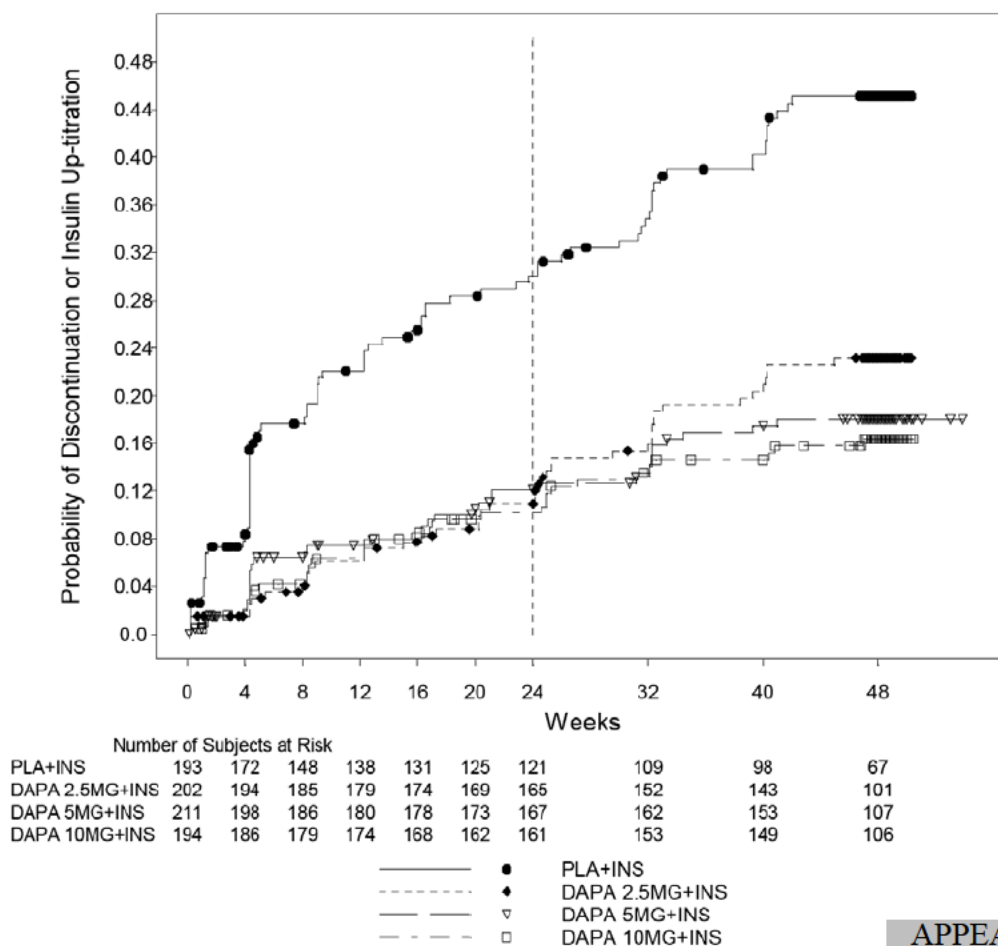
In MB102030 (add-on to TZD), the proportion of subjects rescued or discontinued for lack of efficacy was lower in the dapagliflozin 10 mg group (11.8%) compared to the dapagliflozin 5 mg (18.0%) and placebo (33.8%) groups at week 48. In D1690C00006 add-on insulin, the proportion of insulin up-titration or discontinuation due to lack of efficacy was numerically lower in the dapagliflozin 5 mg (15.3%) and 10 mg (15.6%) groups than in the dapagliflozin 2.5 mg (21.7%) and placebo (42.8%) groups at week 48.

**Figure 19 Time to Rescue or Discontinuation for Failing to Achieve Glycemic Targets to Week 48, Add-on Studies**

**D1690C00005**







Symbols represent censored observations.  
Week is not the scheduled visit week but the actual number of 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.

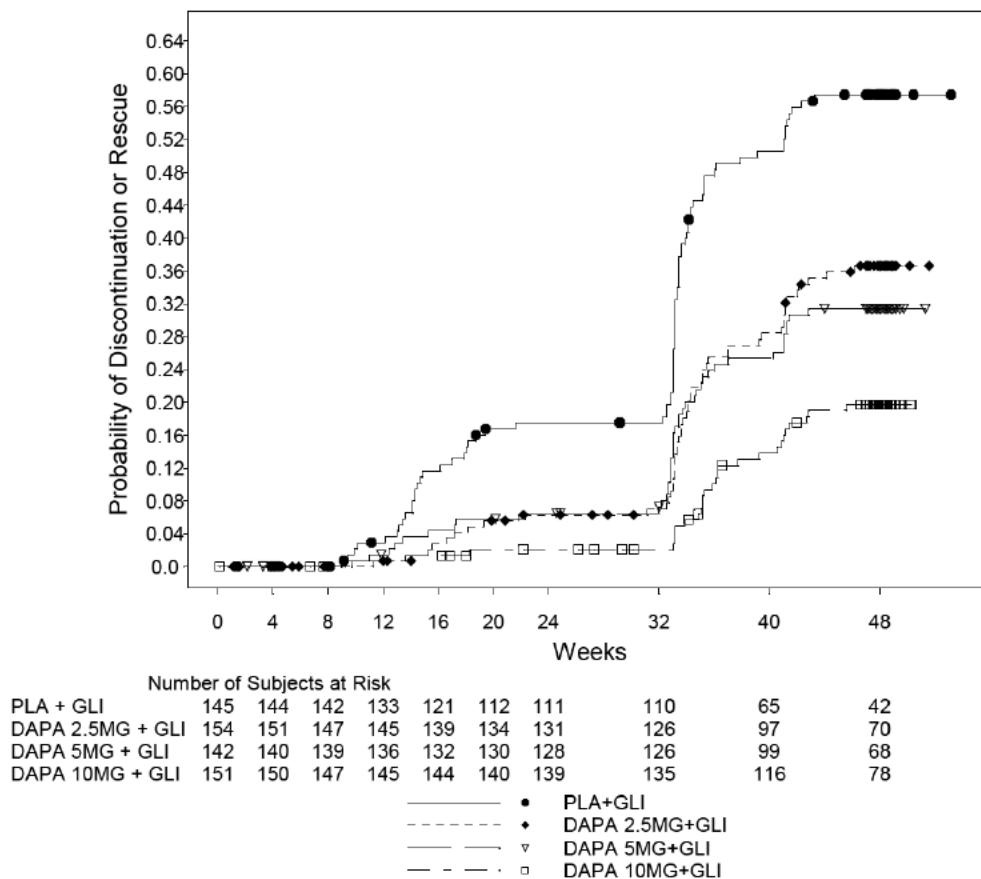
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Source SCE Figures 34-36

In study MB102014 (add-on to metformin), the proportion of subjects requiring rescue or discontinuation as estimated by Kaplan-Meier methodology, was lower for the dapagliflozin treatment groups than the placebo group at all time-points (Figure 20); starting at week 36. The probability was lower in the dapagliflozin 10 mg group compared to the dapagliflozin 5 mg and 2.5 mg groups. The proportion of subjects who were rescued or discontinued for lack of efficacy was lower in the dapagliflozin 5 mg (43.9%) and 10 mg (44.0%) groups than in the dapagliflozin 2.5 mg (53.0%) or placebo (60.1%) groups at week 102.



**Figure 20 Time to Rescue or Discontinuation for Failing to Achieve Glycemic Targets to Week 102, Add-on to Metformin Study**



Symbols represent censored observations.

Week is not the scheduled visit week but the actual number of 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.

Source SCE Figure 34

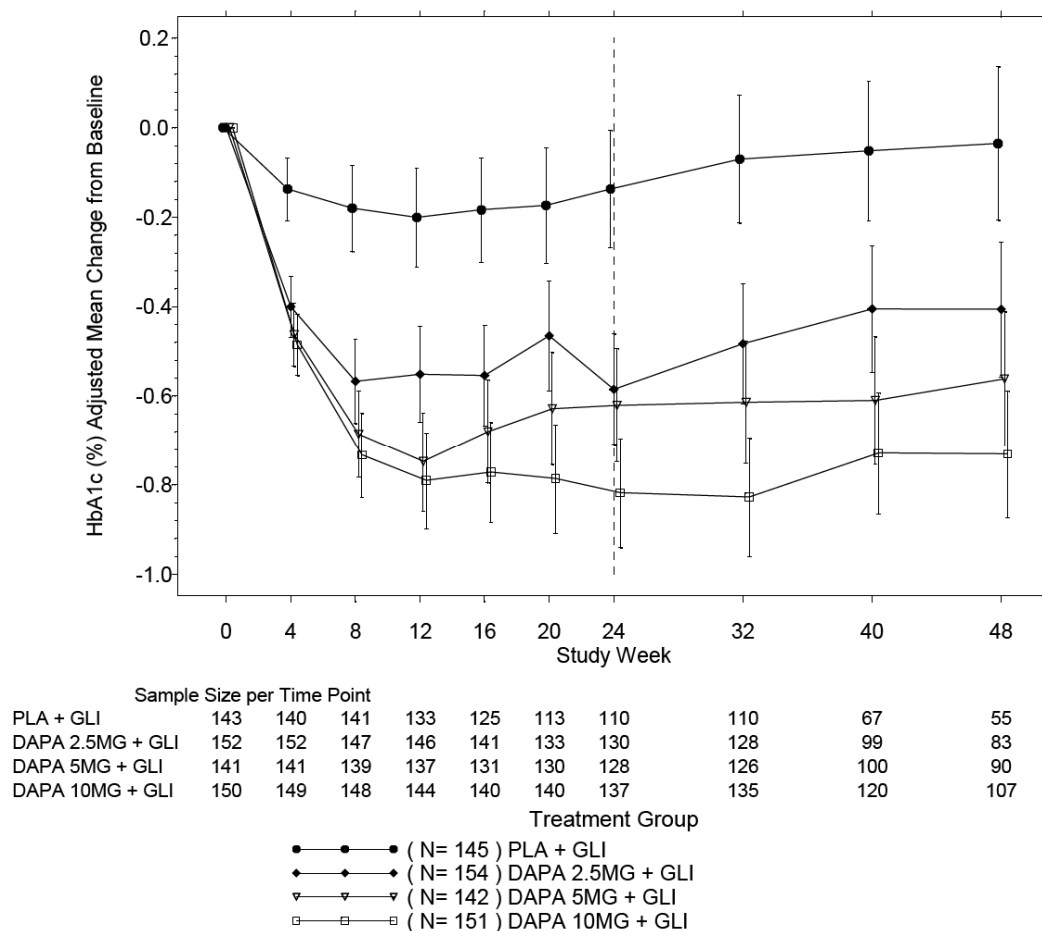
### Long-term Treatment Effects

HbA1c reductions were sustained through week 48 in the three add-on combination studies with 48-week data and reductions were greater in the dapagliflozin groups than in the placebo groups (**Error! Reference source not found.**). (b) (4)

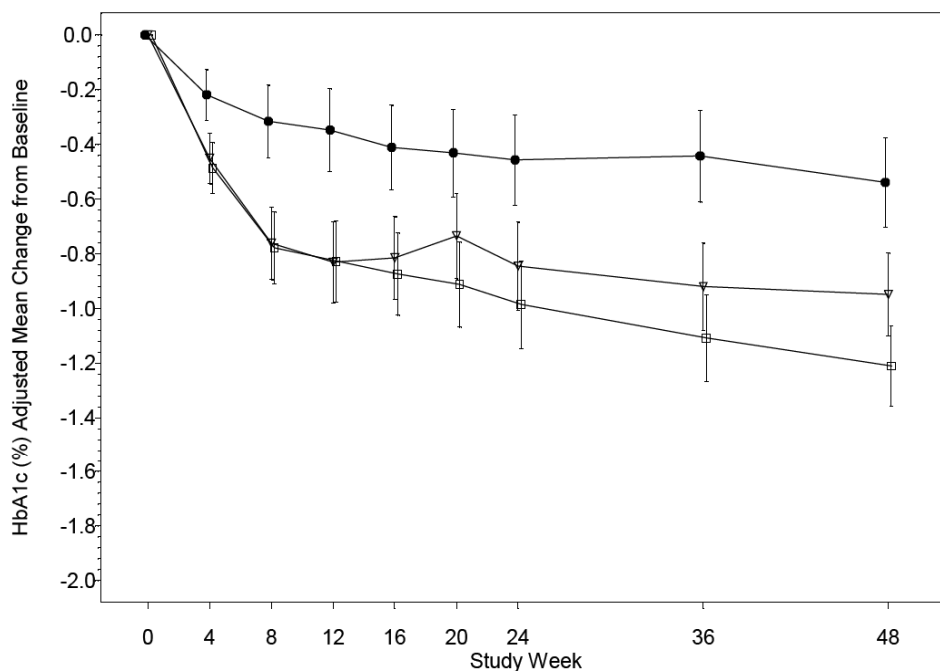
Results were generally dose-dependent but appeared to be similar in the 5 and 10 mg groups in D1690C00006 add-on insulin study.

**Figure 21 HbA1c (%) Adjusted Mean Change Over Time, Short-term Plus Long-term Data—Add-on Studies**

**D1690C00005**



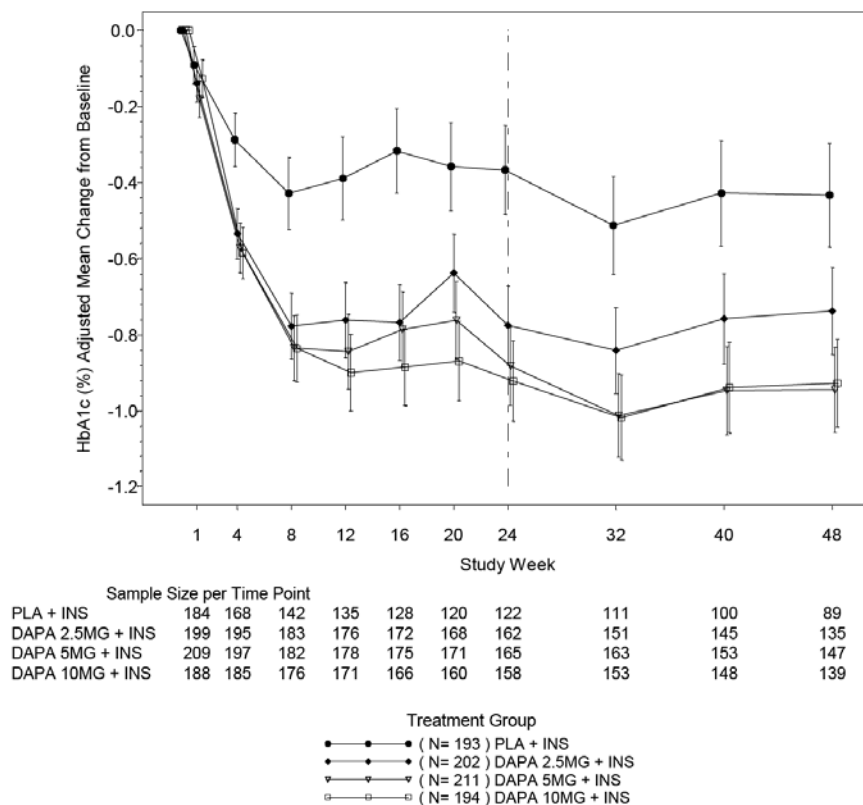
**MB102030**



Sample Size per Time Point									
PLA + PIO	137	136	133	124	115	110	104	99	69
DAPA 5MG + PIO	139	137	131	133	132	126	122	116	89
DAPA 10MG + PIO	139	135	137	134	131	125	123	119	108

Treatment Group

- ( N= 139 ) PLA + PIO
- ▼ ( N= 141 ) DAPA 5MG + PIO
- ( N= 140 ) DAPA 10MG + PIO

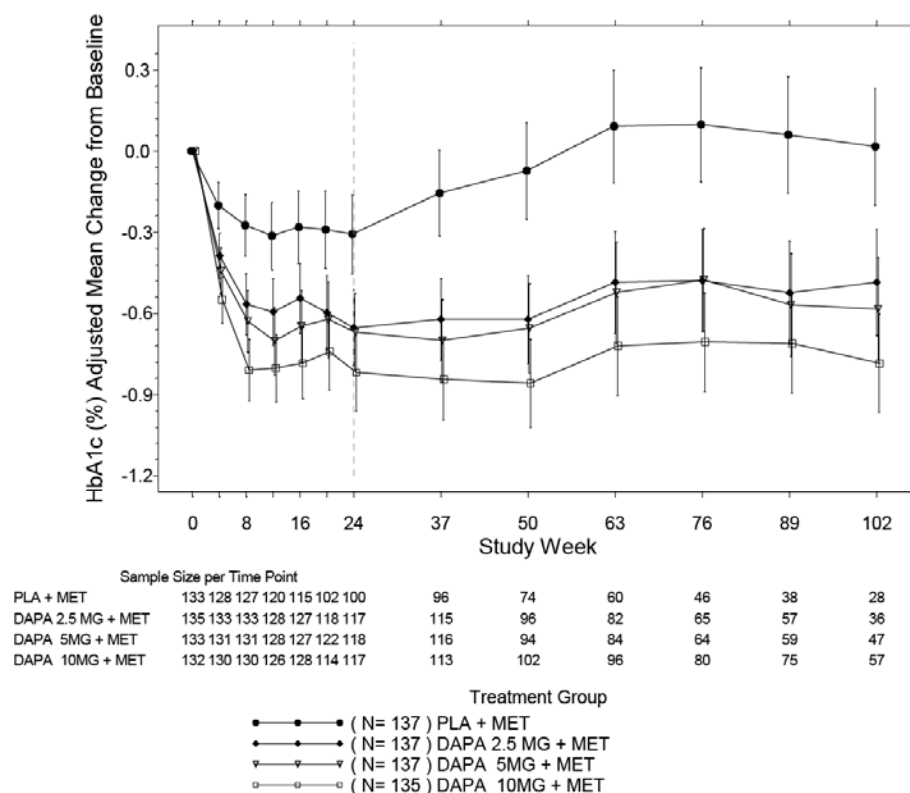


Subjects in the full analysis set.  
Mean value based on repeated measures analysis model:  
post-baseline = baseline treatment stratum week\*baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

## Source SCE Figures 30-32

In study MB102014 (Add-on to metformin), HbA1c reductions observed at week 24 appeared to be maintained through Week 102 in the dapagliflozin treatment groups. The results appeared to be dose dependent throughout the 102 weeks, see Figure 22.

**Figure 22 HbA1c (%) Adjusted Mean Change Over Time, Short-term Plus Long-term Data—Add-on to Metformin Study**



Randomized subjects who took at least one dose of double-blind study medication  
Mean value based on a longitudinal repeated measures model with fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.  
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.  
Treatment symbols shifted horizontally to prevent error bar overlapping

Source SCE Figure 33

Of note, the applicant has included some of the data from the secondary endpoints during the long-term treatment period in the proposed label. These include change in weight and fasting plasma glucose.

**Table 57 Long-term Secondary Endpoints in Add-on Studies**

Study Number— Description/LT Extension Time	Placebo Corrected Reduction in FPG	Mean Changes from Baseline in Body Weight 10 mg Dose
	Dose/Reduction	
D1690C00005— add-on to SU/24 weeks	2.5 mg/ -19.3 5 mg/ -19.3 10 mg/ -31.4	-2.41
MB102030—add-on to TZD/24 weeks	5 mg/ -9.7 10 mg/ -20.0	+0.69 (this was placebo corrected)
D1690C00006— add-on to insulin/24 weeks	2.5 mg/ -12.6 5 mg/ -16.3 10 mg/ -17.1	-1.79
MB102014—add-on to metformin/78 weeks	2.5 mg/ -8.9 5 mg/ -16.0 10 mg/ -14.1	-2.81

### **Reviewer's Comments**

(b) (4)

I recommend only placebo corrected data be presented in the label.

#### **6.1.10 Additional Efficacy Issues/Analyses**

There are no additional issues or analyses to be presented here.

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

All clinical study reports were reviewed for safety. The SAS transport datasets were also reviewed. Selected adverse events (AE) and laboratory abnormalities were cross checked with those provided with the NDA documents. For example, I searched for AEs that pertain to hypovolemia and also looked for liver enzyme elevations in the patient databases. For this safety review, I focused in particular on the *Summary of Clinical Safety* along with the Safety Appendices and the individual Phase 3 study reports.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As mentioned, all studies were reviewed, with particular attention to Phase 3 studies. Pooled groups that are presented in this section are discussed below.

#### Categorization of Adverse Events

AEs are discussed in designated sections on the template (serious AEs [SAEs], common AEs, etc).

Certain categories of AEs reported with imbalances among groups are discussed in detail in section 7.3.4 *Significant Adverse Events* (e.g., cancer imbalances). AEs that were particular to class or noted in the preclinical studies or early in clinical studies are discussed in 7.3.5 *Submission Specific Primary Safety Concerns*. These include hepatic events, genital infections and urinary tract infections.

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

The main pools used for safety are the short-term placebo-controlled pool, short and long-term placebo-controlled pool and the All Phase 2b/3 pool. These are detailed below.

### 7.2 Adequacy of Safety Assessments

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

The phase 1 and 2b studies included 26 clinical pharmacology studies conducted in 688 subjects (635 of these subjects were exposed to dapagliflozin). Of the total number of subjects:

- 554 were healthy subjects (518 exposed to dapagliflozin)
- 32 were subjects with T2DM and renal impairment (all exposed to dapagliflozin)
- 18 were subjects with hepatic impairment (all exposed to dapagliflozin)
- 84 were subjects with T2DM (67 exposed to dapagliflozin)

Over 4000 subjects with T2DM have been exposed to dapagliflozin (2.5 mg or higher) and 2000 subjects were exposed to the 10 mg dose in the Phase 2b and 3 clinical program (Table 58). More than half of these subjects were exposed for > 1 year, 441 subjects were exposed for at least 2 years, and 461 subjects were exposed to the 10 mg dose for at least 77 weeks. Overall, there were 2.2 times more subjects exposed to dapagliflozin (N = 4287) compared with control (N = 1941).

**Table 58 Number of Patients Per Treatment Group**

Population	Placebo/control	Dapagliflozin Dose			Total Dapa
		2.5 mg	5 mg	10 mg	
All Phase 2b and 3 Pool	1941				4287*
Placebo-controlled Pool ST	1393	814	1145	1193	3291*
Placebo-controlled Pool ST + LT	694	625	767	768	2160
Monotherapy ST	251	321	316	245	882
Monotherapy ST + LT	75	132	132	146	410
Dapagliflozin Plus Metformin ST	228			226	226
Dapagliflozin Plus Metformin ST + LT	137	137	137	135	409
Dapagliflozin Plus Insulin	197	202	212	196	610
Dapagliflozin Plus Sulfonylurea	146	154	145	151	450
Dapagliflozin Plus TZD	139		141	140	281
Initial Combination with Metformin 5 mg	201		194 (203)^		397
Initial Combination with Metformin 10 mg	208			211 (219)+	430
Dapagliflozin vs Glipizide	408				406
Moderate Renal Impairment	84		83	85	168
Moderate Renal Impairment	84		83	85	168

Dapa - dapagliflozin, LT - long-term, ST - short-term, TZD - thiazolidinedione

\*Includes DAPA 20 mg and 50 mg

^ Dapa 5 mg + Met (Dapa 5 mg)

+ Dapa 10 mg + Met (Dapa 10 mg)

Source SCS Table 6

### Phase 2b and 3 Pool

Cumulative exposure to dapagliflozin in the Phase 2b and 3 studies was 4009.1 patient-years and 1681.9 patient-years to control.

The studies included in this pool are presented in Table 59. This was the largest pool to explore for safety. It included all available short-term plus long-term data from all 14 studies.

### Placebo-controlled Pool

Mean duration of exposure for subjects treated with dapagliflozin and placebo during short-term treatment was 147.0 and 149.4 days, respectively. Mean duration of exposure for subjects treated with 2.5, 5 and 10 mg doses of dapagliflozin was similar. Median duration of exposure was 168 days for all doses of dapagliflozin and placebo.



Cumulative exposure to dapagliflozin in this population was 1324.4 patient-years and to placebo was 569.9 patient-years. Cumulative exposure to dapagliflozin 10 mg was 491.6 patient-years.

There are two pools for this group: short-term and short plus long-term (see Table 59). This group did not include the moderate renal impairment study.

**Table 59 Pooled Safety Groups**

Population	Treatment Period	Studies	Treatment Groups
<b>1. All Phase 2b and 3 Studies Pool</b>  Data from all Phase 2b and 3 placebo- or active controlled studies, with or without other background antidiabetic medications, were pooled and analyzed.	ST + LT	MB102008	Dapagliflozin 2.5 mg
		MB102009	Dapagliflozin 5 mg
		MB102013	Dapagliflozin 10 mg
		MB102014	Control (placebo with or without background medications or active control including benchmark treatments)
		MB102021	
		MB102029	
		MB102030	
		MB102032	
		MB102034	
		D1690C00004	A total dapagliflozin treatment group includes all subjects who received either dapagliflozin 2.5, 5, or 10 mg as defined above plus dapagliflozin 20 mg and 50 mg. Safety tables for this pool are presented with total dapagliflozin only.
<b>2. Placebo-controlled Pool</b>  Data from placebo-controlled studies, with or without other background antidiabetic medications, are pooled and analyzed.	ST	MB102008	Dapagliflozin 2.5 mg
		MB102009	Dapagliflozin 5 mg (including Dapagliflozin plus metformin from MB102021)
		MB102013	Dapagliflozin 10 mg (including Dapagliflozin plus metformin from MB102034)
		MB102014	
		MB102021	
		MB102030	Control (placebo with or without background medications, and for MB102021 or MB102034, placebo plus metformin)
		MB102032	
		MB102034	
		D1690C00005	
		D1692C00005	
		D1690C00006	
		D1690C00012	A total dapagliflozin treatment group includes all subjects who received dapagliflozin 2.5, 5, or 10 mg (as defined above) plus dapagliflozin 20 mg (MB102008 and Cohort 2 of MB102009) and dapagliflozin 50 mg (MB102008).
	ST + LT	MB102013	Dapagliflozin 2.5 mg
		MB102014	Dapagliflozin 5 mg
		MB102030	Dapagliflozin 10 mg
		D1690C00005	Control (placebo with or without background medications)
		D1690C00006	
			A total dapagliflozin treatment group includes all subjects who received dapagliflozin 2.5, 5, or 10 mg.

Source Modified from SCS Table 3

## 7.2.2 Explorations for Dose Response

The applicant plans to market the 10 mg dose for most T2DM patients. They propose the 5 mg dose for patients at risk for hypovolemia (such as patients on loop diuretics). There is no rationale presented in the NDA to support this chosen dose in this population. There is some dose response seen, both with efficacy and with some safety issues/adverse events; however, the dose response is not seen with hypovolemia events.

### ***Reviewer's Comments***

**An analyses to support the 5 mg dose in this population would have been useful. However, as the 5 mg dose does have efficacy and there is some dose response seen with some of the adverse events (such as genital infection), I think this proposed dose for the intended population is reasonable.**

## 7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. Mukesh Summan's review for full details.

## 7.2.4 Routine Clinical Testing

Routine laboratory and vital sign checks were performed during the course of the trials reviewed here. I did not identify any missing key safety measures during the clinical program.

## 7.2.5 Metabolic, Clearance, and Interaction Workup

Please see *4.4 Clinical Pharmacology* section of this review and also refer to Dr. Ritesh Jain's review for full details.

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

Expected AEs based on the mechanism of action of dapagliflozin were assessed adequately in the clinical program. Dapagliflozin is the first in the class of SGLT2 inhibitors to reach NDA filing, so most of the clinical experience in the class is based on dapagliflozin. The increased presence of glucose in the genital and urinary tract is predicted to result in more frequent urinary infections and genital infections, such as candidiasis. The diuretic effect may cause more hypovolemia and orthostasis. The renal mechanism requires increased monitoring for effects on renal functions. Bone findings in animals, and effects on excretion of minerals prompt for a more thorough examination of these metabolic bone effects in clinical trials.

An early finding with another SGLT2 inhibitor (increased SAEs related to thromboembolic events) was not reported with dapagliflozin or with other more SGLT2 inhibitors in more advanced stages of development. Canagliflozin has been reported to

increase renal, testicular and adrenal tumors in rats, an effect attributed by the IND sponsor to effects on SGLT1.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

Thirty-three deaths occurred, all in the Phase 2b and 3 studies, and were balanced across the dapagliflozin and control groups (Table 60). The most common cause of death was related to cardiac disorders.

**Table 60 Deaths in Phase 2b and 3 Studies**

<b>All Control (N= 1941)</b>	<b>Dapagliflozin Total (N = 4287)</b>
10 (0.5%)	21 (0.5%)

Note: All deaths regardless of time from last dose are included, however 2 subjects are not included in the table: D1692C00005-26-6 because he was treated with dapagliflozin 1 mg and MB102029-72-623 because the death was reported in the lead-in period, prior to receipt of study medication and randomization.

Source SCS Table 34

The patient on 1 mg of dapagliflozin that was excluded from the table above died from multiple organ failure and is included in Table 61 below. The final three cases in Table 61 are cases of death that occurred after the follow up visit.

**Table 61 Cause of Death in the Clinical Program**

<b>Dapagliflozin Dose (mg)</b>	<b>Date of Treatment</b>	<b>Cause of Death</b>
5	566	Pulmonary embolism
10	133	Pulmonary embolism
5	151	Cardiogenic shock
5	119	Septic shock
10	68	Esophageal varices hemorrhage
10	2	Thoracic contusion
10	448	Angina pectoris
2.5	269	Sudden cardiac death
2.5	156	Cardiopulmonary arrest
2.5	593	Cardiopulmonary arrest
2.5	722	Myocardial infarction
5	325	Myocardial infarction
10	157	Myocardial infarction
5	233	Acute myocardial infarction
10	507	Cardiac failure
5	64	Cardio-pulmonary failure
10	360	Multi-organ failure
1	101	Multiple organ failure
2.5	59	Acute liver failure
2.5	350	Acute renal failure
10	112	Pancreatic carcinoma
10	83	Hepatocellular carcinoma

#### **Four Month Safety Update**

Three subjects died in the 4-month period after the database lock date for the SCS. All 3 were from study MB102029 (subjects with moderate renal impairment). These patients are listed here:

- 1 in the dapagliflozin 10 mg group due to sepsis
- 2 in the placebo group: 1 due to an acute myocardial infarction (MI; positively adjudicated by the Clinical Event Committee as both MI and CV death) and 1 due to general physical health deterioration

#### **7.3.2 Nonfatal Serious Adverse Events**

##### **Placebo-controlled Pool—Short-Term Treatment**

Serious Adverse Events (SAEs) were reported in 4.5%, 3.5%, and 3.5% of subjects in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 3.3% in the placebo group (Table 62). No dose-dependent trend in SAE reporting by system organ class (SOC) or preferred term (PT) was apparent. Most SAEs were reported in 1 subject each per

treatment group. Table 62 presents all of the SAEs that were reported in at least 2 subjects in any dapagliflozin treatment group.

**Table 62 SAEs in the Short-term Treated Placebo-controlled Pool**

System Organ Class (%) Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193
TOTAL SUBJECTS WITH AN EVENT	46 ( 3.3)	37 ( 4.5)	40 ( 3.5)	42 ( 3.5)
INFECTIONS AND INFESTATIONS	4 ( 0.3)	6 ( 0.7)	6 ( 0.5)	8 ( 0.7)
PNEUMONIA	0	2 ( 0.2)	1 ( 0.1)	6 ( 0.5)
PULMONARY TUBERCULOSIS	1 ( 0.1)	0	3 ( 0.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 ( 0.2)	2 ( 0.2)	4 ( 0.3)	6 ( 0.5)
ARTHRALGIA	0	0	0	2 ( 0.2)
ROTATOR CUFF SYNDROME	0	0	1 ( 0.1)	2 ( 0.2)
CARDIAC DISORDERS	8 ( 0.6)	8 ( 1.0)	9 ( 0.8)	5 ( 0.4)
MYOCARDIAL INFARCTION	1 ( 0.1)	0	0	2 ( 0.2)
ACUTE MYOCARDIAL INFARCTION	3 ( 0.2)	1 ( 0.1)	3 ( 0.3)	0
ANGINA PECTORIS	0	2 ( 0.2)	3 ( 0.3)	0
CORONARY ARTERY DISEASE	0	1 ( 0.1)	2 ( 0.2)	0
VASCULAR DISORDERS	1 ( 0.1)	1 ( 0.1)	2 ( 0.2)	4 ( 0.3)
HYPERTENSION	0	0	0	2 ( 0.2)
NERVOUS SYSTEM DISORDERS	7 ( 0.5)	4 ( 0.5)	0	3 ( 0.3)
CEREBROVASCULAR ACCIDENT	2 ( 0.1)	1 ( 0.1)	0	2 ( 0.2)
HEPATOBIILIARY DISORDERS	1 ( 0.1)	2 ( 0.2)	2 ( 0.2)	0
CHOLELITHIASIS	0	2 ( 0.2)	1 ( 0.1)	0
METABOLISM AND NUTRITION DISORDERS	1 ( 0.1)	1 ( 0.1)	4 ( 0.3)	0
DIABETES MELLITUS	0	0	2 ( 0.2)	0
HYPOGLYCAEMIA	0	0	2 ( 0.2)	0

Source SCS Table 35

A similar table for this pool was not presented in the 4MSU. However, rates of SAEs were presented and were similar:

- 4MSU: 13.3%, 9.3%, and 9.4% in dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 10.8% in placebo

In the short-term pool from the original NDA, the table presented above, there was an imbalance in pneumonia with 9 patients in the dapagliflozin treated pool (0.3%) versus 0 patients in the placebo group. However, in the larger pool at the time of the 4MSU, this was no longer evident as there were 17 patients in the dapagliflozin treated group (0.4%) versus all control 5 (0.3%).

There is also an imbalance in angina pectoris: 5 patients (0.2%) versus 0 patients in the placebo group. However, dapagliflozin has been found to not have increased cardiovascular risk and this is discussed in further detail with the cardiovascular meta-analysis.

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### **Placebo-controlled Pool—Short Plus Long-Term Treatment**

Compared with the short-term period for the Placebo-controlled Pool, the proportions of patients with SAEs were 2.5 to 3 times higher in each treatment group in the short-term plus long-term period; however, these proportions remained balanced across treatment groups (9.0%, and 8.6% in the dapagliflozin 5 and 10 mg groups, respectively, and 10.1% in the placebo group). Again, all SAEs were reviewed, and no dose dependent SAE by SOC or PT was evident. This pool showed an imbalance in breast cancer with 6 patients being diagnosed (0.3%) versus 0 patients in the placebo group. This will be addressed further in the review.

### **Active Comparator Study D169C00004**

The proportion of subjects with an SAE during the 52-week double-blind treatment period was similar in both treatment groups (35 patients—8.6% patients in the dapagliflozin treated group and 46 patients—11.3% in the glipizide treated group). On the PT level, there was only one SAE that occurred in more than one patient in the dapagliflozin treated group—prostate cancer in three patients (0.7%) versus only one patient in the glipizide group (0.2%).

### **Renal Impairment MB102029**

During the 24-week short-term period, SAEs were reported in a total of 28 subjects, and occurred in a similar proportion of subjects in the placebo (10.7%) and dapagliflozin 5 mg (8.4%) groups and in a higher proportion of subjects in the dapagliflozin 10 mg group (14.1%). However, there were no SAEs by PT that occurred in more than one patient in a dapagliflozin treated group, other than hypoglycemia. This occurred in two patients (2.4%) in the 10 mg treated group. The long-term treatment results were similar, with the only additional PT occurring in more than one patient being anemia (two patients—2.4% in the 5 mg group).

#### **7.3.3 Dropouts and/or Discontinuations**

### **Placebo-controlled Pool Short-term Treatment**

Most AEs leading to discontinuation were reported in one patient each per treatment group. Table 63 presents AEs leading to discontinuation reported in at least two subjects in any dapagliflozin treatment group.

**Table 63 AEs Leading to Discontinuation in at Least 2 Patients—Short-term Treatment**

System Organ Class (%) Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193
TOTAL SUBJECTS WITH AN EVENT	35 ( 2.5)	18 ( 2.2)	32 ( 2.8)	38 ( 3.2)
INVESTIGATIONS	7 ( 0.5)	2 ( 0.2)	4 ( 0.3)	7 ( 0.6)
BLOOD CREATININE INCREASED	2 ( 0.1)	1 ( 0.1)	2 ( 0.2)	5 ( 0.4)
GASTROINTESTINAL DISORDERS	8 ( 0.6)	3 ( 0.4)	3 ( 0.3)	5 ( 0.4)
NAUSEA	1 ( 0.1)	1 ( 0.1)	2 ( 0.2)	2 ( 0.2)
INFECTIONS AND INFESTATIONS	2 ( 0.1)	3 ( 0.4)	5 ( 0.4)	5 ( 0.4)
URINARY TRACT INFECTION	0	1 ( 0.1)	2 ( 0.2)	3 ( 0.3)
PULMONARY TUBERCULOSIS	1 ( 0.1)	0	2 ( 0.2)	0
PYELONEPHRITIS	1 ( 0.1)	2 ( 0.2)	0	0
NERVOUS SYSTEM DISORDERS	1 ( 0.1)	1 ( 0.1)	1 ( 0.1)	4 ( 0.3)
DIZZINESS	0	1 ( 0.1)	1 ( 0.1)	2 ( 0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 ( 0.1)	1 ( 0.1)	4 ( 0.3)	3 ( 0.3)
RASH	0	0	0	2 ( 0.2)
PRURITUS	0	0	2 ( 0.2)	0
RASH GENERALISED	0	0	2 ( 0.2)	0
BALANITIS	0	0	0	1 ( 0.1)
CARDIAC DISORDERS	3 ( 0.2)	0	3 ( 0.3)	1 ( 0.1)
ACUTE MYOCARDIAL INFARCTION	0	0	2 ( 0.2)	0

Source SCS Table 39

### Placebo-controlled Pool—Short Plus Long-Term Treatment

Similar proportions of subjects in each treatment group had an AE leading to discontinuation: 4.3%, 5.7%, and 4.7% in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 5.0% in the placebo group. The most commonly reported AEs leading to discontinuation (in the dapagliflozin 2.5, 5, and 10 mg groups vs. the placebo group) were blood creatinine increased (0.5%, 0.5%, and 0.9% vs. 0.1%) and UTI (0.2%, 0.4%, and 0.4% vs. 0%). All other AEs leading to discontinuation were reported in at most two patients per treatment group.

### Active Comparator Study D169C00004

A higher proportion of subjects in dapagliflozin (9.1%) than in the glipizide group (5.9%) had an AE leading to discontinuation from double-blind study medication. There was a higher number of subjects discontinued due to an AE of creatinine renal clearance decreased in the dapagliflozin group (13 subjects), compared to glipizide (6 subjects). The difference in the proportion of subjects with an AE of creatinine renal clearance decreased was not reflected in marked abnormalities.

AEs that led to discontinuation that occurred in more than two patients are presented in Table 64.

**Table 64 AEs Leading to Discontinuation Active Comparator Study**

<b>AE Leading to Discontinuation</b>	<b>Dapagliflozin N=406</b>	<b>Glipizide N=408</b>
Creatinine Renal Clearance Decreased	14 (3.4)	8 (2.0)
Blood Creatinine Increased	13 (3.2)	6 (1.5)
Renal Impairment	2 (0.5)	2 (0.5)
Prostate Cancer	2 (0.5)	0
Balanitis	2. (0.5)	0

Source CSR Table 11.3.5.1.1

### **Renal Impairment Study**

The discontinuation rate due to AE was higher in the placebo treated patients in the short-term study period—24 weeks. In the short-term period there were 13 events in placebo (15.5%), seven in dapagliflozin 5 mg (8.4%), and six events in dapagliflozin 10 mg (7.1%). The long-term period had a higher rate of events but similar distribution of events among the groups.

#### **7.3.4 Significant Adverse Events**

##### **Bladder Cancer**

In the All Phase 2b and 3 Pool updated for the 4MSU there were a total of 7 (0.2%) cases of bladder cancer in dapagliflozin treated patients versus 0 subjects treated with control. All 7 subjects with bladder cancer were male; all were ≥ 60 years of age and all received dapagliflozin: 1, 3, and 3 in the 2.5, 5, and 10 mg groups, respectively (one subject in the 10 mg group had his dapagliflozin dose titrated from 2.5 to 5 to 10 mg). The 7 events of bladder cancer in subjects receiving dapagliflozin were reported within two years of beginning dapagliflozin treatment, with a median time for appearance of 399 days, ranging from 43 to 727 days.

The 7 subjects were from 7 different countries across 4 continents. Six of the 7 subjects with bladder cancer received concomitant antidiabetic medication: insulin (3 subjects), metformin (2 subjects), and pioglitazone (1 subject). Five of the subjects with bladder cancer were either current or former smokers. Microscopic hematuria was noted in 3 of the 7 subjects prior to taking the first dose of dapagliflozin and 1 additional subject had trace hematuria before or at randomization. Table 65 displays the characteristics of these patients and their diagnoses.



Table 65 Bladder Cancer Patients in the 4MSU

Subject No. Age/Sex/Race	Country	Study Drugs	Preferred Term	Diagnosis Study Day	Action (Study Drugs)	Smoking History	Microscopic Hematuria (Y/N) <sup>a</sup>	Relevant Medical History/AEs	Histology
D1692C00005 -1-11 75/male/Asian	Japan	Dapa 2.5 mg	Bladder cancer	43	Disc	Former smoker, 20 cigarettes/ day for 50 years	Yes (2+)	AE: Occult blood positive onset Day 36	Papillary and broad base elevated lesion from neck to trigone of the bladder, Urinary cytology results revealed Class IV malignant cells
D1690C00006 -1004-6 63/male/white	Austria	Dapa 5 mg + insulin	Bladder cancer	393	None	Current smoker, 40 cigarettes/ d	No (Negative)	AEs: Benign prostatic hyperplasia Day 136, AE: Bladder neoplasm Day 358	Urothelial carcinoma pTa G2, noninvasive
MB102014- 34-524 60/male/white	Canada	Dapa 5 mg + metformin	Bladder transitional cell carcinoma	512	None	Former smoker, 25 cigarettes/ d for 25 y, stopped 1989	Yes (2+)	AE: Calculus ureteric Day 509	Location: Right ureteric orifice, Growth pattern: Papillary, Histological type: transitional, TNM classification: pTa, pNo, Mo., Grade/Stage: Stage 0
MB102030- 90-880 67/male/white	Argentina	Dapa 5 mg + pio- glitazone	Squamous cell carcinoma	144	Disc	Never smoked	No (trace)	AEs: Genital candidiasis Day 19, UTI Day 84, Urinary symptoms: urgency, pollakiuria, AEs: Haematuria Day 130, Urinary bladder polyp Day 144	Location: fundus, Growth pattern: nests and cords, Histological type: squamous, TNM classification: unknown Grade/Stage: unknown
D1690C00004 -4916-2 76/male/white	Germany	Dapa 10 mg <sup>b</sup> + metformin	Bladder transitional cell carcinoma	727	None	Former smoker, 20 pack years until 1980	No (Negative)	AE: Benign prostatic hyperplasia Day 727	Papillary, submucosal, stroma-invasive urothelial carcinoma, high-grade (formerly G3) with partial squamous cell differentiation
D1690C00006 -1501-6 67/male/white	Hungary	Dapa 10 mg + insulin	Bladder transitional cell carcinoma stage II	399	None	Never smoked	Yes (3+)	AE: Haematuria Day 372	Carcinoma transitional grade II of the urinary bladder
D1690C00006 -2206-14 66/male/white	United States	Dapa 10 mg + insulin	Bladder transitional cell carcinoma	581	None	Former smoker 30 cigarettes/ d for 42 y, stopped 2001	No (Negative)	AE: Haematuria Day 577	Non-invasive low grade papillary urothelial carcinoma.

<sup>a</sup> Highest value before or at randomization.

<sup>b</sup> The dapagliflozin dose for this subject was up-titrated from 2.5 to 5 to 10 mg. At the time of event, the dose was 10 mg.

#### Source 4MSU Table 10

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. One of the dapagliflozin treated patients was a 49 year old white male in an ongoing study, D1690C00018. He had a history of renal stones and hematuria several years prior to trial initiation. After approximately 10 weeks of treatment with dapagliflozin 10 mg, he was diagnosed with non-invasive low-grade papillary urothelial carcinoma of the urinary bladder (grade 2). There was no history noted of smoking.

The other case recently reported that was treated with dapagliflozin was in the same trial referenced above. This case was in a 56 year old man who was treated with dapagliflozin 10 mg for six months. There was no smoking or hematuria at baseline noted. The patient had three months of intermittent hematuria prior to diagnosis. Post surgical diagnosis was papillary urothelial carcinoma, low grade (papillary transitional cell carcinoma, grade 1).

The baseline characteristics of risk factors for bladder cancer in the dapagliflozin-treated patients and the control group were similar (Table 66), reducing the likelihood that any imbalance of risk might have contributed to the numerically higher number of cases observed with dapagliflozin.

**Table 66 Baseline Risk Factors for Bladder Cancer Phase 2b/3 Pool**

	DAPA TOTAL N=4310	ALL CONTROL N=1962
HEMATURIA AT BASELINE SUBJECTS WITH AT LEAST ONE URINE DIPSTICK PRIOR TO RECEIVING STUDY DRUG SHOWING 1+, 2+, 3+ OR GREATER BLOOD	387 ( 9.0)	176 ( 9.0)
SMOKING STATUS (%)		
NEVER	2589 (60.1)	1172 (59.7)
CURRENT	711 (16.5)	318 (16.2)
FORMER	1007 (23.4)	472 (24.1)
UNKNOWN	3 ( 0.1)	0 ( 0.0)
GENDER		
MALE	2192 (50.9)	1033 (52.7)
FEMALE	2118 (49.1)	929 (47.3)
RACE		
WHITE	3486 (80.9)	1591 (81.1)
BLACK/AFRICAN AMERICAN	158 ( 3.7)	73 ( 3.7)
ASIAN	558 (12.9)	242 (12.3)
OTHER	108 ( 2.5)	56 ( 2.9)
HISTORY OF CHRONIC CYSTITIS	4 ( 0.1)	5 ( 0.3)
USE OF CYCLOPHOSPHAMIDE	0	0

Source Response to FDA Information Request May 20, 2011

These data were consulted to epidemiology experts in the Division of Epidemiology, Office of Surveillance and Epidemiology. For a full discussion of bladder cancer in patients with T2DM compared to that seen and expected in the dapagliflozin clinical program, please refer to the consult report prepared by Dr. Christian Hampp..

Dr. Hampp's findings took into account the patient year exposure with the ongoing trials since updated cases came from these trials. The estimated incidence rate with updated cases in the dapagliflozin arms are based on an exposure of 3007 subject-years in males. This extrapolates to 299 per 100,000 subject-years (95% CI, 137 – 568). This can be compared to the single case in 1697 subject-years in male controls which

extrapolates to 59 cases per 100,000 subject-years (95% CI, 0.8 – 328). The rate ratio comparing incidence of bladder cancer dapagliflozin versus controls in males is 5.08 (95% CI, 0.70 – 222.6);  $p=0.15$ . This is not significant; however, the trials were not powered to distinguish between incidence of bladder cancer in male dapagliflozin subjects versus controls.

The review included a comparison to the bladder cancer incidence in the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute. The rate was adjusted with a literature-based factor by 40%. The adjustment was made for the increased risk for bladder cancer in a diabetic population and also adjusted for smoking and other risk factors. A Standardized Incidence Ratio (SIR) was calculated which compares observed incidence of bladder cancer in dapagliflozin treated patients with expected incidence in an age- and sex-matched background population. The SIR of observed versus expected cases in males exposed to dapagliflozin was 2.98 (95% CI, 1.36 – 5.65),  $p=0.008$ .

#### ***Reviewer's Comments***

**The baseline bladder cancer risk factors are balanced. This raises concern that a signal for bladder cancer exists in spite of a lack of nonclinical/carcinogenic findings. While some cases were diagnosed earlier in treatment making them less likely to be attributed to dapagliflozin, the five-fold risk is concerning. If dapagliflozin is approved, I would recommend that the applicant conduct an epidemiology study to further assess this risk as a post marketing requirement. The applicant has proposed such a study with their AC briefing document. This AE would also need to be followed in the long-term cardiovascular study (which is also planned and would be required as a post marketing study).**

#### **Breast Cancer**

Nine (0.2% of the total population, 0.4% of the female population) patients treated with dapagliflozin and none treated with control reported breast cancer at the time of NDA submission. During the course of the review, one additional case was reported in the control group. All cases were reported in female subjects. The 9 dapagliflozin-treated subjects include 8 subjects in the All Phase 2b and 3 Pool and 1 additional subject in study D1690C00012 (body weight and composition study) from the supplemental short-term plus long-term period. Descriptions of these patients and their cancer staging are categorized in Table 67.

**Table 67 Breast Cancer Cases in Phase 2b and 3 Studies Short-term Plus Long-term Treatment**

Subject Number	Age/Sex/Race	Diagnosis (Study Day)	Weight Change at Diagnosis (kg)	<u>Histological Grade/Stage/</u> <u>Histologic Type</u> <sup>a</sup>
<b>Dapagliflozin 2.5 mg</b>				
MB102013-33-261	74/Female/White	321	-2.5	Stage 1, grade 2 ductal carcinoma
D1690C00006-1403-2	63/Female/White	6	-1.1	<u>Grade 2, invasive ductal</u> <del>Not provided</del>
D1690C00006-1803-7	58/Female/White	292	+1.0	<u>Not provided</u> Grade 2 breast cancer
<b>Dapagliflozin 5 mg</b>				
MB102021-59-482	53/Female/White	39	-1.2	<u>Not provided</u> Grade 3 intraductal carcinoma
<b>Dapagliflozin 10 mg</b>				
D1690C00004-4405-20 <sup>b</sup>	60/Female/White	193	0	Grade 1 ductal carcinoma
MB102014-50-151	64/Female/White	285	-10.0	<u>Grade is reported as high, Grade 3</u> adenocarcinoma
D1690C00005-4012-46	69/Female/Asian	334	-3.4	<u>Not provided</u> <del>Grade 1</del>
D1690C00006-1005-18	61/Female/White	204	-9.0	<u>Grade 2, multifocal, invasive, lobular carcinoma</u> <del>Not provided</del>
D1690C00012-202-4	64/Female/White	211	-0.3	<u>Grade 2-3, invasive ductal carcinoma with TNM classification of PT1c, pN1M0</u>

<sup>a</sup> Provided when biopsy information was available.

<sup>b</sup> The dapagliflozin dose for this subject was up-titrated from 2.5 to 5 to 10 mg.

#### Source SCS Erratum Table 36

The applicant conducted an epidemiology study where the age- and sex-specific person-time of the dapagliflozin-treated patients was multiplied by the age- and sex-specific rates of breast cancer in the SEER population. An “expected” number of cases

was calculated for each age- and sex-stratum. These stratum-specific expected numbers were summed to provide an overall expected number of cases in the dapagliflozin-treated population. This study was done prior the report of the control case.

Table 68 displays the expected number of breast cancer cases among the female patients that took dapagliflozin.

**Table 68 Dapagliflozin Data and Calculations for Expected Breast Cancer Cases**

<b>Table 1: Dapagliflozin data and Calculations for Expected Breast Cancer Cases</b>				
Age Group	Dapagliflozin Breast Cancer Cases	Dapagliflozin Female Person-Time	SEER Female Breast Cancer Rates	Expected Breast Cancer in Dapagliflozin Patients
20-24	0	5.6	0.000016	0.0001
25-29	0	14.3	0.000083	0.0012
30-34	0	28.8	0.000259	0.0075
35-39	0	59.6	0.000589	0.0351
40-44	0	126.8	0.001209	0.1533
45-49	0	229.4	0.001861	0.4269
50-54	1	357.7	0.002258	0.8077
55-59	1	463.6	0.002802	1.2990
60-64	4	409.5	0.003489	1.4287
65-69	1	222.7	0.003942	0.8779
70-74	1	153.7	0.004100	0.6302
75-79	1	43.1	0.004337	0.1869
80-84	0	6.9	0.004223	0.0291
85+	0	1.0	0.003392	0.0034
<b>Total</b>	<b>9</b>	<b>2122.7</b>	<b>-</b>	<b>5.9</b>
SEER data 2003-2007, SEER 17 crude incidence rates by age, females, breast cancer. Obtained from SEER*Stat November 22, 2010				

Source Breast Cancer Epidemiology Study Table 1

The adjusted SIR for breast cancer among dapagliflozin-treated females in the dapagliflozin clinical program was 1.27 and was not statistically significant (95% CI:

0.58 to 2.41). The SIR point estimate is mildly elevated but the confidence intervals are wide given the few number of cases (n=9).

**Table 69 Standardized Incidence Ratio for Dapagliflozin-Exposed Patients**

<b>Table 2. Standardized Incidence Ratio for Dapagliflozin-Exposed Patients</b>					
	Observed Cases	Expected Cases	Calculated SIR	SIR (95% LL)	SIR (95% UL)
Breast Cancer <u>without</u> type 2 diabetes risk adjustment	9	5.9	1.53	0.7	2.9
Breast Cancer <u>with</u> type 2 diabetes risk adjustment <sup>††</sup>	9	7.1	1.27	0.58	2.41
<sup>††</sup> Risk Adjustment: Meta-analysis of 20 observational studies ( <a href="#">Larsson et al., 2007</a> ) found that women with type 2 diabetes versus without had a statistically significant 20% increased risk of breast cancer. RR=1.20, 95% CI, 1.12-1.28					

Source Breast Cancer Epidemiology Study Table 2

Based on the updated control case, FDA epidemiologist Dr. Julia Ju, calculated that in the dapagliflozin arm the exposure of 2416 subject-years in female patients can be extrapolated to 372 cases per 100,000 subject-years (95% CI, 170-707). Exposure in the control is 1085 subject-years for females. This can be extrapolated to 92 cases per 100,000 subject-years (95% CI, 23-5138). For a full analysis of the breast cancer incidence please see her consultation review.

Dr. Ju calculated that the rate ratio of breast cancer among female dapagliflozin-treated patients versus controls is 4.04 (9% CI, 0.56-177.1); p=0.27. While not statistically significant, the clinical trials were not powered to distinguish the incidence of breast cancer in dapagliflozin treated patients versus controls. Dr. Ju also conducted a literature search on breast cancer in diabetes. Age specific incidence rates of female breast cancer in dapagliflozin treated women compared to what is seen in the literature are summarized in Table 70. The rate for all age groups is higher than what would be expected in the dapagliflozin treated women.

**Table 70 Age Specific Incidence of Breast Cancer in the Literature and in Dapagliflozin Treated Women**

Age	Study	Incidence rate of breast cancer per 1,000 person-years	
		Literature	Dapagliflozin clinical trials*
55-64	Lipscombe (Canada)	2.90	5.73
65-79		3.02	7.15
40-69	Inoue (Japan)	0.62	3.87
50-75	Michels (U.S)	3.41	4.98
45-64	Mink (U.S)	4.04	4.11

Source Dr. Ju's epidemiology review

All the cases of breast cancer were diagnosed within one year of treatment with dapagliflozin. Two of these cases were diagnosed within two months of beginning treatment. However, baseline characteristics for breast cancer risk for women in the Phase 2b/3 pool were similar, see Table 71.

Table 71 Breast Cancer Risk Factors at Baseline Females Phase 2b/3 Pool

	DAPA TOTAL N=2110		ALL CONTROL N=922	
BODY MASS INDEX (KG/M2)				
N	2110		922	
MEAN	32.24		32.17	
MEDIAN	32.00		31.90	
MIN , MAX	16.90 , 48.40		17.50 , 45.20	
Q1 , Q3	28.10 , 36.20		28.00 , 36.20	
STANDARD DEVIATION	5.643		5.794	
BODY MASS INDEX CATEGORIZATION (%)				
< 30 KG/M2	768 (36.4)		351 (38.1)	
>= 30 KG/M2	1342 (63.6)		571 (61.9)	
NOT REPORTED	0		0	
AGE CATEGORIZATION (%)				
<=50 YEARS	576 (27.3)		256 (27.8)	
>50 YEARS	1534 (72.7)		666 (72.2)	
< 45	271 (12.8)		128 (13.9)	
>= 45 - < 55	589 (27.9)		248 (26.9)	
>= 55 - < 65	823 (39.0)		320 (34.7)	
>= 65 - < 75	376 (17.8)		194 (21.0)	
>= 75	51 (2.4)		32 (3.5)	
NOT REPORTED	0		0	
BODY MASS INDEX AND AGE CATEGORIZATION (%)				
>=30 KG/M2 AND >50 YEARS	940 (44.5)		409 (44.4)	
ALCOHOL CONSUMPTION AT BASELINE (%)				
YES	654 (31.0)		273 (29.6)	
NO	1456 (69.0)		649 (70.4)	
NOT REPORTED	0		0	
TOBACO USE AT BASELINE (%)				
NEVER	1608 (76.2)		713 (77.3)	
CURRENT	235 (11.1)		88 (9.5)	
FORMER	267 (12.7)		121 (13.1)	
UNKNOWN	0		0	
PRE-RANDOMIZATION USE OF OESTROGEN MEDICATION				
YES	79 (3.7)		45 (4.9)	
NO	2031 (96.3)		877 (95.1)	
NOT REPORTED	0		0	

Source Applicant Response to Inquiry 5/4/11

### Reviewer's Comments

Given the early diagnosis timing of these cases, an association with dapagliflozin treatment is difficult to make. However, the imbalance is clear despite appropriate randomization. As with the bladder cancer cases, the applicant proposes an epidemiology study to provide data that will lower the current calculated risk. I agree with this plan as well as following these cases as AE of special interest in the long-term CV trial.



## Other Neoplasms

As part of ongoing assessment of malignancies, due to the imbalance in both breast and bladder cancer, the applicant submitted a Neoplasm Summary Report in May 2011, approximately one month after the 4MSU. This report showed that the overall incidence rates of unspecified and malignant neoplasms are similar between dapagliflozin and control. Some individual cancer types were more common with comparator than with dapagliflozin, while others were more common for dapagliflozin than comparator. Overall, malignant and unspecified tumors were observed more frequently in patients treated with dapagliflozin than control in the All Phase 2b and 3 Pool for both the initial NDA and the 4MSU. With additional data collected since the 4MSU, these differences were smaller, and the overall incidence rates were similar between dapagliflozin and control. In the table presented by preferred term for all neoplasms, the only neoplasm other than breast and bladder that was reported with higher incidence of at least 0.05% in dapagliflozin treated patients compared to control was prostate cancer.

**Table 72 Prostate Cancer Incidence in Neoplasm Report, All Phase 2b/3 Pool**

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
PROSTATE (MALES ONLY)	8 (0.34)	(0.15, 0.67)	2587.97	0.31 (0.13, 0.61)		2 (0.17)	(0.02, 0.61)	1277.54	0.16 (0.02, 0.57)	
PROSTATE CANCER	6 (0.26)					2 (0.17)				
NEOPLASM PROSTATE	1 (0.04)					0 (0.00)				
PROSTATE CANCER RECURRENT	1 (0.04)					0 (0.00)				

Source Neoplasm Report Table 2

Submission Specific Primary Safety Concerns

## Liver Injury

The applicant had a hepatic adjudication report submitted with the 4MSU. The adjudication process was to include all clinical Phase 2 and 3 studies; however, three of the studies (D1691C00003, D1693C00002, and MB102077) had not been initiated before the cutoff date of 15-Oct-2010, and are therefore not included. An additional two studies (D1692C00006 and D1692C00012) did not enroll any subjects before 15-Oct-2010 and are not included in this analysis. The adjudication process was for liver abnormalities that met the following criteria:

- AST and/or ALT > 3X ULN and TB > 1.5X ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT > 5X ULN
- Liver-related adverse event leading to discontinuation
- Liver-related SAE or AE in any subjects who died

The following scale was used by the three expert hepatologists on the adjudication committee (Table 73).

**Table 73 Hepatic Adjudication Causal Relationship Scale**

<b>Causal Relationship</b>	<b>Likelihood</b>	<b>Description</b>
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	< 25%	There is evidence that an etiological factor other than the study drug caused the injury is clear

#### Source Hepatic Adjudication Report

The adjudication committee found that there were two **probable** cases. When unblinded these were both found to be control patients. There were 15 **possible** cases. Nine of these were in dapagliflozin treated patients, five were in controls and one remained blinded.

There were a total of five cases in the Phase 2b and 3 Pool that met laboratory criteria for Hy's Law (AST or ALT greater than 3x the Upper Limit of Normal [ULN] in addition to elevation of total bilirubin greater than 2x ULN). If these cases do not have other clinical explanations, they are considered Hy's Law cases. These five cases were included in the cases that were adjudicated by the committee. A consult to the FDA Office of Surveillance and Epidemiology (OSE) hepatic experts was sent. This consult requested review of all the cases adjudicated by the applicant's committee, including the five cases that met biochemical Hy's Law criteria. The purpose was to assess for drug induced liver injury. OSE used the same scale as Table 73 above to assess the cases. Of the five cases on dapagliflozin that met the Hy's Law criteria, OSE found that one case was **probable**. Three were unlikely and one was excluded as drug (not dapagliflozin) induced liver injury. For a full discussion of these and other cases that were adjudicated, please see Dr. Leonard Seeff's full consult report.

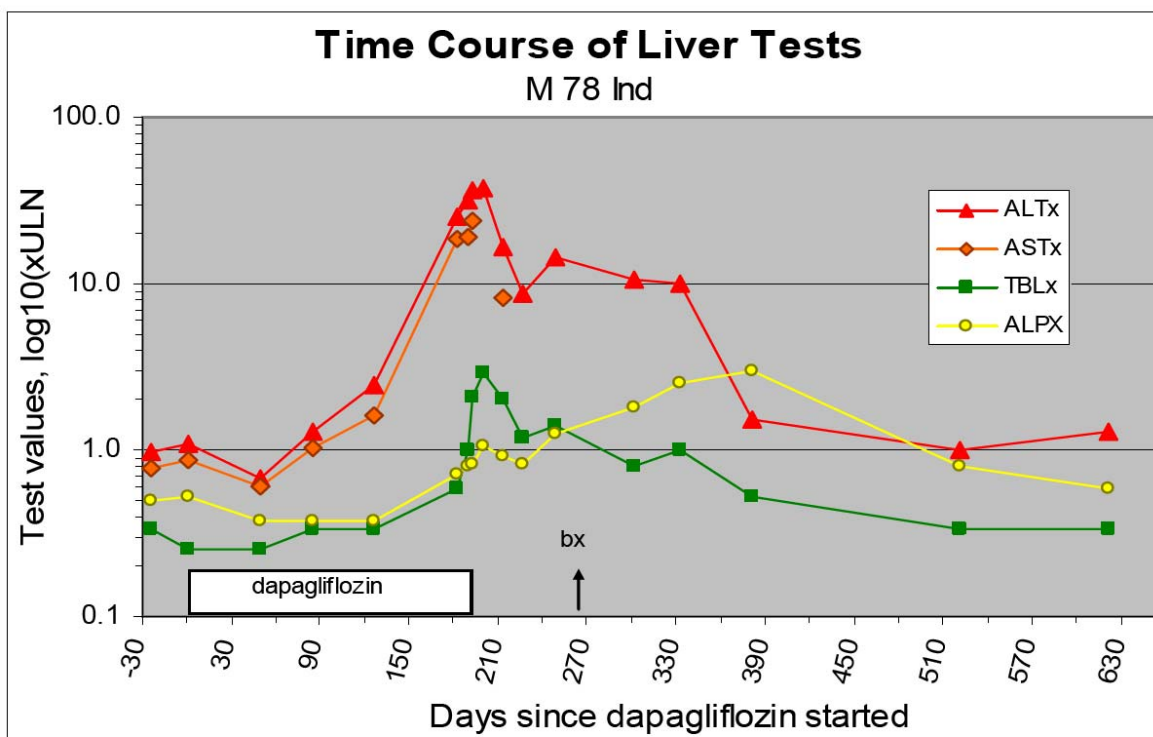
A summary for the probable case is as follows:

D1690C00004-4402-6: The patient was a 78 year old man from India, living in the United Kingdom, with T2DM, coronary artery disease, hypertension, dyslipidemia and benign prostatic hypertrophy. He received the study drug plus metformin. Concomitant

drugs included atorvastatin, cromolyn, lecanidipine, atenolol, parendopril, naproxen, acetylsalicylic acid and herbal products that included senna and ispaghula husk for gastrointestinal upset. The patient was found to be a C282Y/H63D compound heterozygote for hemochromatosis.

Although the patient had a slight increase in ALT on the initial study day, ALT increased from baseline at study day 85. By study day 196, the patient had complaints of dark urine and stool along with upper abdominal discomfort. He was noted to have a "tinge of jaundice." Of note, dapagliflozin was discontinued on day 192. The elevated aminotransferases and bilirubin started to decrease by day 213. Review of a liver biopsy led the treating physicians to a suspicion of autoimmune hepatitis, but prednisolone was only started on day 349; at that point, the serum aminotransferases and bilirubin concentrations had already decreased considerably. The timing of the therapeutic intervention with regard to the oscillation of liver tests suggests a drug induced liver injury diagnosis as opposed to autoimmune hepatitis. The biochemical time course associated with the liver injury event in this study subject is outlined in Figure 23.

**Figure 23 Time Course of Liver Tests for Patient with Possible Drug Induced Liver Injury**



**bx=biopsy**

Source OSE Hepatic Consult Report

During the patient's clinical course, serologic markers for autoimmune hepatitis were negative, although the liver biopsy had some suggestive features of consistent with both

drug induced liver injury and autoimmune hepatitis—fibrosis patterns and acute necroinflammation. In addition, the patient had an elevated IgG 22.4 g/L (reference range 5.3-16.5), IgA 8.93 g/L (0.80-4.00) IgM 2.90 g/L (reference range 0.50-2.00) on day 357. CMV IgG and EBV IgG were both positive implying past infection and the patient had increased transferrin levels. Anti-Hepatitis C was non-reactive at enrollment (b) (6)

There were no subsequent tests for Hepatitis C. The summary of the tests that were done: HBsAg: Negative; HBcAb: Negative; Hepatitis A IgM: Negative; Hepatitis E IgM and IgG: Negative; CMV IgM: Negative; CMV IgG and EBV Nuclear Antigen IgG: both Positive.

The three unlikely cases were as follows:

D1690C00005-6013-3: 83 year old male with choledocholithiasis  
D1690C00005-7002-4: 60 year old female with choledocholithiasis  
MB102030-9-92: 60 year old male choledocholithiasis

The case that was ruled out:

D1690C00006-2004-6: 61 year old that had pancreatic cancer with hepatic metastases

The OSE team clarify in their report that finding one Hy's law case in a clinical program is worrisome and two are predictive that the drug has a potential to cause serious drug induced liver injury (leading to death or liver transplant) in a larger population. With one probable case in this clinical program at the time of 2489 patient year exposure to six months, the estimate would that one in 25,000 patients would develop serious drug induced liver injury. This estimate is based on the relationship between Hy's law and DILI being 10:1. It is virtually impossible to extrapolate with any degree of certainty on the basis of one case of Hy's law.

There was no imbalance in the marked aminotransferase elevations (i.e., 3X, 5X, 10 X or 20 X ULN) across the safety pools. The following three tables show this.

### **Placebo-controlled Pool Short-term Treatment**

Clinical Review  
Somya V. Dunn, M.D.  
NDA 202293

(b) (4) Dapagliflozin

**Table 74 Proportion of Patients with Elevated Liver Tests Short-term Treatment Group**

	X/N#(Percent)				
	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS	55/1382 ( 4.0)	32/814 ( 3.9)	40/1136 ( 3.5)	43/1182 ( 3.6)	120/3270 ( 3.7)
AST ELEVATION					
> 3X ULN	6/1382 ( 0.4)	1/814 ( 0.1)	7/1136 ( 0.6)	9/1182 ( 0.8)	18/3270 ( 0.6)
> 5X ULN	2/1382 ( 0.1)	0/814	0/1136	3/1182 ( 0.3)	4/3270 ( 0.1)
> 10X ULN	1/1382 ( 0.1)	0/814	0/1136	0/1182	0/3270
> 20X ULN	0/1382	0/814	0/1136	0/1182	0/3270
ALT ELEVATION					
> 3X ULN	15/1382 ( 1.1)	4/814 ( 0.5)	11/1136 ( 1.0)	9/1182 ( 0.8)	26/3270 ( 0.8)
> 5X ULN	5/1382 ( 0.4)	1/814 ( 0.1)	2/1136 ( 0.2)	1/1182 ( 0.1)	5/3270 ( 0.2)
> 10X ULN	2/1382 ( 0.1)	0/814	0/1136	0/1182	0/3270
> 20X ULN	1/1382 ( 0.1)	0/814	0/1136	0/1182	0/3270
AST OR ALT ELEVATION					
> 3X ULN	17/1382 ( 1.2)	4/814 ( 0.5)	12/1136 ( 1.1)	15/1182 ( 1.3)	33/3270 ( 1.0)
> 5X ULN	5/1382 ( 0.4)	1/814 ( 0.1)	2/1136 ( 0.2)	3/1182 ( 0.3)	7/3270 ( 0.2)
> 10X ULN	2/1382 ( 0.1)	0/814	0/1136	0/1182	0/3270
> 20X ULN	1/1382 ( 0.1)	0/814	0/1136	0/1182	0/3270
TOTAL BILIRUBIN ELEVATION					
> 1.5X ULN	14/1381 ( 1.0)	8/814 ( 1.0)	11/1136 ( 1.0)	15/1182 ( 1.3)	36/3270 ( 1.1)
> 2X ULN	3/1381 ( 0.2)	3/814 ( 0.4)	3/1136 ( 0.3)	6/1182 ( 0.5)	12/3270 ( 0.4)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION (AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	2/1381 ( 0.1)	0/814	1/1136 ( 0.1)	3/1182 ( 0.3)	4/3270 ( 0.1)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	1/1381 ( 0.1)	0/814	1/1136 ( 0.1)	2/1182 ( 0.2)	3/3270 ( 0.1)
(AST > 3X ULN OR ALT > 3X ULN) AND {(TBL > 2X ULN AND NO ALP >= 2X ULN) WITHIN 14 DAYS ON OR AFTER AT ELEVATION}	1/1381 ( 0.1)	0/814	1/1136 ( 0.1)	1/1182 ( 0.1)	2/3270 ( 0.1)
ALP ELEVATION					
> 1.5X ULN	30/1382 ( 2.2)	20/814 ( 2.5)	22/1136 ( 1.9)	17/1182 ( 1.4)	61/3270 ( 1.9)
> 3X ULN	2/1382 ( 0.1)	1/814 ( 0.1)	1/1136 ( 0.1)	1/1182 ( 0.1)	3/3270 ( 0.1)

Source SCS Table 82

## Placebo-controlled Pool Short-term and Long-term Treatment

**Table 75 Proportion of Patients with Elevated Liver Tests Short-term Plus Long-term Treatment Group**

	X/N# (Percent)				
	PLA N = 785	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 859	DAPA TOTAL N = 2251
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS	42/778 ( 5.4)	36/625 ( 5.8)	39/759 ( 5.1)	44/849 ( 5.2)	119/2233 ( 5.3)
AST ELEVATION					
> 3X ULN	7/778 ( 0.9)	5/625 ( 0.8)	12/759 ( 1.6)	9/849 ( 1.1)	26/2233 ( 1.2)
> 5X ULN	3/778 ( 0.4)	1/625 ( 0.2)	1/759 ( 0.1)	5/849 ( 0.6)	7/2233 ( 0.3)
> 10X ULN	1/778 ( 0.1)	1/625 ( 0.2)	1/759 ( 0.1)	2/849 ( 0.2)	4/2233 ( 0.2)
> 20X ULN	0/778	1/625 ( 0.2)	1/759 ( 0.1)	1/849 ( 0.1)	3/2233 ( 0.1)
ALT ELEVATION					
> 3X ULN	11/778 ( 1.4)	13/625 ( 2.1)	12/759 ( 1.6)	14/849 ( 1.6)	39/2233 ( 1.7)
> 5X ULN	4/778 ( 0.5)	4/625 ( 0.6)	3/759 ( 0.4)	5/849 ( 0.6)	12/2233 ( 0.5)
> 10X ULN	1/778 ( 0.1)	1/625 ( 0.2)	1/759 ( 0.1)	1/849 ( 0.1)	3/2233 ( 0.1)
> 20X ULN	1/778 ( 0.1)	0/625	0/759	1/849 ( 0.1)	1/2233 (<0.1)
AST OR ALT ELEVATION					
> 3X ULN	14/778 ( 1.8)	14/625 ( 2.2)	16/759 ( 2.1)	19/849 ( 2.2)	49/2233 ( 2.2)
> 5X ULN	5/778 ( 0.6)	4/625 ( 0.6)	3/759 ( 0.4)	7/849 ( 0.8)	14/2233 ( 0.6)
> 10X ULN	1/778 ( 0.1)	1/625 ( 0.2)	1/759 ( 0.1)	2/849 ( 0.2)	4/2233 ( 0.2)
> 20X ULN	1/778 ( 0.1)	1/625 ( 0.2)	1/759 ( 0.1)	1/849 ( 0.1)	3/2233 ( 0.1)
TOTAL BILIRUBIN ELEVATION					
> 1.5X ULN	9/778 ( 1.2)	5/625 ( 0.8)	11/759 ( 1.4)	15/849 ( 1.8)	31/2233 ( 1.4)
> 2X ULN	2/778 ( 0.3)	3/625 ( 0.5)	1/759 ( 0.1)	5/849 ( 0.6)	9/2233 ( 0.4)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION (AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	2/778 ( 0.3)	1/625 ( 0.2)	1/759 ( 0.1)	5/849 ( 0.6)	7/2233 ( 0.3)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	2/778 ( 0.3)	1/625 ( 0.2)	1/759 ( 0.1)	2/849 ( 0.2)	4/2233 ( 0.2)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN AND NO ALP >= 2X ULN) WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	2/778 ( 0.3)	0/625	1/759 ( 0.1)	1/849 ( 0.1)	2/2233 ( 0.1)
ALP ELEVATION					
> 1.5X ULN	26/778 ( 3.3)	21/625 ( 3.4)	18/759 ( 2.4)	21/849 ( 2.5)	60/2233 ( 2.7)
> 3X ULN	1/778 ( 0.1)	1/625 ( 0.2)	1/759 ( 0.1)	2/849 ( 0.2)	4/2233 ( 0.2)

Source 4MSU Table 19

## All Phase 2b and 3 Pool

Table 76 Proportion of Patients with Elevated Liver Tests All Phase 2b/3 Pool

	X/N# (Percent)	
	DAPA TOTAL N = 4287	ALL CONTROL N = 1941
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS	206/4258 ( 4.8)	85/1922 ( 4.4)
AST ELEVATION		
> 3X ULN	38/4258 ( 0.9)	16/1922 ( 0.8)
> 5X ULN	11/4258 ( 0.3)	8/1922 ( 0.4)
> 10X ULN	5/4258 ( 0.1)	3/1922 ( 0.2)
> 20X ULN	4/4258 ( 0.1)	0/1922
ALT ELEVATION		
> 3X ULN	61/4258 ( 1.4)	28/1922 ( 1.5)
> 5X ULN	17/4258 ( 0.4)	9/1922 ( 0.5)
> 10X ULN	4/4258 ( 0.1)	3/1922 ( 0.2)
> 20X ULN	2/4258 (<0.1)	1/1922 ( 0.1)
AST OR ALT ELEVATION		
> 3X ULN	73/4258 ( 1.7)	33/1922 ( 1.7)
> 5X ULN	19/4258 ( 0.4)	12/1922 ( 0.6)
> 10X ULN	5/4258 ( 0.1)	5/1922 ( 0.3)
> 20X ULN	4/4258 ( 0.1)	1/1922 ( 0.1)
TOTAL BILIRUBIN ELEVATION		
> 1.5X ULN	55/4258 ( 1.3)	18/1921 ( 0.9)
> 2X ULN	18/4258 ( 0.4)	5/1921 ( 0.3)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION		
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	8/4258 ( 0.2)	4/1921 ( 0.2)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	5/4258 ( 0.1)	3/1921 ( 0.2)
(AST > 3X ULN OR ALT > 3X ULN) AND { (TBL > 2X ULN AND NO ALP ≥ 2X ULN) WITHIN 14 DAYS ON OR AFTER AT ELEVATION }	3/4258 ( 0.1)	2/1921 ( 0.1)
ALP ELEVATION		
> 1.5X ULN	105/4258 ( 2.5)	49/1922 ( 2.5)
> 3X ULN	6/4258 ( 0.1)	4/1922 ( 0.2)

Source SCS Table 84

### Reviewer's Comments

While there is no imbalance in the marked elevations of liver enzymes, the one probable case of Hy's Law is very concerning. If approved, I would consider recommendations on monitoring patients prior to initiation of dapagliflozin therapy and evaluation of elevations. For example, the label for ACTOS (pioglitazone), which has postmarketing reports of hepatic failure, contains a recommendation to obtain liver tests prior to starting therapy. Ongoing monitoring during therapy would not be necessary.

If approved, this premarketing case of Hy's Law should be included in labeling under Warnings and Precautions. In addition, the proposed pharmacoepidemiology study to estimate the incidence and relative risk of liver injury would be extremely important as will be following such cases in the long-term cardiovascular trial. If another such case is found during the pre or post marketing studies, I would not recommend approval of dapagliflozin due to the possibility of drug induced liver injury in a larger population.

## Other Liver Enzyme Laboratory Data

There were no clinically relevant changes from baseline with liver related laboratory data in the short-term placebo-controlled pool, see Table 77.

**Table 77 Changes from Baseline Liver Laboratory Data Short-term Placebo-controlled Pool**

LAB TEST GROUP	
LAB TEST SUBGROUP	
LABORATORY PARAMETER	PLA
SUMMARY STATISTICS	N = 1393
LIVER FUNCTION TESTS	
ALANINE AMINOTRANSFERASE (ALT) (U/L)	
N#	1086
MEAN CHANGE FROM BASELINE (SD)	-1.703 (17.958)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-2.000 (-67.000, 349.000)
LAB TEST GROUP	
LAB TEST SUBGROUP	
LABORATORY PARAMETER	DAPA TOTAL
SUMMARY STATISTICS	N = 3291
LIVER FUNCTION TESTS	
ALANINE AMINOTRANSFERASE (ALT) (U/L)	
N#	2445
MEAN CHANGE FROM BASELINE (SD)	-3.944 (15.095)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-3.000 (-89.000, 294.000)
LAB TEST GROUP	
LAB TEST SUBGROUP	
LABORATORY PARAMETER	PLA
SUMMARY STATISTICS	N = 1393
ALKALINE PHOSPHATASE (ALP) (U/L)	
N#	1088
MEAN CHANGE FROM BASELINE (SD)	-4.020 (14.665)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-3.000 (-114.00, 120.000)
ASPARTATE AMINOTRANSFERASE (AST) (U/L)	
N#	1085
MEAN CHANGE FROM BASELINE (SD)	-1.096 (9.602)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-1.000 (-68.000, 80.000)
BILIRUBIN, TOTAL (MG/DL)	
N#	1083
MEAN CHANGE FROM BASELINE (SD)	-0.011 (0.204)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	0.000 (-1.000, 1.300)



LAB TEST GROUP LAB TEST SUBGROUP LABORATORY PARAMETER SUMMARY STATISTICS	DAPA TOTAL N = 3291
ALKALINE PHOSPHATASE (ALP) (U/L)	
N#	2451
MEAN CHANGE FROM BASELINE (SD)	-3.200 (13.963)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-3.000 (-107.00, 77.000)
ASPARTATE AMINOTRANSFERASE (AST) (U/L)	
N#	2443
MEAN CHANGE FROM BASELINE (SD)	-1.985 (10.319)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	-1.000 (-82.000, 161.000)
BILIRUBIN, TOTAL (MG/DL)	
N#	2441
MEAN CHANGE FROM BASELINE (SD)	0.015 (0.195)
MEDIAN CHANGE FROM BASELINE (MIN, MAX)	0.000 (-1.000, 1.300)

Source Modified from Central Tendency Table Response to FDA Inquiry 5/10/11

## **Genital Infections**

### **Placebo-controlled Pool—Short-term Treatment**

In this analysis of genital infections, prespecified PTs were used to identify genital infections and included both events suggestive of genital infection, as well as actual diagnoses of genital infection. This list was referred to as events suggestive of genital infection. In the short-term treated group, two of the most common events identified by the prespecified list were pruritus genital and vulvovaginal pruritus (Table 78). Pruritus is not a definitive indication of a genital infection as there can be other explanations such as inflammatory skin lesions, abrasions, or chemical irritation.

In the Placebo-controlled Pool, more patients treated with dapagliflozin had events suggestive of genital infection compared with placebo. The number of infections was higher in both the 5 and 10 mg groups compared with the 2.5 mg group. In all treatment groups, events suggestive of genital infection were more common in females than males. Most were mild or moderate in intensity. There was one case that was considered serious; this was a case of balanoposthitis in a patient treated with dapagliflozin 5 mg in study MB102029-moderate renal impairment study.

Most events responded to treatment, resolved and were not recurrent. None of these events were classified as serious. There were three patients in the dapagliflozin treated group who discontinued treatment due to an event of genital infection; there were no patients discontinuing for this reason in the placebo treated group.

**Table 78 Genital Infections in Placebo-controlled Pool Short-term Treatment**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	29 ( 2.1)	47 ( 5.8)	80 ( 7.0)	83 ( 7.0)	223 ( 6.8)
VULVOVAGINAL MYCOTIC INFECTION	5 ( 0.4)	8 ( 1.0)	13 ( 1.1)	20 ( 1.7)	45 ( 1.4)
PRURITUS GENITAL	7 ( 0.5)	7 ( 0.9)	7 ( 0.6)	15 ( 1.3)	29 ( 0.9)
VAGINAL INFECTION	1 ( 0.1)	6 ( 0.7)	14 ( 1.2)	10 ( 0.8)	33 ( 1.0)
VULVOVAGINAL PRURITUS	6 ( 0.4)	5 ( 0.6)	11 ( 1.0)	9 ( 0.8)	26 ( 0.8)
BALANITIS	1 ( 0.1)	4 ( 0.5)	7 ( 0.6)	7 ( 0.6)	18 ( 0.5)
GENITAL INFECTION FUNGAL	1 ( 0.1)	6 ( 0.7)	7 ( 0.6)	6 ( 0.5)	20 ( 0.6)
VULVOVAGINAL CANDIDIASIS	1 ( 0.1)	3 ( 0.4)	10 ( 0.9)	4 ( 0.3)	18 ( 0.5)
VULVOVAGINITIS	0	2 ( 0.2)	4 ( 0.3)	3 ( 0.3)	9 ( 0.3)
BALANITIS CANDIDA	0	2 ( 0.2)	2 ( 0.2)	2 ( 0.2)	7 ( 0.2)
GENITAL CANDIDIASIS	0	0	3 ( 0.3)	2 ( 0.2)	5 ( 0.2)
GENITAL INFECTION	0	0	2 ( 0.2)	2 ( 0.2)	4 ( 0.1)
GENITAL BURNING SENSATION	2 ( 0.1)	1 ( 0.1)	0	1 ( 0.1)	2 ( 0.1)
GENITAL DISCHARGE	1 ( 0.1)	0	0	1 ( 0.1)	1 ( <0.1)
GENITAL INFECTION MALE	0	0	0	1 ( 0.1)	1 ( <0.1)
GENITAL RASH	0	1 ( 0.1)	0	1 ( 0.1)	2 ( 0.1)
PENILE INFECTION	0	0	0	1 ( 0.1)	2 ( 0.1)
VAGINAL DISCHARGE	3 ( 0.2)	0	0	1 ( 0.1)	1 ( <0.1)
VAGINAL INFLAMMATION	0	0	0	1 ( 0.1)	1 ( <0.1)
VULVITIS	0	2 ( 0.2)	1 ( 0.1)	1 ( 0.1)	4 ( 0.1)
BALANOPOSTHITIS	0	1 ( 0.1)	1 ( 0.1)	0	2 ( 0.1)
BALANOPOSTHITIS INFECTIVE	0	0	1 ( 0.1)	0	1 ( <0.1)
GENITOURINARY TRACT INFECTION	0	0	1 ( 0.1)	0	1 ( <0.1)
POSTHITIS	0	0	1 ( 0.1)	0	1 ( <0.1)
VAGINITIS BACTERIAL	2 ( 0.1)	1 ( 0.1)	1 ( 0.1)	0	3 ( 0.1)
VULVAL ABSCESS	1 ( 0.1)	0	0	0	0
VULVOVAGINAL BURNING SENSATION	1 ( 0.1)	1 ( 0.1)	1 ( 0.1)	0	2 ( 0.1)
VULVOVAGINAL ERYTHEMA	0	0	1 ( 0.1)	0	1 ( <0.1)

Source SCS Table 49

AEs suggestive of genital infection search results were also presented by gender. In females, the most common event was vulvovaginal mycotic infection. Pruritus was a common event in the male patients accounting for almost a quarter of events suggestive of genital infection in males (Table 79 and Table 80).

**Table 79 Genital Infections in Placebo-controlled Pool Short-term Treatment—Females**

Preferred Term (%)	PLA N = 677	DAPA 2.5MG N = 400	DAPA 5MG N = 581	DAPA 10MG N = 598	DAPA TOTAL N = 1648
TOTAL SUBJECTS WITH AN EVENT	23 ( 3.4)	34 ( 8.5)	63 ( 10.8)	58 ( 9.7)	165 ( 10.0)
VULVOVAGINAL MYCOTIC INFECTION	5 ( 0.7)	8 ( 2.0)	13 ( 2.2)	20 ( 3.3)	45 ( 2.7)
VAGINAL INFECTION	1 ( 0.1)	6 ( 1.5)	14 ( 2.4)	10 ( 1.7)	33 ( 2.0)
VULVOVAGINAL PRURITUS	6 ( 0.9)	5 ( 1.3)	11 ( 1.9)	9 ( 1.5)	26 ( 1.6)
PRURITUS GENITAL	3 ( 0.4)	5 ( 1.3)	6 ( 1.0)	7 ( 1.2)	18 ( 1.1)
VULVOVAGINAL CANDIDIASIS	1 ( 0.1)	3 ( 0.8)	10 ( 1.7)	4 ( 0.7)	18 ( 1.1)
VULVOVAGINITIS	0	2 ( 0.5)	4 ( 0.7)	3 ( 0.5)	9 ( 0.5)
GENITAL INFECTION	0	0	1 ( 0.2)	2 ( 0.3)	3 ( 0.2)
GENITAL BURNING SENSATION	1 ( 0.1)	1 ( 0.3)	0	1 ( 0.2)	2 ( 0.1)
GENITAL CANDIDIASIS	0	0	1 ( 0.2)	1 ( 0.2)	2 ( 0.1)
GENITAL DISCHARGE	1 ( 0.1)	0	0	1 ( 0.2)	1 ( 0.1)
GENITAL INFECTION FUNGAL	0	3 ( 0.8)	6 ( 1.0)	1 ( 0.2)	10 ( 0.6)
VAGINAL DISCHARGE	3 ( 0.4)	0	0	1 ( 0.2)	1 ( 0.1)
VAGINAL INFLAMMATION	0	0	0	1 ( 0.2)	1 ( 0.1)
VULVITIS	0	2 ( 0.5)	1 ( 0.2)	1 ( 0.2)	4 ( 0.2)

Source SCS Table 50—females

**Table 80 Genital Infections in Placebo-controlled Pool Short-term Treatment—Males**

Preferred Term (%)	PLA N = 716	DAPA 2.5MG N = 414	DAPA 5MG N = 564	DAPA 10MG N = 595	DAPA TOTAL N = 1643
TOTAL SUBJECTS WITH AN EVENT	6 ( 0.8)	13 ( 3.1)	17 ( 3.0)	25 ( 4.2)	58 ( 3.5)
PRURITUS GENITAL	4 ( 0.6)	2 ( 0.5)	1 ( 0.2)	8 ( 1.3)	11 ( 0.7)
BALANITIS	1 ( 0.1)	4 ( 1.0)	7 ( 1.2)	7 ( 1.2)	18 ( 1.1)
GENITAL INFECTION FUNGAL	1 ( 0.1)	3 ( 0.7)	1 ( 0.2)	5 ( 0.8)	10 ( 0.6)
BALANITIS CANDIDA	0	2 ( 0.5)	2 ( 0.4)	2 ( 0.3)	7 ( 0.4)
GENITAL CANDIDIASIS	0	0	2 ( 0.4)	1 ( 0.2)	3 ( 0.2)
GENITAL INFECTION MALE	0	0	0	1 ( 0.2)	1 ( 0.1)
GENITAL RASH	0	1 ( 0.2)	0	1 ( 0.2)	2 ( 0.1)
PENILE INFECTION	0	0	0	1 ( 0.2)	2 ( 0.1)
BALANOPOSTHITIS	0	1 ( 0.2)	1 ( 0.2)	0	2 ( 0.1)
BALANOPOSTHITIS INFECTIVE	0	0	1 ( 0.2)	0	1 ( 0.1)
GENITAL BURNING SENSATION	1 ( 0.1)	0	0	0	0
GENITAL INFECTION	0	0	1 ( 0.2)	0	1 ( 0.1)
POSTHITIS	0	0	1 ( 0.2)	0	1 ( 0.1)

Source SCS Table 51

The rate of recurrence for these events did not differ between the placebo and the dapagliflozin treatment arms.

**Table 81 Genital Infection Recurrence Short-term Plus Long-term Placebo-Controlled Pool**

	PLA N = 694	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 2160
SUBJECTS (N#)	20	53	77	83	213
NUMBER OF SUBJECTS EXPERIENCING: (A)					
1 EVENT	16 ( 80.0)	41 ( 77.4)	53 ( 68.8)	63 ( 75.9)	157 ( 73.7)
2 EVENTS	4 ( 20.0)	7 ( 13.2)	12 ( 15.6)	9 ( 10.8)	28 ( 13.1)
3 EVENTS	0	5 ( 9.4)	6 ( 7.8)	6 ( 7.2)	17 ( 8.0)
>3 EVENTS	0	0	6 ( 7.8)	5 ( 6.0)	11 ( 5.2)
TOTAL EVENTS	24	70	163	121	354
NUMBER OF SEVERE OR VERY SEVERE EVENTS	1	1	2	3	6
GIVEN ANTIMICROBIAL TREATMENT? (B)					
YES	14 ( 58.3)	49 ( 70.0)	138 ( 84.7)	89 ( 73.6)	276 ( 78.0)
NO	9 ( 37.5)	19 ( 27.1)	22 ( 13.5)	29 ( 24.0)	70 ( 19.8)
UNKNOWN	1 ( 4.2)	2 ( 2.9)	3 ( 1.8)	3 ( 2.5)	8 ( 2.3)
ADDITIONAL TREATMENT GIVEN DUE TO INADEQUATE RESPONSE TO INITIAL COURSE (B)					
YES	0	1 ( 1.4)	11 ( 6.7)	4 ( 3.3)	16 ( 4.5)
NO	14 ( 58.3)	48 ( 68.6)	127 ( 77.9)	85 ( 70.2)	260 ( 73.4)
UNKNOWN	0	0	0	0	0
NOT APPLICABLE	10 ( 41.7)	21 ( 30.0)	25 ( 15.3)	32 ( 26.4)	78 ( 22.0)

Source SCS Table 56

The results from the short-term pool were consistent with the long plus short-term treatment period, however the proportions were higher in this longer term pool.

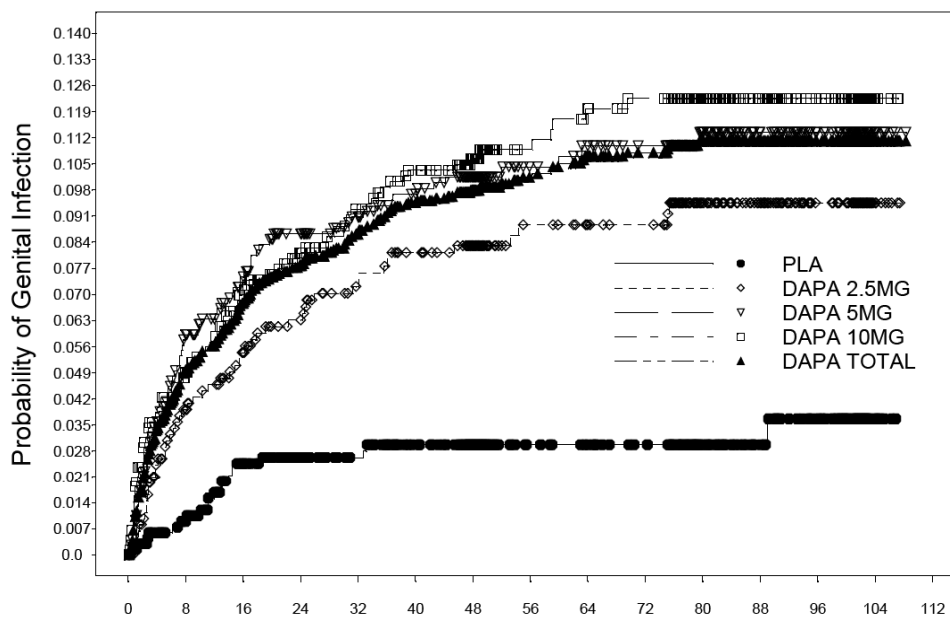
**Table 82 Genital Infections in Placebo-controlled Pool Long-term Treatment**

Preferred Term (%)	PLA N = 347	DAPA 2.5MG N = 313	DAPA 5MG N = 388	DAPA 10MG N = 405	DAPA TOTAL N = 1106
TOTAL SUBJECTS WITH AN EVENT	18 ( 5.2)	37 ( 11.8)	63 ( 16.2)	60 ( 14.8)	160 ( 14.5)
VULVOVAGINAL MYCOTIC INFECTION	6 ( 1.7)	6 ( 1.9)	15 ( 3.9)	18 ( 4.4)	39 ( 3.5)
VAGINAL INFECTION	1 ( 0.3)	6 ( 1.9)	18 ( 4.6)	12 ( 3.0)	36 ( 3.3)
VULVOVAGINAL PRURITUS	4 ( 1.2)	4 ( 1.3)	11 ( 2.8)	9 ( 2.2)	24 ( 2.2)
VULVOVAGINAL CANDIDIASIS	1 ( 0.3)	5 ( 1.6)	8 ( 2.1)	7 ( 1.7)	20 ( 1.8)
PRURITUS GENITAL	3 ( 0.9)	5 ( 1.6)	5 ( 1.3)	5 ( 1.2)	15 ( 1.4)
VULVOVAGINITIS	0	4 ( 1.3)	5 ( 1.3)	4 ( 1.0)	13 ( 1.2)
GENITAL CANDIDIASIS	0	0	0	3 ( 0.7)	3 ( 0.3)
GENITAL INFECTION FUNGAL	0	5 ( 1.6)	6 ( 1.5)	2 ( 0.5)	13 ( 1.2)
VULVITIS	0	2 ( 0.6)	1 ( 0.3)	2 ( 0.5)	5 ( 0.5)
GENITAL INFECTION	0	1 ( 0.3)	1 ( 0.3)	1 ( 0.2)	3 ( 0.3)
GENITAL INFECTION FEMALE	0	0	0	1 ( 0.2)	1 ( 0.1)
VAGINAL DISCHARGE	0	0	0	1 ( 0.2)	1 ( 0.1)
VAGINAL INFLAMMATION	0	0	0	1 ( 0.2)	1 ( 0.1)

Source SCS Table 54

The Kaplan-Meier curves of the time to onset of first event suggestive of genital infection dapagliflozin showed that patients were at greater risk for a first event than those treated with placebo as early as one month after treatment initiation (Figure 24). By 8 weeks, those treated with dapagliflozin 5 and 10 mg were at more risk than the 2.5 mg treated patients. Overall, a first event occurred more often in the first 24 weeks than after 24 weeks in all groups.

Figure 24 Kaplan-Meier Curves of the Time to Onset of First Event of Genital Infection



	Number of Subjects at Risk														
	Weeks														
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 SCS Figure 2

### Reviewer's Comments

Dose response is evident with this AE. The recurrence rates are reassuring. This higher rate of genital infections observed in patients treated with dapagliflozin could be explained by the mechanism of action and potential increased glucose concentration in the genital region. The applicant has appropriately labeled this finding under the Adverse Reaction section of the label both in tabular and detailed textual format.

The (b) (4) patients who had a history of recurrent genital tract infection were more likely to have an event of genital tract infection (25.0% of patients with history of infection treated with dapagliflozin 10 mg and 10.0% of patients with

history of infection on placebo) during the study than those without (5.0% on dapagliflozin 10 mg and 0.8% on placebo). This is based off the following tables (Table 83 and Table 84).

**Table 83 Genital Infection in Patients with History of Genital Infection Short-term Placebo-controlled Pool**

Preferred Term (%)	PLA N = 10	DAPA 2.5MG N = 8	DAPA 5MG N = 13	DAPA 10MG N = 12	DAPA TOTAL N = 33
TOTAL SUBJECTS WITH AN EVENT	1 ( 10.0)	4 ( 50.0)	3 ( 23.1)	3 ( 25.0)	10 ( 30.3)
VULVOVAGINAL MYCOTIC INFECTION	1 ( 10.0)	0	0	2 ( 16.7)	2 ( 6.1)
GENITAL INFECTION FUNGAL	0	3 ( 37.5)	2 ( 15.4)	1 ( 8.3)	6 ( 18.2)
BALANITIS	0	1 ( 12.5)	0	0	1 ( 3.0)
GENITAL CANDIDIASIS	0	0	1 ( 7.7)	0	1 ( 3.0)

Source SCS App 367B

**Table 84 Genital Infection in Patients without History of Genital Infection Short-term Placebo-controlled Pool**

Preferred Term (%)	PLA N = 1247	DAPA 2.5MG N = 685	DAPA 5MG N = 1013	DAPA 10MG N = 1053	DAPA TOTAL N = 2751
TOTAL SUBJECTS WITH AN EVENT	10 ( 0.8)	27 ( 3.9)	60 ( 5.9)	53 ( 5.0)	140 ( 5.1)
VULVOVAGINAL MYCOTIC INFECTION	4 ( 0.3)	6 ( 0.9)	12 ( 1.2)	17 ( 1.6)	35 ( 1.3)
VAGINAL INFECTION	1 ( 0.1)	6 ( 0.9)	14 ( 1.4)	10 ( 0.9)	30 ( 1.1)
BALANITIS	1 ( 0.1)	3 ( 0.4)	6 ( 0.6)	7 ( 0.7)	16 ( 0.6)
GENITAL INFECTION FUNGAL	0	3 ( 0.4)	5 ( 0.5)	5 ( 0.5)	13 ( 0.5)
VULVOVAGINAL CANDIDIASIS	1 ( 0.1)	3 ( 0.4)	10 ( 1.0)	4 ( 0.4)	17 ( 0.6)
VULVOVAGINITIS	0	2 ( 0.3)	4 ( 0.4)	3 ( 0.3)	9 ( 0.3)
BALANITIS CANDIDA	0	2 ( 0.3)	2 ( 0.2)	2 ( 0.2)	6 ( 0.2)
GENITAL CANDIDIASIS	0	0	2 ( 0.2)	2 ( 0.2)	4 ( 0.1)
GENITAL INFECTION	0	0	2 ( 0.2)	2 ( 0.2)	4 ( 0.1)
GENITAL INFECTION MALE	0	0	0	1 ( 0.1)	1 ( <0.1)
PENILE INFECTION	0	0	0	1 ( 0.1)	1 ( <0.1)
VULVITIS	0	2 ( 0.3)	1 ( 0.1)	1 ( 0.1)	4 ( 0.1)
BALANOPOSTHITIS	0	1 ( 0.1)	1 ( 0.1)	0	2 ( 0.1)
BALANOPOSTHITIS INFECTIVE	0	0	1 ( 0.1)	0	1 ( <0.1)
GENITOURINARY TRACT INFECTION	0	0	1 ( 0.1)	0	1 ( <0.1)
POSTHITIS	0	0	1 ( 0.1)	0	1 ( <0.1)
VAGINITIS BACTERIAL	2 ( 0.2)	1 ( 0.1)	1 ( 0.1)	0	2 ( 0.1)
VULVAL ABSCESS	1 ( 0.1)	0	0	0	0

Source SCS App 367B

### Reviewer's Comments

(b) (4)

The numbers of patients in the group of patients with history of infection is very small and cannot be compared to those without.

### Active Control Study

The rate of genital infections in this study was higher in patients treated with dapagliflozin, consistent with results presented above. In patients treated with dapagliflozin 50 patients (12.3%) experienced AEs related to genital infection versus 11 patients in the glipizide treated group (2.7%).

## Urinary Tract Infections (UTI)

### **Placebo-controlled Pool—Short-term Treatment**

A prespecified list of PTs was used to identify cases of UTI (with confirmed positive culture in some cases). This list contained the terms for diagnoses, symptoms, signs, and abnormal laboratory findings suggestive of UTI, as well as events indicating specific involvement of the kidney. Events identified with this list are termed events suggestive of UTI. These events were reported spontaneously as well as in response to questions proactively posed to patients during all study visits that were related to the signs and symptoms of these infections.

In the Placebo-controlled Pool, more patients reported events suggestive of UTI in the dapagliflozin group than the placebo group. These events were more common overall in females than males. Most events were mild or moderate in intensity and resolved while the patients were on study medication.

The PT UTI was most common for this category and dysuria was the second most common term identified (Table 85).

**Table 85 UTI Related Events in the Placebo-controlled Pool Short-term Treatment**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	63 ( 4.5)	34 ( 4.2)	84 ( 7.3)	77 ( 6.5)	209 ( 6.4)
URINARY TRACT INFECTION	38 ( 2.7)	25 ( 3.1)	54 ( 4.7)	43 ( 3.6)	131 ( 4.0)
DYSURIA	10 ( 0.7)	5 ( 0.6)	18 ( 1.6)	25 ( 2.1)	49 ( 1.5)
CYSTITIS	11 ( 0.8)	2 ( 0.2)	7 ( 0.6)	8 ( 0.7)	21 ( 0.6)
LEUKOCYTURIA	0	0	0	2 ( 0.2)	2 ( 0.1)
CANDIDURIA	0	0	0	1 ( 0.1)	1 ( <0.1)
ESCHERICHIA URINARY TRACT INFECTION	0	0	1 ( 0.1)	1 ( 0.1)	2 ( 0.1)
TRIGONITIS	0	0	0	1 ( 0.1)	1 ( <0.1)
BACTERIURIA	2 ( 0.1)	0	1 ( 0.1)	0	1 ( <0.1)
GENITOURINARY TRACT INFECTION	0	0	1 ( 0.1)	0	1 ( <0.1)
PROSTATITIS	2 ( 0.1)	1 ( 0.1)	2 ( 0.2)	0	3 ( 0.1)
PYELONEPHRITIS	1 ( 0.1)	2 ( 0.2)	1 ( 0.1)	0	3 ( 0.1)
PYURIA	2 ( 0.1)	0	1 ( 0.1)	0	1 ( <0.1)
URETHRITIS	1 ( 0.1)	0	0	0	0
URINARY TRACT INFECTION FUNGAL	0	0	1 ( 0.1)	0	2 ( 0.1)
URINARY TRACT INFLAMMATION	0	0	1 ( 0.1)	0	1 ( <0.1)
WHITE BLOOD CELLS URINE POSITIVE	1 ( 0.1)	0	0	0	0

Source SCS Table 57

In the short-term period, pyelonephritis was reported in 4 patients: 2 (0.2%), 1 (0.1%), and 0 in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 1 (0.1%) placebo

treated patient. Of these patients, the only one that was considered serious was the one that occurred in the placebo treated male patient.

Events in males and females suggestive of UTI were also presented. For males, the PT dysuria was the most common PT (Table 86 and Table 87).

**Table 86 UTI in Placebo-controlled Pool Short-term Treatment—Females**

Preferred Term (%)	PLA N = 677	DAPA 2.5MG N = 400	DAPA 5MG N = 581	DAPA 10MG N = 598	DAPA TOTAL N = 1648
TOTAL SUBJECTS WITH AN EVENT	52 ( 7.7)	26 ( 6.5)	66 ( 11.4)	60 ( 10.0)	165 ( 10.0)
URINARY TRACT INFECTION	35 ( 5.2)	21 ( 5.3)	48 ( 8.3)	39 ( 6.5)	117 ( 7.1)
DYSURIA	6 ( 0.9)	3 ( 0.8)	10 ( 1.7)	12 ( 2.0)	26 ( 1.6)
CYSTITIS	10 ( 1.5)	2 ( 0.5)	7 ( 1.2)	7 ( 1.2)	19 ( 1.2)
LEUKOCYTURIA	0	0	0	2 ( 0.3)	2 ( 0.1)
CANDIDURIA	0	0	0	1 ( 0.2)	1 ( 0.1)
ESCHERICHIA URINARY TRACT INFECTION	0	0	1 ( 0.2)	1 ( 0.2)	2 ( 0.1)
TRIGONITIS	0	0	0	1 ( 0.2)	1 ( 0.1)
BACTERIURIA	2 ( 0.3)	0	1 ( 0.2)	0	1 ( 0.1)
GENITOURINARY TRACT INFECTION	0	0	1 ( 0.2)	0	1 ( 0.1)
PYELONEPHRITIS	0	1 ( 0.3)	0	0	1 ( 0.1)
PYURIA	2 ( 0.3)	0	1 ( 0.2)	0	1 ( 0.1)
URINARY TRACT INFECTION FUNGAL	0	0	0	0	1 ( 0.1)
WHITE BLOOD CELLS URINE POSITIVE	1 ( 0.1)	0	0	0	0

Source SCS Table 58

**Table 87 UTI in Placebo-controlled Pool Short-term Treatment—Males**

Preferred Term (%)	PLA N = 716	DAPA 2.5MG N = 414	DAPA 5MG N = 564	DAPA 10MG N = 595	DAPA TOTAL N = 1643
TOTAL SUBJECTS WITH AN EVENT	11 ( 1.5)	8 ( 1.9)	18 ( 3.2)	17 ( 2.9)	44 ( 2.7)
DYSURIA	4 ( 0.6)	2 ( 0.5)	8 ( 1.4)	13 ( 2.2)	23 ( 1.4)
URINARY TRACT INFECTION	3 ( 0.4)	4 ( 1.0)	6 ( 1.1)	4 ( 0.7)	14 ( 0.9)
CYSTITIS	1 ( 0.1)	0	0	1 ( 0.2)	2 ( 0.1)
PROSTATITIS	2 ( 0.3)	1 ( 0.2)	2 ( 0.4)	0	3 ( 0.2)
PYELONEPHRITIS	1 ( 0.1)	1 ( 0.2)	1 ( 0.2)	0	2 ( 0.1)
URETHRITIS	1 ( 0.1)	0	0	0	0
URINARY TRACT INFECTION FUNGAL	0	0	1 ( 0.2)	0	1 ( 0.1)
URINARY TRACT INFLAMMATION	0	0	1 ( 0.2)	0	1 ( 0.1)

Source SCS Table 59

In the short-term period, urine culture was obtained for 42% and 50% of the events suggestive of UTI in the dapagliflozin total group and the placebo group, respectively. Recurrence occurred in 14.7-18.2% of patients taking dapagliflozin of any dose compared to 9.5% of placebo patients (Table 88). This table also depicts the proportion of patients that had a positive urine culture. Of patients that had events suggestive of UTI, around a quarter to one third of patients had positive cultures. Most of the organisms obtained from urine culture are well established causes of UTI in the general population and include Escherichia coli, with skin flora or sample contamination, such as Staphylococcus epidermidis, or fungi such as Candida.



**Table 88 UTI Recurrence and Culture Data**

	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
SUBJECTS (N#)	63	34	84	77	209
NUMBER OF SUBJECTS EXPERIENCING: (A)					
1 EVENT	56 ( 88.9)	28 ( 82.4)	70 ( 83.3)	61 ( 79.2)	172 ( 82.3)
2 EVENTS	6 ( 9.5)	5 ( 14.7)	13 ( 15.5)	14 ( 18.2)	33 ( 15.8)
3 EVENTS	0	1 ( 2.9)	1 ( 1.2)	2 ( 2.6)	4 ( 1.9)
>3 EVENTS	1 ( 1.6)	0	0	0	0
TOTAL EVENTS	72	41	99	95	250
NUMBER OF SEVERE OR VERY SEVERE EVENTS	1	0	4	0	4
GIVEN ANTIMICROBIAL TREATMENT? (B)					
YES	54 ( 75.0)	31 ( 75.6)	57 ( 57.6)	59 ( 62.1)	147 ( 58.8)
NO	14 ( 19.4)	6 ( 14.6)	29 ( 29.3)	27 ( 28.4)	62 ( 24.8)
UNKNOWN	4 ( 5.6)	4 ( 9.8)	13 ( 13.1)	9 ( 9.5)	41 ( 16.4)
ADDITIONAL TREATMENT GIVEN DUE TO INADEQUATE RESPONSE TO INITIAL COURSE (B)					
YES	8 ( 11.1)	2 ( 4.9)	1 ( 1.0)	11 ( 11.6)	14 ( 5.6)
NO	45 ( 62.5)	29 ( 70.7)	56 ( 56.6)	48 ( 50.5)	133 ( 53.2)
UNKNOWN	1 ( 1.4)	0	0	0	0
NOT APPLICABLE	18 ( 25.0)	10 ( 24.4)	42 ( 42.4)	36 ( 37.9)	103 ( 41.2)
URINE CULTURE OBTAINED? (B)					
YES	36 ( 50.0)	19 ( 46.3)	49 ( 49.5)	37 ( 38.9)	105 ( 42.0)
NO	27 ( 37.5)	14 ( 34.1)	34 ( 34.3)	39 ( 41.1)	88 ( 35.2)
UNKNOWN	9 ( 12.5)	8 ( 19.5)	16 ( 16.2)	19 ( 20.0)	57 ( 22.8)
POSITIVE URINE CULTURE? (B)					
YES	21 ( 29.2)	13 ( 31.7)	30 ( 30.3)	24 ( 25.3)	67 ( 26.8)
NO	15 ( 20.8)	6 ( 14.6)	19 ( 19.2)	13 ( 13.7)	38 ( 15.2)
UNKNOWN	0	0	0	0	0

Source SCS Table 60

## Placebo-controlled Pool Short Plus Long-Term Treatment

The proportions were slightly higher in the short-term plus long-term treatment period (Table 89).

**Table 89 UTI in Placebo-controlled Short Plus Long-term Pool**

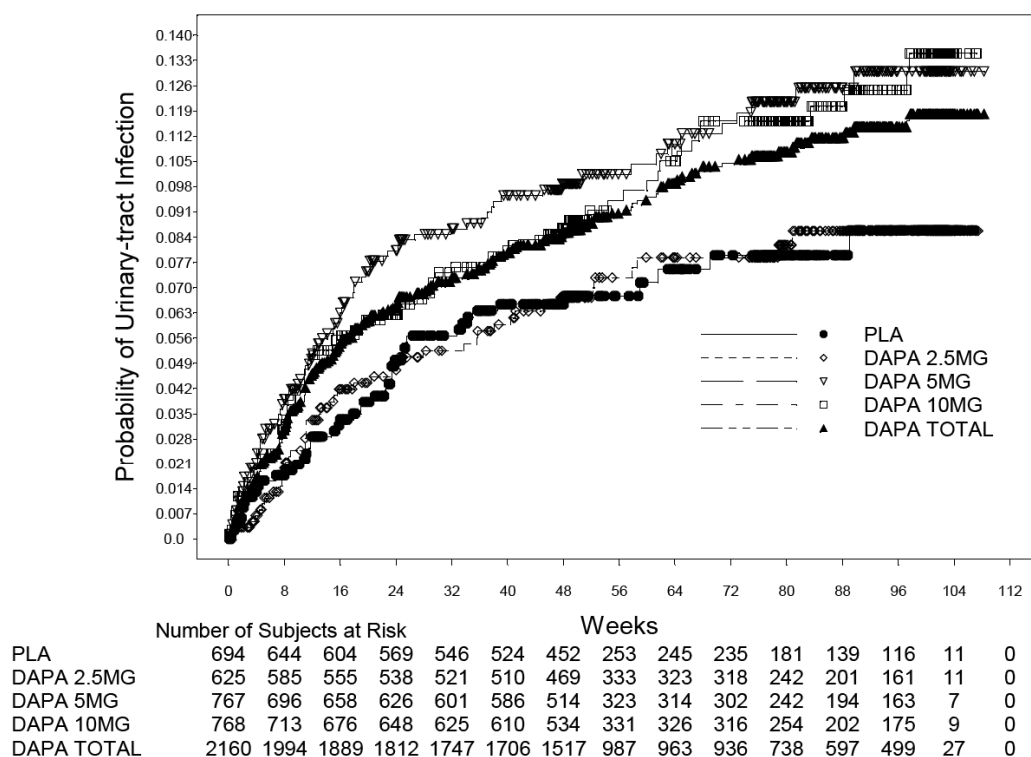
Preferred Term (%)	PLA N = 694	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 2160
TOTAL SUBJECTS WITH AN EVENT	46 ( 6.6)	45 ( 7.2)	80 ( 10.4)	77 ( 10.0)	202 ( 9.4)
URINARY TRACT INFECTION	32 ( 4.6)	29 ( 4.6)	51 ( 6.6)	52 ( 6.8)	132 ( 6.1)
DYSURIA	4 ( 0.6)	11 ( 1.8)	15 ( 2.0)	20 ( 2.6)	46 ( 2.1)
CYSTITIS	11 ( 1.6)	3 ( 0.5)	9 ( 1.2)	5 ( 0.7)	17 ( 0.8)
PROSTATITIS	1 ( 0.1)	2 ( 0.3)	2 ( 0.3)	2 ( 0.3)	6 ( 0.3)
ESCHERICHIA URINARY TRACT INFECTION	0	0	0	1 ( 0.1)	1 ( <0.1)
PYURIA	1 ( 0.1)	0	1 ( 0.1)	1 ( 0.1)	2 ( 0.1)
TRIGONITIS	0	0	0	1 ( 0.1)	1 ( <0.1)
BACTERIURIA	0	0	1 ( 0.1)	0	1 ( <0.1)
GENITOURINARY TRACT INFECTION	0	0	1 ( 0.1)	0	1 ( <0.1)
LEUKOCYTURIA	0	0	1 ( 0.1)	0	1 ( <0.1)
MALACOPOLAKIA VESICAE	0	1 ( 0.2)	0	0	1 ( <0.1)
PYELONEPHRITIS	0	2 ( 0.3)	1 ( 0.1)	0	3 ( 0.1)
URETHRITIS	1 ( 0.1)	0	0	0	0
URINARY TRACT INFECTION FUNGAL	0	0	1 ( 0.1)	0	1 ( <0.1)
URINARY TRACT INFLAMMATION	0	0	1 ( 0.1)	0	1 ( <0.1)

Source SCS Table 61

In this pool, the rates in females for these events remained 2-3 times that seen in males.

The Kaplan-Meier curves of the time to onset of first event suggestive of UTI show separation of the curves for the dapagliflozin (5 mg, 10 mg, and dapagliflozin total) groups from the dapagliflozin 2.5 mg and placebo groups starting at approximately 8 weeks and continuing through Week 104 (Figure 25). A first event suggestive of UTI was reported more often in the first 24 weeks than after 24 weeks in all treatment groups.

**Figure 25 Kaplan-Meier Curves of the Time to Onset of First Event of UTI**



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 SCS Figure 3

### Active Control Study

The rate of UTI was similar to that seen in the placebo treated short-term group. In total 44 patients (10.8%) treated with dapagliflozin had events related to UTI versus 26 treated with glipizide (6.4%).

### Reviewer's Comments

There does not appear to be a dose related association with these events or with recurrence of these events, but recurrence to two events is higher in the dapagliflozin treated group. It is reassuring that cases of pyelonephritis and/or SAEs of pyelonephritis are uncommon. The applicant appropriately labeled this AE. (b) (4)

### Both Genital Infection and Urinary Tract Infection

The proportion of patients that had both types of infection was small compared to that seen with each type of event alone (Table 90). This suggests that urinary tract infection, or treatment of infection, was not a predisposition to developing a genital infection or vice versa.

**Table 90 Patients with Both Events of Genital Infection and UTI Short-term Placebo-controlled Pool**

	Number of Subjects (Percent)				
	PLACEBO N=1393	DAPA 2.5MG N=814	DAPA 5MG N=1145	DAPA 10MG N=1193	DAPA TOTAL N=3291
BOTH URINARY TRACT INFECTION AND GENITAL INFECTION					
TOTAL	7/1393 ( 0.5)	3/ 814 ( 0.4)	16/1145 ( 1.4)	19/1193 ( 1.6)	40/3291 ( 1.2)
MALES	1/ 716 ( 0.1)	1/ 414 ( 0.2)	1/ 564 ( 0.2)	5/ 595 ( 0.8)	7/1643 ( 0.4)
FEMALES	6/ 677 ( 0.9)	2/ 400 ( 0.5)	15/ 581 ( 2.6)	14/ 598 ( 2.3)	33/1648 ( 2.0)

Source Response to FDA Information Request May 18, 2011

### Hypersensitivity Reactions

Possible anaphylactic or drug reactions were searched with several PTs. The PTs that most likely would be due to the drug are presented in Table 91. There were more patients with events in the dapagliflozin treated groups; however rates were fairly balanced.

**Table 91 Possible Anaphylactic or Drug Reactions by PT All Phase 2b and 3 Pool**

Possible Anaphylactic or Drug Reaction AE	Dapagliflozin	All Control
	N=4287	N=1941
<b>Total Subjects</b>	N (%)	N (%)
<b>Urticaria</b>	19 (0.4)	3 (0.2)
<b>Erythema</b>	18 (0.4)	4 (0.2)
<b>Edema</b>	12 (0.3)	8 (0.4)
<b>Hypersensitivity</b>	11 (0.3)	8 (0.4)
<b>Pruritis Generalized</b>	10 (0.2)	6 (0.3)
<b>Angioedema</b>	6 (0.1)	1 (0.1)
<b>Drug hypersensitivity</b>	6 (0.1)	1 (0.1)
<b>Flushing</b>	3 (0.1)	1 (0.1)
<b>Swelling face</b>	3 (0.1)	3 (0.2)
<b>Generalized edema</b>	2 (<0.1)	0
<b>Mouth ulceration</b>	2 (<0.1)	1 (0.1)
<b>Skin exfoliation</b>	2 (<0.1)	1 (0.1)
<b>Allergic edema</b>	1 (<0.1)	0
<b>Drug eruption</b>	1 (<0.1)	0

Source Adapted from SCS App 330A

## **Volume Depletion**

### **Placebo-controlled Pool—Short-term Treatment**

In the Placebo-controlled Pool, events of that are defined as volume depletion events (hypotension/hypovolemia/dehydration) were slightly more common in the dapagliflozin groups compared with the comparator (0.7% vs 0.4% in the short-term period), with no clear dose dependence. This was expected based on dapagliflozin's mechanism of action. Hypotension was the most common event and there were no events of dehydration or hypovolemia. No events in dapagliflozin-treated subjects led to discontinuation.

**Table 92 Events of Hypovolemia Short-term Placebo-controlled Pool**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	5 ( 0.4)	8 ( 1.0)	7 ( 0.6)	8 ( 0.7)	24 ( 0.7)
HYPOTENSION	2 ( 0.1)	6 ( 0.7)	5 ( 0.4)	5 ( 0.4)	16 ( 0.5)
SYNCOPE	1 ( 0.1)	0	0	2 ( 0.2)	2 ( 0.1)
URINE FLOW DECREASED	0	0	0	1 ( 0.1)	1 ( <0.1)
BLOOD PRESSURE DECREASED	1 ( 0.1)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	1 ( 0.1)	2 ( 0.2)	0	4 ( 0.1)
URINE OUTPUT DECREASED	1 ( 0.1)	1 ( 0.1)	0	0	1 ( <0.1)

## Source SCS Table 72

Most events occurred after more than three weeks of therapy. Only two events in dapagliflozin treated patients occurred within 10 days of starting therapy: orthostatic hypotension (Day 3) and hypotension (Day 1) in the dapagliflozin 2.5 mg group.

During the review process, the applicant submitted information indicating that dehydration was left out of the PT search for these events. There was no change to number or rate in placebo or dapagliflozin 5mg due to dehydration events. Dapagliflozin 10mg: 8 events (0.7%) changed to 9 events (0.8%).

In proposed labeling, the applicant includes volume depletion under the AE section. They report that in the 24 week treatment data, the subgroup of patients that received loop diuretics and subgroup of patients ≥ 65 years of age treated with dapagliflozin had a higher rate of hypovolemic events. All subgroups were reviewed, the (b) (4)

**Table 93 Events of Hypovolemia in Patients on Loop Diuretics**

Preferred Term (%)	PLA N = 55	DAPA 2.5MG N = 37	DAPA 5MG N = 40	DAPA 10MG N = 31	DAPA TOTAL N = 114
TOTAL SUBJECTS WITH AN EVENT	1 ( 1.8)	3 ( 8.1)	0	2 ( 6.5)	6 ( 5.3)
HYPOTENSION	0	3 ( 8.1)	0	1 ( 3.2)	4 ( 3.5)
SYNCOPE	0	0	0	1 ( 3.2)	1 ( 0.9)
BLOOD PRESSURE DECREASED	1 ( 1.8)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	0	0	0	1 ( 0.9)

## Source SCS App 222B

**Table 94 Events of Hypovolemia in Patients ≥ 65 Years of Age**

Preferred Term (%)	PLA N = 276	DAPA 2.5MG N = 193	DAPA 5MG N = 216	DAPA 10MG N = 204	DAPA TOTAL N = 631
TOTAL SUBJECTS WITH AN EVENT	1 ( 0.4)	5 ( 2.6)	1 ( 0.5)	2 ( 1.0)	8 ( 1.3)
SYNCOPE	0	0	0	1 ( 0.5)	1 ( 0.2)
URINE FLOW DECREASED	0	0	0	1 ( 0.5)	1 ( 0.2)
HYPOTENSION	1 ( 0.4)	5 ( 2.6)	0	0	5 ( 0.8)
ORTHOSTATIC HYPOTENSION	0	0	1 ( 0.5)	0	1 ( 0.2)

Source SCS App 228B page 9654

Of note, the rate of these events was higher in patients on dapagliflozin that had been treated with thiazides as well (24 week data--1.3%--8 patients in the dapagliflozin total group versus 0.8%--2 patients in the placebo group). This was also the case with both ACE-I or ARBs (1.0%--17 patients in the dapagliflozin total group versus 0.5%--4 patients in the placebo group). These trends were consistent with those seen across long-term treatment as well.

### **Reviewer's Comments**

**These data are useful for the prescribing practitioners and I recommend they remain in the label.**

### **Placebo-controlled Pool—Short-term Plus Long-Term Treatment**

In the short-term plus long-term period, SAEs of hypotension/dehydration/hypovolemia (volume depletion) occurred in 2 subjects treated with dapagliflozin and in 2 subjects treated with placebo; all 4 of these events were syncope.

### **Hemoconcentration, Pulmonary Embolism and Deep Venous Thrombosis (DVT)**

Also related to volume depletion as well is the potential for DVT and/or pulmonary embolism. Dapagliflozin has diuretic effect and this can result in hemoconcentration. A degree of this is observed in the treated patients and can be seen in the hematology laboratory data.

### **Hematology Laboratory Data**

In the Placebo-controlled Pool of Phase 2b and 3 studies, small increases from baseline were observed in hematocrit, hemoglobin, red blood cells, and decreases were observed in platelets. These hematologic changes were consistent across the program and either normalized or trended toward normalization after dapagliflozin discontinuation. These changes from baseline were not associated with an increase in potentially related AEs such as embolic or atherothrombotic events (identified using the standardized medDRA queries (SMQ) for embolic and thrombotic events) or events

related to thrombocytopenia. This was true in both the short-term and long-term treatment periods.

### Placebo-controlled Pool—Short-term Treatment

In the dapagliflozin groups, there were small increases in mean hematocrit and hemoglobin levels starting at week 1 and continuing up to week 16, when the maximum difference from baseline was observed. At week 24, the mean changes from baseline in hematocrit were 1.57%, 1.81%, and 2.15% in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and -0.40% in the placebo group (Table 95).

**Table 95 Hematocrit (%) Change from Baseline Short-term Placebo-controlled Pool**

Period Visit	Treatment Group	N#	Mean	SD	Percentiles					Change From Baseline				
					Min	25	Median	75	Max	N#	Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1063	42.08	3.859	24.3	39.40	42.00	44.70	55.8	1063	-0.40	0.0713	-0.30	2.80
	DAPA 2.5MG	610	43.60	4.182	29.9	40.90	43.70	46.40	58.1	610	1.57	0.0971	1.60	2.80
	DAPA 5MG	875	44.09	3.921	29.1	41.40	44.20	46.70	58.6	875	1.81	0.0789	1.90	2.80
	DAPA 10MG	911	44.46	4.098	28.9	41.70	44.40	47.40	57.8	911	2.15	0.0834	2.20	2.80
	DAPA TOTAL	2396	44.11	4.068	28.9	41.40	44.10	46.80	58.6	2396	1.88	0.0497	1.90	2.80

Source SCS App 20B modified

The mean change from baseline in hemoglobin at week 16 ranged from 0.45 to 0.58 g/dL in the dapagliflozin groups and -0.13 g/dL in the placebo group. By week 24, the mean changes from baseline in hemoglobin were 0.41, 0.47, and 0.58 g/dL in the dapagliflozin 2.5, 5, and 10 mg groups and -0.19 g/dL in the placebo group (Table 96).

**Table 96 Hemoglobin (g/dL) Change from Baseline Short-term Placebo-controlled Pool**

Period Visit	Treatment Group	N#	Mean	SD	Percentiles					Change From Baseline				
					Min	25	Median	75	Max	N#	Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1073	14.07	1.321	7.4	13.20	14.00	14.90	18.4	1073	-0.19	0.0223	-0.20	0.80
	DAPA 2.5MG	614	14.55	1.436	9.4	13.60	14.60	15.50	19.2	614	0.41	0.0316	0.40	1.00
	DAPA 5MG	890	14.65	1.346	10.0	13.80	14.70	15.50	18.5	890	0.47	0.0254	0.50	0.90
	DAPA 10MG	922	14.76	1.448	9.3	13.90	14.80	15.80	19.1	922	0.58	0.0263	0.60	0.90
	DAPA TOTAL	2426	14.67	1.410	9.3	13.80	14.70	15.60	19.2	2426	0.49	0.0159	0.50	1.00

Source SCS App 22B modified

One patient in the dapagliflozin 2.5 mg group reported an AE of increased hemoglobin that led to discontinuation of study drug. No patients who had an AE of increased hemoglobin, increased hematocrit, or polycythemia had a cerebrovascular disorder, ischemic heart disease, embolic or thrombotic event, venous or embolic and thrombotic event, vessel type unspecified and mixed arterial and venous.

There was a small decrease in mean platelet levels in all treatment groups. This decrease was slightly larger in the dapagliflozin groups than in the placebo group.

**Table 97 Platelet (c/L) Change from Baseline Short-term Placebo-controlled Pool**

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Max	Change From Baseline				
						25	Median	75	N#		Mean	SE	Median	IQR	
ST TREAT SCS WK 24	PLA	1047	240.2	63.05	78	194.0	236.0	274.0	558	1047	-5.1	1.080	-6.0	38.0	
	DAPA 2.5MG	603	237.6	64.22	72	194.0	234.0	276.0	536	603	-7.4	1.337	-8.0	34.0	
	DAPA 5MG	876	240.1	65.30	101	196.0	235.0	272.0	888	876	-7.3	1.169	-8.0	35.0	
	DAPA 10MG	899	238.4	65.46	51	194.0	233.0	274.0	611	899	-8.4	1.195	-9.0	34.0	
	DAPA TOTAL	2378	238.8	65.07	51	195.0	234.0	273.0	888	2378	-7.7	0.710	-8.0	35.0	

Source SCS App 24B modified

One subject in the dapagliflozin 10 mg group had an AE of thrombocytopenia and one subject in the placebo group had an SAE of thrombocytopenia leading to discontinuation.

### **Reviewer's Comments**

These hematology changes appear dose related. However, the changes are small and not associated with AEs or SAEs. There is a dose recommendation of 5 mg for patients at risk for volume depletion. The related AEs do not show a dose response, but these hematology data do.

### **Placebo-controlled Pool—Short-term Plus Long-term Treatment**

At Week 76, the mean change from baseline in hematocrit ranged from 1.79% to 2.54% in the dapagliflozin groups and -0.17% in the placebo group. At week 76, the mean change from baseline in hemoglobin ranged from 0.38 to 0.62 g/dL in the dapagliflozin groups and -0.26 g/dL in the placebo group. No further increases were observed at Week 89 and up to Week 102.

For platelet changes, after week 76, there was a further small decrease in platelet counts in all treatment groups, with no difference in the levels between the dapagliflozin and placebo groups, and across dapagliflozin dose groups. At week 102, the mean changes were -28.3, -24.9, -27.1 x 10<sup>9</sup> c/L, for dapagliflozin 2.5, 5, and 10 mg, respectively, and -29.6 x 10<sup>9</sup> c/L for placebo.

### **Reviewer's Comments**

The hematology changes level after several weeks of treatment and are not related to AEs. These changes are unlikely to be clinically relevant.

During the short-term period, 4 patients (0.3%) of placebo treated patients had marked abnormalities (MAs) of hematocrit > 55% versus 40—1.2% in the dapagliflozin treated group. The applicant notes that of those who met this MA criterion, 16 of these patients in the dapagliflozin group and 3 patients in the placebo group had an elevated hematocrit at baseline.



A small proportion of subjects in each treatment group had MAs of hemoglobin > 18 g/dL: 55 patient—1.7% the dapagliflozin treated group and 7 patients—0.5% in the placebo group.

### Placebo-controlled Short-term Plus Long-term Treatment

The findings in this group were consistent with that in the short-term group. MAs of hematocrit remain imbalanced.

Hematocrit >55: 3 (0.4%) placebo patients vs. 43 (2.0%) dapagliflozin treated  
Hemoglobin >18: 4 (0.6%) placebo patients vs. 51 (2.4%) dapagliflozin treated

### Hematology Related AEs All Phase 2b/3 Pool

I selected this pool to review in order to capture the most number of events to evaluate for any notable difference. Overall, there were few events related to venous thrombosis in this pool. Although there were more events in patients treated with dapagliflozin, the rates are very similar.

Table 98 Hematology Related AEs

Event	Control	All Dapagliflozin
	N=1941	N=4287
DVT	0	4 (0.1)
Thrombosis	2 (0.1)	2(<0.1)
Pulmonary Embolism	1 (0.1)	4 (0.1)

Source SCS Appendices 89A

### Hypoglycemic Events

Hypoglycemia was seen more frequently in dapagliflozin patients that were taking insulin or an SU than when taken in monotherapy. Study D1690C00006 add-on to insulin, had the highest rate of patients with hypoglycemia. However, groups on dapagliflozin had higher rates of hypoglycemia, even in the monotherapy studies. The difference in monotherapy studies, however, is very small.

Table 99 depicts the incidence of hypoglycemia in the **Placebo-controlled pool** overall, and type of event.

**Table 99 Hypoglycemic Events in the Short-term Placebo-controlled Pool**

	Number of Subjects (Percent)									
	PLA		DAPA 2.5MG		DAPA 5MG		DAPA 10MG		DAPA TOTAL	
TOTAL SUBJECTS WITH HYPOGLYCEMIA	98/1393	(7.0)	126/814	(15.5)	125/1145	(10.9)	122/1193	(10.2)	387/3291	(11.8)
MAJOR EPISODE OF HYPOGLYCEMIA	1/1393	(0.1)	3/814	(0.4)	1/1145	(0.1)	1/1193	(0.1)	5/3291	(0.2)
MINOR EPISODE OF HYPOGLYCEMIA	75/1393	(5.4)	107/814	(13.1)	107/1145	(9.3)	99/1193	(8.3)	316/3291	(9.6)
OTHER EPISODE OF HYPOGLYCEMIA	19/1393	(1.4)	20/814	(2.5)	17/1145	(1.5)	22/1193	(1.8)	66/3291	(2.0)
OTHER EPISODE OF HYPOGLYCEMIA WITH PLASMA VALUE => 63 MG/DL (a)	15/1051	(1.4)	14/556	(2.5)	14/875	(1.6)	17/854	(2.0)	51/2424	(2.1)

Source SCS Table 44

When separated by study type, higher rates in dapagliflozin treated groups continue to be seen. In the **monotherapy studies** (Table 100), the rate was only 0.5% higher and did not appear dose dependent. Hypoglycemia led to discontinuation of study drug in only one patient; this patient was on 10 mg and was also in the long-term study period.

**Table 100 Hypoglycemic Events in Monotherapy Studies**

	Number of Subjects (Percent)									
	PLA		DAPA 2.5MG		DAPA 5MG		DAPA 10MG		DAPA TOTAL	
TOTAL SUBJECTS WITH HYPOGLYCEMIA	5/251	(2.0)	8/321	(2.5)	7/316	(2.2)	7/245	(2.9)	22/882	(2.5)
MAJOR EPISODE OF HYPOGLYCEMIA	0/251		0/321		0/316		0/245		0/882	
MINOR EPISODE OF HYPOGLYCEMIA	0/251		2/321	(0.6)	0/316		1/245	(0.4)	3/882	(0.3)
OTHER EPISODE OF HYPOGLYCEMIA	2/251	(0.8)	3/321	(0.9)	3/316	(0.9)	6/245	(2.4)	12/882	(1.4)
OTHER EPISODE OF HYPOGLYCEMIA WITH PLASMA VALUE => 63 MG/DL (a)	3/197	(1.5)	5/265	(1.9)	4/258	(1.6)	2/193	(1.0)	11/716	(1.5)

Source SCS Table 42

As indicated above, the highest rates of hypoglycemia were observed in the add-on to insulin study. However, the rates are higher in the patients receiving dapagliflozin and do not appear dose dependent.

**Table 101 Hypoglycemic Events in Add-on Insulin Study**

	Number of Subjects (Percent)							
	PLA + INS N = 197		DAPA 2.5MG + INS N = 202		DAPA 5MG + INS N = 212		DAPA 10MG + INS N = 196	
TOTAL SUBJECTS WITH HYPOGLYCEMIA	69	(35.0)	104	(51.5)	96	(45.3)	83	(42.3)
MAJOR EPISODE OF HYPOGLYCEMIA	1	(0.5)	2	(1.0)	1	(0.5)	1	(0.5)
MINOR EPISODE OF HYPOGLYCEMIA	67	(34.0)	100	(49.5)	92	(43.4)	79	(40.3)
OTHER EPISODE OF HYPOGLYCEMIA	9	(4.6)	16	(7.9)	14	(6.6)	14	(7.1)

Source SCS Table 43

In the add-on to SU study, the rate of hypoglycemia was higher in the dapagliflozin treated patients as well. Hypoglycemic events were reported in 6.9% to 7.3% of the subjects in the dapagliflozin groups and by 4.8% in the placebo group. One major episode of hypoglycemia was reported in the dapagliflozin 2.5 mg group and was associated with watery diarrhea and decreased oral intake.

**Table 102 Hypoglycemic Events Add-on SU Study**

	Number of Subjects (Percent)							
	PLA + GLI N = 146		DAPA 2.5MG + GLI N = 154		DAPA 5MG + GLI N = 145		DAPA 10MG + GLI N = 151	
TOTAL SUBJECTS WITH HYPOGLYCEMIA	7	(4.8)	11	(7.1)	10	(6.9)	12	(7.9)
MAJOR EPISODE OF HYPOGLYCEMIA	0		1	(0.6)	0		0	
MINOR EPISODE OF HYPOGLYCEMIA	3	(2.1)	3	(1.9)	8	(5.5)	10	(6.6)
OTHER EPISODE OF HYPOGLYCEMIA	5	(3.4)	7	(4.5)	3	(2.1)	3	(2.0)

Source CTR Table 31

The following tables show rates of hypoglycemia in the other studies. When added to metformin, rates are higher with dapagliflozin.

**Table 103 Hypoglycemic Events Add-on TZD Study**

	Number of Subjects (Percent)					
	PLA + PIO N=139		DAPA 5MG + PIO N=141		DAPA 10MG + PIO N=140	
TOTAL SUBJECTS WITH HYPOGLYCEMIA	1	(0.7)	3	(2.1)	0	
MAJOR EPISODE OF HYPOGLYCEMIA	0		0		0	
MINOR EPISODE OF HYPOGLYCEMIA	0		3	(2.1)	0	
OTHER EPISODE OF HYPOGLYCEMIA	1	(0.7)	1	(0.7)	0	-

Source CTR Table 8.6.1

**Table 104 Hypoglycemic Events Initial Combination Studies**

Number (%) of Subjects						
MB102021			MB102034			
	Dapa 5 mg + Metformin N=194	Dapa 5 mg N=203	Metformin N=201	Dapa 10 mg + Metformin N=211	Dapa 10 mg N=219	Metformin N=208
Total	5 (2.6)	0	0	7 (3.3)	2 (0.9)	6 (2.9)
Major	0	0	0	0	0	0
Minor	2 (1.0)	0	0	1 (0.5)	0	1 (0.5)
Other	3 (1.5)	0	0	6 (2.8)	2 (0.9)	5 (2.4)

Source SCS Table 45

### Active Comparator Study D1690C0004

The number of patients with at least one episode of hypoglycemia was substantially lower in the in the dapagliflozin plus metformin (3%) group compared with the glipizide plus metformin group (40%). Hypoglycemic events were a secondary efficacy endpoint in study D1690C00004; the difference between the proportions of subjects with at least 1 event of hypoglycemia in the dapagliflozin plus metformin was significantly ( $p < 0.0001$ ) lower compared with the glipizide plus metformin group.

### Reviewer's Comments

The rates of hypoglycemia only differ substantially from placebo when combined with insulin or an insulin secretagogue (SU glipizide in the Add on to metformin study). This is appropriately labeled in proposed applicant labeling.

## Bone Health

### *Fractures*

#### Placebo-controlled Pool—Short-term Treatment

Fractures were reported in  $< 1\%$  of subjects, with no imbalance across treatment groups (Table 105). Overall, ankle fracture ( $\leq 0.2\%$  per treatment group) was the most commonly reported event.

**Table 105 Fracture Incidence in the Placebo-controlled Pool—Short-term Treatment**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	10 ( 0.7)	1 ( 0.1)	7 ( 0.6)	6 ( 0.5)	14 ( 0.4)
ANKLE FRACTURE	2 ( 0.1)	0	2 ( 0.2)	2 ( 0.2)	4 ( 0.1)
FOOT FRACTURE	1 ( 0.1)	0	1 ( 0.1)	2 ( 0.2)	3 ( 0.1)
FACIAL BONES FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
HIP FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
SPINAL COMPRESSION FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
BONE FISSURE	0	0	1 ( 0.1)	0	1 ( <0.1)
FEMORAL NECK FRACTURE	1 ( 0.1)	0	0	0	0
HAND FRACTURE	1 ( 0.1)	0	2 ( 0.2)	0	2 ( 0.1)
RADIUS FRACTURE	2 ( 0.1)	0	0	0	0
RIB FRACTURE	1 ( 0.1)	0	0	0	0
TIBIA FRACTURE	1 ( 0.1)	0	1 ( 0.1)	0	1 ( <0.1)
TRAUMATIC FRACTURE	0	1 ( 0.1)	0	0	1 ( <0.1)
UPPER LIMB FRACTURE	1 ( 0.1)	0	0	0	0

Source SCS Table 77

In subgroups by baseline eGFR, very similar proportions of patients with fracture were observed across treatment groups for baseline eGFR  $\geq 30$  and  $< 60$  and  $\geq 60$  and  $< 90$  mL/min/1.73 m<sup>2</sup>. However, in the subgroup of patients with eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>, events of fracture were reported in 1 (0.2%), 1 (0.3%), 3 (0.7%) and 3 (0.6%) patients in the placebo and dapagliflozin 2.5, 5, and 10 mg groups, respectively.

**Table 106 Fracture Incidence in the Placebo-controlled Pool Short-term Treatment in Normal Renal Function**

Preferred Term (%)	PLA N = 528	DAPA 2.5MG N = 300	DAPA 5MG N = 429	DAPA 10MG N = 474	DAPA TOTAL N = 1250
TOTAL SUBJECTS WITH AN EVENT	1 ( 0.2)	1 ( 0.3)	3 ( 0.7)	3 ( 0.6)	7 ( 0.6)
FOOT FRACTURE	0	0	1 ( 0.2)	2 ( 0.4)	3 ( 0.2)
FACIAL BONES FRACTURE	0	0	0	1 ( 0.2)	1 ( 0.1)
ANKLE FRACTURE	0	0	1 ( 0.2)	0	1 ( 0.1)
HAND FRACTURE	0	0	1 ( 0.2)	0	1 ( 0.1)
RIB FRACTURE	1 ( 0.2)	0	0	0	0
TRAUMATIC FRACTURE	0	1 ( 0.3)	0	0	1 ( 0.1)

Source SCS App 319B

### Placebo-controlled Pool Short-term Plus Long-term Treatment Period

Rates of fracture in the short-term plus long-term treatment period were higher than the short-term only but evenly distributed as seen in the short-term period only.

**Table 107 Fracture Incidence in the Placebo-controlled Pool—Short-term plus Long-term Treatment**

Preferred Term (%)	PLA N = 694	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 2160
TOTAL SUBJECTS WITH AN EVENT	10 ( 1.4)	7 ( 1.1)	12 ( 1.6)	11 ( 1.4)	30 ( 1.4)
ANKLE FRACTURE	2 ( 0.3)	1 ( 0.2)	1 ( 0.1)	4 ( 0.5)	6 ( 0.3)
FOOT FRACTURE	1 ( 0.1)	0	2 ( 0.3)	3 ( 0.4)	5 ( 0.2)
HIP FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
HUMERUS FRACTURE	1 ( 0.1)	0	0	1 ( 0.1)	1 ( <0.1)
OPEN FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
SPINAL COMPRESSION FRACTURE	0	0	0	1 ( 0.1)	1 ( <0.1)
TRAUMATIC FRACTURE	0	1 ( 0.2)	1 ( 0.1)	1 ( 0.1)	3 ( 0.1)
BONE FISSURE	0	0	2 ( 0.3)	0	2 ( 0.1)
FACIAL BONES FRACTURE	0	1 ( 0.2)	1 ( 0.1)	0	2 ( 0.1)
FEMORAL NECK FRACTURE	1 ( 0.1)	0	0	0	0
HAND FRACTURE	1 ( 0.1)	0	3 ( 0.4)	0	3 ( 0.1)
LOWER LIMB FRACTURE	0	1 ( 0.2)	0	0	1 ( <0.1)
LUMBAR VERTEBRAL FRACTURE	1 ( 0.1)	0	0	0	0
MULTIPLE FRACTURES	0	1 ( 0.2)	0	0	1 ( <0.1)
PATELLA FRACTURE	1 ( 0.1)	0	0	0	0
RADIUS FRACTURE	1 ( 0.1)	0	0	0	0
RIB FRACTURE	1 ( 0.1)	1 ( 0.2)	0	0	1 ( <0.1)
TIBIA FRACTURE	0	0	1 ( 0.1)	0	1 ( <0.1)
UPPER LIMB FRACTURE	0	2 ( 0.3)	0	0	2 ( 0.1)
WRIST FRACTURE	0	0	1 ( 0.1)	0	1 ( <0.1)

Source SCS Table 78

These fracture data along with relevant bone health laboratory data were consulted for review by the bone metabolism team in the Division of Reproductive and Urologic Products. For the full review, please see Dr. Marcea Whitaker's report. Dr. Whitaker reviewed all the data presented in this section along with the applicant's submitted bone data. In addition, individual case narratives for fractures were also reviewed. Overall, in the safety pools reviewed for fractures, the rates are very low, less than 1%. In the short-term plus long-term pool, about two thirds of the fractures were considered fragility, or osteoporotic fractures based on location (ankle, hip, humerus, vertebral, limb, rib, wrist). The rate of fragility fractures, which would be the concern if dapagliflozin was compromising bone health, was lower in the dapagliflozin treated patients.

### Renal Impairment Study—MB102029

During the 52-week short-term plus long-term period, fractures were reported for 10 patients in the dapagliflozin groups (3 in the 5 mg group, 7 in 10 mg group) (Table 108). No one in the placebo group had a reported fracture. Most of these fractures (70%) were reported during the 28-week long-term treatment period.

None of the fractures resulted in discontinuation, and all were mild or moderate in intensity. There was one reported as an SAE: an upper limb fracture (elbow) on day 292 of treatment. There was no apparent pattern with respect to site of fracture.

**Table 108 Adverse Events of Fracture in Renal Impairment Study**

Preferred Term (%)	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL SUBJECTS WITH AN EVENT	0	3 ( 3.6)	7 ( 8.2)
FOOT FRACTURE	0	2 ( 2.4)	1 ( 1.2)
LUMBAR VERTEBRAL FRACTURE	0	0	1 ( 1.2)
PATELLA FRACTURE	0	0	1 ( 1.2)
RADIUS FRACTURE	0	0	1 ( 1.2)
TRAUMATIC FRACTURE	0	0	1 ( 1.2)
UPPER LIMB FRACTURE	0	0	1 ( 1.2)
WRIST FRACTURE	0	0	1 ( 1.2)
HUMERUS FRACTURE	0	1 ( 1.2)	0

The applicant included a subanalysis by moderate renal impairment in their AC background briefing document. They report that by the time of the 4MSU, events of fracture were reported for 12 patients treated with dapagliflozin and remained none treated with placebo in this moderate renal impairment study. They then subdivide this data by moderate renal impairment subgroup. Four of the patients with events of fracture in the special study (4.8%) were classified as stage 3A (2 in the 5 mg group, 2 in the 10 mg group) and 8 (9.4%) as stage 3B (2 in the 5 mg group, 6 in the 10 mg group) renal impairment.

Dr. Whitaker notes that 70% of the fractures occurred during the time period between weeks 24 and 52. There was no apparent pattern with respect to the site of fracture, or with reported occurrences of hypotension or hypoglycemia. Hypoglycemia was reported in at least one narrative. All fractures were assessed as mild or moderate in intensity and did not lead to discontinuation. After 52 weeks, two subjects had a fall or trauma, and the sponsor reports 6 of 10 subjects with either diabetic neuropathy or orthostatic hypotension at either baseline or during the treatment. None had a history of osteoporosis. Negligible changes in laboratory values were noted (laboratory discussed below). Dr. Whitaker could not make conclusions based on the presence or absence of fragility fractures between groups in this study based on the following: 1) Fractures generally occurred in subjects who were at risk for osteoporosis based on age. Subjects in study MB102029 could have had osteoporosis at baseline. 2) Fracture events were associated with various risks for falls (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state) or sustained significant trauma. It is well-recognized that the propensity to fall is a risk factor for fracture which is independent of bone mineral density.

### ***Reviewer's Comments***

**In the renal impairment study, the overall higher rate of fracture noted in the dapagliflozin treated patients is due in part to the 2:1 randomization. The numbers of patients in this study and 52 week treatment time make it difficult to draw an association between the treatment and fracture.**

## Relevant Laboratory Data

### Placebo-controlled Pool—Short-term Treatment

The change in **calcium** from baseline did not show a clinical difference between placebo and dapagliflozin groups (placebo -0.4 mg/dL [SE 0.024] dapagliflozin -0.01 [SE 0.012]).

Small changes from baseline in mean serum **magnesium** levels were reported at week 24 in the dapagliflozin (0.05 - 0.07 mEq/L [SE 0.009-0.007]) and placebo (-0.04 mEq/L [0.006]) groups.

Small mean increases from baseline at week 24 in **serum phosphorus** levels were observed in all dapagliflozin treatment groups, with greater increases in the dapagliflozin groups compared with the placebo group (0.03 mg/dL).

**Table 109 Change in Inorganic Phosphorus (mg/dL) from Baseline Placebo-controlled Pool, Short-term Treatment**

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Max	Change From Baseline				
						25	Median	75	N#		Mean	SE	Median	IQR	
ST TREAT SCS WK 24	PLA	1087	3.62	0.524	2.0	3.30	3.60	4.00	5.4	1087	0.03	0.0155	0.00	0.60	
	DAPA 2.5MG	618	3.63	0.510	2.4	3.30	3.60	3.90	5.9	618	0.10	0.0201	0.10	0.60	
	DAPA 5MG	898	3.74	0.516	2.1	3.40	3.70	4.10	5.3	898	0.16	0.0174	0.10	0.70	
	DAPA 10MG	935	3.74	0.513	2.1	3.40	3.70	4.10	5.5	935	0.17	0.0161	0.20	0.60	
	DAPA TOTAL	2451	3.71	0.515	2.1	3.40	3.70	4.10	5.9	2451	0.15	0.0102	0.10	0.70	

Source SCS App 66 B

From baseline to week 24, mean parathyroid hormone (**PTH**) levels decreased in the placebo group (0.6 pg/mL) and increased (1.8 - 2.6 pg/mL) in each dapagliflozin group.

**Table 110 Change in Parathyroid Hormone Level (pg/mL) from Baseline Placebo-controlled Pool, Short-term Treatment**

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Change From Baseline				
						25	Median	75	Max	N#	Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1069	35.8	20.00	3	23.0	32.0	44.0	243	1069	-0.6	0.502	-1.0	16.0
	DAPA 2.5MG	598	40.7	21.32	3	26.0	36.0	49.0	155	598	2.6	0.681	2.0	19.0
	DAPA 5MG	879	38.2	18.11	5	25.0	35.0	48.0	127	879	1.9	0.516	2.0	16.0
	DAPA 10MG	914	39.5	21.86	3	25.0	36.0	49.0	271	914	1.8	0.583	1.0	17.0
	DAPA TOTAL	2391	39.3	20.43	3	25.0	35.0	49.0	271	2391	2.0	0.339	2.0	17.0

Source SCS App 58B

There was a similar mean decrease (-0.3—1.0 ng/mL) in **25[OH]Vitamin D** in all treatment groups from baseline to week 24.



### Placebo-controlled Pool—Short-term Plus Long-Term Treatment

Again, in this treated pool as with the short-term pool, **calcium** differences between placebo and dapagliflozin treated patients was minimal (at 102 weeks placebo change from baseline was 0.08 mg/dL [SE 0.056] and total dapagliflozin change was 0.11 mg/dL [0.021]). Dr. Whitaker remarks that these changes are not significant. Changes with magnesium were seen with a small decrease, these remained within normal range and were not clinically significant.

**Inorganic phosphorus** differences were minimal by 102 weeks of treatment.

**Table 111 Inorganic Phosphorus (mg/dL): Summary Statistics for Short Plus Long-term Period Placebo-controlled Pool**

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
ST Treatment SCS WK 24	PLA	598	3.59	0.523	0	0.0204
	Dapa 2.5mg	554	3.63	0.506	0.9	0.0214
	Dapa 5mg	668	3.71	0.507	0.12	0.0201
	Dapa 10 mg	676	3.73	0.520	0.14	0.0192
	Dapa total	1898	3.69	0.513	0.12	0.0117
LT Treatment SCS WK 102	PLA	107	3.71	0.673	0.10	0.0656
	Dapa 2.5mg	136	3.65	0.454	0.04	0.0403
	Dapa 5mg	159	3.58	0.489	0.04	0.0390
	Dapa 10 mg	166	3.70	0.499	0.06	0.0384
	Dapa total	461	3.64	0.484	0.05	0.0226

Source: Appendix 67B ISS

Source Dr. Whitaker's review Table 12

Small increases in the mean change from baseline **PTH** were seen in dapagliflozin treated patients compared to placebo.

**Table 112 Intact PTH (pg/mL): Summary Statistics for Short Plus Long-term Period Placebo-controlled Pool**

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
ST Treatment SCS WK 24	PLA	586	36.9	20.92	0.1	0.639
	Dapa 2.5mg	535	40.5	21.21	2.5	0.718
	Dapa 5mg	656	38.3	18.10	2.4	0.549
	Dapa 10 mg	656	39.6	21.95	2.3	0.713
	Dapa total	1847	39.4	20.45	2.4	0.381
LT Treatment SCS WK 102	PLA	102	35.3	17.77	-2.9	1.561
	Dapa 2.5mg	131	38.6	19.75	1.5	1.375
	Dapa 5mg	151	39.8	21.64	3.1	1.174
	Dapa 10 mg	158	37.9	18.74	1.6	1.068
	Dapa total	440	38.7	20.05	2.1	0.690

Source: appendix 59B

Source Dr. Whitaker's review Table 14

There was no long-term difference maintained in measurements of **[25]OH Vitamin D**.

## Renal Impairment Study—MB102029

In the 52 week data, there was no notable change in **calcium** levels. However, there was a greater increase in inorganic phosphorus in patients treated with dapagliflozin compared to those treated with placebo.

**Table 113 Change in Inorganic Phosphorus (mg/dL) from Baseline Renal Impairment Study**

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles			Max	N	Change from Baseline			
						25	Median	75			Mean	SE	Median	IQR
WEEK 52	Placebo	49	3.82	0.666	2.5	3.40	3.80	4.20	6.2	49	0.05	0.0787	0.10	0.90
	DAPA 5MG	64	3.88	0.659	2.6	3.50	3.90	4.40	5.8	64	0.19	0.0619	0.20	0.65
	DAPA 10MG	63	3.86	0.590	2.5	3.40	3.80	4.20	5.3	63	0.30	0.0748	0.20	0.80

Source CSR Appendix 7.32

Increases were also noted in **magnesium**.

**Table 114 Change in Magnesium (mEq/L) from Baseline Renal Impairment Study**

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles			Max	N	Change from Baseline			
						25	Median	75			Mean	SE	Median	IQR
WEEK 52	Placebo	48	1.65	0.191	1.0	1.55	1.70	1.70	2.0	48	-0.04	0.0243	0.00	0.15
	DAPA 5MG	64	1.83	0.198	1.4	1.70	1.80	1.90	2.4	64	0.16	0.0293	0.10	0.30
	DAPA 10MG	63	1.81	0.176	1.4	1.70	1.80	1.90	2.3	63	0.12	0.0244	0.10	0.20

Source CSR Appendix 7.33

Greater increases in PTH were seen in the moderate renal failure study (MB102029) (Table 115) where all treatment groups had an increase in PTH levels from baseline with a larger increase in each dapagliflozin group compared with placebo, particularly in the dapagliflozin 10 mg group at weeks 24 and 52. All subjects had elevated PTH at baseline (mean 66-70). At 24 weeks, the mean values ranged from 77-96 pg/ml in the dapa groups compared to 68 pg/ml in the placebo group (mean change from baseline of 4 and 26 pg/ml, for the 5 and 10 mg groups, respectively). At 104 weeks, the mean values ranged from 79-105 pg/ml, with mean change from baseline of 23 and 19 pg/ml, for the 5 and 10 mg groups, respectively. The changes were overall dose-dependent.

**Table 115 Change in PTH (pg/mL) from Baseline Renal Impairment Study**

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
Lead-in Baseline	PLA	81	66.52	52.993		
	Dapa 5 mg	78	70.15	57.448		
	Dapa 10 mg	79	68.53	48.855		
ST Treatment WK 24	PLA	58	68.48	52.728	2.90	4.73
	Dapa 5 mg	64	77.22	67.553	4.05	5.25
	Dapa 10 mg	63	96.59	124.379	25.95	14.80
LT Treatment WK 52	PLA	45	62.49	43.994	1.13	4.61
	Dapa 5 mg	60	76.58	60.201	9.25	5.41
	Dapa 10 mg	60	84.10	54.828	11.93	5.15
LT Treatment WK 104	PLA	2	30.50	7.778	-4.00	11.00
	Dapa 5 mg	8	79.88	28.352	23.50	9.67
	Dapa 10 mg	10	105.70	64.515	19.20	5.77
Source: Appendix 7.36C						

Source Dr. Whitaker's review Table 15

Dr. Whitaker explains that elevated baseline PTH levels are common in renal insufficiency. As vitamin D conversion is compromised, serum calcium decreases leading to increased levels of PTH, as well as increases in PTH due to hyperphosphatemia. The mean values listed above for study MB101029 fall at or somewhat above the target range for moderate renal insufficiency.

### ***Bone Resorption Markers***

Bone markers were evaluated in some of the phase 3 studies as seen in Table 116.

**Table 116 Bone Markers in Phase Three Studies**

Study/Table Number	<u>Laboratory Test</u>						
	Serum CTx	Urine CTx	Serum NTx	Urine NTx	Serum OC	Serum P1NP	Serum BAP
<b>MB102013</b>	X	–	X	–	X	X	–
Table 1-week 24, Table 2-week 24, Table 3-week 102, Table 4-week 102							
<b>MB102014</b>	X	–	X	–	X	X	–
Table 5-week 24, Table 6-week 102							
<b>MB102030</b>	X	–	X	–	X	X	–
Table 7-week 24							
<b>MB102032</b>	X	–	X	–	X	X	–
Table 8-week 24							
<b>D1690C00012</b>	X	X	X	X	X	X	X
Table 9-week 24, Table 10-week 50							

BAP = bone alkaline phosphatase, CTx = type I collagen crosslinked C-telopeptide, NTx = type I collagen crosslinked N-telopeptide, OC = osteocalcin, P1NP = Procollagen type 1 propeptide

Source Response FDA Inquiry Table 2.1 May 13, 2011

The applicant reports that the mean change from baseline in the markers of bone resorption was found to be slightly higher in dapagliflozin-treated subjects compared with placebo-treated subjects. However, change in bone formation markers was inconsistent. The mean change and range for each biomarker are listed in Table 117.

Clinical Review  
Somya V. Dunn, M.D.  
NDA 202293

(b) (4) Dapagliflozin

Table 117 Bone Turnover Markers

	Study /biomarker	Mean baseline value (Min, max) Long-term exposure population		Short Term Mean Range Across dose groups Mean min, Mean max	Mean Placebo Group	Long-term Mean (mean change from baseline) Across dose groups	Placebo Mean (mean change from baseline)	DAPA Trend
Dapagliflozin 2.5 5mg 10 mg  Vs placebo	<b>MB102013*</b>			24 weeks		102 weeks		
	CTX	All subjects*	0.333 (0.030, 1.54) N=537	0.392, 0.435 (0.044, 0.090)	0.3614 (0.002)	0.2403 – 0.3137 (-0.72, -0.019)	0.2687 (-0.085)	equivocal sCTX ↑ in ST but small ↓ in LT
		Pre-MP*	0.310 (0.030, 0.962) N=249					
		Post-MP *	0.385 (0.077, 1.54) N=162					
	NTX	All subjects*	8.536 (3.4, 29.2) N=541	8.88, 10.10 (0.79, 1.41)	9.46 (0.44)	9.33 – 10.53 (0.79, 1.76)	10.77 (1.82)	↑ sNTX Not dose-related
		Pre-MP*	7.6 (3.4, 19.4) N=113					
		Post-MP *	9.325 (4.2, 29.2) N=161					
	OC	All subjects*	16.035 (5.3, 57.3) N=538	16.28, 18.86 (0.81, 3.03)	18.32 (0.39)	14.39, 18.51 (-1.10, 1.23)	15.90 (-1.79)	Equivocal OC ↑ in ST, ↔ in LT
		Pre-MP*	13.442 (5.3, 30.7) N=111					
		Post-MP *	18.470 (6, 57.3) N=160					
	P1NP	All subjects*	40.307 (10, 117.7) N=536	38.72, 41.71 (-1.37, 4.43)	41.52 (-1.31)	25.65, 36.50 (-11.78, -3.81)	30.18 (-11.18)	↓ P1NP Not dose-related
		Pre-MP*	36.865 (11.6, 106.6) N=109					
		Post-MP *	43.988 (10, 117.7) N=161					
Dapagliflozin 2.5mg 5 mg 10 mg + open label metformin  Vs placebo	<b>MB102014</b>			24 weeks		102 weeks		
	CTX	All subjects*	0.27 (0.03, 1.0) N=519	0.30 - 0.31 (0.04, 0.06)	0.26 (-0.01)	0.26, 0.30 (-0.01, 0.01)	0.25 (-0.03)	No change sCTX
		Pre-MP*	0.23 (0.05, 1.0) N=92					
		Post-MP *	0.33 (0.06, 0.96) N=150					
	NTX	All subjects*	8.14 (5.3, 25.1) N=518	8.80-9.48 (0.70, 0.90)	8.05 (0.18)	10.29, 10.76 (1.87, 2.42)	9.82 (1.58)	↑ sNTX
		Pre-MP*	7.34 (5.3, 19.2) N=93					
		Post-MP *	9.2 (5.3, 25.1) N=150					
	OC	All subjects*	13.8 (3.2, 38.9) N=520	13.09, 15.10 (-0.31, -0.20)	13.07 (-0.89)	13.78, 14.56 (-0.95, 0.46)	13.67 (-0.14)	slight ↑ OC
		Pre-MP*	12.4 (4.3, 30.7) N=93					
		Post-MP *	16.2 (4, 38.9) N=150					
	P1NP	All subjects*	34.80 (6.3, 125.5) N=520	30.27, 36.91 (-1.73, -2.76)	31.37 (-3.29)	27.74, 29.63 (-9.61, 5.46)	26.29 (-10.31)	↓ P1NP
		Pre-MP*	32.70 (10.2, 125.5) N=92					
		Post-MP *	41.54 (13, 120.6) N=150					
Dapagliflozin 5 mg 10 mg + pioglitazone  vs placebo	<b>MB102030</b>			24 weeks		N/A		
	Serum CTX	All subjects	PLA+PIO 0.32 DAP+PIO 0.32, 0.35	0.37, 0.45 (0.05, 0.09)	0.31 (-0.013)			↑ sCTX dose effect†
	Serum NTX	All subjects	PLA+PIO 9.41 DAP+PIO 9.35, 9.68	11.33, 12.31 (2.05, 2.27)	9.85 (0.319)			↑ sNTX dose effect

	Study /biomarker	Mean baseline value (Min, max) Long-term exposure population		Short Term Mean Range Across dose groups Mean min, Mean max	Mean Placebo Group	Long-term Mean (mean change from baseline) Across dose groups	Placebo Mean (mean change from baseline)	DAPA Trend
+ pioglitazone	OC	All subjects	PLA+PIO 15.22 DAP+PIO 15.14, 16.28	17.09, 19.32 (1.08, 2.88)	16.57 (1.068)			↑ OC dose effect
	P1NP	All subjects	PLA+PIO 33.97 DAP+PIO 32.49, 35.54	34.49, 41.14 (1.61, 5.24)	34.43 (-0.107)			↑ P1NP dose effect
Dapagliflozin 1 mg 2.5 mg 5 mg Vs placebo	MB10232			24 weeks		N/A		
	Serum CTX	All subjects	PLA 0.29 DAPA 1-5mg 0.30, 0.31	0.35, 0.43 (0.05, 0.07)	0.33 (0.04)			↑ CTX No dose effect
	Serum NTX	All subjects	PLA 8.56 DAPA (1-5mg) 8.68, 10.11	9.95, 11.73 (1.30, 1.97)	10.61 (2.01)			↑ NTX No dose effect
	OC	All subjects	PLA 15.77 DAPA (1-5mg) 15.54, 18.32	17.15, 20.38 (0.58, 1.80)	17.21 (1.36)			↑ OC No dose effect
	P1NP	All subjects	PLA 35.31 DAPA (1-5mg) 33.35, 38.36	35.56-41.22 (-1.45, 2.37)	34.88 (-0.51)			↑ P1NP
Dapagliflozin 10 + metformin Vs placebo + metformin	D1690C00012			24 weeks		50 weeks		
	Serum CTX	All subjects	0.22 Dapag 0.24 PLA	NR (0.03)	NR -0.01	0.26 (0.04)	0.26 (0.02)	no change compared to PBO sCTX
		PMP pop	Not available					
	Serum NTX	All subjects	8.91 PLA 9.00 DAPAG	NR (0.27)	NR (-0.15)	8.64 (-0.36)	8.34 (-0.57)	decrease but effect not greater than PBOsNTX
		PMP pop	Not available					
	OC	All subjects	14.07 DAPA 15.20 PLA	NR (-0.46)	NR (-1.50)	13.67 (-0.40)	13.21 (-1.99)	↓ OC
		PMP pop	Not available					
	P1NP	All subjects	26.72 DAPA 28.19 Pla	NR (-0.04)	NR (-1.96)	25.93 (-0.79)	24.45 (-3.74)	↓ P1NP
		PMP pop	Not available					
	Urine CTX	All subjects	8.76 DAPAG 10.49 PLA	NR (0.69)	NR (-0.06)	9.86 (1.10)	10.21 (-0.27)	↑ uCTX
		PMP pop	Not available					
	Urine NTX	All subjects	275.2 DAPAG 314.4 PLA	NR (-24.32)	NR (-11.10)	243.4 (-31.8)	271.4 (-43.0)	↓ uNTX
		PMP pop	Not available					
	BSAP	All subjects	17.06 DAPA 17.03 PLA	NR (-0.97)	NR (-1.33)	16.26 (-0.80)	15.42 (-1.61)	↓ BSAP
		PMP pop	Not available					

\*data from long term study datasets  
Values for study MB102013 represent Group 1 only (Hb 7-10)  
ST=short term, LT=long term, NR=not reported  
Pre-MP=premenopausal, post-MP=postmenopausal

Source Dr. Whitaker's review Table 16

Dr. Whitaker notes that the mean baseline range in bone turnover markers for postmenopausal subjects appeared only slightly higher than those for the premenopausal subjects. Therefore, these data may not be applicable to postmenopausal women in whom one would expect to see increased bone turnover. While there were small inconsistent changes in bone turnover markers, including bone resorption. No conclusions can be made from these data. This is in agreement with the applicant's overall assessment.

### Bone Mineral Density—Body Composition Study

The effects of dapagliflozin on bone mineral density (BMD) were measured by DXA, the preferred technique for diagnosis of osteoporosis, in study D1690C00012—body

composition study, biochemical markers of bone formation and bone resorption were also evaluated. The bone mineral density data are based on the 03-Feb-2011 database lock and were presented for the first time in the 4-MSU.

Of the 182 randomized, 165 remained after the 50 week visit (84 on placebo and 81 on dapagliflozin). Nine subjects were discontinued due to pre-specified change in T-score BMD (T-score <-2.5 or T-score change >5% - 3 on placebo, 6 on dapagliflozin). All discontinuations were due to 5 to 10% decrease at one site. Updated mean change data was requested by the consult reviewer and reported here, see Table 118.

**Table 118 Mean Percent Change in BMD at 50 weeks (minimum change, maximal change)**

	Dapa 10mg + Met (n=82)	Placebo + Met (n=84)
LS BMD	0.26 (-8.5, 8.9)	0.18 (-9.4, 8.1)
Femoral Neck	-0.42 (-8, 4.6)	0.17 (-6.4, 12.7)
Total Hip	0.1 (-7.2, 36.1)	-0.23 (-5.3, 4.6)

Source Dr. Whitaker's review Table 18

Overall, Dr. Whitaker remarks that mean data suggest minimal effects of dapagliflozin on BMD at 50 weeks. Outliers show that there were 7 subjects in the dapagliflozin group and three subjects in the placebo group with losses of approximately 9%. Conversely, many subjects had BMD increases (5 dapagliflozin, and 11 placebo). A difficult to explain 36% increase in BMD was seen in one subject, but generally increases ranged up to about 12%.

#### **Reviewer's Comments**

**There is no clear association between treatment with dapagliflozin and fractures or clinically significant changes in bone mineral density, bone markers or bone related laboratories.**

**Dr. Whitaker's conclusions were as follows:**

***From the bone safety data reviewed, there is no indication that dapagliflozin exerts a clinically significant effect on bone loss or fracture. Full review of the 2-year data would be reassuring but generally would not be required for approval from a bone standpoint. While bone loss due to weight loss is a primary concern, further surveillance of bone formation/hyperostosis based on nonclinical evidence of vascular tissue mineralization, and increased bone resorption should also be monitored.***

**The applicant continues to follow bone health in their ongoing body composition study and also plans to continue to follow fracture as an AE of special interest in the long-term cardiovascular study.**

## Renal Related AEs and Renal Lab Changes

Urinary stone events were infrequent therefore analyses were conducted on the largest pool of data (All Phase 2b and 3 Pool). In the Phase 2b and 3 Pool, a lower proportion of subjects treated with dapagliflozin compared with comparator (0.6% versus 1.2%) reported events of urinary stones. Most events were mild to moderate in intensity; few were serious or led to discontinuation of study drug.

### Placebo-controlled Pool—Short-term Treatment

Across treatment groups, similar proportions of subjects remained within their baseline urine albumin to creatinine ratio (UACR) category or moved to a higher or lower category by week 24.

**Table 119 UACR Shift Ratios Short-term Placebo-controlled Pool**

Treatment Group: PLA (N = 1393)

Lab Test Description	Baseline	Week 24 LOCF Value				TOTAL
		NORMOALBUMINURIA	MICROALBUMINURIA	MACROALBUMINURIA	NOT REPORTED	
ALBUM TO CREAT RATIO (MG/G)	NORMOALBUMINURIA	971 (92.0)	75 (7.1)	0	9 (0.9)	1055
	MICROALBUMINURIA	115 (38.7)	166 (55.9)	8 (2.7)	8 (2.7)	297
	MACROALBUMINURIA	0	15 (38.5)	24 (61.5)	0	39
	NOT REPORTED	2 (100.0)	0	0	0	2

Treatment Group: DAPA TOTAL (N = 3291)

Lab Test Description	Baseline	Week 24 LOCF Value				TOTAL
		NORMOALBUMINURIA	MICROALBUMINURIA	MACROALBUMINURIA	NOT REPORTED	
ALBUM TO CREAT RATIO (MG/G)	NORMOALBUMINURIA	2281 (90.9)	195 (7.8)	3 (0.1)	31 (1.2)	2510
	MICROALBUMINURIA	254 (37.7)	391 (58.1)	20 (3.0)	8 (1.2)	673
	MACROALBUMINURIA	5 (6.0)	32 (38.1)	46 (54.8)	1 (1.2)	84
	NOT REPORTED	21 (87.5)	2 (8.3)	0	1 (4.2)	24

### Source SCS Appendix 64B

Within each subgroup of baseline eGFR category, a similar proportion of subjects in each treatment group remained within their baseline albumin:creatinine category or moved to a higher or lower category by week 24.

In an Adverse Events list compiled for investigator suspected drug related AEs, microalbuminuria was reported. This list reported AEs in at least 0.2% of subjects and at least 0.1% more and in at least three subjects more in the dapagliflozin group. Microalbuminuria was reported in more dapagliflozin patients. There were 4 dapagliflozin treated patients (0.1%) and no placebo patients.



Comparison of renal related AEs of predetermined PTs from the Placebo-controlled Pool did not show evidence of new or worsening renal impairment, progression of diabetic nephropathy, acute nephrotoxicity, such as acute tubular necrosis, or other events that would suggest increased or worsening nephropathy in dapagliflozin-treated subjects.

**Table 120 Renal Related AEs in the Short-term Placebo-controlled Pool**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	12 ( 0.9)	11 ( 1.4)	15 ( 1.3)	11 ( 0.9)	38 ( 1.2)
BLOOD CREATININE INCREASED	7 ( 0.5)	6 ( 0.7)	6 ( 0.5)	9 ( 0.8)	22 ( 0.7)
CREATININE RENAL CLEARANCE DECREASED	0	0	0	1 ( 0.1)	1 ( <0.1)
CYSTATIN C INCREASED	0	0	0	1 ( 0.1)	1 ( <0.1)
GLOMERULAR FILTRATION RATE DECREASED	0	1 ( 0.1)	3 ( 0.3)	1 ( 0.1)	5 ( 0.2)
RENAL FAILURE	3 ( 0.2)	0	2 ( 0.2)	1 ( 0.1)	3 ( 0.1)
URINE FLOW DECREASED	0	0	0	1 ( 0.1)	1 ( <0.1)
BLOOD CREATININE ABNORMAL	0	0	1 ( 0.1)	0	1 ( <0.1)
OBSTRUCTIVE UROPATHY	0	0	1 ( 0.1)	0	1 ( <0.1)
OLIGURIA	0	1 ( 0.1)	0	0	1 ( <0.1)
RENAL FUNCTION TEST ABNORMAL	0	0	1 ( 0.1)	0	1 ( <0.1)
RENAL IMPAIRMENT	1 ( 0.1)	2 ( 0.2)	2 ( 0.2)	0	4 ( 0.1)
URINE OUTPUT DECREASED	1 ( 0.1)	1 ( 0.1)	0	0	1 ( <0.1)

Source SCS Table 65

### MB102029 Moderate Renal Impairment Study

AEs related to renal impairment were reported in a higher proportion of patients treated with dapagliflozin 10 mg in the special moderate renal impairment study during short-term treatment. Increased blood creatinine was the only event reported for any treatment group in the special study; it was also the most commonly reported event in the short-term Placebo-controlled Pool.

**Table 121 Renal AEs in Moderate Renal Impairment Study**

Special Moderate Renal Impairment Study (Short-term Treatment up to Week 24)*	Number (%) of Patients		
	Dapa 5 mg N = 83	Dapa 10 mg N = 85	Placebo N = 84
Renal Adverse Event	0	4 (4.7)	1 (1.2)

Source BMS AC Modified from Briefing Document Table 51

### Mean Changes from Baseline—Renal Labs

Of note, the Abbreviated Modification of Diet in Renal Disease Study (MDRD) equation was used throughout the dapagliflozin clinical program to calculate estimated glomerular filtration rate.

**Uric acid** levels decreased in all dapagliflozin groups in the studies in which it was analyzed (MB102013, MB102032, MB102014, MB102021, and MB102034); placebo-corrected mean reductions ranged from -0.45 mg/dL to -0.8 mg/dL in studies MB102013, MB102032, and MB102014. In the initial combination therapy studies, mean reductions were also observed for the combination therapy groups versus the metformin monotherapy groups (-0.75 mg/dL and -0.72 mg/dL in MB102021 and MB102034, respectively).

### Placebo-controlled Pool—Short-term Treatment

Mean changes from baseline in renal function tests were observed for the Placebo-controlled Pool. In the dapagliflozin groups, estimated glomerular filtration rate (eGFR) decreased initially then increased toward or above baseline values by week 24.

**Table 122 Estimated GFR (mL/min/1.73 m<sup>2</sup>) Mean Changes from Baseline at 4 and 24 Weeks**

Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
<b>4 Weeks (SE)</b>	N=1347 0.6 (0.3)	N=796 -2.2 (0.4)	N=1109 -1.9 (0.4)	N=1149 -2.1 (0.3)	N=3187 -2.0 (0.2)
<b>24 Weeks (SE)</b>	N=1087 0.8 (0.3)	N=619 -0.9 (0.4)	N=899 0.8 (0.4)	N=935 0.3 (0.4)	N=2453 0.2 (0.2)

Source Applicant's SCS App 40B

Mean estimated creatinine clearance (eCrCl) decreased from baseline to week 24 in all treatment groups; this decrease was greater in the dapagliflozin treated groups.

**Table 123 Estimated CrCl (mL/min) Mean Changes from Baseline at 4 and 24 Weeks**

Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
<b>4 Weeks (SE)</b>	N=1324 0.1 (0.4)	N=794 -4.0 (0.4)	N=1108 -3.7 (0.4)	N=1125 -4.4 (0.4)	N=3136 -4.0 (0.3)
<b>24 Weeks (SE)</b>	N=1086 -0.4 (0.4)	N=618 -4.0 (0.4)	N=898 -2.2 (0.5)	N=934 -3.5 (0.5)	N=2450 -3.1 (0.3)

Source Applicant's SCS App 38B

Mean serum creatinine levels changed minimally from baseline to week 24 in all treatment groups.

Mean blood urea nitrogen (BUN) levels increased 0.3 mg/dL in the placebo group and 1.5 to 1.8 mg/dL in each dapagliflozin group from baseline to week 24.

Table 124 Estimated BUN (mg/dL) Mean Changes from Baseline at 4 and 24 Weeks

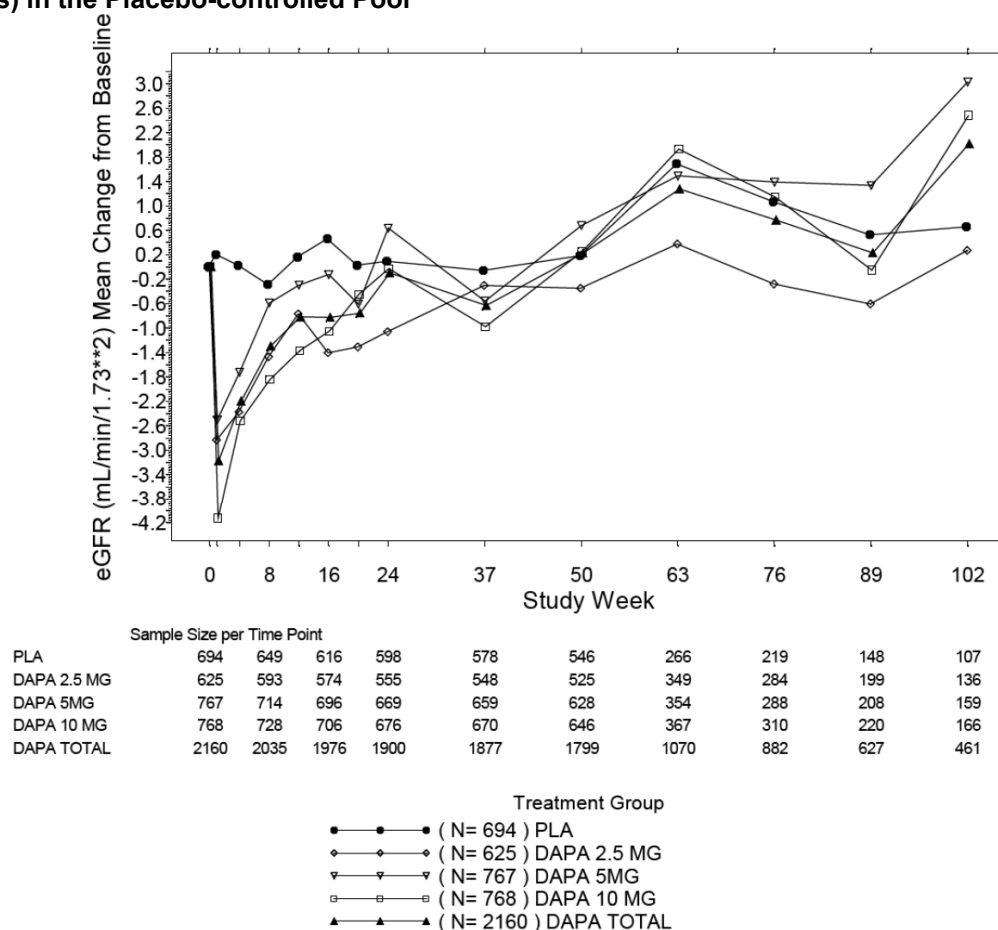
Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
<b>4 Weeks (SE)</b>	N=1347 0.0 (1.0)	N=797 1.1 (0.1)	N=1109 1.2 (0.1)	N=1149 1.3 (0.1)	N=3188 1.2 (0.1)
<b>24 Weeks (SE)</b>	N=1087 0.3 (0.1)	N=619 1.5 (0.2)	N=899 1.4 (0.1)	N=935 1.6 (0.1)	N=2453 1.5 (0.1)

Source Applicant's SCS App 36B

## Placebo-controlled Pool—Long-term Treatment

Small mean decreases in eGFR from baseline were reported in dapagliflozin-treated patients at Week 1 in the short-term plus long-term Placebo-controlled Pool. Following this initial drop in eGFR, there was a gradual return to baseline over 16-24 weeks without evidence of progressive renal dysfunction (Figure 26). These small and transient changes were dose-dependent.

Figure 26 Mean changes in estimated GFR from Baseline to Week 102 (short-term and long-term periods) in the Placebo-controlled Pool



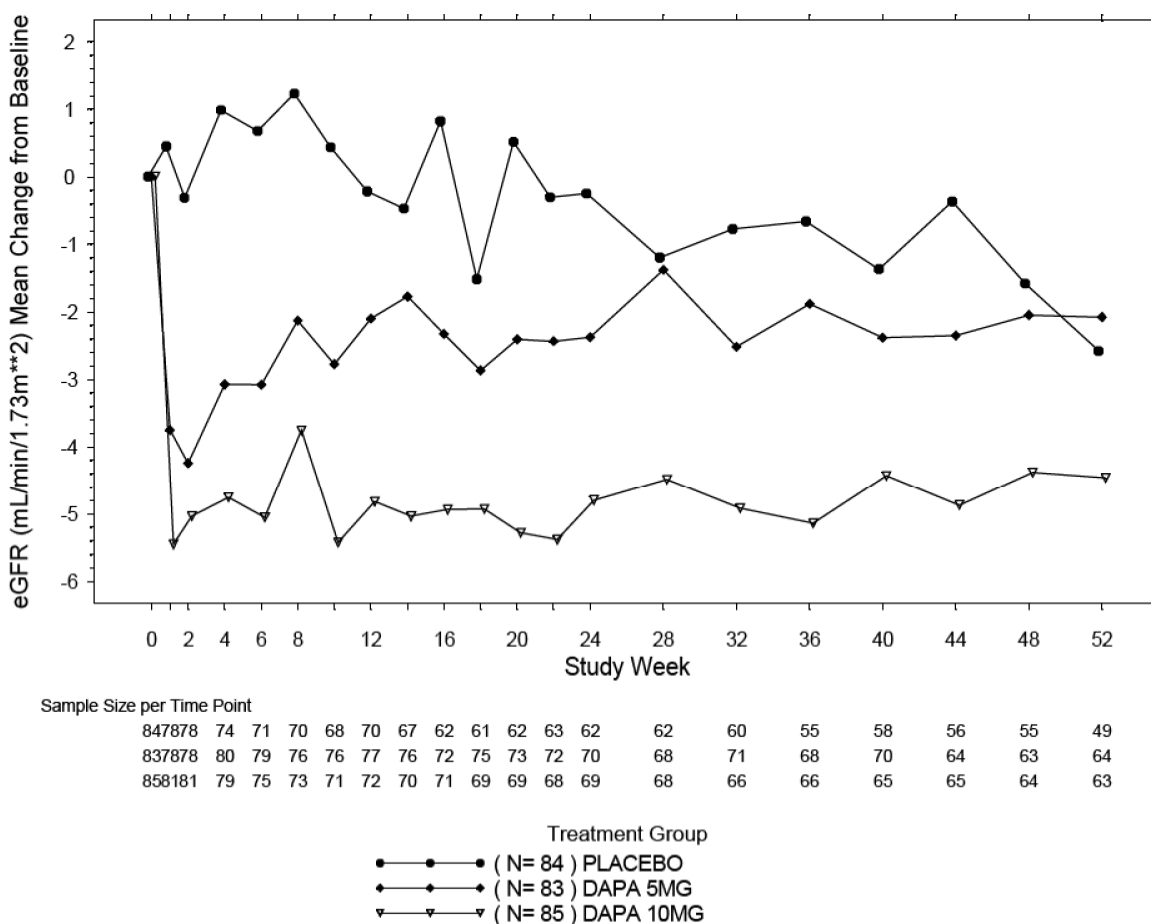
Source: Applicant's SCS Figure 4

Small mean decreases (-1 to -5 mL/min) in eCrCl were reported in all dapagliflozin groups compared to placebo (-1 mL/min) that persisted to week 102. These are not clinically relevant.

### MB102029 Moderate Renal Impairment Study

Estimated GFR and eCrCl decreased from baseline to week 1 in the dapagliflozin 5 and 10 mg groups then stabilized, with mean reductions from baseline at week 52 that were slightly less than those seen at week 1. By comparison, the mean eGFR and eCrCl in the placebo group were essentially unchanged from baseline to week 24 and then decreased slowly (Figure 27). While mean reductions from baseline to week 52 in eGFR and eCrCl were observed in all treatment groups for subgroups of subjects with baseline GFR 45 to 59 mL/min/1.73 m<sup>2</sup> and 30 to 44 mL/min/1.73 m<sup>2</sup>, the magnitude of the mean decreases were consistently larger in the 45 to 59 mL/min/1.73 m<sup>2</sup> subgroup compared with the 30 to 44 mL/min/1.73 m<sup>2</sup> subgroup.

**Figure 27 Change in eGFR (mL/min/1.73m<sup>2</sup>) from Baseline to week 52 in the Short-term Plus Longterm in Study MB102029**



Source CTR Table 8.8.3.1

### **Markedly Abnormal Renal Laboratory Values**

Marked abnormalities for BUN (> 60 mg/dL) or creatinine (> 2.5 mg/dL) were reported in similar proportions of subjects in all treatment groups: 0% to 0.2% in the dapagliflozin groups and 0% in the placebo group. Similar proportions of subjects in each dapagliflozin group and the placebo group had elevated renal tests based on laboratory values (creatinine:  $\geq 1.5$ X pre-treatment creatinine [1.4% - 1.9% in the dapagliflozin groups; 1.6% in the placebo group] or creatinine  $\geq 2.5$  mg/dL [0% - 0.2% in the dapagliflozin groups; 0% in the placebo group]). Similar proportions of subjects in each dapagliflozin group and the placebo group had elevated renal tests based on laboratory values and/or reported AEs of renal impairment or failure (< 3% in each treatment group). In addition, marked abnormalities of BUN and serum creatinine were noted in similar proportions of subjects across treatment groups, including subjects using diuretics or ACE-I or ARB anti-hypertensive agents.

#### ***Reviewer's comments***

**Overall, renal AEs and lab changes are not concerning in the larger pools. The AE rate being higher in the dapagliflozin treated patients compared to placebo in the moderate renal impairment study is concerning. Overall, I do not recommend that dapagliflozin be approved for this group, or any subgroup of patients in the moderate renal impairment category. However, due to the nature of T2DM progression and worsening renal disease, studying this population is necessary.**

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

#### **Placebo-controlled Pool Short-term Treatment**

The most common AEs ( $\geq 2\%$ ) in the dapagliflozin 10 mg group in descending order of frequency were nasopharyngitis, back pain, headache, diarrhea, upper respiratory tract infection, urinary tract infection, dyslipidemia, nausea, hypertension, influenza, pollakiuria, and dysuria (Table 125). Most did not appear to be associated with the mechanism of action of dapagliflozin and were reported in similar proportions across treatment groups, with the exception of urinary tract infection, back pain, and dysuria, which were more common in the dapagliflozin 10 mg group than in the placebo group. The most common AEs reported in subjects in the dapagliflozin 2.5 and 5 mg groups were consistent with those reported in subjects in the dapagliflozin 10 mg group.

**Table 125 Common AEs Short-term Placebo-controlled Pool**

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
NASOPHARYNGITIS	87 ( 6.2)	71 ( 8.7)	76 ( 6.6)	75 ( 6.3)	227 ( 6.9)
BACK PAIN	44 ( 3.2)	25 ( 3.1)	35 ( 3.1)	50 ( 4.2)	115 ( 3.5)
HEADACHE	63 ( 4.5)	32 ( 3.9)	51 ( 4.5)	48 ( 4.0)	135 ( 4.1)
DIARRHOEA	66 ( 4.7)	23 ( 2.8)	47 ( 4.1)	44 ( 3.7)	121 ( 3.7)
UPPER RESPIRATORY TRACT INFECTION	61 ( 4.4)	20 ( 2.5)	38 ( 3.3)	43 ( 3.6)	105 ( 3.2)
URINARY TRACT INFECTION	38 ( 2.7)	25 ( 3.1)	54 ( 4.7)	43 ( 3.6)	131 ( 4.0)
DYSLIPIDAEMIA	21 ( 1.5)	9 ( 1.1)	24 ( 2.1)	30 ( 2.5)	63 ( 1.9)
NAUSEA	33 ( 2.4)	16 ( 2.0)	32 ( 2.8)	30 ( 2.5)	86 ( 2.6)
HYPERTENSION	54 ( 3.9)	35 ( 4.3)	32 ( 2.8)	28 ( 2.3)	95 ( 2.9)
INFLUENZA	32 ( 2.3)	20 ( 2.5)	31 ( 2.7)	28 ( 2.3)	82 ( 2.5)
POLAKIURIA	14 ( 1.0)	9 ( 1.1)	13 ( 1.1)	26 ( 2.2)	53 ( 1.6)
DYSURIA	10 ( 0.7)	5 ( 0.6)	18 ( 1.6)	25 ( 2.1)	49 ( 1.5)
CONSTIPATION	21 ( 1.5)	23 ( 2.8)	25 ( 2.2)	23 ( 1.9)	75 ( 2.3)
COUGH	25 ( 1.8)	17 ( 2.1)	22 ( 1.9)	23 ( 1.9)	65 ( 2.0)
ARTHRALGIA	28 ( 2.0)	26 ( 3.2)	22 ( 1.9)	20 ( 1.7)	69 ( 2.1)
DIZZINESS	31 ( 2.2)	25 ( 3.1)	25 ( 2.2)	20 ( 1.7)	77 ( 2.3)
OEDEMA PERIPHERAL	33 ( 2.4)	10 ( 1.2)	10 ( 0.9)	20 ( 1.7)	44 ( 1.3)
PAIN IN EXTREMITY	20 ( 1.4)	10 ( 1.2)	23 ( 2.0)	20 ( 1.7)	55 ( 1.7)

Source SCS Table 29

### Placebo-controlled Pool Short-term Plus Long-Term Treatment

The profile of this pool is very similar to the short-term period. The difference noted in dyslipidemia is more pronounced at almost 1% (2.4% of placebo treated patients versus 3.3% of dapagliflozin treated patients. There is no clear dose response for these AEs.

Table 126 Common AEs Short Plus Long-term Placebo-controlled Pool

Preferred Term (%)	PLA N = 694	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 2160
NASOPHARYNGITIS	61 ( 8.8)	78 ( 12.5)	77 ( 10.0)	82 ( 10.7)	237 ( 11.0)
BACK PAIN	36 ( 5.2)	32 ( 5.1)	35 ( 4.6)	58 ( 7.6)	125 ( 5.8)
URINARY TRACT INFECTION	32 ( 4.6)	29 ( 4.6)	51 ( 6.6)	52 ( 6.8)	132 ( 6.1)
DIARRHOEA	36 ( 5.2)	30 ( 4.8)	41 ( 5.3)	48 ( 6.3)	119 ( 5.5)
HEADACHE	46 ( 6.6)	34 ( 5.4)	47 ( 6.1)	44 ( 5.7)	125 ( 5.8)
UPPER RESPIRATORY TRACT INFECTION	44 ( 6.3)	30 ( 4.8)	35 ( 4.6)	43 ( 5.6)	108 ( 5.0)
INFLUENZA	24 ( 3.5)	36 ( 5.8)	45 ( 5.9)	37 ( 4.8)	118 ( 5.5)
DYSLIPIDAEMIA	17 ( 2.4)	14 ( 2.2)	23 ( 3.0)	35 ( 4.6)	72 ( 3.3)
HYPERTENSION	54 ( 7.8)	50 ( 8.0)	45 ( 5.9)	34 ( 4.4)	129 ( 6.0)
ARTHRALGIA	29 ( 4.2)	33 ( 5.3)	36 ( 4.7)	31 ( 4.0)	100 ( 4.6)
BRONCHITIS	25 ( 3.6)	19 ( 3.0)	28 ( 3.7)	31 ( 4.0)	78 ( 3.6)
COUGH	25 ( 3.6)	18 ( 2.9)	23 ( 3.0)	28 ( 3.6)	69 ( 3.2)
PHARYNGITIS	20 ( 2.9)	15 ( 2.4)	21 ( 2.7)	28 ( 3.6)	64 ( 3.0)
NAUSEA	19 ( 2.7)	17 ( 2.7)	21 ( 2.7)	26 ( 3.4)	64 ( 3.0)
OEDEMA PERIPHERAL	36 ( 5.2)	14 ( 2.2)	18 ( 2.3)	24 ( 3.1)	56 ( 2.6)
PAIN IN EXTREMITY	23 ( 3.3)	26 ( 4.2)	33 ( 4.3)	23 ( 3.0)	82 ( 3.8)
POLAKIURIA	9 ( 1.3)	9 ( 1.4)	14 ( 1.8)	23 ( 3.0)	46 ( 2.1)

Source SCS Table 30

### Active Comparator Study

Table 127 presents AEs that occurred in  $\geq 2\%$  of patients in the trial. As noted in the *Discontinuations* section, there were more patients with decreased creatinine clearance in the patients treated with dapagliflozin compared to glipizide. This is also consistent with laboratory findings for the placebo-controlled pool. UTI,

headache, bronchitis, vulvovaginal candidiasis, vaginal mycotic infection and decreased creatinine clearance are all AEs by PT in more than 1% of patients greater in the dapagliflozin treated pool than glipizide.

**Table 127 Common AEs Active Comparator Study**

Preferred Term (%)	DAPA + MET N = 406	GLIP + MET N = 408
TOTAL SUBJECTS WITH AN EVENT	318 ( 78.3)	318 ( 77.9)
NASOPHARYNGITIS	43 ( 10.6)	61 ( 15.0)
HYPERTENSION	30 ( 7.4)	35 ( 8.6)
INFLUENZA	30 ( 7.4)	30 ( 7.4)
URINARY TRACT INFECTION	30 ( 7.4)	17 ( 4.2)
UPPER RESPIRATORY TRACT INFECTION	24 ( 5.9)	31 ( 7.6)
HEADACHE	21 ( 5.2)	17 ( 4.2)
BACK PAIN	19 ( 4.7)	20 ( 4.9)
BRONCHITIS	19 ( 4.7)	14 ( 3.4)
DIARRHOEA	19 ( 4.7)	26 ( 6.4)
CREATININE RENAL CLEARANCE DECREASED	17 ( 4.2)	7 ( 1.7)
COUGH	15 ( 3.7)	20 ( 4.9)
DIZZINESS	15 ( 3.7)	37 ( 9.1)
GASTROENTERITIS	14 ( 3.4)	14 ( 3.4)
NAUSEA	14 ( 3.4)	15 ( 3.7)
VULVOVAGINAL CANDIDIASIS	14 ( 3.4)	2 ( 0.5)
ARTHRALGIA	11 ( 2.7)	21 ( 5.1)
DYSURIA	11 ( 2.7)	4 ( 1.0)
MUSCLE SPASMS	11 ( 2.7)	8 ( 2.0)
OEDEMA PERIPHERAL	11 ( 2.7)	13 ( 3.2)
VULVOVAGINAL MYCOTIC INFECTION	11 ( 2.7)	3 ( 0.7)
FATIGUE	10 ( 2.5)	17 ( 4.2)
DYSPEPSIA	9 ( 2.2)	9 ( 2.2)
MUSCULOSKELETAL PAIN	9 ( 2.2)	6 ( 1.5)
ABDOMINAL PAIN UPPER	8 ( 2.0)	8 ( 2.0)
CONSTIPATION	8 ( 2.0)	10 ( 2.5)
ECZEMA	8 ( 2.0)	2 ( 0.5)
PALPITATIONS	8 ( 2.0)	5 ( 1.2)
VOMITING	7 ( 1.7)	8 ( 2.0)
OSTEOARTHRITIS	6 ( 1.5)	9 ( 2.2)
ASYMPTOMATIC BACTERIURIA	5 ( 1.2)	8 ( 2.0)
HYPERHIDROSIS	5 ( 1.2)	27 ( 6.6)
PARAESTHESIA	5 ( 1.2)	9 ( 2.2)
ASTHENIA	3 ( 0.7)	9 ( 2.2)
TREMOR	1 ( 0.2)	31 ( 7.6)

Source CTR Table 39

## Renal Impairment Study

In this trial, there were several AEs that occurred at higher frequency in patients treated with dapagliflozin. Most notably, pollakiuria, blood creatinine increased and polyuria.

**Table 128 Common AEs Moderate Renal Impairment Study**

Preferred Term (%)	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL SUBJECTS WITH AN EVENT	68 (81.0)	71 (85.5)	65 (76.5)
POLAKIURIA	3 ( 3.6)	5 ( 6.0)	10 (11.8)
COUGH	2 ( 2.4)	8 ( 9.6)	8 ( 9.4)
DIARRHOEA	3 ( 3.6)	3 ( 3.6)	8 ( 9.4)
MUSCULOSKELETAL PAIN	3 ( 3.6)	3 ( 3.6)	7 ( 8.2)
NAUSEA	1 ( 1.2)	3 ( 3.6)	7 ( 8.2)
HYPERKALAEMIA	10 (11.9)	7 ( 8.4)	6 ( 7.1)
UPPER RESPIRATORY TRACT INFECTION	3 ( 3.6)	3 ( 3.6)	6 ( 7.1)
DIZZINESS	4 ( 4.8)	10 (12.0)	5 ( 5.9)
HYPERTENSION	5 ( 6.0)	1 ( 1.2)	5 ( 5.9)
HYPOTENSION	0	3 ( 3.6)	5 ( 5.9)
BLOOD CREATININE INCREASED	1 ( 1.2)	0	4 ( 4.7)
HEADACHE	2 ( 2.4)	1 ( 1.2)	4 ( 4.7)
NASOPHARYNGITIS	5 ( 6.0)	6 ( 7.2)	4 ( 4.7)
OEDEMA PERIPHERAL	4 ( 4.8)	8 ( 9.6)	4 ( 4.7)
URINE OUTPUT INCREASED	1 ( 1.2)	2 ( 2.4)	4 ( 4.7)
VOMITING	1 ( 1.2)	0	4 ( 4.7)
DECREASED APPETITE	0	2 ( 2.4)	3 ( 3.5)
DYSURIA	3 ( 3.6)	1 ( 1.2)	3 ( 3.5)
EXCORIATION	0	0	3 ( 3.5)
FALL	4 ( 4.8)	1 ( 1.2)	3 ( 3.5)
FATIGUE	1 ( 1.2)	2 ( 2.4)	3 ( 3.5)
HYPOGLYCAEMIA	2 ( 2.4)	0	3 ( 3.5)
MUSCLE SPASMS	0	1 ( 1.2)	3 ( 3.5)
POLYURIA	1 ( 1.2)	2 ( 2.4)	3 ( 3.5)
SKIN LACERATION	2 ( 2.4)	0	3 ( 3.5)
ARTHRALGIA	5 ( 6.0)	5 ( 6.0)	2 ( 2.4)
ASTHENIA	1 ( 1.2)	2 ( 2.4)	2 ( 2.4)
BACK PAIN	6 ( 7.1)	7 ( 8.4)	2 ( 2.4)
BLOOD BICARBONATE DECREASED	1 ( 1.2)	0	2 ( 2.4)
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 ( 1.2)	0	2 ( 2.4)
BRONCHITIS	4 ( 4.8)	2 ( 2.4)	2 ( 2.4)
CHILLS	0	1 ( 1.2)	2 ( 2.4)
CONSTIPATION	2 ( 2.4)	2 ( 2.4)	2 ( 2.4)
CONTUSION	2 ( 2.4)	1 ( 1.2)	2 ( 2.4)
DEHYDRATION	1 ( 1.2)	0	2 ( 2.4)
DEPRESSION	0	0	2 ( 2.4)

Source CTR Table 8.7.1

### Reviewer's Comments

In general, the common AEs are expected from a large group of patients. Of note, UTI is a common AE that is particular to dapagliflozin. The AEs seen in the moderate renal impairment study appear different than in the larger pools and this is a reflection of the patient population having more comorbidity and also increased renal disease.

### Laboratory Findings

Many of the laboratory findings from the clinical program are discussed in clinically relevant sections of this review. For example, renal related laboratory is discussed in the section above. All central tendency laboratory values/changes from baseline were reviewed and clinically relevant changes are mentioned in this section or relevant sections throughout this safety review.

- No notable changes from baseline in mean serum creatinine kinase, serum total protein and serum albumin in the dapagliflozin-treated groups were observed during the short-term or short-term plus long-term treatment.



- No notable mean changes from baseline in serum electrolytes were observed in the dapagliflozin groups compared with placebo with the exception of a small mean increase in serum magnesium and serum phosphorus; these were discussed in the *Bone Health* section.
- No clinically meaningful differences were observed in fasting lipid profiles (total cholesterol, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, free fatty acids) in the dapagliflozin treatment groups compared with placebo during the short-term or the short-term plus long-term period.
- In the pooled and unpooled populations, the mean change from baseline in all serum chemistry parameters measured in the dapagliflozin treatment groups during short-term plus long-term treatment was consistent with that in short-term treatment.
- Results for each pooled population were consistent with the results for the Placebo-controlled Pool.

Overall, marked abnormalities (MAs) were reported in small proportions of subjects, with no imbalance across the treatment groups with the exception of high serum potassium and both low and high serum sodium. MAs for high serum potassium and low serum sodium were more common in the dapagliflozin 2.5 mg group than in the rest of the treatment groups. MAs for high serum sodium were more common in the dapagliflozin 2.5 and 10 mg groups. Table 129 shows the definitions of the MAs and these results. There was no imbalance across the treatment groups in the proportions of subjects with creatine kinase > 5X ULN or > 10X ULN and no cases of rhabdomyolysis were reported. No MAs of creatine kinase were associated with renal failure.

**Table 129 Marked Abnormalities Short-term Placebo-controlled Pool**

Laboratory Test, n (%)	Placebo N = 1393	Dapa 2.5 mg N = 814	Dapa 5 mg N = 1145	Dapa 10 mg N = 1193
Creatine kinase > 5x ULN	12 (0.9)	6 (0.7)	12 (1.1)	13 (1.1)
Creatine kinase > 10x ULN	4 (0.3)	2 (0.2)	3 (0.3)	5 (0.4)
Bicarbonate ≤ 13 mEq/L	1 (0.1)	0	2 (0.2)	5 (0.4)
Serum potassium ≤ 2.5 mEq/L	0	0	0	0
Serum potassium ≥ 6 mEq/L	36 (2.6)	33 (4.1)	32 (2.8)	34 (2.9)
Serum magnesium < 1 mEq/L	4 (0.3)	0	2 (0.2)	1 (0.1)
Serum magnesium > 4 mEq/L	0	0	0	0
Serum sodium < 130 mEq/L	7 (0.5)	10 (1.2)	7 (0.6)	3 (0.3)
Serum sodium < 120 mEq/L	2 (0.1)	1 (0.1)	0	0
Serum sodium > 150 mEq/L	11 (0.8)	13 (1.6)	6 (0.5)	15 (1.3)

Source SCS Table 40

### Placebo-controlled Short-term Plus Long-term Treatment

The pattern of MAs seen with short-term plus long-term treatment in the Placebo-controlled Pool was consistent with that seen in short-term treatment, except that the slight differences between the low levels for serum sodium in the short-term period were balanced across the treatment groups in this time period. In addition, elevations in potassium were more pronounced (115 patients—5.4% in dapagliflozin treated patients and 29 placebo patients—4.2%). Inorganic phosphorus levels remained imbalanced (49—2.3% dapagliflozin treated patients and 10—1.5% placebo treated patients).

### Vital Signs

#### Blood Pressure

Mean decreases in seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 24 in the dapagliflozin groups were larger compared with the placebo group (Table 130). These mean decreases were similar across the dapagliflozin groups. Decreases in SBP and DBP were observed at the first week and throughout the short-term period.

**Table 130 Mean Changes in Seated Systolic (Top) and Diastolic (Bottom) Blood Pressure at 24 Weeks Short-term Placebo-controlled Pool**

Period Visit	Treatment Group	Change From Baseline						
		N#	Mean	SD	Min , Max	Mean	SD	Min, Max
ST TREAT WEEK 24	PLA	1096	129.2	14.33	88 , 178	-0.9	13.13	-54 , 36
	DAPA 2.5MG	621	128.4	15.60	89 , 198	-4.0	14.16	-58 , 43
	DAPA 5MG	908	125.5	15.02	83 , 211	-3.5	13.36	-56 , 58
	DAPA 10MG	949	126.0	14.44	89 , 185	-4.4	13.92	-55 , 42
	DAPA TOTAL	2478	126.4	14.99	83 , 211	-4.0	13.78	-58 , 58

Change From Baseline Period								
Visit	Treatment Group	N#	Mean	SD	Min , Max	Mean	SD	Min , Max
ST TREAT WEEK 24	PLA	1096	79.2	8.44	53 , 111	-0.5	8.31	-35 , 33
	DAPA 2.5MG	621	77.8	9.06	50 , 113	-1.8	8.45	-31 , 32
	DAPA 5MG	908	77.2	8.36	50 , 106	-2.1	7.92	-34 , 29
	DAPA 10MG	949	77.1	8.35	47 , 104	-2.1	8.44	-39 , 30
	DAPA TOTAL	2478	77.3	8.54	47 , 113	-2.0	8.25	-39 , 32

Source SCS Table 88 and 89

Based upon routine assessment of supine and standing BP measurements, the proportion of subjects with orthostatic hypotension in the dapagliflozin and placebo groups was similar.

(b) (4)

### Reviewer's Comments

(b) (4)

### Heart Rate (HR)

No clinically relevant mean changes from baseline in seated heart rate were observed during the short-term period or the short-term plus long-term period in the Placebo-controlled Pool. At week 24, mean changes from baseline ranged from -1.1 to -0.4 bpm for seated HR in the dapagliflozin groups; and mean change from baseline in the placebo group was 0.5 bpm. At Week 102 mean changes from baseline ranged from -1.0 to 0.3 bpm for seated HR in the dapagliflozin groups; and mean change from baseline in the placebo group was 1.0 bpm. However, there was a smaller number of subjects in this dataset.

#### 7.4.4 Electrocardiograms (ECGs)

In the individual completed Phase 2b and 3 studies, there was little difference between ECGs at baseline and at weeks 12, 24, or 52. No pooled analyses were performed for ECGs. The majority of subjects in the dapagliflozin and placebo groups with normal ECG tracings at baseline also had normal ECG tracings at weeks 12, 24, or 52. No clinically relevant rhythm disturbances were captured at ECG readings. Results were similar during the short-term plus long-term periods.

In a study to assess the effect on cardiac ventricular repolarization by QTcX (QT interval corrected for heart rate using a study-specific factor) (study D1690C00001), dapagliflozin had no clinically relevant effect, compared with placebo, during the first 24 hours after administration of single oral doses of dapagliflozin 20 or 150 mg to healthy male subjects. The supra-therapeutic dose of 150 mg of dapagliflozin provided exposures more than 10X higher than the anticipated therapeutic dose of 10 mg at steady state. This study was reviewed during the IND phase at our agency.

#### Special Safety Studies/Clinical Trials

##### **Cardiovascular Meta-analysis**

Please refer to Dr. Anita Abraham's cardiovascular meta-analysis review for a full discussion on the applicant's meta-analysis.

Phase 2 studies of at least 12 weeks duration and all Phase 3 trials that were unblinded before data cut-off (30-Jul-2010) were used in the applicant's analysis. In addition, data from study MB102029 (moderate renal impairment) was also included in the analysis although data was unblinded 10-Aug-2010.

Most Phase 3 studies consist of qualification and lead-in periods, followed by a double-blind short-term treatment period of at least 24 weeks duration. Phase 3 studies ranged in length from 24 to 102 weeks.

CV events were adjudicated by an independent adjudication committee at (b) (4). For the majority of the trials the adjudication was done prospectively: studies D169000004, D1690C00005, D169000006, D169000012, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, and D1692C00005. One event in each of the following studies was adjudicated after study database lock: D1692C00005, MB102034 and MB102021. Two Phase 2 trials, MB102008 and MB102009, were completed when the adjudication process was initiated and the adjudication of the events was done retrospectively. The independent adjudication committee was at all times blinded to treatment allocation.

## Exposure

The meta-analysis study population included 6228 subjects: 4287 in the dapagliflozin group and 1941 in the comparator group. The observed population was representative of the intended T2DM population. Total years of exposure with respect to all-cause death were 6230: 4366 in the dapagliflozin group and 1864 in the comparator group. On average, the amount of exposure was one year/subject.

## Baseline Characteristics

In the 14 Phase 2 and 3 studies contributing to the meta-analysis, the study population had a mean age of around 56 years and approximately 20% were ≥65 years of age (Table 131). Mean body mass index (BMI) was 31.5 kg/m<sup>2</sup>. The mean duration of T2DM was 6 years, and approximately 20% had a duration of diabetes of over 10 years.

**Table 131 Baseline Characteristics and Risk Factors for Patients in the CV Meta-analysis**

		Dapagliflozin (a)	Comparator (b)
AGE CATEGORIZATION (%)	< 65 YEARS	3408 (79.5%)	1485 (76.5%)
	≥ 65 YEARS	879 (20.5%)	456 (23.5%)
	< 75 YEARS	4172 (97.3%)	1887 (97.2%)
	≥ 75 YEARS	115 (2.7%)	54 (2.8%)
GENDER (%)	MALE	2177 (50.8%)	1019 (52.5%)
	FEMALE	2110 (49.2%)	922 (47.5%)
PRIOR HISTORY OF CV DISEASE (%)	YES	841 (19.6%)	353 (18.2%)
	NO	3446 (80.4%)	1588 (81.8%)
PRIOR HISTORY OF HYPERTENSION (%)	YES	2635 (61.5%)	1248 (64.3%)
	NO	1652 (38.5%)	693 (35.7%)
PRIOR HISTORY OF DYSLIPIDEMIA (%)	YES	2116 (49.4%)	947 (48.8%)
	NO	2171 (50.6%)	994 (51.2%)
PRIOR HISTORY OF CONGESTIVE HEART FAILURE (%)	YES	93 (2.2%)	33 (1.7%)
	NO	4194 (97.8%)	1908 (98.3%)
GEOGRAPHIC REGION (%)	NORTH AMERICA	1355 (31.6%)	525 (27.0%)
	LATIN AMERICA	917 (21.4%)	412 (21.2%)
	EUROPE	1529 (35.7%)	813 (41.9%)
	ASIA/PACIFIC	486 (11.3%)	191 (9.8%)
DURATION OF DIABETES (%)	< 3 YEARS	1918 (44.7%)	868 (44.7%)
	≥ 3 AND ≤ 10 YEARS	1419 (33.1%)	663 (34.2%)
	> 10 YEARS	950 (22.2%)	409 (21.1%)
DURATION OF DIABETES (%)	UNKNOWN	0 (0.0%)	1 (0.1%)
eGFR (%)	< 30 ML/MIN/1.73M**2	8 (0.2%)	5 (0.3%)
	≥ 30 AND < 60 ML/MIN/1.73M**2	477 (11.1%)	207 (10.7%)
	≥ 60 AND < 90 ML/MIN/1.73M**2	2190 (51.1%)	976 (50.3%)
	≥ 90 ML/MIN/1.73M**2	1612 (37.6%)	753 (38.8%)

Source CV Meta-analysis Table 5

## Results

The CV safety analysis was performed for the primary composite endpoint, comprised of first event of adjudicated CV death, MI, stroke and hospitalization for unstable angina.

This composite endpoint is consistent with FDA guidance. There were a total of 78 patients with first events: 48 on dapagliflozin and 30 on comparator. In the dapagliflozin group, 8 were CV death, 18 were MI, 11 were stroke, and 11 were hospitalization for unstable angina. In the comparator group, 4 were CV death, 18 were MI, 5 were stroke, and 3 were hospitalization for unstable angina. Table 132 lists the primary CV events by study.

**Table 132 Events Contributing to Primary CV Composite Endpoint by Trial (BMS Analysis Population)**

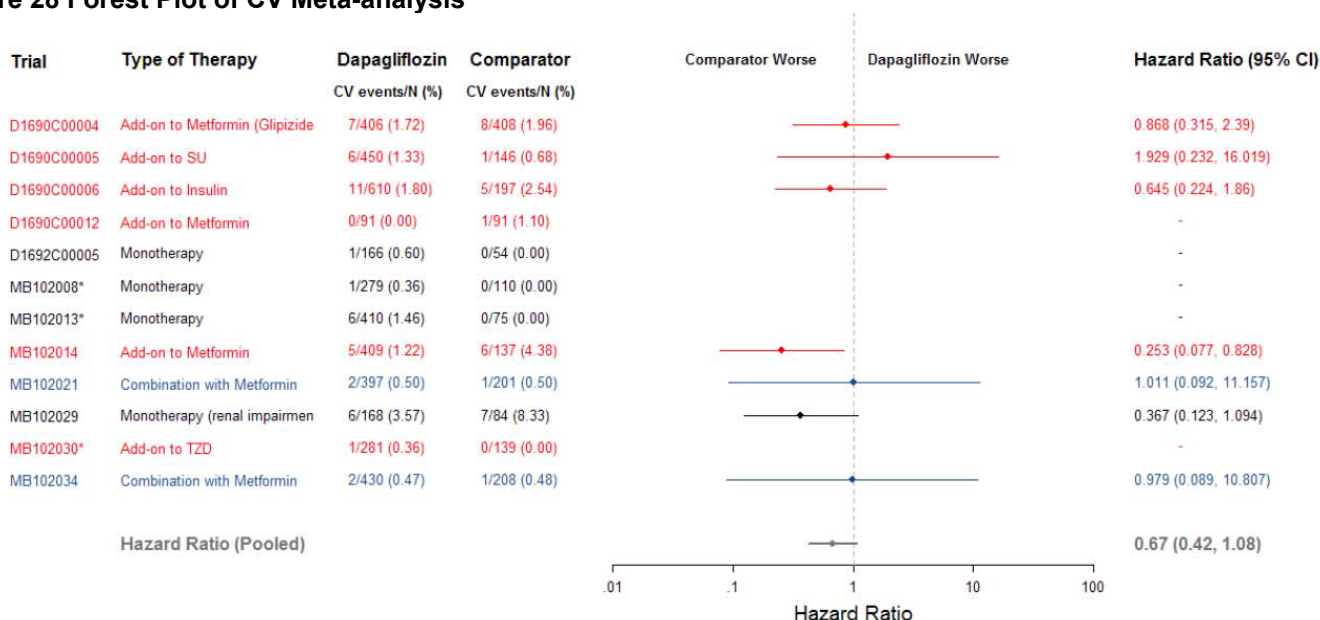
Trial	Arms	Sample Size	Primary Composite Endpoint	CV Death	Non-Fatal MI	Non-Fatal Stroke
<b>D1690C00004</b>	dapagliflozin	406	7 (1.72)	0 (0.00)	3 (0.74)	3 (0.74)
	glipizide	408	8 (1.96)	2 (0.50)	5 (1.22)	1 (0.25)
<b>D1690C00005</b>	dapagliflozin/glimepiride	450	6 (1.33)	0 (0.00)	1 (0.22)	2 (0.44)
	placebo/glimepiride	146	1 (0.66)	0 (0.00)	1 (0.68)	0 (0.00)
<b>D1690C00006</b>	dapagliflozin/insulin	610	11 (1.80)	3 (0.49)	2 (0.33)	3 (0.49)
	placebo/insulin	197	5 (2.53)	0 (0.00)	3 (1.52)	2 (1.01)
<b>D1690C00012</b>	dapagliflozin/metformin	91	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo/metformin	91	1 (1.10)	0 (0.00)	1 (1.10)	0 (0.00)
<b>D1692C00005</b>	dapagliflozin	166	1 (0.60)	0 (0.00)	1 (0.60)	0 (0.00)
	placebo	54	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102008</b>	dapagliflozin	279	1 (0.36)	0 (0.00)	1 (0.36)	0 (0.00)
	metformin	56	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo	54	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102009</b>	dapagliflozin/insulin	48	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo/insulin	23	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102013</b>	dapagliflozin	410	6 (1.46)	1 (0.24)	3 (0.73)	1 (0.24)
	placebo	75	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102014</b>	dapagliflozin/metformin	409	5 (1.22)	2 (0.49)	2 (0.49)	0 (0.00)
	placebo/metformin	137	6 (4.38)	0 (0.00)	3 (2.19)	1 (0.73)
<b>MB102021</b>	dapagliflozin	203	2 (0.98)	0 (0.00)	1 (0.49)	0 (0.00)
	dapagliflozin/metformin	194	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo/metformin	201	1 (0.50)	0 (0.00)	0 (0.00)	1 (0.50)
<b>MB102029</b>	dapagliflozin	168	6 (3.57)	1 (0.60)	2 (1.19)	2 (1.19)
	placebo	84	7 (8.33)	1 (1.19)	5 (5.95)	0 (0.00)
<b>MB102030</b>	dapagliflozin/pioglitazone	281	1 (0.36)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo/pioglitazone	139	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102032</b>	dapagliflozin	142	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	placebo	68	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>MB102034</b>	dapagliflozin	219	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	dapagliflozin/metformin	211	2 (0.95)	0 (0.00)	1 (0.47)	0 (0.00)
	placebo/metformin	208	1 (0.48)	1 (0.48)	0 (0.00)	0 (0.00)

<sup>1</sup> UA with Hosp = Hospitalization due to unstable angina

Source Modified from Dr. Abraham

The hazard ratio versus comparator was 0.674 with an upper limit of the 98<sup>th</sup> percentile confidence interval at 1.178 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078). Figure 28 is a forest plot of the meta-analysis and of the hazard ratio. Two trials had zero events in both arms and were not included in the stratified Cox proportional hazards model.

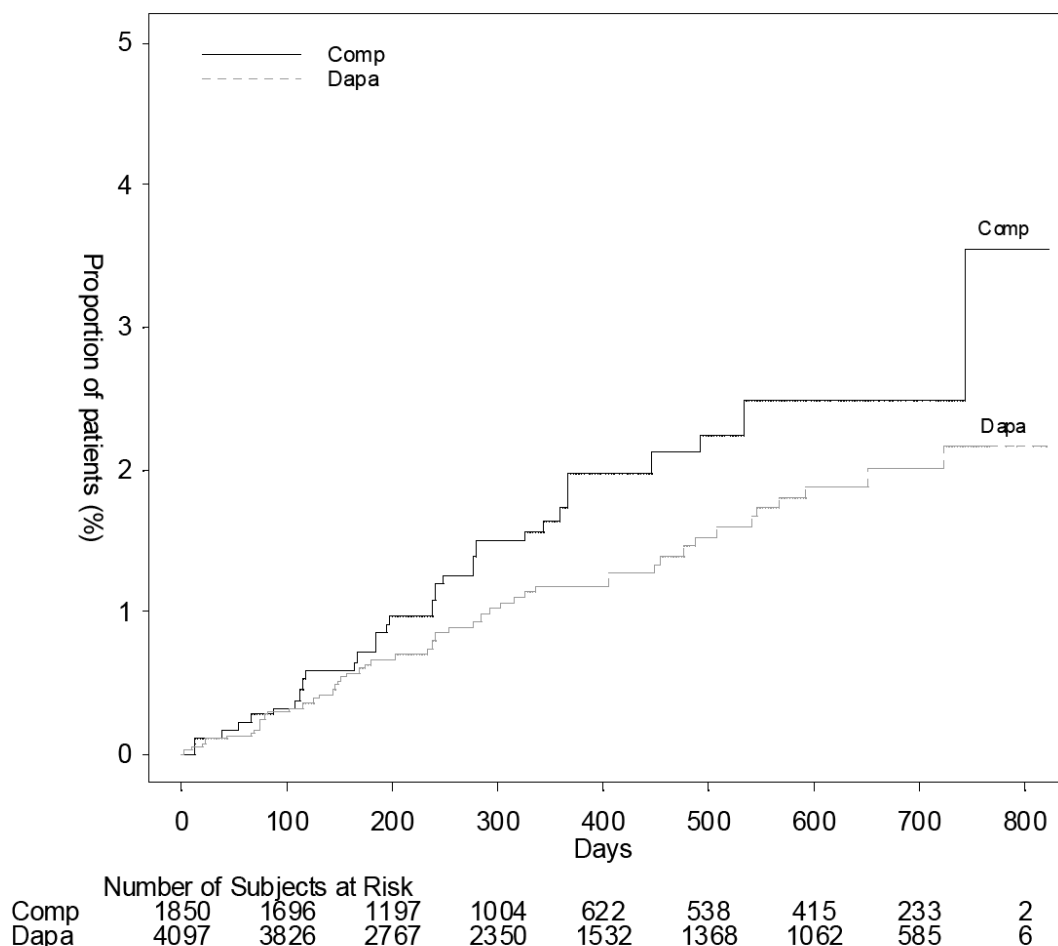
**Figure 28 Forest Plot of CV Meta-analysis**



Source Dr. Anita Abraham

The crude event rate (subjects with events/1000 subject years) was 11.3 in the dapagliflozin group and 16.6 in the comparator group. A Kaplan-Meier curve for the cumulative probability of the primary composite endpoint over time is shown in Figure 29. The cumulative probability of the primary endpoint shows a separation of the two curves starting at approximately 200 days and then continuously increasing during the treatment period.

**Figure 29 Cumulative Probability of Primary CV Composite Endpoint over Time (Kaplan-Meier Estimate). During Short-term and Long-term Periods. Overall Stratified Analysis**



Source CV Meta-analysis Figure 1

Overall, there is no evidence at this time of increased cardiovascular risk with dapagliflozin.

### ***Reviewer's Comments***

During the review process, the applicant was informed that if approved, dapagliflozin will require a dedicated cardiovascular study to rule out cardiovascular risk, along with other safety concerns uncovered during the NDA review. They plan to conduct a study to show cardiovascular benefit.



#### 7.4.6 Immunogenicity

Dapagliflozin is not a protein and not expected to cause immunogenic reactions.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Some dose dependency for adverse events was noted (such as genital infections). However, this was not clinically significant for the doses tested. The proposed dose of 10 mg in the general T2DM population is appropriate. The 5 mg dose proposed for patients at risk for volume depletion is also acceptable.

#### 7.5.2 Time Dependency for Adverse Events

Exposure data, time to AE and long-term studies are presented throughout the safety review.

#### 7.5.3 Drug-Demographic Interactions

Where relevant, AEs are discussed with respect to demographics such as gender or age. However, there was no pooled analyses for AEs and demographics. This was presented by study, where some patient numbers (such as race) would be too few to determine interactions. Overall, there was no evidence of drug-demographic interactions in the pharmacology, phase 2b or phase 3 studies.

#### 7.5.4 Drug-Disease Interactions

Again, where relevant this was discussed. For example, patients with renal impairment are discussed throughout this review.

#### 7.5.5 Drug-Drug Interactions

Please see section 4.4.3. *Pharmacokinetics* for details on studies of drug-drug interactions. For more details, please refer to Dr. Ritesh Jain's review.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

While there was no preclinical signal, there is an imbalance in the clinical program for both bladder and breast cancer. Mechanisms are unclear. Epidemiology studies for

further evaluation of the relative risk as well as following these cancers as AEs of special interest in pending and ongoing studies would be very informative.

#### 7.6.2 Human Reproduction and Pregnancy Data

Because of renal pelvic dilation in the 2nd/3rd trimesters of pregnancy, stunted growth following in utero and lactational exposure and weight loss in pregnancy in preclinical studies, dapagliflozin should not be used during pregnancy, lactation, or in small children.

Dapagliflozin has not been studied in pregnant women or nursing mothers. Three pregnancies were reported in subjects treated with dapagliflozin up to the data cutoff date; no additional data was provided. The applicant was asked for additional data on these patients during the review process, but could not provide this.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

Studies in pediatric patients have not been performed.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Orally-administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the maximum recommended human dose [MRHD]). In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia was slightly higher than placebo and was not dose-related.

In both studies, rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function.

Drug abuse with dapagliflozin has not been studied.

### 7.7 Additional Submissions / Safety Issues

Not applicable.

## 7 Postmarket Experience

Not applicable.

## 9 Appendices

Not applicable.

### 9.1 Literature Review/References

1. Smith, D. et al. *Urinary Protein Binding, Kinetics, and Dynamics of Furosemide in Nephrotic Patients*. J of Pharm Sciences; 1985 (6) 604-607.
2. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet. Downloaded at [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf).

### 9.2 Labeling Recommendations

Labeling recommendations were made throughout this review.

### 9.3 Advisory Committee Meeting

The advisory committee meeting for dapagliflozin was held on July 19, 2011 in Silver Spring, Maryland. Applicant presentations were followed by FDA presentations on both efficacy and safety. The committee was allowed to ask several questions and then discuss questions posed by the FDA. Finally, there was a vote for approval of dapagliflozin. Important points from the day's discussion are presented here.

#### Discussion Points

**Discuss implications of this reduced efficacy in T2DM where renal impairment can impact a sizeable proportion of individuals with this disease.**

**Discuss whether additional studies should be conducted (e.g., in specific populations) to better characterize the efficacy of dapagliflozin in T2DM or whether monitoring for renal function should be performed prior to and/or during treatment with dapagliflozin**

Both Dr. Erica Brittain (Mathematical Statistician) and Dr. Kevin McBryde (Pediatric Nephrologist) agreed that the applicant's proposal to split the moderate renal impairment group (3A and 3B) and allow dapagliflozin to be given to patients in the 3A group should not be allowed. Both Dr. Ellen Seely (Endocrinologist) and Dr. Sanjay Kaul (Cardiologist) agreed. Dr. McBryde also made the point that the MDRD formula has only been validated in patients with stage 3 or worse chronic kidney disease and MDRD has no validity above 60 ml/minute. Both Dr. McBryde and Dr. Abraham Thomas (Endocrinologist) made the point that since the medication or drug is protein bound, there could be impact of albuminuria at its effect on the SGLT2 site in the

kidney and the S1/S2 segment of the tubule. Studies of populations with micro or macroalbuminuria to see if the efficacy is diminished would be very informative. As mentioned earlier in the review, this data has since been requested and is being compiled by the applicant.

For monitoring of patients, the panel members agreed that the most conservative method would be to get an estimated GFR or another appropriate measure of creatinine clearance. If there is no presence of micro or macroalbuminuria, dapagliflozin could be prescribed.

**Comment on the clinical relevance of the one case and whether sufficient evaluation has been conducted premarketing to determine if dapagliflozin is associated with a risk of hepatotoxicity.**

Dr. Doris Strader (Hepatologist) brought up the point that baseline liver disease and background medication knowledge is very important to evaluate hepatotoxicity. There was also discussion amongst the panel members and FDA about the guidance suggestions for how to follow patients with possible hepatotoxicity and what should or should not be mandated. The one “probable” case is certainly a “red flag” as Dr. Thomas indicated and having criteria to work up such patients would be useful.

**Breast and Bladder Cancer**

- **For both types of cancer, discuss:**
  - **Whether these imbalances signify a risk of carcinogenic potential associated with dapagliflozin?**
- **For both types of cancer, comment whether the numeric imbalances were impacted by:**
  - **Any imbalances of baseline risk factors**
  - **Any detection bias.**

For this discussion, Dr. Piantadosi (Oncologist) expressed his concern over the cancer relative risks and the possible extrapolation out into the general T2DM population. He recommended that if approved, the applicant perform a large additional study whose design specifically permits the assessment of the index cancers. Discussion on the possibility of detection bias also took place, especially in light of the increased UTI risk. There was a general consensus that these cancers would need to be studied in more detail to further determine the risk. The long-term Cardiovascular safety study would be one way to obtain needed long-term data. The applicant has also proposed epidemiology studies.

**Please discuss the clinical significance of the following in the type II diabetes mellitus population:**

- **increased genital/urinary infections associated with dapagliflozin therapy**
- **bone safety concerns**

- **any other safety issues identified in the pre-marketing application**

The panel members agreed that long-term data would be needed to evaluate the increased genital-urinary infections and bone safety concerns that exist.

- **Do the efficacy and safety data provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM?**
  - **Please vote Yes or No.**

The committee voted not in favor of approval 9:6.

Many of the panel members explained that they felt that the safety issues (predominantly discussed above, cancers and hepatic risk) needed further study. Panel members that thought this could be done post marketing, tended to vote in favor of approval.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOMYA VERMA  
09/02/2011

ILAN IRONY  
09/02/2011  
Please see the CDTL review. I concur with Dr. Dunn's review.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 202293**

**Applicant: Bristol Myer  
Squibb**

**Stamp Date: 12/29/2010**

**Drug Name: Dapagliflozin**

**NDA/BLA Type: New NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?				SCS and Appendices in place of ISS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?				SCE and Appendices in place of ISE
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			In the Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?  MB102008 A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-512148 as Monotherapy in Subjects With Type 2 Diabetes Mellitus Who Are Treatment Naive And Have Inadequate Glycemic Control on Diet and Exercise  MB102009 A Pilot Study of the Efficacy and Safety of BMS-512148 on Glycemic Control in Subjects with Type 2 Diabetes Treated Aggressively but Not Controlled on	x			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Combination Antihyperglycemic Therapy with Metformin and/or Thiazolidinedione (TZD) and Insulin</p> <p>DC1692C00005 A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control</p> <p>MB102008 A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-512148 as Monotherapy in Subjects With Type 2 Diabetes Mellitus Who Are Treatment Naive And Have Inadequate Glycemic Control on Diet and Exercise</p>				
<b>EFFICACY</b>					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>1. MB102013— A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise</p> <p>2. MB102032—A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise</p> <p>3. MB102014—A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Alone</p> <p>4. D1690C00005—A 24-Week, International, Randomized, Double-blind, Parallel-group, Multi-center, Placebo-controlled Phase III Study with a 24-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination with Glimepiride (a Sulfonylurea) in Subjects with Type 2 Diabetes who Have Inadequate Glycemic Control on Glimepiride Therapy Alone</p> <p>5. MB102030 –A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone</p>	x			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>6. D1690C00006—A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycemic control on insulin.</p> <p>7. D1690C00004—A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination with Metformin compared with Sulfonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Therapy Alone</p> <p>8. MB102034 –A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control</p> <p>9. MB102021—A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control</p> <p>10. MB102029—A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase 2/3 Trial to Evaluate the Glycemic Efficacy, Renal Safety, Pharmacokinetics, and Pharmacodynamics of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Moderate Renal Impairment Who Have Inadequate Glycemic Control</p>				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			Applicability of foreign data and few African American patients, addressed in Clinical Overview,

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					page 20 and 22
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?	x			Report submitted December 2008. Reviewed with no concerns.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	x			*>4000 T2D pts treated (2.5 mg or higher) *2000 to 10 mg *>1/2 for 1 year *441 pts for 2 years *Overall ratio 2.2 : 1 (dapagliflozin : control)
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Section 5.3.5.1 of the eCTD application
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			CV meta-analysis, bone safety, section 5.3.5.3
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver for < 10 years Deferral 10-17 years
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to	x			

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

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

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	assess the abuse liability of the product?				
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			See 17.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** yes

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

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

- Few patients are of African American origin (84% white, 10% Asian, 3% African American). You state in your *Clinical Overview* that available data suggests that SGLT2 polymorphisms are rare and your data should be applicable to all regions and races. Please submit your references.
- Were there any reports indicating drug-induced liver toxicity, including those meeting Hy's Law, during the dapagliflozin clinical program? We know that you will provide narratives with the Four Month Safety Update, but we would like to know of any such cases that have occurred.
- As some of your studies are ongoing, please clarify your plan to submit updated analyses of cardiovascular safety based on accrued cardiovascular events

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

contributing to the overall dapagliflozin cardiovascular meta-analysis. Please submit this plan within one month receipt of these comments.

Somya Dunn, MD	February 18, 2011
Reviewing Medical Officer	Date
Ilan Irony, MD	February 18, 2011
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOMYA VERMA  
02/18/2011

ILAN IRONY  
02/22/2011

I concur with Dr. Dunn's recommendation to file the NDA and with the comments to the applicant in the 74-day letter.