



BACKGROUND DOCUMENT

DAPAGLIFLOZIN

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EXECUTIVE SUMMARY

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) are seeking approval of dapagliflozin for the treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin is a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT2), the transporter responsible for the majority of renal glucose re-absorption. Dapagliflozin's mechanism of action (MOA) results in the direct elimination of glucose in the urine. Dapagliflozin improves glycemic control with efficacy equivalent to current foundational oral treatments for T2DM - metformin and sulfonylureas (SUs) - with low intrinsic hypoglycemia risk. Excreting glucose in the urine brings the additional benefits of weight loss and blood pressure (BP) reduction.

Dapagliflozin is effective across age, race, gender, duration of diabetes, and body mass index (BMI). Its mechanism is complementary to the mechanisms of other antidiabetic drug classes, enabling it to work in combination with metformin, SUs, thiazolidinedione (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin. The mechanism of dapagliflozin is dependent, however, upon renal function, with decreased efficacy in patients with moderate or greater renal impairment.

The clinical pharmacology properties of dapagliflozin allow it to be dosed once daily without regard to meals. Dapagliflozin has no clinically meaningful drug-drug interactions.

The safety profile of dapagliflozin has been defined based on an evaluation of data in preclinical studies, clinical pharmacology studies, and from a comprehensive clinical trials program. The adverse effects associated with dapagliflozin treatment are related to its MOA and can be handled within standard clinical practice, generally without interruption of dapagliflozin treatment. Glucosuria from dapagliflozin is associated with increases in urogenital infections and because it is also a diuretic, it is associated with reversible volume depletion-related symptoms in a small number of patients.

The proposed indication for dapagliflozin is for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The recommended dose is 10 mg once daily, at any time of the day, regardless of meals. A 5 mg dose may be appropriate for patients at risk for volume depletion. Because of decreased clinical efficacy, dapagliflozin should not be initiated in patients with estimated glomerular filtration rates (eGFR) $< 60 \text{ mL/min/1.73m}^2$.

Overview of Clinical Development Program

The dapagliflozin clinical development program was designed to test the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. The program was comprised of 24 Phase 2b and 3 studies, including both placebo-controlled and active comparator designs, with durations ranging from 12 weeks to 4 years. More than 11,000 patients were randomized in these studies, with over 6,000 receiving dapagliflozin. Patient populations examined covered the range of diabetes progression: drug-naïve patients, patients failing oral therapies, and patients on insulin-based regimens. The program also provided significant experience in elderly patients, patients with a history of cardiovascular (CV) disease, overweight and obese patients, patients with poorly controlled hypertension, and patients with mild to moderate renal impairment.

Key Regulatory History

The initial dapagliflozin New Drug Application (NDA) and other global marketing applications were submitted beginning on 28-Dec-2010. Dapagliflozin is currently approved and available in the following countries: European Union (EU; Nov-2012), Australia (Oct-2012), Mexico (Mar-2013), New Zealand (June-2013), Brazil (July-2013), and Argentina (Sep-2013).

Dapagliflozin was presented before the Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) on 19-Jul-2011. The EMDAC voted 9 to 6 against approval of dapagliflozin based on the data presented. The EMDAC members' comments indicated that they were encouraged by the drug's potential for treating T2DM, but remained concerned about imbalances in bladder and breast cancer and the potential for risk of drug induced liver injury (DILI).

Subsequent to the July-2011 Advisory Committee meeting, additional data were submitted at the request of the Food and Drug Administration (FDA) which triggered a major amendment. These additional data provided additional breast cancer cases, reducing the imbalance for this cancer. FDA remained concerned, however, regarding bladder cancer and DILI. In addition, while the CV data in the original NDA suggested a CV benefit for dapagliflozin, the Agency noted that some of the CV data in the major amendment, and specifically from 2 studies in the program, D1690C00018 and D1690C00019, did not support the suggestion of CV benefit originally observed in the meta-analysis of CV events in the NDA. Thus, the Agency determined that suggestive CV benefit could not be used in a benefit-risk consideration to offset concerns around safety signals.

On 17-Jan-2012, the FDA issued a complete response letter (CRL) stating that in order to address their concerns, BMS/AZ needed to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and controls. The FDA requested at a minimum that the resubmission include 1-year data from the then ongoing Studies D1690C00018 and D1690C00019. The CRL stated that the NDA resubmission needed to include a safety update including updated information on the 2 key issues of bladder cancer and liver safety, as well as an updated CV meta-analysis.

In subsequent discussions, the FDA indicated that the original concerns about breast cancer risk were likely unfounded. The imbalance of bladder cancer cases remained a concern, however, and it was suggested that a preclinical tumor promotion study to evaluate the effect of dapagliflozin on transitional cell tumor growth within the bladder could help provide reassurance about any potential risk. The FDA noted that it is reasonable to conduct this preclinical study in the post-marketing period, unless the review of the resubmitted NDA raises new concerns about bladder cancer. That said, additional nonclinical studies that address the question of tumor promotion from a complimentary perspective were conducted and are included in the NDA resubmission to add to the overall weight-of-evidence. Regarding DILI, the single case of severe hepatotoxicity in the NDA database, which was complicated by features of autoimmune hepatitis, was not as concerning as it would be if it had been in the setting of a strong signal of transaminitis among dapagliflozin patients (Hy's Law). The FDA did not think this absolved the

drug of any hepatotoxic risk, but it also did not indicate a high risk of liver toxicity that might result in transplant or mortality. The FDA also noted that the additional information on this case, which had not yet been considered, should be included in the NDA resubmission. Finally, the need for additional follow-up data on CV safety, especially from Studies D1690C00018 and D1690C00019, which were seen as having raised questions about the otherwise promising CV profile once other CV risk factors are operative, was reiterated. As agreed with the FDA, on 11-Jul-2013, BMS/AZ resubmitted the dapagliflozin NDA.

NDA Resubmission

All of the safety analyses requested by the FDA in the CRL were included in the dapagliflozin NDA resubmission. The dapagliflozin NDA resubmission plan was agreed to with the FDA and included data from 9 new Phase 2b and 3 clinical studies along with long term (LT) data from previously submitted studies for a total of 24 studies (see [Table 1](#)). These data provided > 50% increase in patient-years exposure since the initial NDA. Of the 9 new Phase 2b and 3 clinical studies, 6 are core studies supporting use in patients with T2DM in the United States (US) and 3 are region-specific studies supporting registration in China and Japan. The safety update also included limited data from 2 additional studies: a pilot study in type 1 diabetes and a study of twice daily dosing.

Although no additional bladder cancer cases were reported up to the data cut for the NDA resubmission, 1 bladder cancer case was subsequently detected in an ongoing study. While this study was not included in the NDA resubmission, the new bladder cancer case was included for transparency.

Along with the clinical data, new preclinical studies were submitted that further assessed whether dapagliflozin or glucosuria could enhance the growth of existing bladder tumors.

No new safety signals were identified for dapagliflozin in the NDA resubmission, and the additional data provide additional perspective to address the key issues raised in the CRL.

First, the weight-of-evidence does not support a causal relationship linking dapagliflozin to bladder cancer. The clinical data, including the additional patient-years of clinical experience, show no overall imbalance in malignancies, with some tumor types, such as bladder cancer, more common on dapagliflozin than control, but others, such as renal cancer, less common on dapagliflozin than control. None of these imbalances was statistically significant. The nonclinical data, which are highly predictive, show no evidence with dapagliflozin for tumor initiation or tumor promotion, and no biologically plausibility link between dapagliflozin and increased bladder cancer risk. Further, the clinical cases of bladder cancer in the dapagliflozin program had time courses inconsistent with carcinogenesis. Of the clinical cases of bladder cancer in the program, all but 1 were diagnosed or showed the first clinical sign (hematuria) of bladder cancer within 6 months of starting dapagliflozin therapy. This timeframe is too short to realistically reflect causality, and is indicative of pre-existing tumors. Finally, new nonclinical studies show no growth-enhancing effect of dapagliflozin or glucosuria on bladder cancer cells or bladder tumors.

Second, the concern for a possible risk of DILI has been addressed. There continues to be no increase in liver test abnormalities with dapagliflozin therapy. The issue of potential DILI was based on a single clinical case for which there was partial information at the time of the previous Advisory Committee meeting and the CRL. Subsequent additional data on the case show the probable diagnosis to be idiopathic autoimmune hepatitis rather than DILI.

Third, the updated CV events meta-analysis continues to show no evidence of increased CV risk, both in the overall population and in the high CV risk subpopulation. The updated primary, secondary, and major adverse cardiac event (MACE) endpoints for the overall population as well as for the high CV risk subpopulation show beneficial hazard ratio point estimates, consistent with previous analyses. The upper bound of the confidence interval (CI) for the primary endpoint is well within the margin required by FDA guidance to rule out an unacceptable increase in CV risk prior to approval. In addition, the updated analyses of Studies D1690C00018 and D1690C00019 show neutral hazard ratio point estimates. Finally, the newly completed Studies MB102073 and MB102077 show that in hypertensive patients with T2DM, dapagliflozin lowers systolic BP (SBP), thus improving an important cardiac risk factor and common comorbidity in patients with T2DM. These data taken together, while not proving CV benefit, strongly support the hypothesis that dapagliflozin confers CV benefit. This hypothesis is being tested in the Dapagliflozin Effect on Cardiovascular Events (DECLARE [TIMI-58]), outcomes study. DECLARE is the largest randomized prospective clinical outcomes study undertaken in a diabetes population to date, and was initiated in April of this year, with more than 1400 patients randomized as of 15-Oct-2013 of a total planned enrollment of 17,150 patients. The study will randomize patients with T2DM and either established CV disease or at least 2 CV risk factors and provide up to 6 years of exposure to dapagliflozin (see [Section 6.2](#) for additional details).

Benefit-Risk

The benefit-risk ratio of dapagliflozin is favorable and warrants approval of the drug.

A substantial proportion of patients with T2DM have difficulty controlling their blood sugar. This treatment challenge is exacerbated by obesity, and by the weight gain caused by many current antidiabetic therapies. Many patients with T2DM also struggle with hypertension, a common co-morbidity.

The data from the clinical development program firmly establish the benefits of dapagliflozin as an oral therapy for T2DM. Dapagliflozin provides substantial glycemic efficacy, demonstrated in head-to-head clinical trials to be comparable in magnitude to metformin and SUs, the most frequently used agents in the treatment of patients with T2DM. Dapagliflozin brings the additional important benefits of weight loss and modest BP reduction, with a low intrinsic risk of hypoglycemia.

Adverse effects associated with dapagliflozin treatment are related to its MOA, and are consequences of glucosuria and diuresis. Urogenital infections, volume depletion, and transient changes in renal function are familiar to physicians, recognizable, and can be handled within standard clinical practice, generally without interruption of dapagliflozin treatment. Further, glucosuria and associated physiological effects due to diuresis are rapidly reversible.

It is not possible to completely assess potential risks from rare events of new drugs prior to approval. For this reason, assessment of risk continues after approval. An example of this approach is the FDA requirement to demonstrate reasonable evidence of CV safety prior to approval, and more definitive evidence after approval. Similarly, while the weight-of-evidence supports no causal relationship of dapagliflozin to bladder cancer or to DILI, bladder cancer and liver safety will continue to be studied after approval. The recently started DECLARE outcomes study, in addition to its primary CV endpoint, will formally adjudicate and assess cancer incidence and liver injury over the course of the study (see [Section 6.2](#) for additional details). Additionally, pharmacoepidemiology studies, including studies of cancer and liver injury incidence with dapagliflozin therapy, are underway in Europe, where dapagliflozin is already on the market, and will be expanded to the US upon approval. Finally, bladder cancer is being assessed by routine and enhanced pharmacovigilance practices in the countries where dapagliflozin is already approved and marketed (EU, Australia, Mexico, New Zealand, Brazil, Argentina).

Patients struggle to improve their glycemic control while maintaining control of weight and BP. With the addition of new data since the time of the previous Advisory Committee meeting and CRL, the benefit-risk ratio of dapagliflozin for the treatment of T2DM is clearly positive and warrants approval of dapagliflozin to help address this unmet medical need. More choices are needed for treating T2DM; and dapagliflozin represents an important new treatment option for patients and health care providers.

Topics of Focus

Because dapagliflozin was presented to the EMDAC in July-2011, the discussion in this briefing document provides a brief overview of the efficacy and safety program and then focuses primarily on issues raised by FDA in the CRL, as well as class safety issues raised in the EMDAC review of the SGLT2 inhibitor canagliflozin.¹ (see [Section 5.2](#), Safety Topics of Interest).

The following topics are presented in this document:

- Introduction ([Section 1](#))
- Clinical Development Program ([Section 2](#))
- Overview of Clinical Pharmacology and Dosing Evaluations ([Section 3](#))
- Overview of Efficacy ([Section 4](#); active comparator studies, placebo-controlled studies, durability of effect, efficacy in key subgroups)
- Overview of Safety ([Section 5](#))
 - Adverse Event (AE) Profile ([Section 5.1](#); deaths, serious adverse events (SAEs), discontinuations, hypoglycemia, urinary tract infections [UTIs], genital infections, volume depletion/hematocrit, AEs related to renal function, fractures and bone health, and clinical laboratory evaluations [electrolytes, lipids])
 - Safety Topics of Interest ([Section 5.2](#); hepatic safety, malignancies, CV safety)
- Post-marketing Pharmacoepidemiology Studies ([Section 6](#))
- Benefit-Risk Conclusions ([Section 7](#))

1 INTRODUCTION

1.1 Development Rationale and Unmet Medical Need

The incidence and prevalence of T2DM continue to rise by epidemic proportions. In the US approximately 10% of the population has diabetes. The American Diabetes Association (ADA) estimates that 1 in 3 American adults will have diabetes in 2050 if this trend continues.² Approximately 50% of patients in the US with T2DM do not reach glycemic goals. Because of its established efficacy and safety profile, metformin is recommended by ADA guidelines as a first-line pharmacological treatment for glycemic control in most of the patients with T2DM. Despite a high propensity for hypoglycemia and concerns around CV safety, SUs are the second most used class of drugs to treat T2DM in the US. Diabetes is, however, a progressive disease and as such glycemia and hemoglobin A1c (HbA1c) rise over time requiring gradual addition of new drugs to reduce blood glucose. Dapagliflozin provides a novel insulin-independent MOA with demonstrated non-inferiority for HbA1c-lowering compared with metformin and SUs in head-to-head studies.

Efforts by patients with T2DM to lose weight as part of a diet and exercise program are undermined by therapies that lead to weight gain, such as TZDs, insulin, and SUs. Over 85% of patients with T2DM are overweight or obese and additional weight gain augments insulin resistance, which, in turn, exacerbates the progression of diabetes. Reducing body weight in T2DM patients is a major unmet medical need; even modest weight loss has noticeable beneficial effects on glycemic control and BP.

Hypertension, which is also common (> 70% prevalence) among patients with T2DM, contributes to the increased risk of macro- and microvascular complications of T2DM.³ The combination of hypertension and T2DM impacts the health-related quality of life (including physical and social functioning, mental health, and general health) of patients with T2DM⁴ and increases diabetes-related healthcare expenditures.⁵

Hypoglycemia is a clinically important barrier to optimizing treatment with insulin and SUs, both of which are preferred second-line treatment options in the ADA/European Association for the Study of Diabetes (EASD) diabetes treatment algorithm.⁶

If approved, dapagliflozin would offer an oral medication indicated for glycemic control in T2DM with demonstrated additional benefits of reduction in weight and BP, and with a low intrinsic risk for hypoglycemia. In addition, dapagliflozin does not depend on insulin secretion or action for its efficacy. Thus, dapagliflozin is effective regardless of insulin sensitivity, secretion, or administration. This characteristic enables it to be successfully added to any anti-hyperglycemic therapy, at any stage of T2DM.

Finally, if approved, dapagliflozin would add another member of the SGLT2 class to available treatment choices for health care professionals and their patients to manage T2DM in the US. Long-term (LT) uncertainties related to rare clinical events exist at approval for any drug class. Thus, potential future clinical event findings possibly resulting from labeled precautions for dapagliflozin along with the potential clinical event findings and imbalances noted and addressed

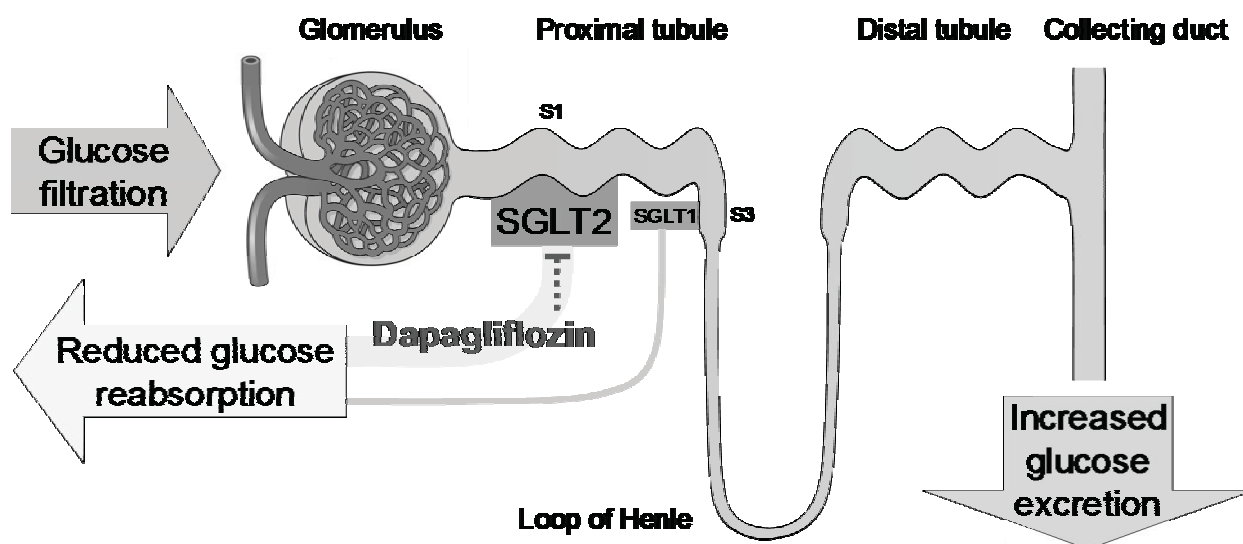
for dapagliflozin in this NDA resubmission, argue for ensuring that several members of the SGLT2 inhibitors drug class are made available for prescription use and future post-approval assessments.

1.2 Mechanism of Action

Dapagliflozin (BMS-512148) is a stable, competitive, reversible, highly selective, and orally active inhibitor of SGLT2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin inhibits human SGLT2 ($K_i = 0.55$ nM) selectively vs. human sodium-dependent glucose transporter 1 (SGLT1), the major glucose transporter responsible for the absorption of glucose in the small intestine, as well as other members of the SGLT protein family (SGLT1, SGLT4, SGLT6) with >1400-fold selectivity vs. each of these cotransporters. The selectivity is not uniform across the class, with somewhat lower selectivity for canagliflozin.⁷ This is in contrast to Dapagliflozin is also highly selective against facilitative glucose transporters (GLUT1, GLUT4, GLUT2) and a panel of > 300 unrelated enzymes, transporters, and receptors. Dapagliflozin's MOA is different from and complementary to the mechanisms of existing medications in other drug classes for T2DM, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. Further, as SGLT2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target (ie, non-kidney) effects. Therefore, no effects are observed on glucose and/or other carbohydrate transport or absorption in any other organs, including the gut, and no other transporters are affected. As such, dapagliflozin offers an important additional strategy for improving glycemic control in patients with T2DM.

Urinary glucose excretion induced by dapagliflozin depends upon the amount of glucose filtered by the kidney (Figure 1). This filtered load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR). Therefore, 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, which translates into a low risk of hypoglycemia. Furthermore, because the mechanism reduces hyperglycemia independent of insulin secretion or action, this approach to antidiabetic therapy provides an opportunity to achieve clinically important glycemic efficacy in a broad spectrum of patients with T2DM.

The steady excretion of glucose due to SGLT2 inhibition results in a continual loss of calories that ultimately leads to a decrease in weight and adiposity, a supplemental benefit that addresses one of the basic underlying problems in the pathogenesis of T2DM, namely over-nutrition and caloric excess. SGLT2 inhibition leads to inhibition of sodium and glucose transport in the proximal tubule, dapagliflozin therefore causes a mild diuretic effect, with potential for modest BP lowering in hypertensive patients with T2DM.

Figure 1: How Dapagliflozin Works (Mechanism of Action)

1.3 Proposed Indications and Use

Overall, dapagliflozin has the potential to be effective in patients with T2DM regardless of disease stage or severity. Dapagliflozin improves HbA1c with a low risk of hypoglycemia, while demonstrating positive trends for common co-morbidities (weight gain and systolic hypertension) associated with increased CV risk. Dapagliflozin is proposed as an adjunct to diet and exercise to improved glycemic control in adults with T2DM.

The recommended dose is 10 mg once daily at any time of the day regardless of meals and 5 mg for patients at risk for volume depletion due to coexisting conditions. Dapagliflozin's action is dependent upon renal function, and as agreed with the FDA, it should not be initiated in patients with moderate or severe renal impairment (defined as $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ by the Modification of Diet in Renal Disease (MDRD) formula or creatinine clearance $[\text{CrCl}] < 60 \text{ mL/min}$ as calculated by Cockcroft-Gault formula) or end stage renal disease.

2 CLINICAL DEVELOPMENT PROGRAM

2.1 Clinical Pharmacology Studies (Phase 1 and 2a)

As of the 30-month update (30-MU), there were 28 clinical pharmacology studies conducted in 728 subjects/patients (675 of these subjects were exposed to dapagliflozin). These studies, summarized in [Figure 2](#), included healthy subjects (560 subjects, 524 exposed to dapagliflozin) as well as patients with T2DM (130 subjects, 113 exposed to dapagliflozin) and patients with renal or hepatic impairment (20 and 18 patients respectively, all exposed to dapagliflozin).

Figure 2: Summary of Clinical Pharmacology Program for Dapagliflozin

PK/PD/Safety	Drug-Drug Interactions	Specific Populations	Exposure-Response	Biopharm Studies
MB102001 SAD (2.5 to 500mg)	MB102026 Metformin (20mg)	MB102007 Renal Impairment (50mg SD + 20mg QD x 7d)	Multiple Studies Population PK and E-R Analysis	MB102005 Caps vs Tabs Rel BA (50mg)
MB120002 MAD (2.5 to 100mg)	MB102037 Glimepiride (20mg)			
MB102003 Phase 2a (5-100mg)	MB102037 Sitagliptin (20mg)	MB102027 Hepatic Impairment (10mg)		MB102019 Definitive Food Effect (10mg)
MB102006 14C ADME (50mg)	MB102017 Pioglitazone (50mg)			MB102062 Heat Stressed BE (10mg)
D1690C00001 Thorough QT/QTc (20 and 150mg)	D1692C00002 Voglibose (10mg)	MB102010 Japanese SAD (2.5 to 50mg)		MB102090 Heat Stressed BE (2.5mg)
MB102088 Low dose PK/PD (0.001 to 2.5mg)	MB102058 Digoxin (10mg)	MB102025 Japanese MAD (2.5 to 20mg) T2DM patients		
MB102059 Absolute Bioavailability (10mg)	MB102058 Warfarin (10mg)			
MB102066 Tm _G /Splay (10mg)	MB102036 Valsartan (20mg)			
	MB102036 Simvastatin (20mg)			
	MB102004 Hydrochlorothiazide (50mg)			
	MB102057 Bumetanide (10mg)			
	MB102074 Rifampin (10mg)			
	MB102093 Mefenamic Acid (10mg)			

ADME = absorption, distribution, metabolism, and excretion; BA = bioavailability; BE = bioequivalence; Caps = capsules; d = day; E-R = exposure-response; MAD = multiple-ascending dose; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; rel = relative; SAD = single-ascending dose; SD = single dose; T2DM = type 2 diabetes mellitus; Tabs = tablets; Tm_G = maximum tubular glucose transport

Notes: Doses are doses of dapagliflozin. Some drug-drug interaction studies examined more than one interacting drug.

There were in total 8 single and multiple dose safety/pharmacokinetic (PK)/pharmacodynamic (PD) studies. Single oral doses from 2.5 to 500 mg and multiple oral doses from 2.5 to 100 mg of dapagliflozin for up to 14 days were evaluated in healthy subjects. Multiple oral doses from 5 to 100 mg of dapagliflozin for up to 14 days were evaluated in patients with T2DM. These studies showed that these doses of dapagliflozin were well-tolerated. An MOA study (MB102066) showed that dapagliflozin reduces renal glucose reabsorption such that maximum tubular glucose transport (Tm_G) is reduced by 55% and glucosuria is evident at normal plasma glucose levels. In addition, 4 studies were conducted in specific populations (renal impairment, hepatic impairment and 2 studies in Japanese patients) and 4 bioavailability (BA)/bioequivalence (BE) and food interaction studies were conducted. The program also included 10 drug-drug interactions studies in healthy subjects evaluating dapagliflozin in combination with other oral antidiabetic (OAD) medicines, commonly co-prescribed CV medicines, with rifampin (rifampicin), which is an inducer of several drug metabolizing enzymes, and with mefenamic acid, which is an inhibitor of

uridine diphosphate glucuronosyltransferase (UGT) 1A9, the enzyme responsible for the formation of dapagliflozin's major metabolite.

2.2 Dose Rationale

The Phase 1 and 2 studies for dapagliflozin established that doses of > 20 mg once daily did not result in greater glucosuria or incremental improvements of glycemic control. In the dose ranging Phase 2b study, a clinically meaningful incremental reduction in HbA1c was not observed in doses > 10 mg. Based on the comparative PD, glycemic markers, and safety and tolerability findings from these studies, doses of 2.5, 5, and 10 mg dapagliflozin once daily were selected as the core doses to be studied in the Phase 3 program.

Dose selection was further narrowed in the early Phase 3 program. In 4 of the 5 initial Phase 3 studies including the 2.5 mg dose, glycemic efficacy at this dose was shown to be suboptimal compared to the 5 and 10 mg doses. In one monotherapy study (MB102013), the HbA1c reduction with the 2.5 mg dose was not statistically different from placebo. The effects of 2.5 mg on fasting plasma glucose (FPG) and glycemic control (evaluated as proportion of patients achieving HbA1c < 7%) were also not statistically significant from placebo in most of the studies where this dose was evaluated. On the basis of these findings, doses of 2.5 mg (and lower) did not demonstrate consistent clinical benefit for the treatment of T2DM. Therefore, further Phase 3 studies focused on the 5 and 10 mg doses, with the 10 mg dose being the most studied dose for efficacy and safety evaluations.

In studies where both the 5 and 10 mg doses were tested, the 10 mg dose consistently showed greater mean HbA1c reductions than the 5 mg dose. Greater reductions were also consistently seen at the 10 mg dose for FPG, postprandial glucose (PPG), and the proportion of patients achieving a target HbA1c < 7%. At the same time, the safety profiles of 5 mg and 10 mg are similar; no risks were identified that increased in frequency or severity as the dose increased from 5 to 10 mg. In summary, of the 3 core doses of the Phase 3 program, 2.5 mg showed inconsistent efficacy, and 10 mg showed greater glycemic benefit than 5 mg with a similar safety profile. Thus, 10 mg is proposed as the usual daily dose of dapagliflozin.

While AEs of volume depletion were similar across the 5 and 10 mg doses, the PD effect of dapagliflozin - glucosuria and diuresis - was modestly greater at 10 mg than at 5 mg. Therefore, the option of treatment with the 5 mg dose may be appropriate for patients at risk for volume depletion.

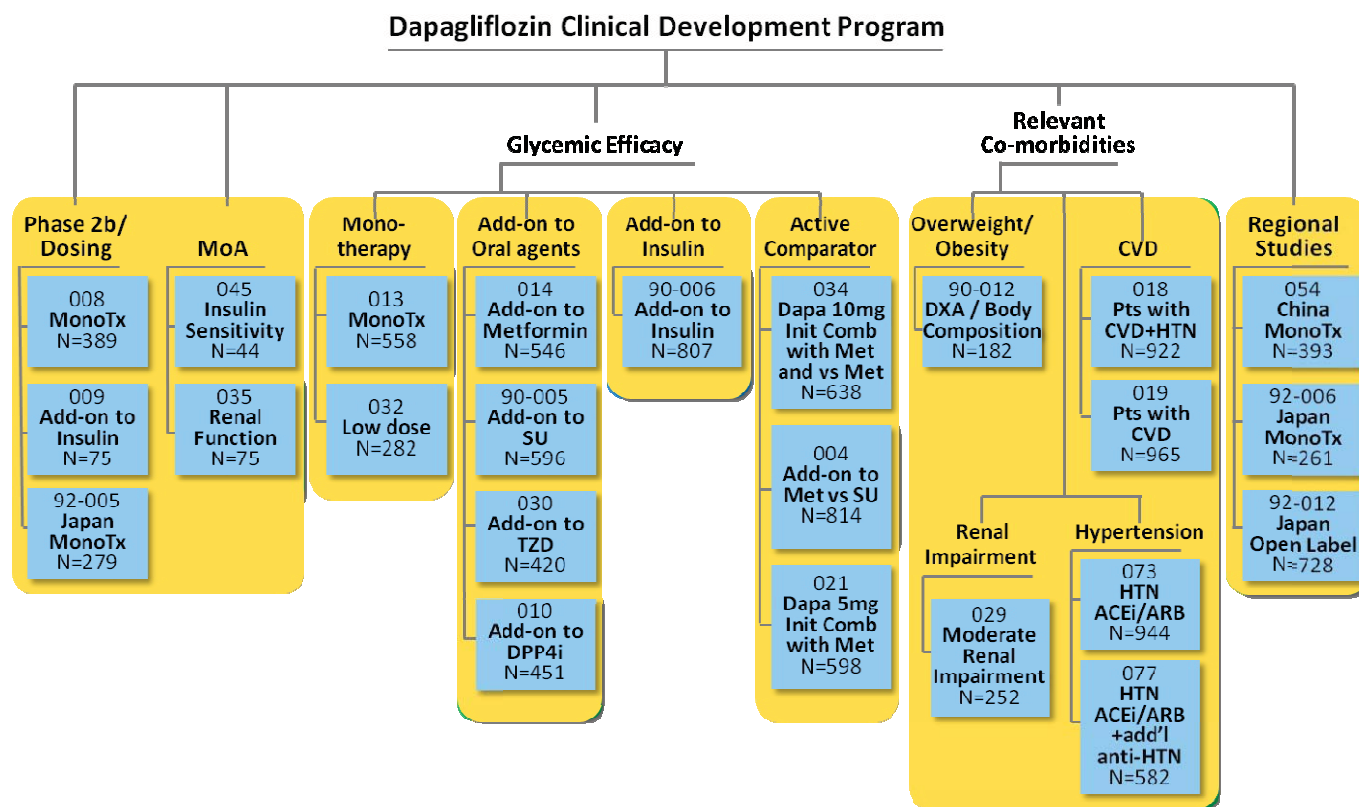
2.3 Phase 2b and 3 Clinical Studies

The dapagliflozin Phase 2b and 3 clinical development program was designed to examine the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. The program included both placebo-controlled and standard-of-care active comparator studies in a broad spectrum of patients ranging from those who were drug-naïve at an early stage of disease through those who required additional therapy after failure to reach adequate glycemic control with their current regimen (dapagliflozin group mean duration of disease = 6.95 years; range = 0.0 to 54.4 years). In addition, the development program included a large proportion of patients on insulin-based regimens.

Given its insulin-independent MOA that causes excretion of glucose in the urine, dapagliflozin was expected to be effective when used as monotherapy as well as effective and complementary when used with other antidiabetic drugs; the clinical program was designed to evaluate this broad therapeutic potential. The program also examined the persistent loss of calories in the urine due to glucosuria and the resulting potential for weight loss and a reduction in body fat. In addition, the potential for beneficial BP effects was assessed. The clinical studies were not designed to study patients with severe renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$) because glycemic efficacy was not expected in the absence of adequate renal function.

An overview of the clinical Phase 2b and 3 clinical studies is presented in [Figure 3](#) and described in more detail in [Table 1](#).

Figure 3: Summary of Clinical Phase 2b and 3 Development Program in Patients with T2DM



Source: 30-MU, Appendix 1

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; Comb = combination; Comp = compared; CV CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; DXA = dual-x-ray absorbiometry; HTN = hypertension; Init = initial; Met = metformin; MOA = mechanism of action; MonoTx = monotherapy treatment; Pts = patients; SU = sulfonylurea; TZD = thiazolidinedione

Note: Studies with partial data included in the file: D1691C00003 – different dosing paradigm, not completed in time for the submission; MB102072 indication. The additional new bladder cancer case was from ongoing study D1693C00005.

Study numbers:

008 = MB102008; 009 = MB102009; 92-005 = D1692C00005; 09-012 = D1690C00012; 045 = MB102045; 035 = MB102035; 013 = MB102013
032 = MB102032; 014 = MB102014; 030 = MB102030; 90-005 = D1690C00005; 010 = D1690C00010; 90-006 = D1690C00006; 034 = MB102034;
021 - MB102021; 004 = D1690C00004; 029 = MB102029; 018 = D1690C00018; 019 = D1690C00019; 073 = MB102073; 077 = MB102077;
054 = MB102054; 92-006 = D1692C00006; 92-012 = D1692C00012

Table 1: Dapagliflozin Clinical Development Program

Study Description/Period/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment
PHASE 2B/DOSING					
MB102008 Phase 2b Monotherapy	Drug naive subjects with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	47 – 59/ 279/ 389	12 weeks	Dapagliflozin 2.5, 5, 10, 20 or 50 mg or placebo Additional group: metformin XR 750/1500 mg/ Background therapy: None	None
MB102009 Phase 2b Add-on to insulin	Subjects on insulin sensitizer (metformin and/or TZD) and insulin with HbA1c $\geq 7.5\%$ to $\leq 10.0\%$	<u>Cohort 1:</u> single blind, unrandomized 4/ 4/ 4 <u>Cohort 2:</u> double-blind: 23-24/ 48/ 71	12 weeks	Dapagliflozin 20 mg (to determine insulin dose level for Cohort 2) Dapagliflozin 10 or 20 mg or placebo/ Background therapy: 50% original insulin dose + metformin or TZD	Insulin up-titration
D1692C00005 Phase 2b Japan monotherapy	Japanese subjects with inadequate glycemic control with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	54-59/ 225/ 279	12 weeks	Dapagliflozin 1, 2.5, 5, or 10 mg or placebo/ Background therapy: None	None
MECHANISM OF ACTION (MOA)					
MB102045 Phase 2b Insulin sensitivity	Subjects on metformin \pm an insulin secretagogue (SU, DPP-4, or glinide) with HbA1c \geq 7.0% to $\leq 10.0\%$	21-23/ 23/ 44	12 weeks	Dapagliflozin 5 mg or placebo/ Background therapy: metformin \pm insulin secretagogue	None
MB102035* Phase 2b Renal function	Subjects on metformin \pm SU + inadequate BP control (HbA1c ≥ 6.6 to \leq 9.5%, SBP ≥ 130 and \leq 165mmHg and/or DBP \geq 80 and ≤ 105 mmHg)	24-26/ 24/ 75	12 weeks	Dapagliflozin 10 mg, HCTZ 25 mg, or placebo/ Background therapy: metformin \pm SU	Upward titration or initiation of metformin or SU

Table 1: Dapagliflozin Clinical Development Program

Study Description/Period/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment
GLYCEMIC EFFICACY					
<i>Monotherapy</i>					
MB102013 Phase 3 Monotherapy	<u>Group 1</u> : drug-naïve, baseline HbA1c $\geq 7.0\%$ - $\leq 10.0\%$. <u>Group 2</u> : drug-naïve with baseline HbA1c $\geq 10.1\%$ - $\leq 12.0\%$	64 – 76/ 410/ 485 34 -39/ 73/ 73	24 weeks + 78 weeks 24 weeks + 78 weeks	<u>Group 1</u> : Dapagliflozin 2.5, 5 or 10 mg, QAM or QPM, or placebo <u>Group 2</u> : Dapagliflozin 5 or 10 mg, QAM/ Background therapy: None	Metformin
MB102032 Phase 3 Low-dose monotherapy	Drug-naïve subjects with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	68 – 74/ 214/ 282	24 weeks	Dapagliflozin 1, 2.5, or 5 mg, or placebo/ Background therapy: None	Metformin
<i>Add-on Oral Agents or Insulin</i>					
MB102014 Phase 3 Add-on to metformin	Subjects on metformin ≥ 1500 mg/day with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	135 – 137/ 409/ 546	24 weeks + 78 weeks	Dapagliflozin 2.5, 5, 10 mg, or placebo/ Background therapy: metformin ≥ 1500 mg/day	Pioglitazone (or acarbose)
MB102030 Phase 3 Add-on to TZD	Subjects on pioglitazone with HbA1c $\geq 7.0\%$ to $\leq 10.5\%$	139 – 141/ 281/ 420	24 weeks + 24 weeks	Dapagliflozin 5 or 10 mg or placebo/ Background therapy: pioglitazone ≥ 30 mg/day	Metformin or SU
D1690C00005 Phase 3 Add-on to SU	Subjects on SU with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	146 – 154/ 450/ 596	24 weeks + 24 weeks	Dapagliflozin 2.5, 5, or 10 mg or placebo/ Background therapy: glimepiride 4 mg/day	Metformin or TZD
D1690C00010* Phase 3 Add-on to DPP-4i	Subjects on DPP-4 inhibitor \pm metformin with HbA1c $\geq 7.0\%$ to $\leq 10.0\%$	225-226/ 225/ 451	24 weeks + 24 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: Sitagliptin 100mg/day and/or metformin ≥ 1500 mg/day	Glimeperide
D1690C00006 Phase 3 Add-on to insulin	Subjects on insulin ≥ 30 IU/day \pm maximum 2 OAD with HbA1c $\geq 7.5\%$ to $\leq 10.5\%$	196 – 212/ 610/ 807	24 weeks + 24 weeks + 56 weeks	Dapagliflozin 2.5, 5, or 10 mg or placebo/ Background therapy: Insulin ≥ 30 IU/day \pm max 2 OAD	Insulin up-titration

Table 1: Dapagliflozin Clinical Development Program

Study Description/Period/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment
Active Comparator					
MB102021 Phase 3 Dapagliflozin 5 mg, Initial combination with metformin	Treatment-naïve subjects with HbA1c ≥ 7.5% to ≤ 12.0%	194 – 203/ 397/ 598	24 weeks	Dapagliflozin 5 mg + metformin XR up to 2000 mg, Dapagliflozin 5 mg, or Metformin XR up to 2000 mg/ Background therapy: None	Pioglitazone, acarbose, or sitagliptin
MB102034 Phase 3 Dapagliflozin 10 mg, Initial combination with metformin	Treatment-naïve subjects with HbA1c ≥ 7.5% to ≤ 12.0%	208 – 219/ 430/ 638	24 weeks	Dapagliflozin 10 mg + metformin XR up to 2000 mg, Dapagliflozin 10 mg, or Metformin XR up to 2000 mg/ Background therapy: None	Pioglitazone, acarbose, or sitagliptin
D1690C00004 Phase 3 Add-on to metformin vs. SU	Subjects on metformin ≥ 1500 mg/day with HbA1c > 6.5% to ≤ 10.0%	406 – 408/ 406/ 814	52 weeks + 52 weeks + 104 weeks	Dapagliflozin titrated 2.5, 5, or 10 mg or Glipizide titrated 5, 10, or 20 mg/ Background therapy: Metformin ≥ 1500 mg/day	None ≤ 104 weeks. Allowed after 104 weeks
RELEVANT CO-MORBIDITIES					
Overweight/Obesity					
D1690C00012 Phase 3 DXA/body composition, Add-on to met	Subjects on metformin ≥ 1500 mg/day with HbA1c with ≥ 6.5% to ≤ 8.5%	91/ 91/ 182	24 weeks + 78 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: Metformin ≥ 1500 mg/day	Sitagliptin
Cardiovascular Disease (CVD)					
D1690C00018* Phase 3 Patients with a history of CVD and hypertension	Patients on usual care of diabetes with CVD and hypertension and HbA1c ≥ 7.0% to ≤ 10.0%	460-462/ 460/ 922	24 weeks + 28 weeks + 52 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: OADs and/or insulin	At discretion of investigator

Table 1: Dapagliflozin Clinical Development Program

Study Description/Period/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment
D1690C00019* Phase 3 Patients with a history of CVD	Patients on usual care of diabetes with CVD and HbA1c $\geq 7.0\%$ to \leq 10.0%	482-483/ 482/ 965	24 weeks + 28 weeks + 52 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: OADs and/or Insulin	At discretion of investigator
Renal Impairment					
MB102029 Phase 2b and 3 Moderate renal impairment	Subjects on a stable anti-diabetic regimen with HbA1c $\geq 7\%$ to $\geq 11\%$	83 - 85/ 168/ 252	24 weeks + 28 weeks + 52 weeks	Dapagliflozin 5 or 10 mg or placebo/ Background therapy: Any except metformin	Any approved therapy per investigator except metformin
Hypertension					
MB102073* Phase 3 Patients with HTN + ACEi/ARB	Subjects on stable dose of OAD + inadequately controlled hypertension on stable dose of ACE-I or ARB and HbA1c $\geq 7.0\%$ to $\leq 10.5\%$)	302-311/ 302/ 613**	12 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: OADs and/or Insulin, and ACEi or ARB	Anti- hypertensive medication
MB102077* Phase 3 Patients with HTN + ACEi/ARB + additional anti-hypertensive	Subjects on stable dose of OAD + inadequately controlled hypertension treated with an ACEi or ARB and additional antihypertensive drug and HbA1c $\geq 7.0\%$ to $\leq 10.5\%$	224-225/ 225/ 449**	12 weeks	Dapagliflozin 10 mg or placebo/ Background therapy: OADs and/or Insulin, and ACEi or ARB and one additional antihypertensive medication	Anti- hypertensive medication

Table 1: Dapagliflozin Clinical Development Program

Study Description/Period/ Current Status	Subject Population	N per Group/ N treated with Dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment
REGION SPECIFIC STUDIES					
D1692C00006* Phase 3 Japan monotherapy	Drug naive subjects (HbA1c \geq 6.5% and \leq 10%) Or Subjects with ongoing anti-diabetic treatment (HbA1c \leq 8% at enrollment)	86-88/ 174/ 261	24 weeks	Dapagliflozin 5mg or 10 mg or placebo/ Background therapy: None	Metformin or Glimeperide
D1692C00012* Phase 3 Japan Open-label	Japan subjects with inadequate glycemic control with or without OAD and HbA1c \geq 6.5% to \leq 10%	728/ 728/ 728	52 weeks	Dapagliflozin 5 mg titrated to 10 mg if HbA1c $>$ 7.5%, Open- label/ Background therapy: None or selected OADs	At discretion of investigator
MB102054* Phase 3 Asian (most in China) Monotherapy	Asian drug naive subjects with HbA1c \geq 7.5% to \leq 10.5% at enrollment	128-133/ 261/ 393	24 weeks	Dapagliflozin 5 mg or 10 mg or placebo/ Background therapy: None	Metformin

Source: 30-MU, Appendix 1

*New studies (9) included in the NDA resubmission

**In the early part of the study, dapagliflozin 2.5 mg and 5 mg were also studied in MB102073 and dapagliflozin 5 mg was also studied in MB102077.

They are not included in the counting here

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; BP = blood pressure; CVD = cardiovascular disease;

DBP = diastolic blood pressure; DPP-4i = dipeptidyl peptidase-4 inhibitor; DXA = dual-x-ray absorbiometry; HbA1c = hemoglobin A1c; HTN = hypertension;

HCTZ = hydrochlorothiazide; MOA = mechanism of action; OAD = oral antidiabetic; SBP = systolic blood pressure; SU = sulfonylure

TZD = thiazolidinedione

The dapagliflozin Phase 2b and 3 development program studied a diverse patient population worldwide and in the US including a similar proportion of men and women, a large proportion of patients over 65 years of age, as well as representative subgroups of African-Americans and patients of Hispanic/Latino ethnicity in the US (Table 2). Race information was collected at all global sites but ethnicity information was only collected at US sites. The dapagliflozin clinical development program studied subgroups of patients with co-morbidities relevant to T2DM and included specific studies dedicated to such populations: CV disease, hypertension, and renal impairment.

Table 2: Patient Demographics: Worldwide and in the United States (All Phase 2b and 3 Pool plus 2 Studies in Hypertensive Patients, 30-MU)

		Patients, n (%)	
		Worldwide N=11,801	U.S. N=2,587
Age	Mean	57.0 yrs	55.6 yrs
	≥65	2818 (23.9)	495 (19.1)
	≥75	367 (3.1)	66 (2.6)
Gender	Male	6612 (56.0)	1494 (57.8)
	Female	5189 (44.0)	1093 (42.2)
Race	White	8372 (70.9)	2117 (81.8)
	Black	428 (3.6)	322 (12.4)
	Asian	2672 (22.6)	78 (3.0)
Ethnicity	Hispanic/Latino	N/A	876 (33.9)

Source: rt-dm-demogsum23plusas023

N/A = not applicable; yrs = years

2.4 Analysis Populations (Phase 2b and 3)

2.4.1 Populations Supporting Efficacy

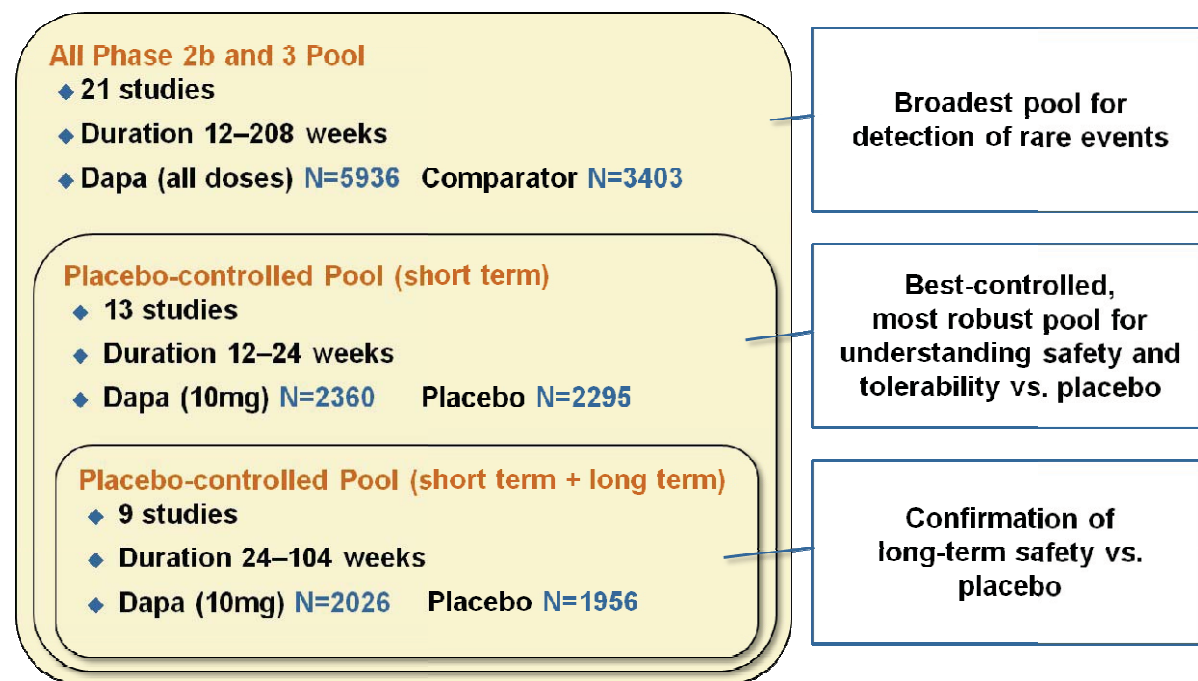
Most of the efficacy data in this document is presented by study. However, some pooling of efficacy data was conducted in order to increase the size of the subgroups to assess the impact of intrinsic and extrinsic factors on efficacy, including different levels of renal function and baseline HbA1c (see [Section 4.2.4](#)).

2.4.2 Populations Supporting Safety

Twenty-one Phase 2b and 3 studies were included in the integrated database for the 30-MU pooled safety analyses and used to create 3 pools to summarize the safety of dapagliflozin as described in [Figure 4](#). Three studies were excluded from this pool: the Japanese open-label study (D1692C00012) because it did not have a control arm, and the 2 studies in diabetic patients with

poorly controlled hypertension (MB102073 and MB102077), because they were completed after the database cutoff for the safety pools. The individual studies included in each pool are listed in Table 3.

Figure 4: Safety Data Pooling Strategy



Source: 30-MU, Tables 2, 3, and 4
Dapa = dapagliflozin

Table 3: Studies Included in the 3 Pools for Clinical Safety Evaluation

All Phase 2b and 3 Pool	Placebo-controlled Pool	
(N=21)	Short-term (N = 13)	Short-term + Long-term (N = 9)
MB102008 (Phase 2b/dosing; monotherapy)	MB102008	*
MB102009 (Phase 2b/dosing; add-on to insulin)	MB102009	*
MB102013 (monotherapy)	MB102013	MB102013
MB102014 (add-on to metformin)	MB102014	MB102014
MB102021 (dapagliflozin 5 mg; initial combination with metformin)	*	*
MB102029 (moderate renal impairment)	*	*
MB102030 (add-on to TZD)	MB102030	MB102030
MB102032 (low dose monotherapy)	*	*
MB102034 (dapagliflozin 10 mg; initial combination with metformin)	MB102034	*

Table 3: Studies Included in the 3 Pools for Clinical Safety Evaluation

All Phase 2b and 3 Pool (N=21)	Placebo-controlled Pool	
	Short-term (N = 13)	Short-term + Long-term (N = 9)
MB102035 (renal function)	*	*
MB102045 (insulin sensitivity)	*	*
MB102054 (China monotherapy)	*	*
D1690C00004 (add-on to metformin vs. SU)	*	*
D1690C00005 (add-on to SU)	D1690C00005	D1690C00005
D1692C00005 (Phase 2b/dosing; Japan monotherapy)	D1692C00005	*
D1690C00006 (add-on to insulin)	D1690C00006	D1690C00006
D1692C00006 (Japan monotherapy)	*	*
D1690C00010 (add-on to DPP-4i)	D1690C00010	D1690C00010
D1690C00012 (DXA/body composition; add-on to metformin)	D1690C00012	D1690C00012
D1690C00018 (patients with CVD + HTN)	D1690C00018	D1690C00018
D1690C00019 (patients with CVD)	D1690C00019	D1690C00019

Source: 30-MU, Table 5

*Eight core studies were not included in the Placebo-controlled Pool: (1) MB102029, patients with moderate renal impairment, (2) D1690C00004, active control study vs. glipizide, (3) D1692C00006 regional study, (4) MB102054 regional study, (5) MB102021 study without dapagliflozin 10 mg group, (6) MB102032 study without dapagliflozin 10 mg group, (7) MB102035: small MOA study, (8) MB102045: small MOA study

CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; DXA = dual-xray absorbiometry; HTN = hypertension; SU = sulfonylurea; TZD = thiazolidinedione

Only studies with dapagliflozin 10 mg and placebo treatment groups are included in the 30-MU Placebo-controlled Pools, as the majority of new data from placebo-controlled studies is in patients treated with dapagliflozin 10 mg or placebo. No studies provide new data from patients on dapagliflozin 2.5 mg and 5 mg for the short-term (ST) Placebo-controlled Pool. Only 1 study, D1690C00006, provided new data for the short-term plus long-term (ST+LT) Placebo-controlled Pool from patients on dapagliflozin 2.5 mg or 5 mg. In total, this study provided less than 16 patient-years additional exposure for each of these doses. Comparative safety assessment across dapagliflozin doses (2.5 mg, 5 mg, 10 mg, dapagliflozin total) is most appropriately performed using the data in the initial NDA, where these doses are each represented. A detailed discussion on dose rationale for the dapagliflozin clinical program is provided in [Section 2.2](#).

2.4.3 Excluded Populations

Most studies excluded patients with significant hepatic disease (including aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3X upper limit of normal [ULN] at enrollment). Other exclusions included patients with elevated creatinine or severe renal impairment, nephrotic levels of proteinuria, recent major cardiac events, uncontrolled

hypertension, or patients at risk in the opinion of the investigator for dehydration or volume depletion.

Patients with a history of New York Heart Association (NYHA) Class I or II heart failure were not excluded from the program. Patients with NYHA Class III and IV heart failure were initially excluded from the Phase 3 clinical development program; a limited number of patients (24 [1.3%]) with NYHA Class III heart failure were included in Studies D1690C00018 and D1690C00019. Appropriate warnings and precautions are included in the proposed label to account for these limitations to the overall study population.

2.5 Extent of Exposure to Dapagliflozin

All Phase 2b and 3 Pool (ST+LT):

The 30-MU provides over 50% additional patient-years of exposure in the All Phase 2b and 3 Pool relative to the initial NDA (Table 4). Since the 4-month safety update (4-MSU, submitted April-2011), new patients were primarily from the following studies:

- 451 patients from **D1690C00010** (add-on to DPP-4, 1-year data): 225 patients in the dapagliflozin 10 mg group and 226 patients in placebo group;
- 922 patients from **D1690C00018** (in patients with CV disease and hypertension, 2-year data): 460 patients in the dapagliflozin 10 mg group and 462 patients in the placebo group;
- 965 patients from **D1690C00019** (in patients with a history of CV disease, 2-year data): 482 patients in the dapagliflozin 10 mg group and 483 patients in the placebo group.

Other new patient data comes from studies MB102035 (renal function), D1692C00006 (Japan monotherapy), and MB102054 (China monotherapy).

In addition, since the 4-MSU, new LT data on patients already in the program comes from studies MB102029 (moderate renal impairment; 2-year data), D1690C00004 (add-on to metformin; up to 4-year data), D1690C00006 (add-on to insulin; 2 year data), and D1690C00012 (DXA/body composition; 2-year data).

More patients were exposed to dapagliflozin than to control in the 30-MU All Phase 2b and 3 Pool. The total patient-years of exposure for dapagliflozin- compared with control-treated patients is 6247:3638, for a ratio of 1.7:1 dapagliflozin:control (Table 5).

In the All Phase 2b and 3 Pool including data after rescue, in the dapagliflozin and control groups, 3214 patients and 1889 patients were exposed to study treatment for ≥ 1 year and 1453 patients and 742 patients were exposed for ≥ 2 years, respectively. There were 113 and 101 (4.4%) patients in the dapagliflozin and control groups, respectively, exposed to study treatment for 4 years.

Table 4: Overall Exposure (Patient-years), 30-Month Update in Comparison to the Summary of Clinical Safety (SCS), Including Data After Rescue

	SCS		30-MU	
All Phase 2b and 3 Pool (ST+LT)	Dapa Total N = 4287	Control N = 1941	Dapa Total N = 5936	Control N = 3403
Cumulative Exposure (p-y)	4009.1 p-y	1681.9 p-y	6247.2 p-y	3637.6 p-y
Placebo-controlled Pool (ST)	Dapa 10 mg N = 1193	Placebo N = 1393	Dapa 10 mg N = 2360	Placebo N = 2295
Cumulative Exposure (p-y)	491.6 p-y	569.9 p-y	997.6 p-y	957.9 p-y
Placebo-controlled Pool (ST+LT)	Dapa 10 mg N = 768	Placebo N = 694	Dapa 10 mg N = 2026	Placebo N = 1956
Cumulative Exposure (p-y)	954.0 p-y	777.6 p-y	2437.9 p-y	2243.6 p-y

Source: SCS: Table 8, Table 9, Appendix 262A; 30-MU: Appendix 104, Appendix 204, and Appendix 304.

30-MU = 30 Month Update; Dapa = dapagliflozin; LT = long-term; p-y = patient years; SCS = Summary of Clinical Safety; ST = short-term

Table 5: Mean Duration (Days) of Exposure to Double-blind Study Medication: Summary by the Population Pools Analyzed for Safety in this 30-Month Update

	All Phase 2b/3 Pool (ST+LT)		Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa Total N = 5936	Control N = 3403	Dapa 10 mg N = 2360	Placebo N = 2295	Dapa 10 mg N = 2026	Placebo N = 1956
Mean Duration of Exposure (days) (including data after rescue)	384.4	390.4	154.4	152.4	439.5	419.0
Mean Duration of Exposure (days) (excluding data after rescue)	330.1	296.5	149.4	136.0	374.8	289.5

Source: **30-MU**: Appendix 104, Appendix 105, Appendix 204, Appendix 205, Appendix 304, and Appendix 305.

Dapa = dapagliflozin; LT = long-term; p-y = patient-years; ST = short-term

Placebo-controlled Pool (ST):

About twice as many patients were exposed to dapagliflozin 10 mg in the 30-MU Placebo-controlled Pool (ST) than in the original Summary of Clinical Safety (SCS; Table 4 and Table 5). Since the SCS, additional patients in the Placebo-controlled Pool (ST) in this 30-MU were from studies D1690C00010, D1690C00018, and D1690C00019, see description above.

The total patient-years of exposure for patients in the Placebo-controlled Pool (ST) treated with dapagliflozin 10 mg compared with patients treated with control is 998:958, for a ratio of 1.04:1 dapagliflozin:control (Table 4).

Most patients in the 30-MU Placebo-controlled Pool (ST) were exposed to dapagliflozin 10 mg or placebo for approximately 6 months (between 121 and 180 days; including data after rescue). The mean duration of exposure, both including and excluding data after rescue, were similar for both treatment groups in the ST treatment period (Table 5).

Placebo-controlled Pool (ST+LT):

About three times more patients were exposed to dapagliflozin 10 mg in the 30-MU Placebo-controlled Pool (ST+LT) than in the original SCS (Table 4 and Table 5). Since the SCS, additional patients in the 30-MU Placebo-controlled Pool (ST+LT) were primarily from the same 3 studies (D1690C00010, D1690C00018, and D1690C00019) described above. The total patient-years of exposure for patients in the Placebo-controlled Pool (ST+LT) treated with dapagliflozin compared with placebo is 2438:2244, for a ratio of 1.09:1 dapagliflozin:control (Table 4).

The mean duration of exposure in the 30-MU Placebo-controlled Pool (ST+LT) including data after rescue was 440 and 419 days in the dapagliflozin 10 mg and placebo groups, respectively. Mean duration of exposure when data after rescue was excluded was shorter than including data after rescue for patients in both treatment groups in the 30-MU. There was a smaller decrease for patients treated with dapagliflozin 10 mg than placebo (375 vs. 290 days; Table 5). This was primarily due to earlier study rescue and discontinuation in the placebo group, consistent with previously reported data. Overall, the exposure data both including and excluding rescue is consistent with data previously reported in the SCS.

2.6 Baseline Characteristics

Dapagliflozin was studied in a broad population of patients with T2DM with respect to duration of diabetes, baseline HbA1c, SBP, BMI, and level of renal impairment.

In the All Phase 2b and 3 Pool, baseline diabetes characteristics were balanced across the dapagliflozin total and all control groups (Table 6). The mean duration of T2DM was 6.95 years in the dapagliflozin total group vs. 7.59 years in the all control group. Mean baseline HbA1c was approximately 8.0% in both treatment groups; however, patients with higher baseline HbA1c were studied in selected trials (Table 6).

More than half of the patients in the All Phase 2b and 3 Pool had a body mass index (BMI) ≥ 30 kg/m² (Table 6). Approximately 90% of patients across all treatment groups had a BMI ≥ 25 kg/m². Mean baseline SBP for the dapagliflozin total and all control groups was 130.4 mmHg and 131.1 mmHg, respectively.

About 88% of patients in the dapagliflozin total and all control groups had normal renal function or mild renal impairment (eGFR ≥ 60 mL/min/1.73m²) at baseline (Table 6). There were 15 patients with severe renal impairment (eGFR < 30 mL/min/1.73m²) at baseline which were equally distributed between the dapagliflozin total and all control groups (0.2% of patients in each group).

Patient baseline characteristics were also balanced across the treatment groups in the Placebo-controlled Pools (ST and ST+LT).

Baseline CV characteristics are discussed in [Section 5.2.3.2](#).

Table 6: Baseline Diabetes and Renal Characteristics Summary, All Phase 2b and 3 Pool (30-MU)

Parameter		Dapa Total N = 5936	Control N = 3403
Baseline HbA1c	mean (%)	8.21	8.14
< 8.0	n (%)	2740 (46.2)	1668 (49.0)
≥ 8.0 - < 9.0		1912 (32.2)	1058 (31.1)
≥ 9.0		1284 (21.6)	677 (19.9)
Duration of T2DM	mean (yrs)	6.95	7.59
≤ 3	n (%)	2421 (40.8)	1250 (36.7)
> 3 - ≤ 10		1937 (32.6)	1161 (34.1)
> 10		1578 (26.6)	989 (29.1)
Systolic BP	mean (mmHg)	130.4	131.1
≥ 140	n (%)	1529 (25.8)	946 (27.8)
BMI			
≥ 25	n (%)	5214 (87.8)	2998 (88.1)
≥ 30		3368 (56.7)	1949 (57.3)
eGFR			
< 30	n (%)	9 (0.2)	6 (0.2)
≥ 30 - < 60		668 (11.3)	387 (11.4)
≥ 60		5259 (88.6)	3009 (88.4)

Source: 30-MU, Tables 9, 10, and 11; rt-dm-sumlt23as059

BMI = body mass index; BP = blood pressure; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; T2DM = type 2 diabetes mellitus

3 CLINICAL PHARMACOLOGY AND DOSING EVALUATIONS

The Clinical Pharmacology program profiled the safety, tolerability, PK, PD, population PK, exposure-response, and biopharmaceutic characteristics of dapagliflozin. At the time of the initial NDA submission, a total of 675 subjects/patients in 28 studies had received at least 1 dose of dapagliflozin over a range of 0.001 to 500 mg.

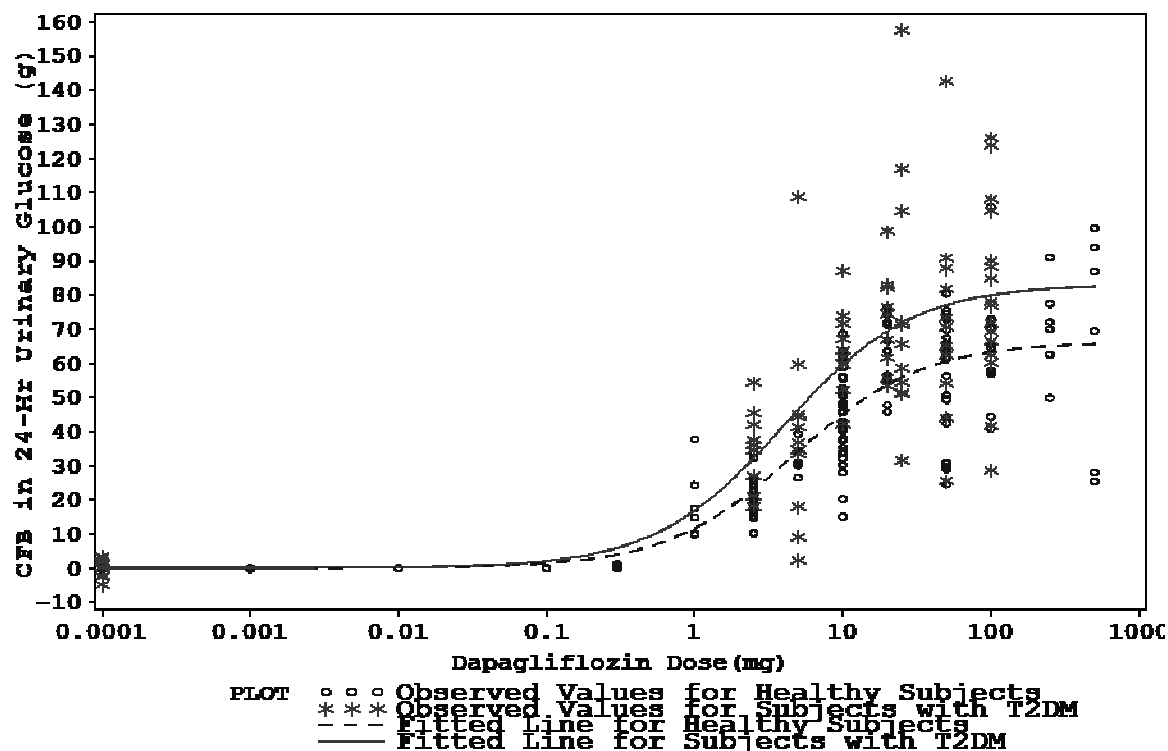
Across the Clinical Pharmacology program, no dose-limiting toxicities were identified in studies conducted in healthy subjects administered single doses of dapagliflozin up to 500 mg or in healthy subjects or those with T2DM administered daily doses up to 100 mg for 2 weeks. These subjects had detectable glucose in the urine for a dose-related period of time (i.e., the time that glucose was detected in the urine was longer as dose increased). The ability of dapagliflozin to promote urinary glucose excretion results in mild osmotic diuresis and an increase in urinary volume. In patients with T2DM, urinary volume increases were sustained at 12 weeks (approximate increase of 375 mL/day). In the Clinical Pharmacology studies there was no signal for dehydration, hypotension or electrolyte imbalance. A dedicated thorough QTc study did not show any dapagliflozin dose or plasma concentration-related effect on QTc interval at doses up

to 150 mg, once a day, which provides a wide safety margin for CV conduction/repolarization effects from the proposed highest dose of 10 mg.

The PK of dapagliflozin has been well-characterized in healthy subjects, patients with T2DM, and in relevant specific populations. Following oral administration, dapagliflozin is rapidly absorbed with a high absolute BA (78%) and dose-proportional systemic exposure across a broad range of doses (0.1 to 500 mg). Dapagliflozin is metabolized by UGT1A9 to a stable glucuronidated metabolite, dapagliflozin 3-O-glucuronide (BMS-801576), which is not a meaningful inhibitor of SGLT2 at clinically relevant doses. Renal excretion of dapagliflozin is minimal (< 2%) but renal excretion of dapagliflozin metabolites is extensive (~73% of dose).

The terminal phase half-life of dapagliflozin (12.5 h) and the sustained inhibition of urinary glucose reabsorption over 24 hours post-dose at the proposed highest clinical dose of 10 mg illustrates that dapagliflozin is suitable for once-daily dosing. The change from baseline in the amount of glucose excreted over 24 hours post dapagliflozin dosing was higher for a given dapagliflozin dose in patients with T2DM compared to healthy subjects (maximum effect [Emax]) values of 83.1 g and 66.2 g, respectively; see [Figure 5](#)). This finding was expected since patients with T2DM and normal renal function have a higher amount of glucose filtered by the kidney due to their higher systemic glucose concentrations. Regardless of the population (healthy or T2DM), the proposed highest dose of 10 mg dapagliflozin is near the upper inflection point of the Emax urinary glucose excretion curve, although relatively small increases in urinary glucose excretion occur with higher doses. The other Phase 3 doses of 1, 2.5 and 5 mg fell on the linear part of the sigmoid curve, indicating that these doses provided proportionally less PD effect than the 10 mg dose.

Figure 5: Scatter Plot and Fitted Line of Change from Baseline in 24-hr Urinary Glucose Amount vs. Dapagliflozin Dose in Healthy Subjects and Patients with T2DM (semi-log plot)



Source: Figure 3.5.4A of CTD Section 2.7.2 Summary of Clinical Pharmacology for Dapagliflozin

In this Semi-Log Plot, the placebo is presented as Dose = 0.0001 mg.

Note: Dapagliflozin alone treatment in fasted state for healthy subjects and patients with T2DM included.

CFB Change from baseline CTD Common technical document; hr Hour; T2DM Type 2 diabetes

Consistent with the MOA, dapagliflozin increased 24-hour urine volume. Increases in urinary volume at Week 12 appeared to be dose-related. Mean changes from baseline at Week 12 were 107, 340, 375, 375 and 470 mL/24h for 2.5-, 5-, 10-, 20- and 50-mg dapagliflozin doses respectively, compared to -111.5 for the placebo group and -95.8 mL/24 h for the metformin group (Study MB102008).

A MOA study showed that T2DM patients have higher TmG than healthy subjects and that dapagliflozin treatment reduced TmG by ~55% in both healthy subjects and T2DM patients. However, the markedly decreased renal glucose threshold was the primary mechanism responsible for the induction of glucosuria with dapagliflozin in both patients with T2DM and healthy subjects.

Compared to appropriate reference populations, dapagliflozin PK is not meaningfully affected by age, T2DM, body weight, gender, race, UGT1A9 polymorphism, mild or moderate hepatic impairment, or mild to moderate renal impairment. The mean systemic exposure to dapagliflozin in patients with severe renal impairment or severe hepatic impairment is less than 2-times higher than reference subjects. Additionally, a pharmacogenetic analysis showed no conclusive evidence for a meaningful difference in dapagliflozin clearance across genotypes for any

UGT1A9 single nucleotide polymorphisms. Patients who are suitable for dapagliflozin therapy have no identified intrinsic factors that will result in extremely high or extremely low drug exposure from the recommended daily 10 mg dose, and dapagliflozin PK data do not indicate a need for dose adjustments.

In vitro metabolism data and clinical drug-drug interaction studies with common concomitant medication used by the T2DM population (metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, simvastatin) or those that may affect its metabolic pathway (mefenamic acid, and rifampin) demonstrate that dapagliflozin has little potential either to affect their metabolism or to have its metabolism meaningfully affected by co-administration of other drugs. In healthy subjects, dapagliflozin's osmotic diuretic properties did not meaningfully interfere with the PD of a loop diuretic (bumetanide) and vice versa. However, the glucosuria of dapagliflozin in T2DM patients receiving treatment with a loop diuretic was not separately evaluated. The PK, PD, and/or efficacy results indicate that dapagliflozin may be given without regards to food or time of day (AM or PM dosing). Thus, there are no identified extrinsic factors that markedly alter dapagliflozin drug exposure in T2DM patients receiving the recommended daily 10 mg dose.

Population-based integrated modeling and simulation analyses were performed for patients with T2DM and normal renal function or mild renal impairment. A separate analysis in patients with T2DM and moderate renal impairment was also performed. These analyses included evaluations of relationships of dapagliflozin systemic exposure to FPG and HbA1c from the Phase 3 program at dapagliflozin doses of 2.5, 5, and 10 mg once daily. Of these doses, 10 mg dapagliflozin once daily provided the optimal therapeutic benefit to patients with T2DM.

In summary, at doses up to 50 times higher than the highest proposed dose of 10 mg, dapagliflozin was generally safe and well-tolerated and had no impact on the QTc interval when tested in a thorough QT study. Dapagliflozin possesses predictable and time-invariant PK with chronic dosing and predictable PD related to its MOA; these characteristics are amenable to once-daily dosing. Dapagliflozin PK is not meaningfully affected by intrinsic factors such as age, race, gender, body weight, or UGT1A9 polymorphism. Dapagliflozin has a low potential for drug-drug interactions and may be given without regard to meals or time of day, indicating that most extrinsic factors have little effect on dapagliflozin PK. Exposure-response analyses support the use of 10 mg or 5 mg once daily as the proposed dose patients with T2DM.

4 OVERVIEW OF EFFICACY

As described in [Section 1.2](#), the dapagliflozin clinical development program was designed to examine the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. The program included both placebo-controlled and standard-of-care active comparator studies in drug-naïve patients at an early stage of disease and patients who require additional therapy after failure to reach adequate glycemic control with their current regimen, including OAD agents or insulin at a later stage of the disease.

Given its insulin-independent MOA that causes excretion of glucose in the urine, dapagliflozin was expected to be effective when used as monotherapy as well as effective and complementary

when used with other antidiabetic drugs; the clinical program was designed to evaluate this broad therapeutic potential. The clinical development program also examined the persistent loss of calories in the urine due to glucosuria and the resulting potential for weight loss with a reduction in total body fat. In addition, the potential for beneficial BP effects was assessed given the mild osmotic diuresis resulting from glucosuria.

Dapagliflozin produced consistent and sustained, clinically important reductions in HbA1c which were equivalent to other therapies for T2DM. In active comparison trials, efficacy of dapagliflozin 10 mg was non-inferior to SU with lower hypoglycemia and the added benefit of weight loss and non-inferior to metformin with better FPG and weight loss. As can be predicted from its MOA, dapagliflozin treatment demonstrated consistent efficacy whether used as monotherapy in drug-naïve patients, as add-on therapy in patients with treatment failure on the background therapy alone, or as initial combination therapy with metformin in poorly controlled drug-naïve patients. Also, as can be predicted from its insulin-independent MOA, dapagliflozin proved to be effective regardless of insulin sensitivity, secretion, or administration. Among the doses tested in Phase 3, clinically meaningful reductions in HbA1c were consistently observed with dapagliflozin 10 mg.

In addition, dapagliflozin's new MOA confers additional benefits:

- Weight loss: The loss of calories due to persistent glucosuria results in reductions in body weight. These reductions are mainly attributable to a decrease in body fat mass rather than fluid or lean tissue mass. The PD effect of glucosuria is maintained over time; the effects of dapagliflozin on glycemic and weight parameters continue to be observed with LT treatment over at least 2 years.
- BP reductions: Dapagliflozin has a BP-lowering effect, which is consistent with its mild diuretic effect due to inhibition of renal tubular glucose and sodium reabsorption. Dapagliflozin has consistently shown reductions in BP in hypertensive, T2DM patients, both in the integrated safety database and in two dedicated studies. There is a minimal effect on measured orthostatic hypotension, and no increase in heart rate, mitigating associated safety concerns.

Dapagliflozin is effective across a range of demographic factors including gender, race, region, BMI, duration of diabetes, and age. Because of the dependence of efficacy on plasma glucose levels and GFR (or the filtered glucose load), the magnitude of effect is correlated with these parameters, such that greater glycemic efficacy is achieved in patients with poor baseline glycemic control, while there is a pattern of declining glycemic efficacy as eGFR decreases.

4.1 Methodology

Data establishing the clinical efficacy of dapagliflozin come from 16 core Phase 3 studies (MB102032, MB102013, MB102014, D1690C00012, D1690C00006, MB102030, D1690C00005, MB102021, MB102034, D1690C00004, MB102029, D1690C00010, D1690C00018, D1690C00019, MB102073, and MB102077).

Each Phase 3 study was conducted in a randomized, controlled, double-blind manner in adult patients with T2DM with placebo or active comparator. All Phase 3 studies had a ST period of 24 weeks duration with the exception of Study D1690C00004, which had a ST period of 52 weeks, and SMB102073 and MB102077, which had ST periods of 12 weeks. LT extensions of up to 156 additional weeks were conducted for 11 of the Phase 3 studies.

In all studies but Study D1690C00004 (in which all patients received active treatment in addition to background metformin), patients who failed to meet pre-specified glycemic targets (which became more stringent as the trials progressed) received rescue medication or were discontinued. Analyses of the ST periods were performed primarily excluding data after rescue and using the last observation carried forward (LOCF). Because of the increasing rescue and discontinuation rates in the LT extension treatment periods, efficacy analyses were performed with a longitudinal repeated measures model without use of LOCF both excluding and including data after rescue.

The investigators, BMS and AZ personnel, and patients were blinded to treatment allocation throughout the ST treatment period. To avoid bias in the analyses of the LT treatment period data, patients, investigators, and BMS and AZ personnel involved in data collection and verification at the study sites remained blinded to the individual treatment assignments until all patients had completed or had withdrawn from the study. Samples for urinary analyses were sent to central laboratories and the results for urinary glucose and HbA1c were masked from investigators and site/study personnel in order to maintain the blind.

4.1.1 Efficacy Endpoints

HbA1c is the clinical and regulatory parameter of choice for monitoring LT glycemic control because of the well-established correlation between HbA1c and diabetic microvascular complications.^{8,9} HbA1c was the primary efficacy variable for the majority of the studies in the Phase 3 program. The exceptions were: Study D1690C00012, which was designed to evaluate changes in weight as the primary endpoint, as well as changes in body composition (by dual-xray absorbiometry [DXA] and magnetic resonance imaging) in overweight patients with T2DM; Studies MB102073 and MB102077, which had co-primary endpoints of changes in HbA1c and seated SBP; and Studies D1690C00018 and D1690C00019, which had co-primary endpoints of changes in HbA1c and a 3-item endpoint of clinical benefit. Other efficacy endpoints evaluated in the clinical development program included, but were not limited, to FPG, PPG, the proportion of patients achieving a therapeutic response of HbA1c < 7.0%, change from baseline in body weight, ambulatory BP, and serum uric acid.

Exploratory endpoints included additional glycemic endpoints, additional weight and body composition endpoints, efficacy assessments of BP and lipid effects, assessments of glucose homeostasis, metabolic and inflammatory markers, and patient-reported outcomes.

4.1.2 Statistical Methods

The following is a brief overview of important pre-specified statistical considerations in the dapagliflozin program. Of particular note is the attention given to (i) control of the overall Type I error within treatment groups for the primary and all secondary endpoints, and (ii) sensitivity

analyses such as those conducted with data collected after initiation of rescue medication to support primary conclusions.

For all studies except Studies MB102073 and MB102077, analysis of covariance (ANCOVA) was used to analyze the primary and all continuous secondary endpoints. All models included effects for treatment group, baseline value, and stratification factor at randomization (other than site) if applicable. The primary endpoint in each study was evaluated by comparing the adjusted mean change from baseline between the dapagliflozin treatment group(s) and the comparator group(s), adjusting for multiple treatment comparisons in most cases with Dunnett's method. Statistical testing of secondary efficacy endpoints proceeded in a sequential manner using 2-sided $\alpha=0.05$ tests for only those treatment groups found to be statistically significant in the primary efficacy analysis (an exception to this rule is Study D1690C00012 where Hochberg's method was used). For each study, the number and order of secondary endpoints was specified prior to breaking of the blind. Sequential testing of secondary endpoints was performed independently within each dapagliflozin arm, with statistical inference stopping at the first endpoint which failed to reject the null hypothesis.

For the dichotomous co-primary endpoint in Studies D1690C00018 and D1690C00019, the statistical comparison was performed with a Cochran-Mantel-Haenszel test accounting for the 3 stratification factors in those studies. For other dichotomous efficacy endpoints across studies, a modified logistic regression was used which included adjustment for baseline value and stratification factor, if applicable.^{10,11}

Missing data from the ST period were handled in main analyses using LOCF methodology, excluding data obtained after rescue (except Study D1690C00004 where no rescue was used, Study D1690C00012 where the primary efficacy variable was weight change, and Studies MB102073 and MB102077 which used longitudinal repeated measures methodology). Robustness of study conclusions was evaluated with respect to the primary endpoint through sensitivity analyses by (i) including versus excluding data after rescue, (ii) using observed values vs. LOCF values, (iii) employing a longitudinal model versus visit-specific analyses, and/or (iv) excluding major protocol violators vs. including all randomized and treated patients.

Generally, primary analyses for the ST period of studies were based on LOCF values while exploratory analyses from the ST plus LT periods were based on longitudinal models using observed values.

Study D1690C00004 was a non-inferiority trial which compared dapagliflozin to glipizide as titrated regimens over 52 weeks of treatment. Non-inferiority to glipizide was 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 non-inferiority margin was based on a literature review and clinical judgment. The same criterion was used in Study MB102034 where a comparison between the dapagliflozin and metformin monotherapy arms was pre-specified.

For change from baseline in HbA1c to Week 24 (LOCF), subgroup analyses were performed within individual studies and in a pooled study population comprised of data from 10 of the

16 Phase 3 studies (Pooled Monotherapy/Combination Therapy Group): MB102013, MB102014, MB102030, MB102034, D1690C00005, D1690C00006, D1690C00012, D1690C00010, D1690C00018, and D1690C00019. Data from the other 6 Phase 3 studies were excluded because they did not contain dapagliflozin 10 mg (MB102021 and MB102032), were active comparator (D1690C00004), special risk population (MB102029) or 12-week duration (MB102073 and MB102077) studies. In both individual studies and pooled data, an ANCOVA model was used to assess the interaction between subgroup and treatment (dapagliflozin vs. placebo) as well as to estimate effects of each dapagliflozin dose within subgroup categories.

For Studies MB102073 and MB102077, based on the feedback received from FDA, a longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and randomization strata, as well as the continuous fixed covariates of baseline value and baseline value-by-week interaction was used for the primary and continuous secondary endpoints, as well as the subgroup efficacy analysis.

The LT efficacy and safety of dapagliflozin was evaluated over the entire duration of the ST combined with the LT treatment period (and extension period if applicable). LT extension phases ranged from 6 months to 3 years in duration. The LT efficacy analyses were considered exploratory and results were not assessed for statistical inference. Analyses were based on observed data without application of LOCF, to avoid carrying forward data over long periods of time. For continuous endpoints, a longitudinal repeated measures model was used.

The evaluation of maintenance of effect of dapagliflozin over the LT extension treatment periods is complicated by the confounding effect of rescue (or up titration of insulin in Study D1690C00006) and the increasing discontinuation rate in the LT treatment period. To help address problems arising from missing data, analyses were performed both excluding as well as including data after rescue. Both analyses have limitations: when excluding data, treatment estimates are derived from a selected subset of the randomized study population; whereas, including data after rescue or insulin up-titration affects HbA1c values, resulting in estimates that reflect the combined effects of investigational product and rescue. These 2 approaches to analyses were performed for the endpoints of HbA1c and weight to help assess whether findings are sensitive to the way data following rescue are handled in the analysis. In addition, the proportion of patients rescued or discontinued due to failing to achieve glycemic targets was analyzed as a separate efficacy endpoint in its own right and time to rescue or discontinuation summarized with Kaplan-Meier curves.

4.2 Key Effects of Dapagliflozin in Patients with T2DM

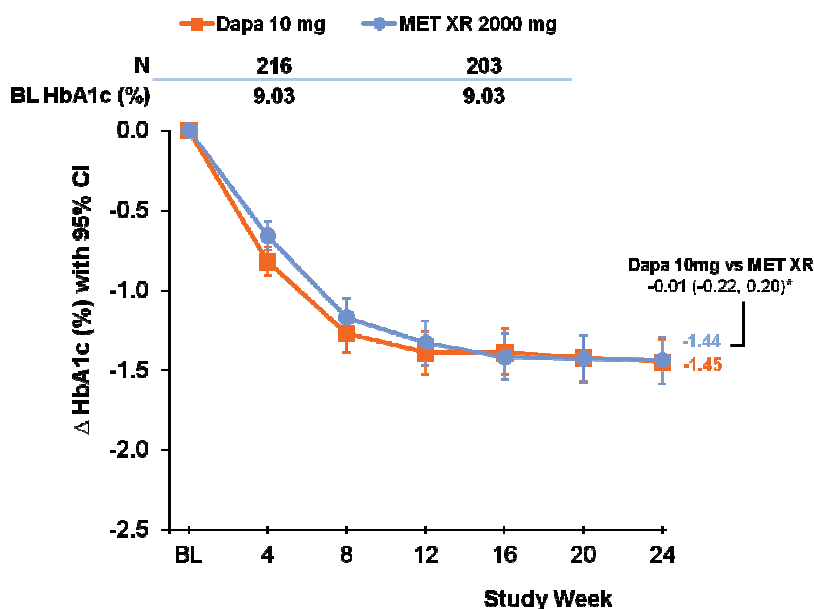
4.2.1 Active Comparator Studies

4.2.1.1 Glycemic Parameters

Two active comparator studies demonstrated non-inferiority of dapagliflozin to the compounds established as the cornerstones of the treatment in T2DM: Studies MB102034 (initial combination with metformin) and D1690C00004 (head-to-head comparison to SU). Non-inferiority to metformin has not been demonstrated for any of the recently approved OADs, such as DPP-4 inhibitors.

Study MB102034 examined the efficacy of dapagliflozin 10 mg plus metformin extended release (XR) as initial combination therapy. Drug-naïve patients with poorly controlled T2DM with mean HbA1c of approximately 9% were recruited into the initial combination with metformin study. In this study, the non-inferiority comparison between the 2 monotherapies was a pre-specified secondary objective. Dapagliflozin was non-inferior to metformin, with HbA1c mean reductions of 1.45% (95% CI = -1.59, -1.31) and 1.44% (95% CI = -1.59, -1.29) for dapagliflozin 10 mg/day and metformin XR 2000 mg/day, respectively, at Week 24 (Figure 6). Dapagliflozin was also superior to metformin in reducing FPG and body weight.

Figure 6: HbA1c (Dapagliflozin 10 mg Equivalent to Metformin XR 2000 mg): Adjusted Mean Change from Baseline to Week 24 (Initial Combination Study MB102034)



*Noninferior compared to limit of 0.35%.

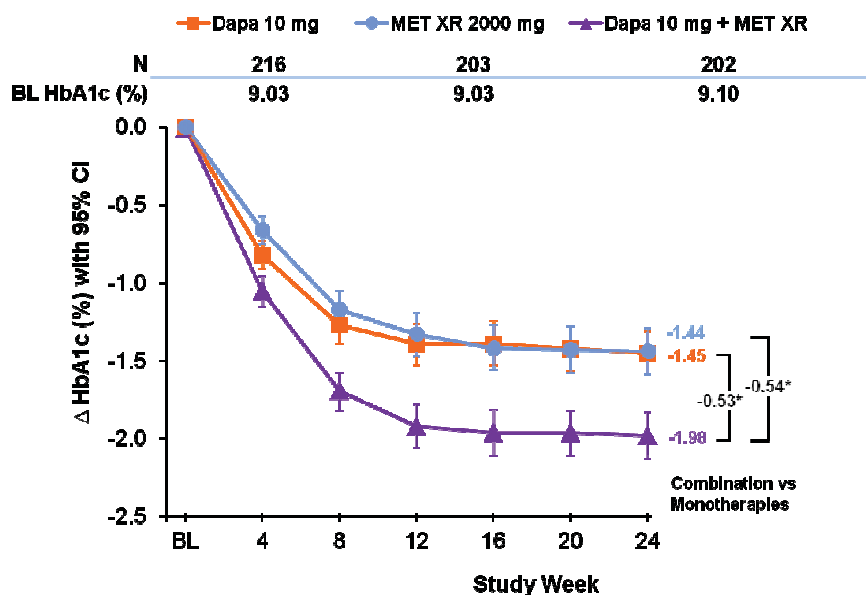
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Source: CSR-034 final

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; Met = metformin; XR = extended release

Treatment with dapagliflozin 10 mg as initial combination therapy with metformin (Study MB102034) was associated with greater reductions in HbA1c compared with dapagliflozin or metformin alone (Figure 7). Almost half (46.6%) of the proportion of patients in the dapagliflozin 10 mg plus metformin group achieved a therapeutic glycemic response, defined as HbA1c < 7.0%, compared to 31.7% in the dapagliflozin monotherapy and 35.2% in the metformin monotherapy treatment groups.

Figure 7: HbA1c (Dapagliflozin + Metformin Superior to Individual Monotherapies): Adjusted Mean Change from Baseline to Week 24 (Excluding Data after Rescue, Initial Combination Study MB102034)



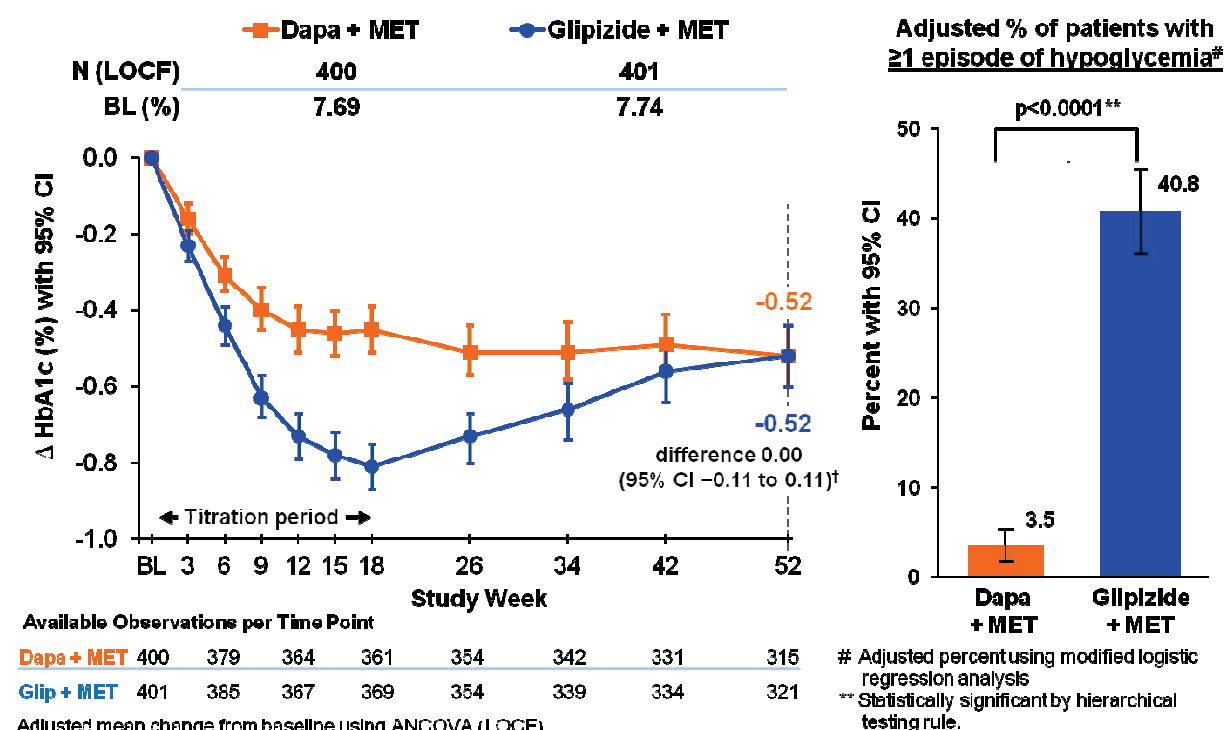
* Significantly superior to monotherapy.
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Source: CSR-034 final

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; Met = metformin; XR = extended release

In the active comparator Study D1690C00004, patients who failed treatment with metformin immediate release (IR) were randomized 1:1 to glipizide 5 mg or dapagliflozin 2.5 mg, and were up-titrated over 18 weeks to optimal glycemic effect (FPG < 110 mg/dL) or to the highest dose tolerated (glipizide 20 mg or dapagliflozin 10 mg). At the end of the titration period, 87% of patients in the dapagliflozin group had been titrated to the maximum study dose vs. 73% in the glipizide group. In total, 0.5% of patients in the dapagliflozin group required down-titration due to hypoglycemia, vs. 5.1% of patients in the glipizide group. At Week 52, both treatments had identical HbA1c mean reductions of 0.52% which met the criteria for non-inferiority (Figure 8). The HbA1c reduction with glipizide waned after the initial titration period, an effect that has been seen in other studies of SUs. Glipizide was also associated with a high risk of hypoglycemia by Week 52: 40.8% of patients in the glipizide group had at least one episode of hypoglycemia compared with 3.5% of patients in the dapagliflozin group (see Section 5.1.5).

Figure 8: HbA1c: Similar Reductions in HbA1c at Week 52 with Significantly Fewer Hypoglycemic Episodes (Active Comparator Study D1690C00004)



Source: CSR-D1690C00004-52 weeks

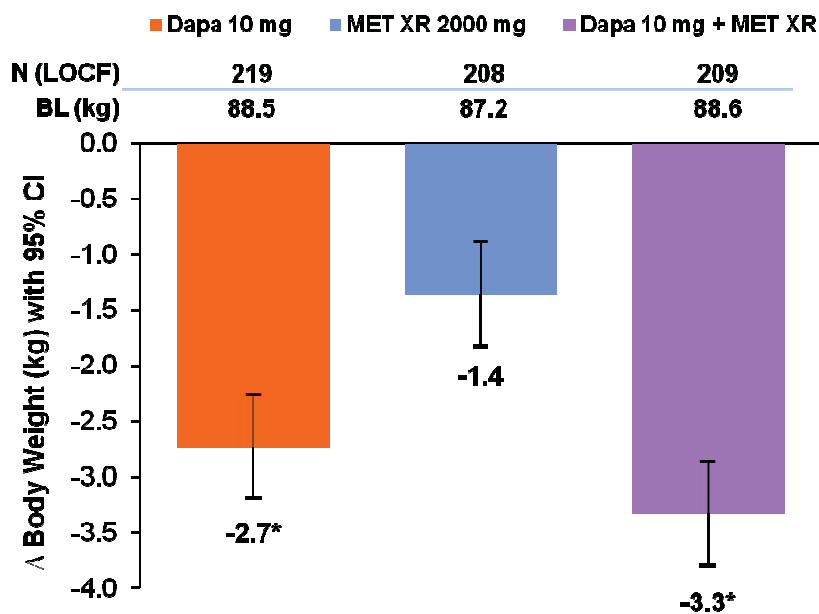
ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Glip = glipizide; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; MET = metformin

4.2.1.2 Body Weight

In Study MB102034, dapagliflozin either as monotherapy or as initial combination therapy with metformin was superior to metformin in reducing body weight. The reduction in mean body weight was -3.33 kg (95% CI = -3.80, -2.86), -2.73 kg (95% CI = -3.19, -2.27), and -1.36 kg (95% CI = -1.83, -0.89) for the dapagliflozin 10 mg plus metformin, dapagliflozin 10 mg, and metformin dose groups, respectively (Figure 9).

In the active comparator Study D1690C00004, treatment with glipizide resulted in weight gain at Week 52 in this study, an effect that is characteristic of treatment with SUs.⁶ Treatment with dapagliflozin resulted in weight loss of -3.22 kg vs. weight gain of 1.44 kg with glipizide (Figure 10). A significantly greater proportion of patients in the dapagliflozin group (33.3%), compared to glipizide (2.5%), experienced weight loss by at least 5% from baseline to Week 52.

Figure 9: Body Weight: Superior Reduction in Body Weight at Week 24 (Initial Combination Study MB102034)



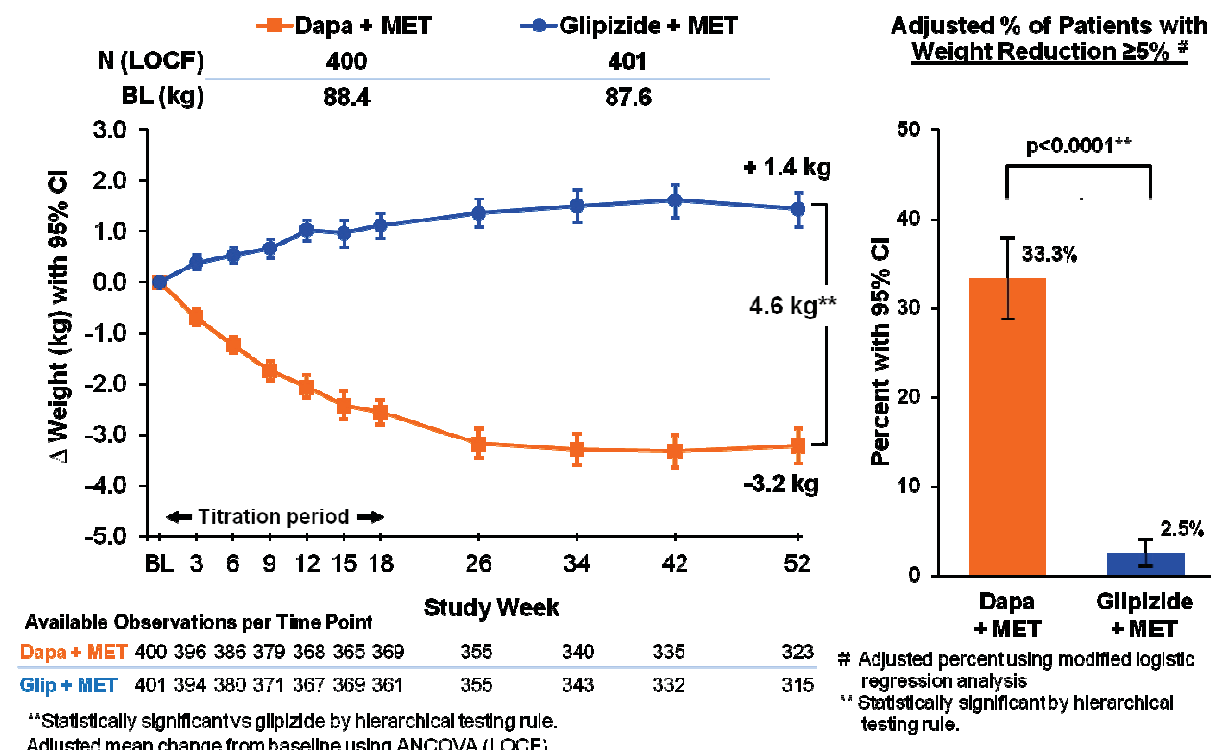
* Significantly superior to metformin XR monotherapy

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

Source: CSR-034 final

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; LOCF = last observation carried forward; Met = metformin; XR = extended release

Figure 10: Body Weight: Significant Reduction in Body Weight at Week 52 (Active Comparator Study D1690C00004)



Source: CSR-D1690C00004-52 weeks

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Glip = glipizide; LOCF = last observation carried forward; MET = metformin

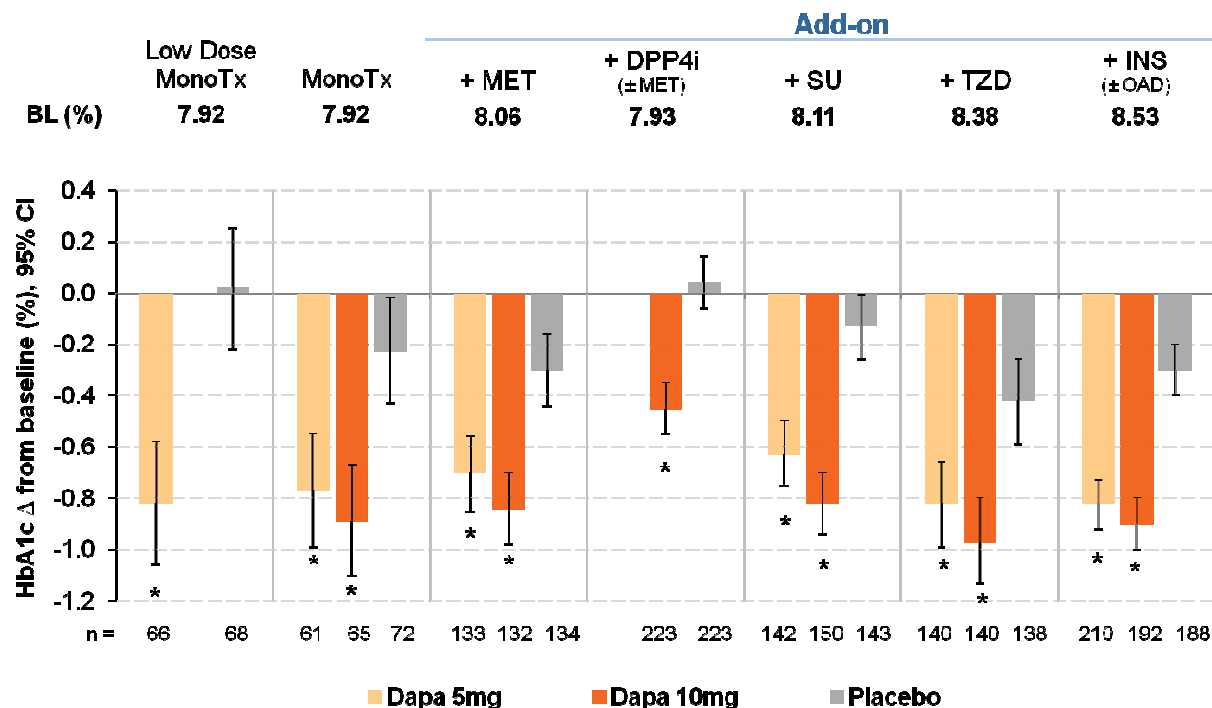
4.2.2 Placebo-controlled Studies

4.2.2.1 Glycemic Parameters

HbA1c

Across the core placebo-controlled Phase 3 studies, dapagliflozin 10 mg treatment resulted in statistically significant and clinically relevant reductions in HbA1c at Week 24 compared with placebo. Dapagliflozin demonstrated consistent efficacy across a broad range of patients, regardless of the background treatment, both as monotherapy and add-on to different antidiabetic agents (Figure 11).

Figure 11: HbA1c: Mean Change from Baseline at Week 24 (Primary Endpoint; Core Placebo-controlled Phase 3 Studies)



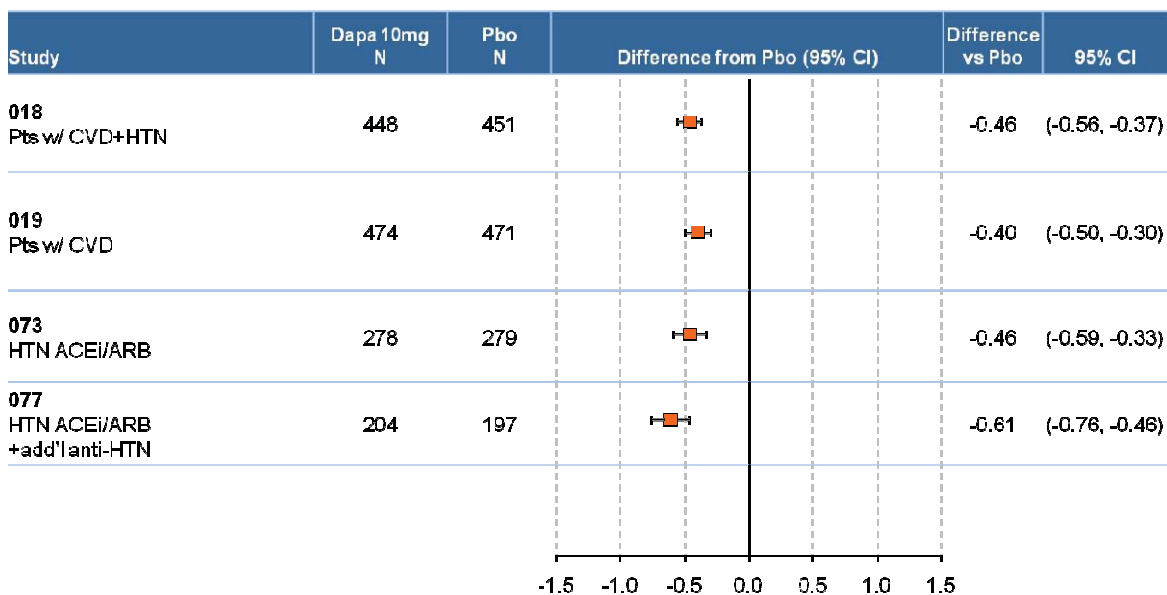
* Statistically significant vs placebo.

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

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; DPP-4i = dipeptidyl peptidase-4 inhibitor; HbA1c = hemoglobin A1c; INS = Insulin; LOCF = last observation carried forward; MET = metformin; MonoTx = monotherapy treatment; OAD = oral antidiabetic; SITA = sitagliptin; SU = sulfonylurea; PBO = placebo; PIO = pioglitazone

HbA1c reduction was also evaluated in 4 studies conducted in special populations (2 studies in patients with hypertension and 2 studies in patients with CV disease). Statistically significant HbA1c reductions with dapagliflozin 10 mg compared to placebo were observed in all 4 studies (Figure 12).

Figure 12: HbA1c Reduction (Dapagliflozin 10 mg vs. Placebo) in Patients with Cardiovascular Co-morbidities (Core Phase 3 Program, Studies D1690C00018, D1690C00019, MB102073, MB102077)



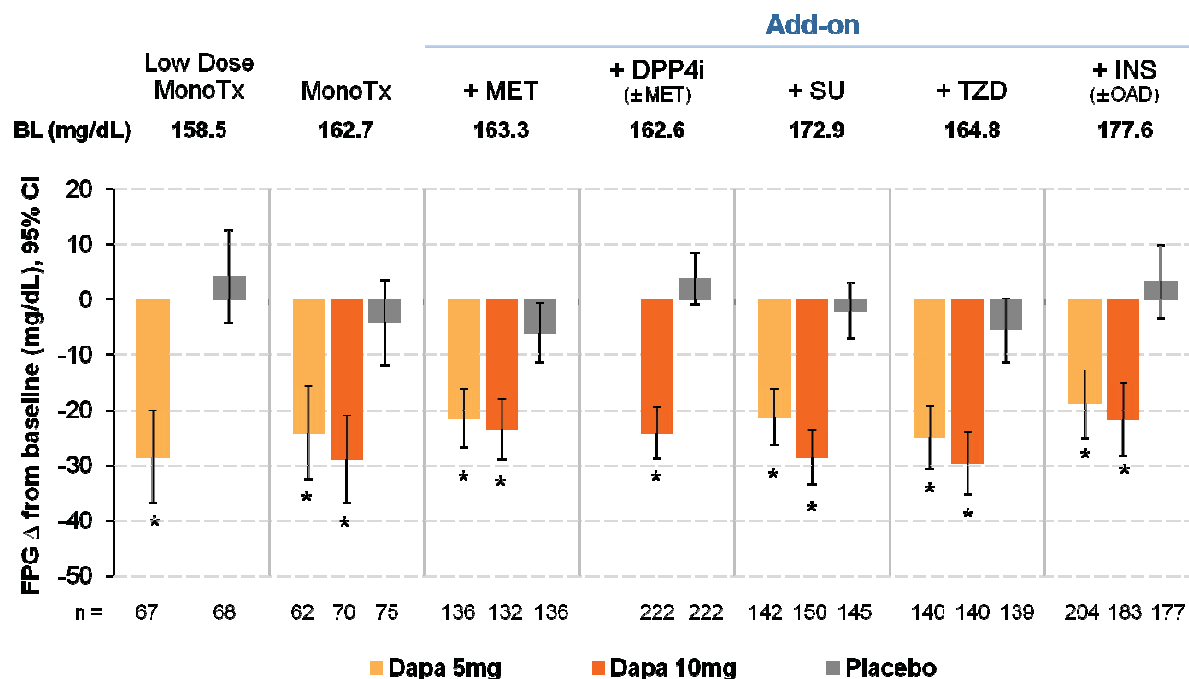
* Statistically significant vs placebo at week 12, repeated measures mixed model for HTN; and
Statistically significant vs placebo at week 24, ANCOVA (LOCF) for CVD

ANCOVA = Analysis of Covariance ; ACEi angiotensin-converting enzyme inhibitor = ; ARB = angiotensin receptor blocker; CI = confidence interval; CVD = cardiovascular disease; Dapa = dapagliflozin; HTN = hypertension; LOCF = last observation carried forward; Pbo = placebo; Pts = patients; w/ = with
Study numbers: 018 = D1690C00018; 019 = D1690C00019; 073 = MB102073; 074 = MB102074

Fasting Plasma Glucose

Mean reductions from baseline in FPG at Week 24 with the dapagliflozin 10 mg dose ranged from -21.7 to -29.6 mg/dL across the placebo-controlled studies (Figure 13). As a consequence of the rapid PD effect of glucosuria, mean decreases from baseline in FPG were seen as early as 1 week following the initiation of therapy.

Figure 13: FPG: Mean Change from Baseline at Week 24 (Core Placebo-controlled Phase 3 Studies)



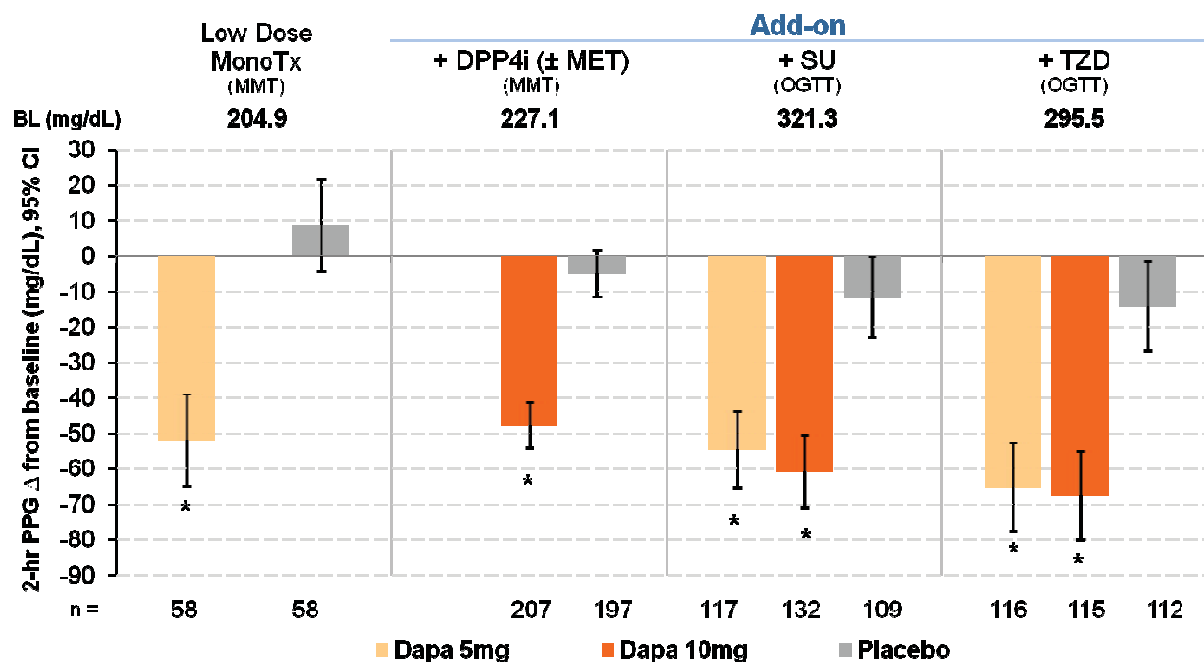
* Statistically significant vs placebo.

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

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; INS = Insulin; LOCF = last observation carried forward; MET = metformin; MonoTx = monotherapy treatment; OAD = oral antidiabetic; SITA = Sitagliptin; SU = sulfonylurea; PBO = placebo; PIO = pioglitazone

Postprandial Glucose

Significant mean reductions in PPG were also observed in those studies where this variable was assessed (Figure 14; D1690C00005, D1690C00010, MB102030, and MB102032).

Figure 14: 2-Hour PPG: Mean Change from Baseline at Week 24 (Core Placebo-controlled Phase 3 Studies)

OGTT = oral glucose tolerance test; MMT = mixed meal test

* Statistically significant vs placebo.

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

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; PPG postprandial glucose; LOCF = last observation carried forward; MET = metformin; MonoTx = monotherapy treatment; SITA = Sitagliptin; SU = sulfonylurea; PBO = placebo; PIO = pioglitazone

A statistically significantly greater proportion of patients treated with dapagliflozin 5 and 10 mg achieved a therapeutic response of HbA1c at Week 24 < 7% vs. those treated with placebo in the add-on to metformin (MB102014: 37.5% and 40.6% for the 5 mg and 10 mg treatment group, respectively vs. 25.9% for placebo), add-on to pioglitazone (MB102030: 32.5% and 38.8% for the 5 mg and 10 mg treatment group, respectively vs. 22.4% for placebo), and add-on to glimepiride (D1690C00005: 30.3% and 32.7% for the 5 mg and 10 mg treatment group, respectively vs. 13.0% for placebo) studies ($p < 0.05$). Similarly, in both monotherapy studies, numerically higher proportions of patients achieved a therapeutic glycemic response of HbA1c < 7% at Week 24 in the 5 and 10 mg dapagliflozin treatment groups compared with placebo (MB102013: 44.2% and 50.8% for the 5 mg and 10 mg treatment group, respectively vs. 31.6% for placebo; and MB102032 [low-dose]: 49.1% for the 5 mg treatment group vs. 31.6% for placebo). Statistical testing of proportions of patients with therapeutic responses in the monotherapy study, MB102013, was not performed due to sequential testing methods used to control family-wise type I error.

Insulin is associated with weight gain and hypoglycemia and progressive insulin dose escalation is often required to achieve or maintain T2DM treatment goals. Secondary endpoints to evaluate changes in insulin requirements as supportive measures of glycemic efficacy were included in the add-on to insulin study (D1690C00006). There was a small reduction in mean total daily

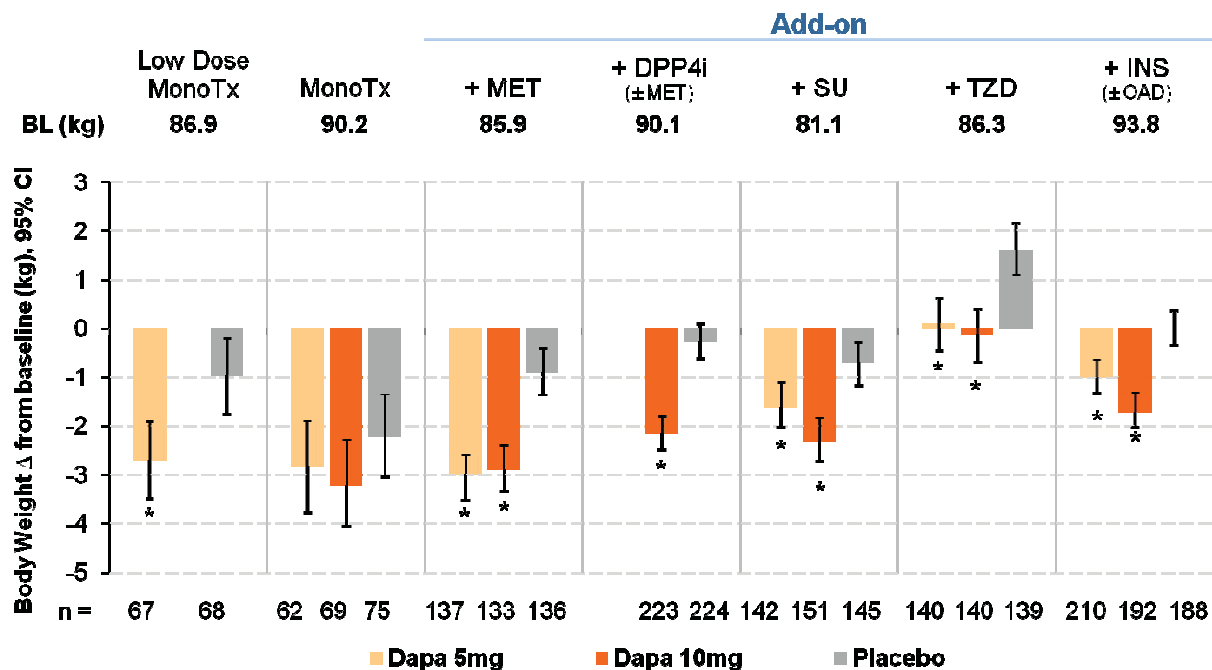
insulin dose (baseline mean: 77.96 international units [IU]) in the dapagliflozin 10 mg treatment group at Week 24 (-1.16 IU) contrasting with an increase in mean insulin dose (baseline mean: 73.96 IU) by 5.08 IU in the placebo group. A statistically significantly higher proportion of patients treated with dapagliflozin 10 mg had mean daily insulin dose reductions of at least 10% (19.6%) vs. placebo (11.0%).

4.2.2.2 Measures of Insulin Resistance and Beta Cell Function

Reduction in glucotoxicity by SGLT inhibition has been shown in animals to improve insulin resistance and beta cell function.^{12,13} Dapagliflozin has been shown to increase insulin sensitivity. Study MB102045 measured insulin sensitivity by the hyperinsulinemic euglycemic clamp (HEC) in patients receiving 5 mg dapagliflozin or placebo with T2DM inadequately controlled with metformin alone or with a combination of metformin and an insulin secretagogue. A placebo-subtracted adjusted mean improvement of 19.97% (p=0.0059) in glucose disposal rate, a measurement of insulin sensitivity, was seen following 12 weeks of dapagliflozin therapy. Insulin sensitivity along with beta cell function was also assessed in several Phase 3 studies by homeostasis model assessment 2 (HOMA-2). Exploratory analyses by HOMA-2 showed placebo-subtracted adjusted mean percent increases in insulin sensitivity of 2.95% to 28.21%, and increases in beta cell function of 0.45% to 17.27%.

4.2.2.3 Body Weight

Treatment with dapagliflozin was associated with clinically meaningful weight loss that was consistently seen across the clinical program ([Figure 15](#)). Dapagliflozin with its unique MOA, persistent loss of calories in the urine, and subsequent negative energy balance, resulted in weight loss that was primarily attributable to a reduction in total body fat ([Figure 16](#)).

Figure 15: Body Weight: Mean Change from Baseline at Week 24 (Core Placebo-controlled Phase 3 Studies)

* Statistically significant vs placebo.

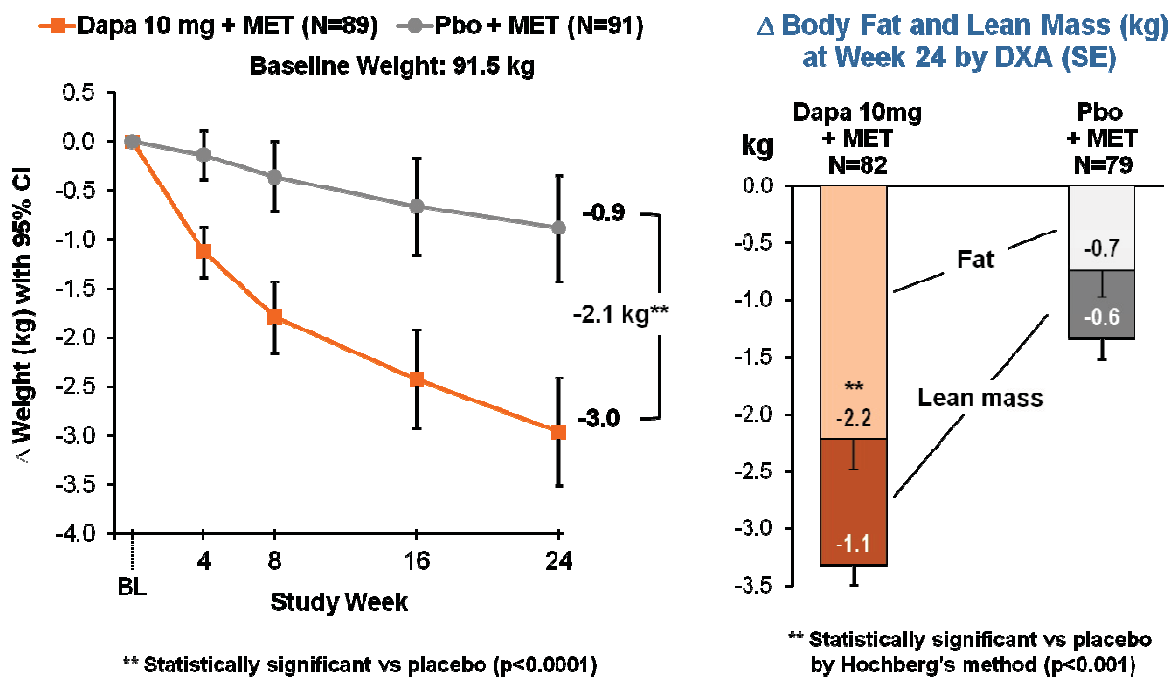
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CVD = cardiovascular disease; Dapa = dapagliflozin; DM = type 2 diabetes mellitus; HTN = hypertension; INS = Insulin; LOCF = last observation carried forward; MET = metformin; MonoTx = monotherapy treatment; OAD = oral antidiabetic; SITA = Sitagliptin; SU = sulfonylurea; PBO = placebo; PIO = pioglitazone

In the placebo-controlled studies, the placebo-corrected mean weight reductions over 24 weeks for dapagliflozin 10 mg ranged from -0.46 to -2.16 kg and, with the exception of study MB102013, were statistically significant for the 10 mg dose of dapagliflozin.

4.2.2.4 Dual X-ray Absorptiometry (DXA) Study

The majority of weight loss due to dapagliflozin was attributable to a reduction in total body fat mass, as measured by DXA evaluated in Study D1690C00012. The type of weight loss achieved is clinically important as total body fat correlates positively with key CV risk factors, most strongly with insulin resistance.¹⁴ Study D1690C00012 was designed to address this question with change from baseline in mean body weight being the primary endpoint. Treatment with dapagliflozin 10 mg as add-on to metformin in patients with treatment failure on metformin resulted in a statistically significant mean weight reduction of -2.1 kg ($p < 0.0001$) compared to placebo plus metformin (Figure 16).

Figure 16: Body Weight and Body Fat: Adjusted Mean Change from Baseline to Week 24 (Add-on to Metformin Study D1690C00012)

DXA = dual X-ray absorptiometry.

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

Source: D1690C00012 24w CSR

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; LOCF = last observation carried forward; MET = metformin; PBO = placebo

Increasing central obesity is associated with an increased risk of morbidity and mortality.¹⁵ A statistically significant mean placebo-corrected reduction of 1.5 cm in waist circumference was observed in the dapagliflozin group. The proportion of patients attaining a weight loss of 5% or more was also statistically significantly greater in the dapagliflozin group (30.5%) compared to the placebo group (4.3%; p-value <0.0001).

Exploratory analyses in Study D1690C00012 also showed favorable effects on the distribution of body mass (Figure 16). Due to the relatively greater amount of fat loss in patients treated with dapagliflozin vs. placebo, there was an increase in the percentage of lean tissue mass (non-fat, non-bone mass, including fluid compartments) relative to total body weight in the dapagliflozin-treated patients (difference between treatment groups of 0.9% as measured by DXA). An exploratory analysis in a subset of patients utilizing magnetic resonance imaging suggested that the decrease in body fat mass was partly attributable to a decrease in visceral adipose tissue, which is associated with abnormalities in glucose and lipid metabolism;¹⁶ an approximately 10% reduction in visceral adipose tissue volume was observed in the dapagliflozin group (-322.6 cm³ [95% CI = -485.1, -160.2]) compared to a < 1.5% change in the placebo group (-8.7 cm³ [95% CI = [-154.8, 137.4]).

4.2.2.5 Blood Pressure Reductions

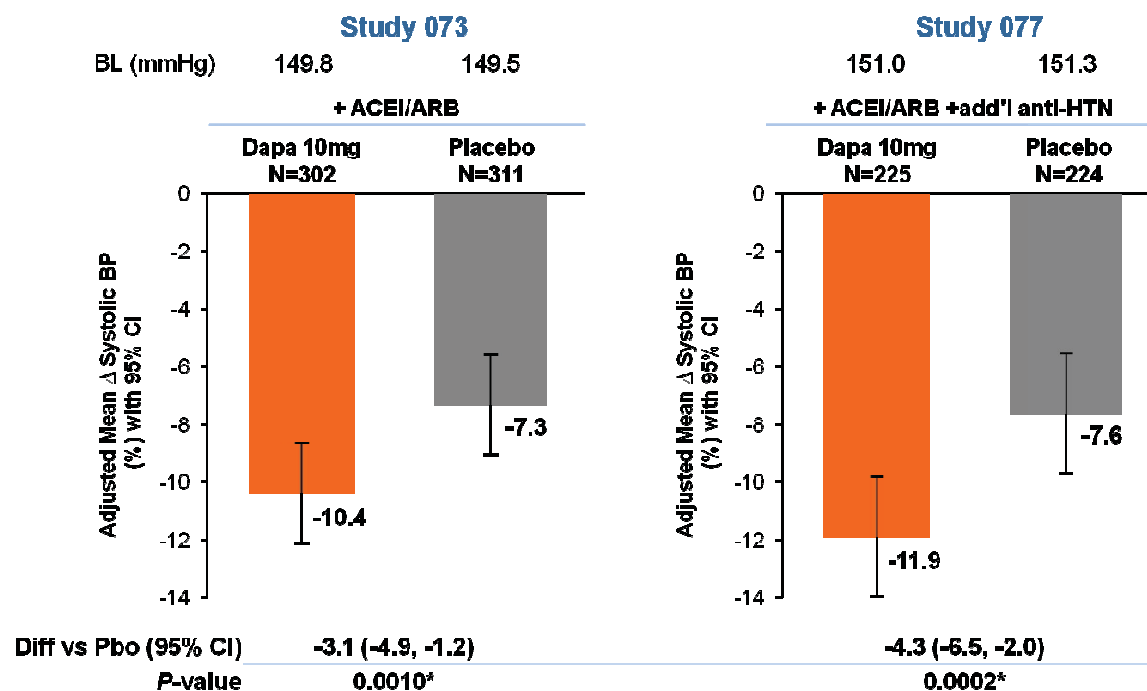
Treatment with dapagliflozin 10 mg resulted in statistically and clinically significant reductions in seated SBP and in 24-hour ambulatory SBP in hypertensive patients with T2DM when added to pre-existing antidiabetic and antihypertensive treatments. These observations are consistent with a mild diuretic effect in combination with weight loss due to inhibition of SGLT2.¹⁷

Studies MB102073 and MB102077 were designed to evaluate the effect of dapagliflozin on BP and HbA1c in patients with T2DM with inadequately controlled hypertension on an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB; MB102073) or an ACEi or ARB plus an additional antihypertensive medication (MB102077). Across the 2 studies, 527 patients were treated with dapagliflozin 10 mg and 535 with placebo. Patients treated with dapagliflozin 10 mg also received the following medications for BP control: ACEs (63%), ARBs (37%), thiazide diuretics (41.8%), calcium channel blockers (21%), beta blockers (16%) and alpha adrenergic blockers (1%). Baseline mean (seated) SBP was 149.5 to 151.3 mmHg (Figure 17) and baseline mean seated diastolic BP (DBP) was 91 mmHg (Table 7). Additionally, 24 hour ambulatory BP was also measured. Baseline 24-hour mean ambulatory BP was 145.9 to 149.2 mmHg systolic over 87.0 to 88.0 mmHg diastolic.

At Week 12 in both studies, dapagliflozin 10 mg provided significant improvement in seated SBP and significant reduction in 24-hour mean ambulatory SBP when added to pre-existing antidiabetic and antihypertensive treatments (Figure 17 and Table 7). Seated DBP showed a reduction from baseline in patients treated with dapagliflozin 10 mg, but the difference from placebo was not statistically significant.

In addition, exploratory analyses in the initial Phase 3 studies showed mean numerical reductions at Week 24 vs. placebo in SBP (-1.3 to -5.3 mmHg placebo-corrected) in the dapagliflozin 10 mg groups in all of the Phase 3 monotherapy and placebo-controlled add-on combination therapy studies. Across the Phase 3 program, there was a minimal effect on measured orthostatic hypotension, mitigating associated safety concerns. No clinically relevant mean changes from baseline in seated heart rate were observed. In the Placebo-controlled Pool (ST), mean changes from baseline at Week 1 (0.4 and 0.1 beats per minute [bpm] and at Week 24 (-0.1 and 0.6 bpm) were observed in the dapagliflozin 10 mg and placebo groups, respectively.

Figure 17: Seated Systolic Blood Pressure Reduction at Week 12 (Studies in Hypertensive Patients with T2DM, MB102073 and MB102077)



* Significant P-value

Source: 30-MU, Table 32

Add'l = additional; BL = baseline; BP = blood pressure; ACEi angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; Dapa = dapagliflozin; HTN = hypertension; Pbo = placebo

Table 7: Ambulatory Systolic Blood Pressure and Seated and Ambulatory Diastolic Blood Pressure Changes at Week 12 (Studies in Hypertensive Patients with T2DM, MB102073 and MB102077)

	MB102073		MB102077	
Efficacy Parameter	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
	N=302 ^a	N=311 ^a	N=225 ^a	N=224 ^a
24-hour Mean Ambulatory Systolic Blood Pressure (mmHg) (LOCF)				
Baseline (mean)	145.9	146.6	146.5	149.2
Change from baseline (adjusted mean ^b)	−9.6	−6.7	−11.3	−6.9
Difference from placebo (adjusted mean ^b)	−2.9 ^c		−4.5 ^c	
(95% CI)	(−4.9, −0.9)		(−7.1, −1.8)	
Seated Diastolic Blood Pressure (mmHg) (LRM)				
Baseline (mean)	91.1	90.8	91.2	91.4
Change from baseline (adjusted mean ^b)	−5.8	−4.8	−6.3	−5.3
Difference from placebo (adjusted mean ^b)	−1.0		−1.0	
(95% CI)	(−2.2, 0.1)		(−2.3, 0.4)	
24-hour Mean Ambulatory Diastolic Blood Pressure (mmHg) (LOCF)				
Baseline (mean)	87.0	87.2	87.5	88.0
Change from baseline (adjusted mean ^b)	−6.2	−5.5	−7.6	−5.6
Difference from placebo (adjusted mean ^b)	−0.6		−2.0	
(95% CI)	(−2.0, 0.7)		(−3.7, −0.3)	

^a Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.^b Least squares mean adjusted for baseline value.^c p-value <0.05.

Source: 30-MU, Table 32

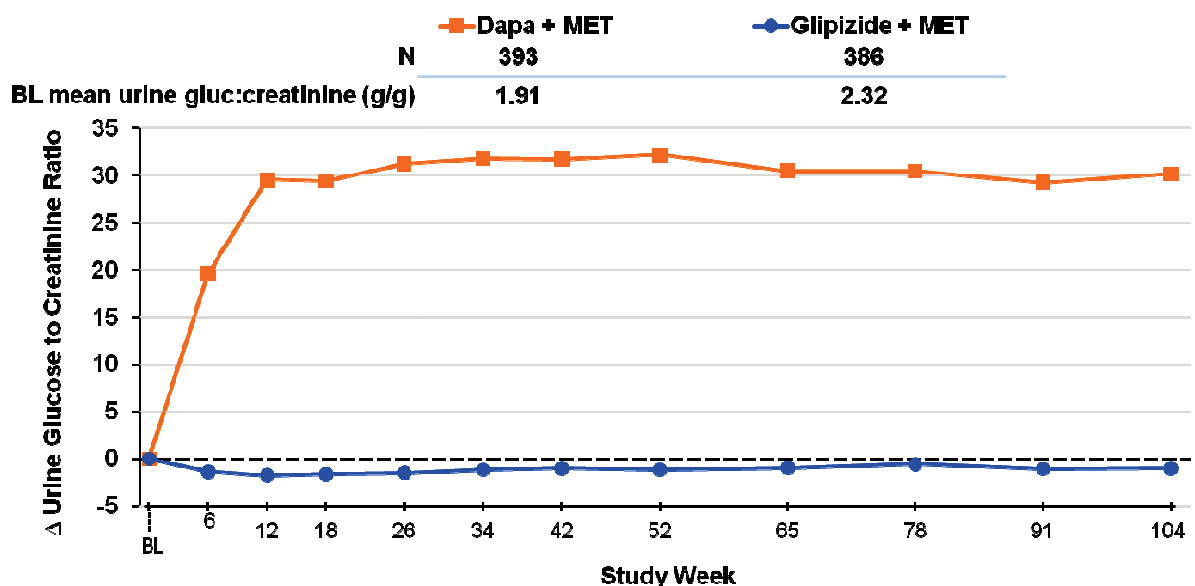
LOCF = last observation carried forward; LRM = longitudinal repeated measures analysis

4.2.3 Durability of Effect

Among the Phase 3 studies included in the resubmission, many of them had LT extensions: 3 studies had 1-year study duration, 7 had 2-year study duration, and 1 had 4-year study duration. While the primary purpose of the LT extension treatment period was to assess safety, exploratory efficacy analyses were also performed to assess the durability of treatment effects on HbA1c, other glycemic endpoints, and body weight. Dapagliflozin treatment resulted in continuing, undiminished urinary glucose excretion for up to 2 years in all placebo-controlled studies, consistent with the undiminished glucosuric PD effects observed during LT dapagliflozin treatment, HbA1c, and weight reductions observed at Week 24 also were maintained through Week 104 relative to placebo.

In the active comparator study, D1690C00004, urinary glucose excretion, here measured as spot urine glucose to creatinine ratio, was maintained through Week 104 indicating LT persistence of PD effect (Figure 18). The numerical decrease in HbA1c with dapagliflozin seen at Week 52 was sustained through Week 91 with some attenuation in effect thereafter through Week 104 (Figure 19). However, in the glipizide treatment group, the attenuation of the HbA1c-lowering effect seen at 18 weeks after the completion of the titration period continued over the remaining treatment period, eventually showing < 0.2% HbA1c difference from baseline HbA1c by Week 104.

Figure 18: Increase in Urine Glucose to Creatinine Ratio Sustained over Time (104 Weeks; Active Comparator Study D1690C00004)



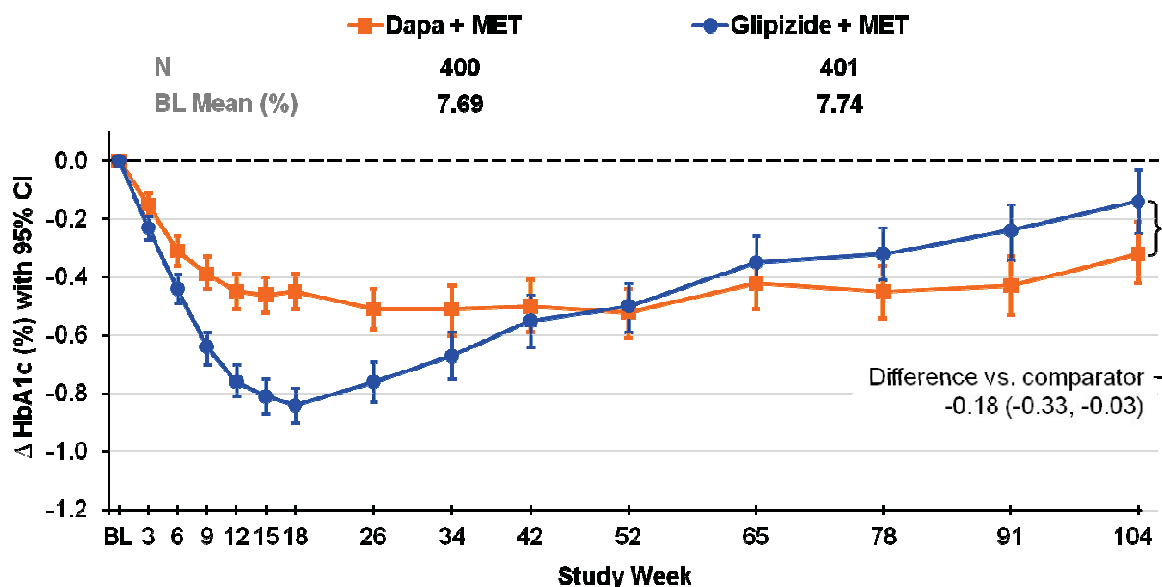
Sample Size Per Time Point

Dapa + MET	393	379	355	362	352	337	329	319	305	264	240	228
Glip + MET	386	373	346	351	352	341	329	310	297	244	221	205

Repeated measures mixed model analysis.

Source: D1690C00004-CSR-104 Weeks

BL = baseline; Dapa = dapagliflozin; Glip = glipizide; MET = metformin

Figure 19: HbA1c: Mean Change from Baseline over Time (104 Weeks; Active Comparator Study D1690C00004)**Sample Size Per Time Point**

Dapa + MET	400	378	369	354	339	334	321	311	271	242	233
Glip + MET	401	370	361	354	342	331	315	303	248	226	208

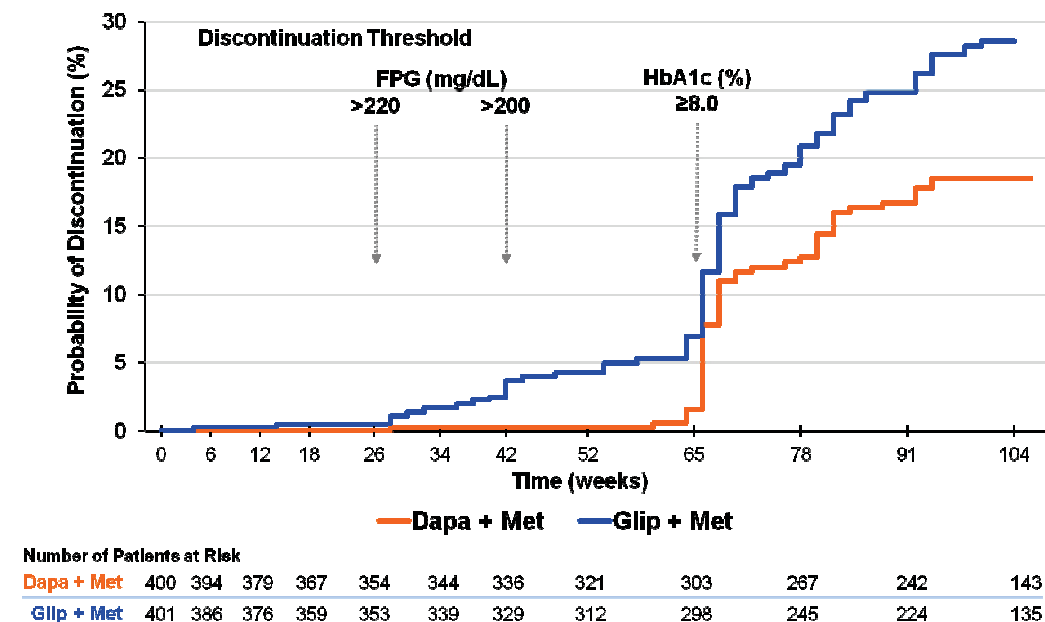
Repeated measures mixed model analysis

Source: D1690C00004-CSR-104 Weeks

BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Glip = glipizide; MET = metformin;

Supportive evidence for LT efficacy is provided in the analyses of rescue or discontinuation for failing to achieve glycemic targets. More patients discontinued from lack of glycemic control in the glipizide group compared to the dapagliflozin group at all time points in Study D1690C00004 (Figure 20). Similarly, the decrease from baseline in mean body weight seen with dapagliflozin at Week 52 was sustained through Week 104. Glipizide resulted in a sustained increase in mean body weight over the same time period (Figure 21).

Figure 20: Time to Discontinuation for Lack of Glycemic Control over 104 Weeks (Active Comparator Study D1690C00004)

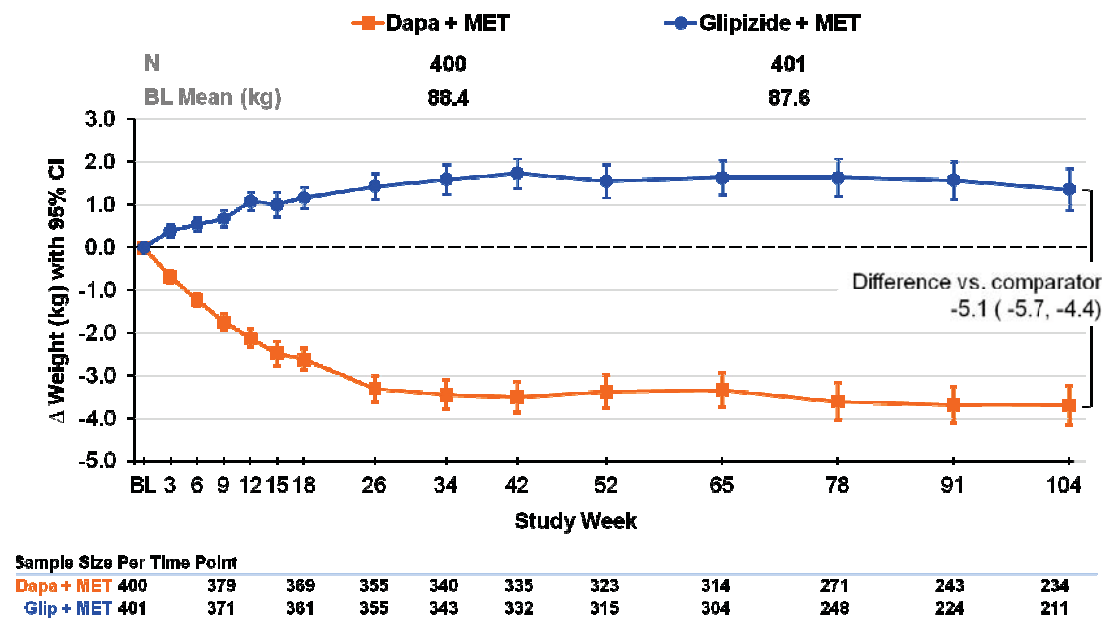


All randomized and treated patients included in the analysis.

Source: D1690C00004-CSR-104 Weeks

Dapa = dapagliflozin; Glip = glipizide; Met = metformin;

Figure 21: Total Body Weight: Mean Change from Baseline over Time (104 Weeks; Active Comparator Study D1690C00004)



Repeated measures mixed model analysis

Source: D1690C00004-CSR-104 Weeks

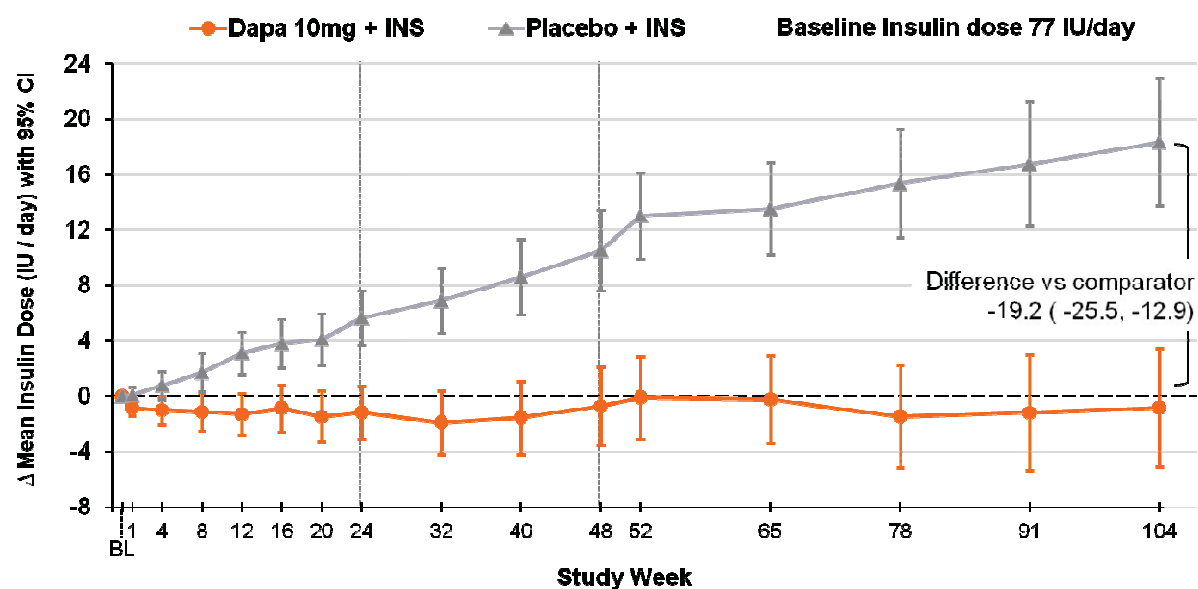
BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Glip = glipizide; MET = metformin;

The findings from Studies MB102030, D1690C00005, MB102013, D1690C00004, D1690C00010, D1690C00012, D1690C00018, and D1690C00019 are also indicative that effects on HbA1c, FPG, and weight, whether including or excluding data after rescue, were maintained during the LT period.

In the add-on to insulin study (D1690C00006), at Week 104, a mean reduction in HbA1c compared to baseline was observed in all dapagliflozin treatment groups using repeated measures analyses and excluding data after insulin up-titration. The HbA1c adjusted mean change from baseline observed in the dapagliflozin 10 mg group at Week 104 (-0.71 [95% CI = -0.86, -0.57]) was similar to those at Week 48 (-0.92 [95% CI = -1.03, -0.80]), whereas in the placebo group the initial reductions in HbA1c observed at Weeks 24 and 48 (-0.43 [95% CI = -0.56, -0.29]) were not observable at Week 104 (-0.06 [95% CI = -0.25, 0.13]).

In addition, there was no meaningful change in mean daily insulin dose at Week 104 in the dapagliflozin treatment groups compared to baseline (range of 4.09 to -0.83 IU/day mean change in the dapagliflozin groups), while a mean numerical increase of 18.34 IU/day was observed in the placebo group compared to baseline ([Figure 22](#)). The increase in calculated mean daily insulin dose in the placebo group observed at Week 48 was nearly doubled at Week 104, whereas there was no notable change in the dapagliflozin groups. Along with the increase in daily insulin dose, a modest weight loss at Week 104 compared to baseline was observed in the dapagliflozin groups, with the most pronounced effect in the dapagliflozin 10 mg group (-1.97 kg [95% CI = -2.69, -1.26]), while patients in the placebo group showed a slight increase in body weight (0.91 kg, [95% CI = -0.05, 1.87]). Given that insulin therapy is often associated with weight gain, this finding may be related to the insulin-sparing effect of dapagliflozin in addition to its effects on urinary caloric loss.

Figure 22: Calculated Mean Daily Insulin Dose (IU/day): Adjusted Mean Change from Baseline over Time up to Week 104 (Add-on to Insulin Study D1690C00006)



Sample Size Per Time Point

Dapa 10mg+INS	189	185	180	177	175	173	166	145	146	144	142	140
Placebo+INS	185	176	170	168	164	158	157	121	118	114	110	104

Repeated measures mixed model analysis, including data after insulin up-titration.

Source: D1690C00006-CSR-104Weeks

CI = confidence interval; Dapa = dapagliflozin; INS = insulin

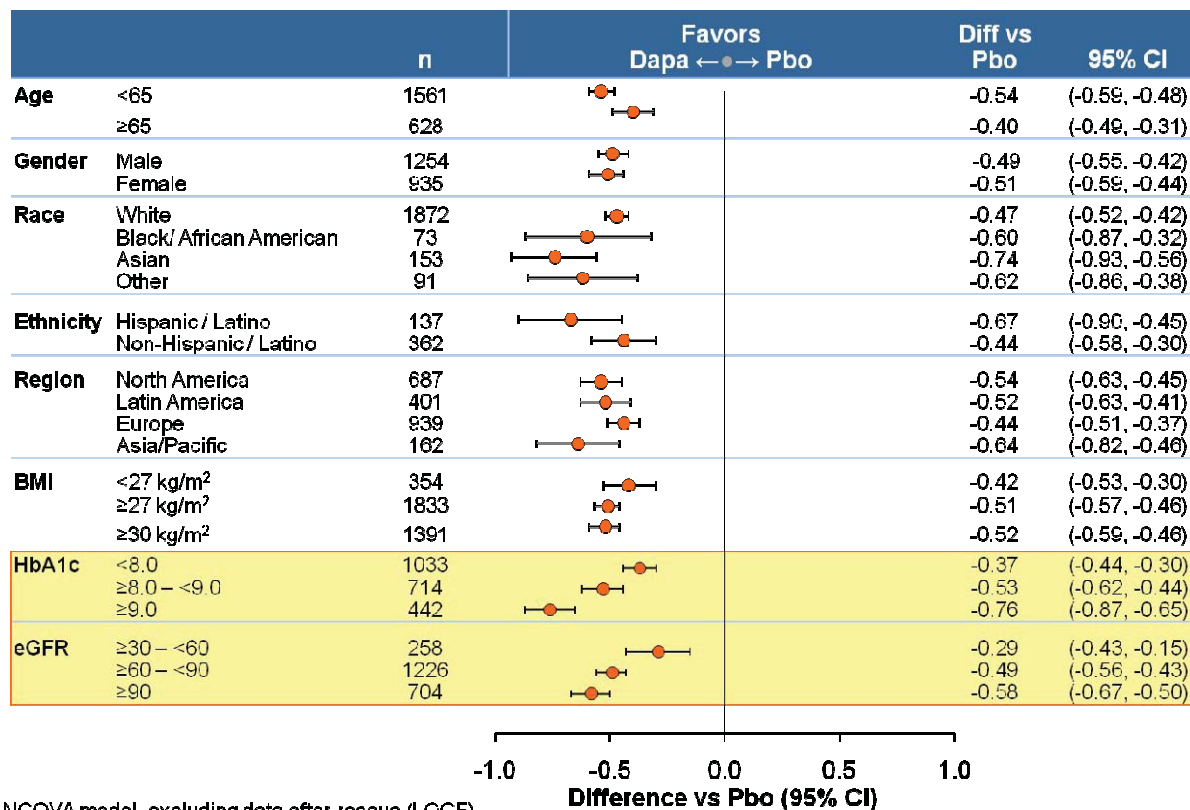
4.2.4 Efficacy in Key Subgroups

To support the overall benefit and risk assessment in key subpopulations, a pool of Phase 3 placebo-controlled studies, as defined below, was created. Criteria for inclusion in the pool were use of the 10 mg dose, use of placebo as comparator, and assessment of the primary endpoint at 24 weeks. Dapagliflozin 10 mg and placebo treatment group data from 10 Phase 3 studies were combined to evaluate consistency of treatment effects across subpopulations. This pool included 1 monotherapy study (MB102013), 8 add-on combination therapy studies (MB102014, MB102030, D1690C00005, D1690C00006, D1690C00010, D1690C00012, D1690C00018, D1690C00019) and 1 initial combination study (MB102034). Data from the other 6 Phase 3 studies were excluded because they did not contain dapagliflozin 10 mg (MB102021 and MB102032), were active comparator (D1690C00004), included special risk populations that were expected to impact HbA1c (MB102029 [moderate renal impaired patients]), or had shorter study durations (12 weeks; MB102073 and MB102077).

The effect of dapagliflozin on the adjusted mean change from baseline in HbA1c vs. placebo was examined in 10 pre-specified subgroups of potential interest: age, gender, race, ethnicity, female age, geographic region, baseline BMI, baseline HbA1c, duration of T2DM, and baseline eGFR (Figure 23).

While dapagliflozin 10 mg showed glycemic efficacy in all of the adequately sized subgroups in the pooled analyses, greater placebo-corrected reductions in HbA1c were observed for groups with higher baseline HbA1c, higher baseline eGFR, and younger age. However since eGFR decreases with advancing age, after adjusting for baseline eGFR, age was no longer a factor affecting the efficacy of dapagliflozin. The individual subgroups of HbA1c and eGFR in the 30-MU Efficacy Pool are discussed in more detail below.

Figure 23: HbA1c Placebo-corrected Difference vs. Placebo by Subgroups at Week 24



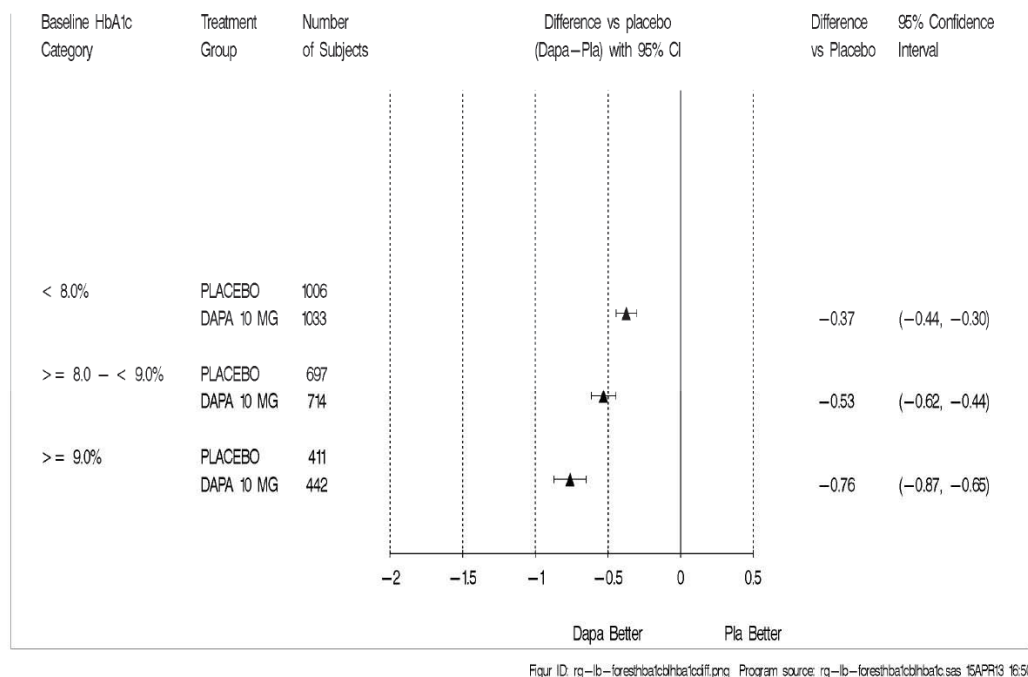
ANCOVA model, excluding data after rescue (LOCF)

Source: 30-MU, Appendices 806, 807, 808, 809, 810, 811, 812, 813, and 815

ANCOVA = analysis of covariance; BMI = body mass index = CI = confidence interval; Dapa = dapagliflozin; Diff = difference; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; Pbo = placebo

4.2.4.1 Effect of Baseline HbA1c Category on HbA1c

Dapagliflozin treatment was consistently effective in reducing HbA1c across baseline HbA1c subgroups (< 8.0%, ≥ 8.0% and < 9.0%, and ≥ 9.0%) and resulted in greater HbA1c reductions from baseline in patients with higher baseline HbA1c (Figure 24). Similar findings are observed with other T2DM therapies.¹⁸ Strong treatment-by-subgroup interactions (p-values < 0.0001) were identified in both the NDA and 30-MU Efficacy Pooled Populations.

Figure 24: HbA1c Difference vs. Placebo at Week 24 by Baseline HbA1c Category (30-MU Efficacy Pooled Population)

Includes study MB102013 (QAM and QPM doses combined, excluding Group 2), MB102014, MB102030, D1690C00005, D1690C00006, D1690C00010, D1690C00012, D1690C00018, D1690C00019 and MB102034 (excluding dapagliflozin alone arm).

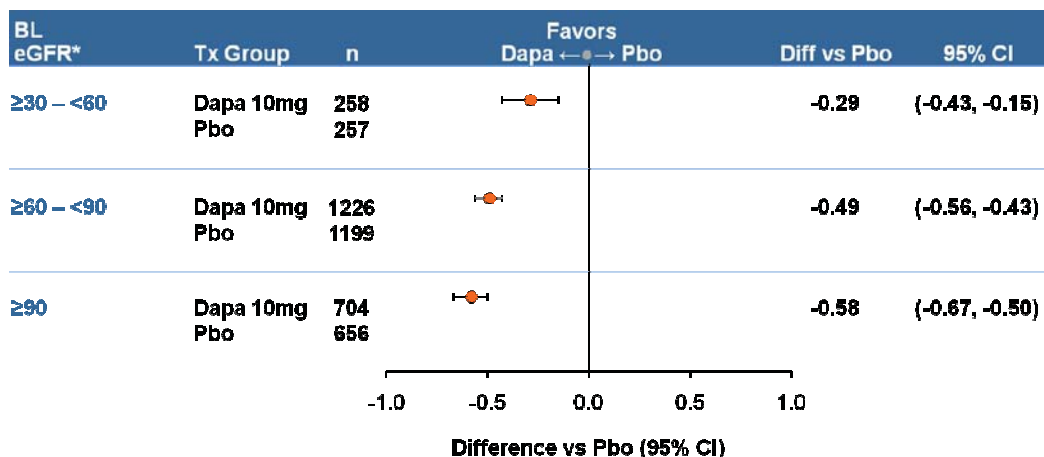
ANCOVA model, excluding data after rescue (LOCF)

Source: 30-MU, Figure 802

ANCOVA = analysis of covariance; CI = confidence interval; Dapa = dapagliflozin; HbA1c = hemoglobin A1c; LOCF = last observation carried forward; Pla = placebo

4.2.4.2 Effect of Baseline eGFR Category on HbA1c

Consistent with the MOA, the efficacy of dapagliflozin is dependent on renal function. Efficacy was evaluated by baseline eGFR in the 30-MU Efficacy Pooled Population (Figure 25). Placebo-corrected HbA1c reductions seen in patients with normal renal function ($\text{eGFR} \geq 90 \text{ mL/min/1.73m}^2$) and mild renal impairment ($\text{eGFR} \geq 60$ and $< 90 \text{ mL/min/1.73m}^2$) were -0.58% and -0.49%, respectively. In patients with moderate renal impairment ($\text{eGFR} \geq 30$ and $< 60 \text{ mL/min/1.73 m}^2$), a lesser placebo-corrected reduction of -0.29% was observed.

Figure 25: HbA1c Difference vs. Placebo at Week 24 by Baseline eGFR (30-MU Efficacy Pooled Population)*Unit: mL/min/1.73 m²

ANCOVA model, excluding data after rescue (LOCF)

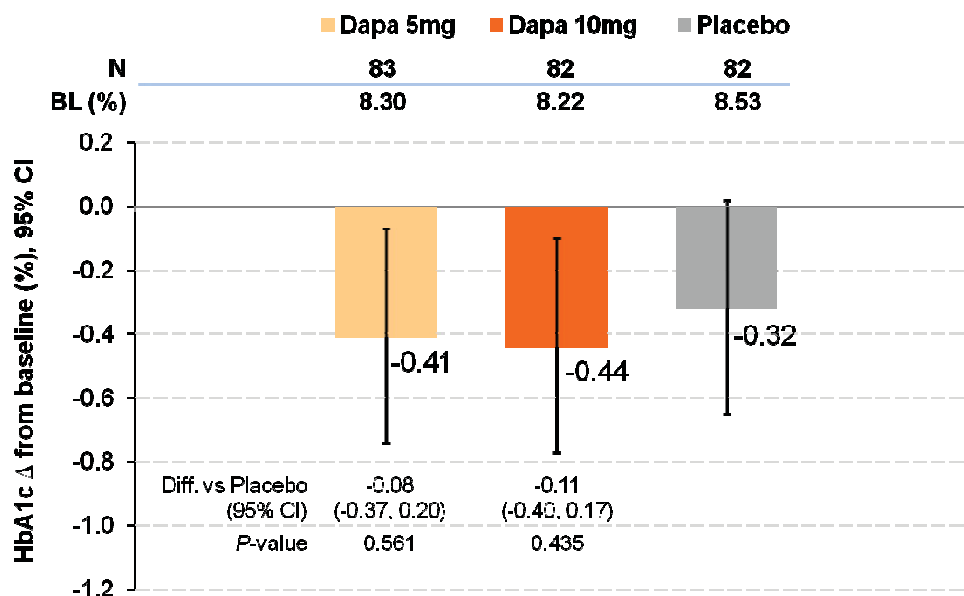
Source: 30-MU, Appendix 803

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Diff = difference; eGFR = estimated glomerular filtration rate; LOCF = last observation carried forward; Pbo = placebo; Tx= treatment group

In line with effect of baseline renal function on HbA1c reduction, a smaller HbA1c reduction was observed in elderly patients which was explained by the reduced renal function with advancing age. Once baseline renal function was accounted for, there was no significant interaction between age category and HbA1c reduction (p-value for treatment by subgroup interaction = 0.4053)

Study MB102029

In Study MB102029 (moderate renal impairment study), which enrolled patients with eGFR between 30 to 60 mL/min/1.73 m², treatment with dapagliflozin 10 mg did not produce a statistically greater reduction in HbA1C compared to placebo (Figure 26). Initiation of dapagliflozin is therefore not recommended in patients with eGFR < 60mL/min/1.73m².

Figure 26: HbA1c Reduction at Week 24 in the Moderate Renal Impairment Study (MB102029)

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

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 24 (LOCF) values.

(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.

Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a covariate.

Source: MB102029 CSR-24 Weeks

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; Diff = difference; LOCF = last observation carried forward

4.3 Conclusion on Efficacy

Dapagliflozin is effective in reducing HbA1c in a broad range of patients regardless of disease progression/duration or concomitant use of anti-diabetic therapies. It is comparable in efficacy to current foundational oral treatments for T2DM, such as metformin and SUs, and can be used as monotherapy, as add-on combination therapy to metformin, SU, TZD, DPP-4 inhibitor, or insulin (\pm OAD), and as initial combination therapy with metformin. Secondary glycemic efficacy parameters support the primary efficacy findings.

Dapagliflozin 10 mg consistently demonstrated numerically superior HbA1c and FPG reductions vs. the 5 mg dose. In addition, the 10 mg dose demonstrated equivalent efficacy to commonly prescribed potent glucose lowering OAD agents in the US such as metformin and glipizide (SU). Overall, though both 5 mg and 10 mg demonstrated clinical efficacy, the 10 mg dose was more effective than the 5 mg dose.

As expected based on its MOA, the glycemic efficacy of dapagliflozin is attenuated in patients with reduced renal function ($\text{eGFR} < 60 \text{ mL/min/1.73m}^2$), and initiation of dapagliflozin is not recommended in this patient population.

Dapagliflozin also reduces total body weight relative to placebo/comparator. The weight loss is mainly attributable to a decrease in body fat mass.

Dapagliflozin has consistently shown reductions in BP in the clinical program regardless of background anti-hypertensive medications as well as in 2 dedicated studies in hypertensive patients with T2DM. There was a minimal effect on measured orthostatic hypotension, and no increase in heart rate, mitigating associated safety concerns.

Placebo-controlled data for over 2 years on similar background and rescue therapies indicate that the PD effects of glucosuria, as well as the beneficial effects of dapagliflozin on HbA1c and weight, are maintained in LT treatment.

5 OVERVIEW OF SAFETY

The safety profile of dapagliflozin has been well-characterized through an extensive development program.

To complement standard safety monitoring practices, a widespread program was implemented to monitor and collect additional information for selected events and laboratory parameters of interest based upon: (1) potential importance to anti-hyperglycemic agents in general; (2) relevance given the MOA of dapagliflozin; (3) suggestions from nonclinical, Phase 1 or Phase 2 safety data; or (4) identification in the Phase 3 trials. They included, in particular, those risks associated with urinary glucose excretion. These events and laboratory parameters of interest are addressed individually in Section 5.1. Due to the selectivity of dapagliflozin's kidney-specific MOA, off-target activity was not expected and not seen.

Dapagliflozin's comprehensive nonclinical testing program did not reveal any findings that would preclude the safe usage of dapagliflozin in patients with T2DM. In particular, dapagliflozin was not associated with any target organ or adverse effects at large multiples of human exposure, was non-genotoxic, and was not associated with any indications of being carcinogenic.

Dapagliflozin (2.5, 5.0, and 10 mg) demonstrated an acceptable safety profile, with a small proportion of patients having either a SAE (5.1% and 5.4% for dapagliflozin and control, respectively) or an AE leading to discontinuation (4.3% and 3.6% for dapagliflozin and control, respectively). In general, the anticipated risks, confirmed in the clinical development program, are manageable with standard clinical practice typical for patients with T2DM, are reversible, and do not cause discontinuations.

5.1 Adverse Event Profile

This section focuses on the results from the 30-MU Placebo-controlled ST Pool except where noted. Results from other pooled and individual study populations, including LT data and specific subgroups, are only discussed if there were dissimilar findings relative to the 30-MU Placebo-controlled ST Pool or if the limited number of events supported reference to the 30-MU All Phase 2b and 3 Studies Pool.

5.1.1 Deaths

Death was an infrequent event across the dapagliflozin clinical program. Cumulatively, 61 deaths occurred out of the 9,339 treated patients in the All Phase 2b and 3 Pool within each study's SAE reporting period. The frequency of death was balanced across the treatment groups (37 [0.6%] and 24 [0.7%] for dapagliflozin and control, respectively; Table 8). In addition, 9 deaths were reported spontaneously after study completion and the last follow-up visit. After inclusion of those deaths in the analysis, the frequency of deaths remained balanced (0.7%).

The most common cause of death was related to cardiac disorders, a common co-morbidity among T2DM patients.

Table 8: Deaths, Including Data after Rescue (30-MU)

Total (%) Patients with an Event	All Phase 2b and 3 Pool (ST+LT)	
	Dapa Total	All Control
	N = 5936	N = 3403
	37 (0.6%)	24 (0.7%)

Source: 30-MU, Appendix 306

Deaths in an additional 3 patients are not included in the table: D1692C00005-26-6 due to treatment with dapagliflozin 1 mg, and MB102029-72-623 and D1690C00010-1016-6 because the deaths were reported in the lead-in period, prior to randomization and receipt of study medication.

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

5.1.2 Serious Adverse Events

Overall, SAEs were reported for a small percent of patients. There was no imbalance in the proportions of patients with SAEs (Placebo-controlled ST Pool: 5.1% in the dapagliflozin 10 mg group vs. 5.4% in the placebo group; Table 9). The most commonly reported SAEs were in the following Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs): cardiac disorders; infections and infestations; gastrointestinal disorders; and musculoskeletal and connective tissue disorders. The most commonly reported SAEs by preferred term (PT) were unstable angina, myocardial infarction (MI), and pneumonia. Most SAEs were reported by 1 patient each (per PT) per treatment group. SAEs specific to the events of special interest are reported in their respective sections. SAEs were not related to dose (Table 10). The frequency of SAEs remains balanced in the Placebo-controlled ST+LT Pool and the All Phase 2b and 3 Pool.

5.1.3 Adverse Events Leading to Discontinuation

Overall, a small proportion of patients reported an AE that led to discontinuation (Placebo-controlled ST Pool: 4.3% in the dapagliflozin 10 mg group vs. 3.6% in placebo; Table 9). The SOC with the greatest proportion of discontinuations was Investigations (1.2% in the dapagliflozin 10 mg group vs. 1.1% in the placebo group). Within this SOC, the most frequent reason for discontinuation in both the dapagliflozin 10 mg and placebo groups was for decreased creatinine renal clearance (0.6% in both groups).

Events from the SOC renal and urinary disorders (1.2% for dapagliflozin vs. 0.4% for placebo), followed by infections and infestations (0.5% vs. 0.2%), and gastrointestinal disorders (0.3% for both groups), were the next most frequent reasons for discontinuation. Renal disorder discontinuations were largely driven by protocol defined study drug discontinuations for specific renal criteria. Renal impairment (0.8% vs. 0.3%) was the most frequently reported PT in the renal and urinary disorders. These events were primarily due to transient changes in serum creatinine or renal CrCl that were rarely associated with SAEs of renal failure or marked abnormalities of serum creatinine > 2.5 g/dL (see [Section 5.1.9](#)). In the infections and infestations SOC, UTI (0.2% vs. 0.1%) was the most frequently reported PT (see [Section 5.1.6](#)).

5.1.4 Overall Adverse Events

In the Placebo-controlled Pools, the proportion of patients reporting at least 1 AE was higher in the dapagliflozin 10 mg group relative to the placebo group during ST treatment (60.0% vs. 55.7%; [Table 9](#)) and ST+LT treatment (74.4% vs. 71.5%). The most common AEs ($\geq 2\%$) in either treatment group during the ST period were (in descending order of frequency for dapagliflozin): nasopharyngitis, UTI, back pain, headache, diarrhea, upper respiratory tract infection, dizziness, pollakiuria, and influenza. Events of UTI, back pain, dizziness pollakiuria, and influenza, were more common in the dapagliflozin 10 mg than the placebo group ([Table 11](#)). The overall frequency of AEs was not related to dose ([Table 10](#)). Hypoglycemia is addressed in [Section 5.1.5](#).

Table 9: Overall Adverse Events Summary, Short-term Double-blind Treatment Period including Data after Rescue - Placebo-controlled Pool, Treated Patients (30-MU and NDA Dataset)

	NDA DATABASE LOCK				30 MONTH SUR DATABASE LOCK			
	PLA N = 1393		DAPA 10MG N = 1193		PLA N = 2295		DAPA 10MG N = 2360	
AT LEAST ONE ADVERSE EVENT	792	(56.9)	734	(61.5)	1279	(55.7)	1416	(60.0)
AT LEAST ONE HYPOGLYCEMIA	112	(8.0)	128	(10.7)	284	(12.4)	324	(13.7)
AT LEAST ONE AE OR HYPOGLYCEMIA	828	(59.4)	771	(64.6)	1373	(59.8)	1513	(64.1)
AT LEAST ONE RELATED ADVERSE EVENT	185	(13.3)	216	(18.1)	261	(11.4)	409	(17.3)
DEATHS	1	(0.1)	3	(0.3)	4	(0.2)	7	(0.3)
AT LEAST ONE SAE	46	(3.3)	42	(3.5)	123	(5.4)	120	(5.1)
AT LEAST ONE RELATED SAE	5	(0.4)	2	(0.2)	7	(0.3)	3	(0.1)
SAE LEADING TO DISC. OF STUDY MED.	11	(0.8)	9	(0.8)	24	(1.0)	16	(0.7)
AE LEADING TO DISC. OF STUDY MED.	35	(2.5)	38	(3.2)	82	(3.6)	102	(4.3)
HYPOGLYCEMIA LEADING TO DISC. OF STUDY MED.	0		0		0		1	(0.0)

MedDRA Version: 15.1

N is the number of treated subjects.

Includes non-serious/serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days/30 days or up to and including the start date of the long-term period or up to the follow-up visit if earlier.

Only hypoglycemia reported as a SAE is included in the AE, related AE, SAE, related SAE, and AE leading to discontinuation summary lines. All reported hypoglycemia events within 4 days of last day of treatment are included in the hypoglycemia line.

Program Source: /gbs/prod/clin/programs/mb/102/iss/30msu/rpt/rt-ae-freq-v01.sas

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Table 10: Overall Adverse Events Summary, Short-term Double-blind Treatment Period including Data after Rescue - Placebo-controlled Pool, Treated Patients (NDA Dataset, By-dose)

	Number (%) of Patients									
	PLA N = 1393		DAPA 2.5MG N = 814		DAPA 5MG N = 1145		DAPA 10MG N = 1193		DAPA TOTAL N = 3291	
AT LEAST ONE ADVERSE EVENT	792	(56.9)	493	(60.6)	709	(61.9)	734	(61.5)	2030	(61.7)
AT LEAST ONE HYPOGLYCEMIA	112	(8.0)	133	(16.3)	130	(11.4)	128	(10.7)	405	(12.3)
AT LEAST ONE AE OR HYPOGLYCEMIA	828	(59.4)	529	(65.0)	747	(65.2)	771	(64.6)	2142	(65.1)
AT LEAST ONE RELATED ADVERSE EVENT	185	(13.3)	121	(14.9)	197	(17.2)	216	(18.1)	568	(17.3)
DEATHS	1	(0.1)	1	(0.1)	2	(0.2)	3	(0.3)	6	(0.2)
AT LEAST ONE SAE	46	(3.3)	37	(4.5)	40	(3.5)	42	(3.5)	122	(3.7)
AT LEAST ONE RELATED SAE	5	(0.4)	0		2	(0.2)	2	(0.2)	5	(0.2)
SAE LEADING TO DISC. OF STUDY MED.	11	(0.8)	5	(0.6)	9	(0.8)	9	(0.8)	23	(0.7)
AE LEADING TO DISC. OF STUDY MED.	35	(2.5)	18	(2.2)	32	(2.8)	38	(3.2)	93	(2.8)
HYPOGLYCEMIA LEADING TO DISC. OF STUDY MED.	0		0		0		0		0	

MedDRA Version: 13.0

N is the number of treated patients. DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Includes nonserious/serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days/30 days or up to and including the start date of the long-term period or up to the follow-up visit if earlier.

Only hypoglycemia reported as a SAE is included in the AE, related AE, SAE, related SAE, and AE leading to discontinuation summary lines. All reported hypoglycemia events within 4 days of last day of treatment are included in the hypoglycemia line.

Table 11: Most Common Adverse Events ($\geq 2\%$ in either Treatment Group), Placebo-controlled ST Pool (30-MU)

	% of Patients	
	Dapa 10 mg N = 2360	Placebo N = 2295
Nasopharyngitis	126 (5.3%)	133 (5.8%)
UTI	91 (3.9%)	61 (2.7%)
Back pain	83 (3.5%)	56 (2.4%)
Headache	81 (3.4%)	83 (3.6%)
Diarrhea	79 (3.3%)	87 (3.8%)
Upper Respiratory Tract Infection	72 (3.1%)	91 (4.0%)
Dizziness	54 (2.3%)	42 (1.8%)
Pollakiuria	49 (2.1%)	16 (0.7%)
Influenza	47 (2.0%)	44 (1.9%)
Edema Peripheral	43 (1.8%)	55 (2.4%)
Arthralgia	41 (1.7%)	46 (2.0%)
Hypertension	41 (1.7%)	66 (2.9%)

Source: 30-MU, Table 14

Bold = Events more common ($> 1\%$) in the dapagliflozin 10 mg than the placebo group

5.1.5 Hypoglycemia

Hypoglycemia was reported as major episodes, minor episodes, or other. Major episodes of hypoglycemia were defined as 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 episodes of hypoglycemia were defined as any episode, regardless of symptoms, with a capillary or plasma glucose measurement < 63 mg/dL that does not qualify as a major episode.

Overall, the available clinical data indicate that dapagliflozin, with its insulin-independent mechanism and direct glucose excretion MOA dependent on baseline glycemia, has a low propensity for hypoglycemia. In the monotherapy and add-on to metformin, pioglitazone, and DPP-4 (sitagliptin) studies, the proportion of patients with events of hypoglycemia was similar on dapagliflozin vs. placebo and occurred in $< 4.0\%$ of patients (Table 12).

However, when used together with agents with known side effects of hypoglycemia, such as SUs and insulin, an increased risk of hypoglycemic events is observed, mainly in minor hypoglycemic events.

Table 12: Events of Hypoglycemia, By-study Type, Excluding Data after Rescue

Study	Number of Patients n/N (%)	
	Dapa 10 mg	Placebo
Active Comparator Studies^a		
Dapa vs. SU (add-on to Metformin)	14/406 (3.5) ^b	162/408 (40.8) ^b
Dapa vs. Metformin	2/219 (0.9)	6/208 (2.9)
Placebo-controlled Studies^a		
Monotherapy	2/70 (2.9)	2/75 (2.7)
Add-on to Metformin	5/135 (3.7)	4/137 (2.9)
Add-on to TZD	0/140 (0.0)	1/139 (0.7)
Add-on to DPP-4	5/225 (2.2)	3/226 (1.3)
Add on to SU	11/151 (7.3)	7/146 (4.8)
Add-on to Insulin	83/196 (42.3)	69/197 (35.0)

30-MU = 30-month update; Dapa = dapagliflozin; DPP-4 = dipeptidyl peptidase-4; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione

^a Data from individual studies, excluding data after rescue

^b Adjusted percent using modified logistic regression analysis

In the Placebo-controlled Pools (ST and ST+LT; which included studies with SU and insulin; excluding data after rescue), the proportion of patients with events of hypoglycemia was higher on dapagliflozin 10 mg compared to placebo (Table 13), which was driven mostly by studies involving insulin use. Major episodes of hypoglycemia were uncommon and balanced across the placebo and dapagliflozin groups.

When 5 and 10 mg doses of dapagliflozin were compared, there was no dose dependence on events of hypoglycemia.

Table 13: Events of Hypoglycemia - Excluding Data after Rescue (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
	N = 2360	N = 2295	N = 2026	N = 1956
All Events of Hypoglycemia	309 (13.1%)	242 (10.5%)	378 (18.7%)	290 (14.8%)
Major Events	2 (0.1%)	1 (<0.1%)	4 (0.2%)	2 (0.1%)
Minor Events	276 (11.7%)	211 (9.2%)	352 (17.4%)	266 (13.6%)

Source: 30-MU. Appendix 133 and Appendix 233

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

5.1.6 Urinary Tract Infection, Including Pyelonephritis

An increase in UTIs has been observed with the approved member of the class, canagliflozin, with the presumed link to the MOA being the increased urinary glucose levels enabling the growth of urinary pathogens.¹⁹ To detect any potential signal for an increased risk of UTIs, the dapagliflozin clinical development program implemented comprehensive measures to collect data regarding this risk. Those measures included proactive questioning by investigators and supplemental case report forms. If the investigator believed that a UTI might be present based on the response to questions or other suggestive signs or symptoms, the investigator was asked to obtain a urine culture. Urinary testing for evidence of infection was not routinely performed in asymptomatic patients in accordance with treatment guidelines.²⁰ Events of UTI were evaluated based on a prespecified PT list of terms indicating a diagnosis of UTI.

The Placebo-controlled Pools showed a small increase in the proportion of patients reporting UTIs with dapagliflozin treatment vs. placebo (Table 14). As with genital infections, this was likely due, in part, to increased urine glucose levels. The UTI signal was, however, less evident than for genital infections and not consistent across studies.

Events of UTIs were more common in females than males and in patients with a history of recurrent UTIs.

Table 14: Events of UTI (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
Events of UTI	N = 2360	N = 2295	N = 2026	N = 1956
	110 (4.7%)	81 (3.5%)	174 (8.6%)	121 (6.2%)
UTI in Females	N = 1003	N = 952	N = 852	N = 799
	85 (8.5%)	64 (6.7%)	121 (14.2%)	86 (10.8%)
UTI in Males	N = 1357	N = 1343	N = 1174	N = 1157
	25 (1.8%)	17 (1.3%)	53 (4.5%)	35 (3.0%)

Source: 30-MU: Table 37, Table 38, Appendix 125, Appendix 128, Appendix 225, and Appendix 228

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term; UTI = urinary tract infection;

Most events were mild or moderate in intensity. Few patients were discontinued from study drug due to events of UTI; most events responded to initial treatment and resolved while the patient continued on study medication. Recurrence of events (in patients who had already experienced 1 event) over the longer term experience (ST+LT) was similar among patients receiving dapagliflozin 10 mg (22.4%) vs. placebo (22.3%). In patients who had cultures available, typical urinary pathogens, such as *E. coli*, were detected. The increased risk of events of UTIs is considered tolerable and manageable.

When 5 and 10 mg doses of dapagliflozin were compared in the original NDA, there was no dose dependence on events of UTI.

Pyelonephritis

The proportion of patients who were reported to have pyelonephritis, based on a prespecified PT list of terms, was low and balanced between treatment groups: 7 (0.1%) in the dapagliflozin total group vs. 7 (0.2%) in the all control group in the All Phase 2b and 3 Pool. Two of the events in each treatment group led to discontinuation. Serious adverse events of pyelonephritis were reported for one subject in the dapagliflozin group compared with four subjects in the placebo group.

5.1.7 Events of Genital Infection

Similar to UTIs, an increase in genital infections has been observed with the approved member of the SGLT2 inhibitor class, canagliflozin.¹⁹ The presumed link to MOA here is genital exposure to increased urinary glucose levels enabling the growth of fungal pathogens. In order to better understand the risk of genital infections, similar measures were implemented as for UTIs; including proactively questioning patients regarding signs, symptoms, and events suggestive of genital infection at each study visit and completion of supplemental case report forms for genital infections in order to obtain more detailed information for assessment. Investigators could confirm the diagnosis by physical examination, culture of the secretion, or positive response to standard treatment. Analyses were performed based on a prespecified PT list of terms indicating diagnosis of genital infection.

In the Placebo-controlled Pools (ST and ST+LT), genital infections were reported more frequently with dapagliflozin treatment than placebo, and events of genital infection were more common in females than males (Table 15). In both Placebo-controlled Pools, the most frequently reported AEs of genital infection were vulvovaginal mycotic infection, balanitis, and vaginal infection. Overall, the AEs of genital infection were typically fungal infections, as observed in patients with T2DM.

Table 15: Events of Genital Infection (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
Genital Infection	N = 2360	N = 2295	N = 2026	N = 1956
	130 (5.5%)	14 (0.6%)	156 (7.7%)	19 (1.0%)
Genital Infection in Females	N = 1003	N = 952	N = 852	N = 799
	84 (8.4%)	11 (1.2%)	98 (11.5%)	15 (1.9%)
Genital Infection in Males	N = 1357	N = 1343	N = 1174	N = 1157
	46 (3.4%)	3 (0.2%)	58 (4.9%)	4 (0.3%)

Source: 30-MU Table 34, Table 35, Appendix 119, Appendix 122, Appendix 219, and Appendix 222.

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term;

In the Placebo-controlled Pool (ST), 5 (0.2%) patients treated with dapagliflozin 10 mg had an AE of genital infection (vulvovaginal mycotic infection [3 patients], balanitis and vulvovaginal candidiasis [1 patient, each]) leading to discontinuation of study drug. No additional patients

discontinued due to AEs of genital infection in the Placebo-controlled Pool (ST+LT). None of the events of genital infection reported in the Placebo-controlled Pools were serious, and most were managed with antimicrobial therapy.

In the All Phase 2b and 3 Pool, there was one SAE of balanoposthitis reported in a male patient treated with 5 mg of dapagliflozin which resulted in discontinuation from the study. The AE resolved following antibiotic and antifungal treatment and was assessed by the investigator as related to study medication.

When 5 and 10 mg doses of dapagliflozin were compared in the original NDA, there was no dose dependence for events of genital infections.

5.1.8 Volume Depletion

Dapagliflozin, a mild diuretic, potentially can lead to volume depletion. To assess this risk in the Phase 2b and 3 program, AEs corresponding to hypotension, dehydration, or hypovolemia were pooled based on a prespecified list of PTs.

In the Placebo-controlled Pools (ST and ST+LT), events of volume depletion (hypotension/hypovolemia/dehydration) were infrequent but more common in patients treated with dapagliflozin 10 mg relative to placebo (Table 16). This result was expected based on dapagliflozin's MOA. Most events were mild or moderate in intensity and few patients were discontinued from study drug due to events of volume depletion.

Table 16: Events of Volume Depletion (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
	N = 2360	N = 2295	N = 2026	N = 1956
	27 (1.1%)	17 (0.7%)	38 (1.9%)	27 (1.4%)

Source: 30-MU: Appendix 135 and Appendix 241

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

In the Placebo-controlled Pool (ST and ST+LT), most of the events identified in this category were reported under the PT "Hypotension" in the dapagliflozin 10 mg (0.6% and 0.9%) and placebo (0.2% and 0.3%) groups, respectively. The distribution of such events across time was similar in both treatment groups. In the dapagliflozin 10 mg group of the Placebo Controlled Pool (ST), 18.5% of volume depletion events occurred during the first 2 weeks of treatment compared with 17.6% in the placebo group. Half of the events occurred by Week 8 in both treatment groups.

In the All Phase 2b and 3 Pool, SAEs of volume depletion were infrequent and occurred in 6 (0.1%) patients treated with dapagliflozin and 8 (0.2%) patients treated with control; the majority of these events were syncope (4 of 6 events in the dapagliflozin group and 7 of 8 events in the control group). Serious adverse events of circulatory collapse (1 event each in the dapagliflozin and control groups) and hypotension (1 event in the dapagliflozin group) were also reported.

When 5 and 10 mg doses of dapagliflozin were compared, there was no clear dose dependence for events of volume depletion. Nevertheless, based on the PD response seen during dose range finding investigations, it can be assumed that there is a dose response relationship for urine output across this dose interval. In line with this, a numerically greater 24-hour urine volume was observed at 10 mg compared to 5 mg in the Phase 2b dose ranging study (MB102008). Therefore, 5 mg may be an appropriate dose for patients at risk for volume depletion.

Volume Depletion Events by Subgroups

Results for events of hypovolemia/hypotension/dehydration by subgroups were generally consistent with those for the overall study population, with the exception of the subgroups of patients ≥ 65 years of age, patients receiving loop diuretics, and patients with eGFR (calculated by MDRD) ≥ 30 and < 60 mL/min/1.73 m² at baseline. In these subgroups, events were infrequent but more common than in the overall population studied, a pattern also seen in the approved SGLT2 inhibitor canagliflozin.

In both Placebo-controlled Pools (ST and ST+LT), patients ≥ 65 years old were more likely to have an event of volume depletion in the dapagliflozin 10 mg than placebo group ([Table 17](#)).

Patients using loop diuretics were more likely to have an event of volume depletion regardless of whether they were treated with dapagliflozin or placebo ([Table 17](#)). In the Placebo-controlled Pool (ST), 10% of the dapagliflozin-treated patients in the clinical program were treated with loop diuretics. The frequency of AEs in patients using loop diuretics is 2.5 times higher in both treatment groups than in patients that are not using loop diuretics.

Patients with eGFR (calculated by MDRD) ≥ 30 and < 60 mL/min/1.73 m² were more likely to have an event of volume depletion regardless of treatment with dapagliflozin or placebo ([Table 17](#)).

Table 17: Events of Volume Depletion by Age Category, Loop Diuretic Use, and Baseline eGFR Category (30-MU)

Total (%) Patients with Event of Volume Depletion	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
Patients < 65 years	N = 1695	N = 1584	N = 1406	N = 1301
	16 (0.9%)	11 (0.7%)	24 (1.7%)	16 (1.2%)
Patients ≥ 65 years	N = 665	N = 711	N = 620	N = 655
	11 (1.7%)	6 (0.8%)	14 (2.3%)	11 (1.7%)
Loop Diuretic Use	N = 236	N = 267	N = 234	N = 260
	6 (2.5%)	4 (1.5%)	7 (3.0%)	7 (2.7%)
No Loop Diuretic Use	N = 2124	N = 2028	N = 1792	N = 1696
	21 (1.0%)	13 (0.6%)	31 (1.7%)	20 (1.2%)
Baseline eGFR	N = 2094	N = 2025	N = 1774	N = 1705
≥ 60 mL/min/1.73 m²	22 (1.1%)	13 (0.6%)	30 (1.7%)	21 (1.2%)
Baseline eGFR	N = 265	N = 268	N = 251	N = 249
≥ 30 to < 60 mL/min/1.73 m²	5 (1.9%)	4 (1.5%)	8 (3.2%)	6 (2.4%)

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

Source: 30-MU: Appendix 136 and Appendix 242; Appendix 137 and Appendix 243; Appendix 142 and Appendix 244

5.1.8.1 Hematocrit

In the Placebo-controlled (ST) Pool small dose-dependent changes from baseline were observed in hematocrit, likely the effect of modest hemoconcentration. Increases in mean hematocrit levels, up to 2.32% absolute mean increase for dapagliflozin 10 mg, were observed up to Week 16 in patients treated with dapagliflozin, after which hematocrit levels remained stable. The observed hematocrit changes are not considered clinically meaningful. Outlier values for elevated absolute hematocrit occurred in few subjects and were not associated with adverse clinical events.

Marked abnormalities (MAs) of increased hemoglobin or hematocrit occurred in few patients and without associated adverse clinical events. In both Placebo-controlled Pools (ST and ST+LT), MAs of hematocrit (> 55%) and hemoglobin (> 18 g/dL) were more common in patients treated with dapagliflozin 10 mg compared with placebo, however MAs of hematocrit (> 60%) and hemoglobin (> 20 g/dL) were rare and occurred in similar proportions of patients in both treatment groups (Table 18). Most patients with MAs of elevated hematocrit or hemoglobin had elevations measured a single time that resolved at subsequent visits.

There was no imbalance in thromboembolic events in patients with MAs of elevated hematocrit. Two dapagliflozin-treated patients with an MA of elevated hematocrit had peripheral arterial occlusive disease, and one placebo-treated patient with an MA of elevated hematocrit had a stroke. In addition, the meta-analysis of adjudicated CV events did not show an imbalance in CV events between dapagliflozin and control (see Section 5.2.1).

Table 18: Marked Abnormalities of Increased Hemoglobin or Hematocrit (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU	N = 2360	N = 2295	N = 2026	N = 1956
Hematocrit (> 55%)	31 (1.3%)	8 (0.4%)	42 (2.1%)	11 (0.6%)
Hematocrit (> 60%)	3 (0.1%)	2 (0.1)	4 (0.2%)	2 (0.1%)
Hemoglobin (> 18 g/dL)	36 (1.5%)	11 (0.5%)	45 (2.2%)	14 (0.7%)
Hemoglobin (> 20 g/dL)	0	2 (0.1%)	0	2 (0.1%)

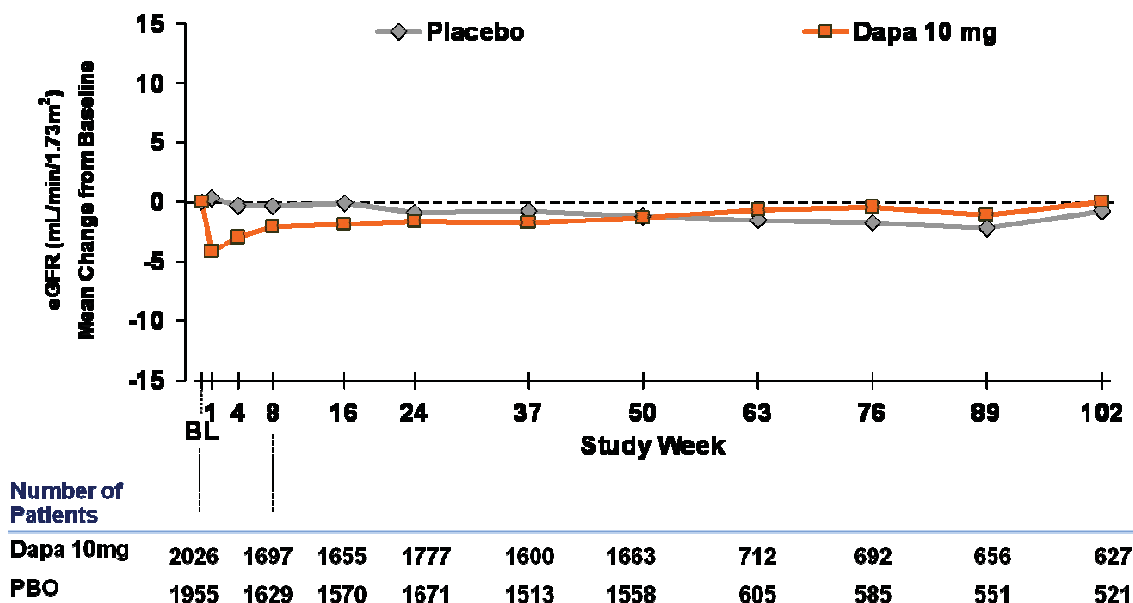
30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

Source: 30-MU: Appendix 156 and Appendix 262

5.1.9 Renal Function

Due to dapagliflozin's MOA of inhibiting glucose reabsorption in the kidneys, renal safety is of special interest. Within the class of SGLT2 inhibitors, the approved drug canagliflozin is associated with a modest decrease in eGFR, which is larger in patients with moderate renal impairment ($\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²).¹⁹ The effect of treatment with dapagliflozin on renal function has been evaluated in both nonclinical and clinical studies. Evaluation in clinical studies included diabetic patients with normal renal function at baseline as well as patients with mild or moderate renal impairment.

The MDRD creatinine-based estimating equation for GFR was used to assess renal function over time. In dapagliflozin-treated patients renal function remained stable over time up to Week 102. Mean eGFR decreased initially by Week 1 (mean change from baseline: -4.2 vs. 0.5 mL/min/1.73m² [dapagliflozin 10 mg vs. placebo]) and then gradually increased toward eGFR baseline values over several weeks. At Week 24, mean change from baseline was -1.4 vs. -0.7 mL/min/1.73m² (dapagliflozin 10 mg vs. placebo; [Figure 27](#)). These early, transient changes were not indicative of progressive renal dysfunction, as demonstrated by the gradual return to baseline in eGFR over time and likely represent auto-regulation through tubuloglomerular feedback due to the increased delivery of sodium to the macula densa. Following the initial decrease, and gradual return to baseline, after Week 24, mean eGFR values remained stable over 2 years in the Placebo Controlled (ST+LT) Pool.

Figure 27: Change in Estimated GFR (by MDRD), Placebo-controlled ST+LT Pool (30-MU)

MDRD = Modification of Diet in Renal Disease

Source: Source: rt-lb-gfrchgltplac.lst.doc

For patients with moderate renal impairment ($\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²), in patients treated with dapagliflozin the initial decrement in eGFR was followed by stability without return to baseline, while placebo-treated patients experienced a modest steady decline in eGFR. In the dedicated Phase 2b/3 study in this population (MB102029), at 104-weeks, the mean change from baseline in eGFR was -3.5 mL/min/1.73 m² for dapagliflozin and -2.4 mL/min/1.73 m² for placebo.

In the Placebo-controlled ST Pool, AEs belonging to a predefined group of PTs related to renal function occurred in 3.2% of patients treated with dapagliflozin 10 mg vs. 1.8% treated with placebo (Table 19). Most events consisted of small and reversible increases in creatinine and were rarely associated with clinically meaningful excursions from baseline in serum creatinine. In the All Phase 2b and 3 Pool, renal SAEs were few and balanced between dapagliflozin and control (0.15% of patients in both treatment groups).

The increased proportion of patients with AEs related to renal function in the dapagliflozin group compared to the placebo group is predominantly driven by the subgroup of patients with $\text{eGFR} < 60$ mL/min/1.73 m² (Table 21). This appears to be a class effect, as the approved SGLT2 inhibitor canagliflozin was associated with an increased incidence of renal-related adverse reactions, particularly in patients with moderate renal impairment.

Table 19: Adverse Events Related to Renal Function

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU	N = 2360	N = 2295	N = 2026	N = 1956
AEs Related to Renal Function	76 (3.2%)	42 (1.8%)	136 (6.7%)	82 (4.2%)

Source: 30-MU: Appendix 143, Appendix 144, Appendix 249, and Appendix 250.

30-MU = 30-month update; AEs = adverse events; Dapa = dapagliflozin; LT = long-term; ST = short-term

There were no events of acute tubular necrosis or acute nephritis, suggestive of toxic or allergic nephropathy, in any dapagliflozin-treated patients. When 5 and 10 mg doses of dapagliflozin were compared, there was no dose dependence on AEs related to renal function.

Renal Laboratory Results

Complementary analyses of laboratory data were performed to assess the effect of dapagliflozin on renal function. Mean changes in renal parameters, marked abnormalities in renal function labs based on pre-specified thresholds, and, in the case of albumin excretion, categorical changes were all calculated.

Mean changes in eGFR were described above (see [Section 5.1.9](#)). In addition, minimal changes from baseline in serum creatinine were consistent with changes in eGFR. There were small increases in blood urea nitrogen (BUN), consistent with previously reported data. In the 30-MU, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.041 vs. -0.008 mg/dL) and decreased toward baseline at Week 24 (mean change from baseline: 0.019 vs. 0.008 mg/dL) in dapagliflozin 10 mg vs. placebo, respectively. There were no further changes through Week 102. Mean BUN levels increased at Week 1 (mean change from baseline: 1.7 vs. -0.1 mg/dL, dapagliflozin 10 mg vs. placebo, respectively. Values remained stable through Weeks 24 and 102.

A small number of patients had MAs of creatinine $\geq 1.5X$ pre-treatment level; a higher proportion of these MAs were reported in patients treated with dapagliflozin 10 mg compared with placebo in both Placebo-controlled Pools (2.1% vs. 1.5% [ST], and 3.8% vs. 3.1% [ST+LT]; [Table 20](#)). In the Placebo-controlled Pools, few and equal percentages of patients in both treatment groups had MAs of creatinine ≥ 2.5 mg/dL (0.1% vs. < 0.1% [ST] and 0.2% vs. 0.2% [ST+LT]) or of BUN > 60 mg/dL or urea > 21.4 mmol/L (0.1% vs. 0.1% [ST] and 0.1% vs. 0.2% [ST+LT]).

Table 20: Marked Laboratory Abnormalities - Kidney Function Tests (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU	N = 2360	N = 2295	N = 2026	N = 1956
BUN > 60 mg/dL or urea > 21.4 mmol/L	2 (0.1%)	2 (0.1%)	3 (0.1%)	4 (0.2%)
Creatinine ≥ 1.5X Pre-treatment Creatinine	48 (2.1%)	34 (1.5%)	75 (3.8%)	61 (3.1%)
Creatinine ≥ 2.5 mg/dL	2 (0.1%)	1 (0.0%)	3 (0.2%)	3 (0.2%)

Source: 30-MU: Appendix 156 and Appendix 262.

30-MU = 30-month update; BUN = blood urea nitrogen; Dapa = dapagliflozin; LT = long-term; ST = short-term

Urine albumin measurements did not show any evidence of a deleterious effect of dapagliflozin. Urine albumin to creatinine ratio measurements were categorized as normoalbuminuria (0 to < 30 mg/g), microalbuminuria (30 to <300 mg/g), or macroalbuminuria (≥ 300 mg/g). A numerically larger proportion of patients on dapagliflozin shifted to a lesser category of albuminuria, and a numerically smaller proportion of patients shifted to a greater category of albuminuria on dapagliflozin, compared to placebo.

In conclusion, there is no evidence from the clinical development program that dapagliflozin is associated with an increased risk of renal adverse effects in the overall population.

5.1.9.1 Renal Events by Subgroups

Of the 9339 patients in the All Phase 2b and 3 Pool, 8268 (88.5%) patients had baseline eGFR ≥ 60 mL/min/1.73m² and 1055 (11.3%) had baseline eGFR ≥ 30 and < 60 mL/min/1.73m². In the Placebo-controlled Pools (ST and ST+LT), the proportion of AEs related to renal function is greater in patients with eGFR ≥ 30 and < 60 mL/min/1.73 m² than in patients with eGFR ≥ 60 mL/min/1.73 m² (Table 21). In both eGFR subgroups, the proportion of patients experiencing AEs related to renal function is greater in patients treated with dapagliflozin vs. placebo. These types of events were 10-fold more common in patients with eGFR ≥ 30 and < 60 mL/min/1.73 m² in both treatment groups. Treatment initiation is not recommended for patients with eGFR < 60 mL/min/1.73 m².

Table 21: Adverse Events Related to Renal Function - eGFR Category Subgroups (30-MU)

Total Number (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
Patients eGFR ≥ 60 mL/min/1.73 m²	N = 2094	N = 2025	N = 1774	N = 1705
	27 (1.3%)	17 (0.8%)	65 (3.7%)	42 (2.5%)
Patients eGFR ≥ 30 and < 60 mL/min/1.73 m²	N = 265	N = 268	N = 251	N = 249
	49 (18.5%)	25 (9.3%)	71 (28.3%)	40 (16.1%)

Source: 30-MU: Appendix 146 and Appendix 252

30-MU = 30-month update; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; LT = long-term; ST = short-term

Elderly patients appear to be more sensitive to the diuretic effects of dapagliflozin, which is in part related to the high proportion of patients in this age group with eGFR ≥ 30 and < 60 mL/min/1.73 m². AEs related to renal function were reported more frequently in patients greater than 65 years of age who were treated with dapagliflozin 10 mg than placebo (Table 22).

Table 22: Adverse Events Related to Renal Function - Age Subgroups (30-MU)

Total (%) Patients with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU				
Patients < 65 yrs	N = 1695	N = 1584	N = 1406	N = 1301
	25 (1.5%)	15 (0.9%)	49 (3.5%)	30 (2.3%)
Patients ≥ 65 yrs	N = 665	N = 711	N = 620	N = 655
	51 (7.7%)	27 (3.8%)	87 (14.0%)	52 (7.9%)

Source: 30-MU: Appendix 143, Appendix 144, Appendix 249, and Appendix 250.

30-MU = 30-month update; Dapa = dapagliflozin; LT = long-term; ST = short-term

Laboratory Results by Subgroups

In the Placebo-controlled Pools (ST and ST+LT), the mean serum creatinine changes over time were the same in the overall study population and the subgroup of patients with eGFR ≥ 60 mL/min/1.73m².

In the Placebo-controlled Pools (ST and ST+LT), the proportions of patients with MAs in kidney function tests were similar in the eGFR subgroups (≥ 30 to < 60 mL/min/1.73m² and ≥ 60 mL/min/1.73m²). No patients in the dapagliflozin 10 mg group (eGFR subgroup ≥ 60 mL/min/1.73m²) had creatinine ≥ 2.5 mg/dL.

5.1.10 Fractures and Bone Health

There was no increase in fractures seen with dapagliflozin, unlike the experience seen with the approved member of the SGLT2 inhibitor class canagliflozin.¹⁹ In the Placebo-controlled Pools (ST and ST+LT), the proportions of patients with fractures were small and balanced with placebo (Table 23).

Table 23: Events of Fracture, Including Data after Rescue (30-MU)

Total (%) Subjects with an Event	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU	N = 2360	N = 2295	N = 2026	N = 1956
	8 (0.3%)	17 (0.7%)	23 (1.1%)	32 (1.6%)

LT = long-term; ST = short-term; 30-MU = 30-month Update

Source: 30-MU: Appendix 149 and Appendix 255

Study D1690C00012 was specifically designed to evaluate the effect of dapagliflozin treatment on bone mineral density (BMD) by DXA at 50 and 102 weeks. All 3 standard locations for BMD measurement were included in order to evaluate the effects on both trabecular (lumbar spine) and cortical (femoral neck and total hip) bone. There was no meaningful difference in mean percent change from baseline in BMD between treatment groups at any of the 3 locations at Week 50 or Week 102 (Table 24). In addition, biochemical markers of bone formation and bone resorption measured in this study did not show any statistically significant or clinically relevant changes with dapagliflozin therapy (Table 25).

Table 24: Bone Mineral Density at Week 102 (Study D1690C00012, DXA Body Composition Study)

	Dapa 10mg N = 91	Placebo N = 91	Difference Dapa vs. Placebo		
Patients in 102 wk DXA eval.	n = 68	n = 71			
Bone Mineral Density (BMD)	Mean % Change from Baseline		(%)	95% CI	p-value
BMD Lumbar Spine (L1-4)	0.69	0.47	0.22	(-0.89, 1.34)	0.7013
BMD Femoral Neck	-0.85	0.09	-0.94	(-2.21, 0.35)	0.1521
BMD Total Hip	-0.82	-0.37	-0.45	(-1.32, 0.43)	0.3105

Source: D1690C00012-CSR-102 Week

CI = confidence interval; Dapa = dapagliflozin; DXA = dual x-ray absorbiometry; eval = evaluation; wk = week

Table 25: Markers of Bone Formation and Resorption at Week 12 (Study D1690C00012, DXA Body Composition Study)

Turnover marker	Dapa 10mg N=91	Placebo N=91	Difference vs Placebo	95% CI	p-value
	(n of patients with measure) Mean change from baseline				
C-terminal Cross-linking Telopeptides of Type 1 Collagen (ng/mL)	(n=69) 0.02	(n=67) 0.02	0.01	(-0.02, 0.04)	0.6918
N-terminal Cross-linking Telopeptides of Type 1 Collagen (nm/BCE)	(n=69) 0.50	(n=67) 0.61	-0.10	(-1.04, 0.83)	0.8275
Osteocalcin (ng/mL)	(n=69) 0.11	(n=68) -0.14	0.25	(-1.35, 1.86)	0.7557
Bone specific ALP (U/L) Week 50	(n=78) -1.58	(n=80) -2.29	0.71	(-0.55, 1.97)	0.2664
Procollagen Type 1 N-terminal Propeptide (µg/L)	(n=69) 1.66	(n=68) 0.50	1.16	(-2.16, 4.48)	0.4906

Source: D1690C00012-CSR-102 Week

ALP = alkaline phosphatase; CI = confidence interval; Dapa = dapagliflozin

The experience was somewhat different in patients with moderate renal impairment ($\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²), a population in whom initiation of dapagliflozin therapy is not recommended. The dedicated Phase 2b/3 study in this population (MB102029) had more fractures in the dapagliflozin groups than the placebo group. Through 104 weeks, 13 (7.7%) patients experienced events of fracture in the dapagliflozin groups vs. 0 on placebo. The majority of the fractures involved a fall mechanism, and the dapagliflozin groups had higher rates of neuropathy and orthostatic hypotension at baseline, conceivably predisposing them to falls. Seven of 13 patients who sustained fractures had a history of diabetic neuropathy or exhibited orthostatic hypotension at baseline. In contrast, no increase in events of fracture was observed in pooled data from patients across the dapagliflozin clinical studies with moderate renal impairment. Of the patients with moderate renal impairment in the Placebo-controlled ST Pool, fractures were experienced by 0 patients on dapagliflozin, and 2 (0.7%) patients on placebo. In the Placebo-controlled ST+LT Pool, fractures were experienced by 1 (0.4%) patient on dapagliflozin, and 5 (2.0%) patients on placebo.

5.1.11 Clinical Laboratory Evaluations

5.1.11.1 Electrolytes

There is no clinically relevant impact of dapagliflozin treatment on serum electrolytes. Few patients had significant excursions in laboratory values outside of normal limits in dapagliflozin- and placebo-treated patients in the Placebo-controlled Pools, and values returned to within normal range at the subsequent measurement for the majority of subjects.

In dapagliflozin-treated patients, no clinically meaningful changes from baseline were observed in mean serum sodium, potassium, calcium, bicarbonate, or chloride after 24 weeks of treatment. Small changes from baseline in mean serum phosphorus, magnesium, and uric acid were observed after 24 weeks of dapagliflozin treatment and are described below. Similar to the SGLT2 inhibitor canagliflozin, there was a small increase from baseline in parathyroid hormone; at Week 24 the change was 4.1 pg/mL for the dapagliflozin 10 mg group vs. 1.4 pg/mL for the placebo group.

An increased risk of hyperkalemia has been seen with the SGLT2 inhibitor canagliflozin. This was especially apparent in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications such as ACEi, ARB, or potassium-sparing diuretics.¹⁹ Serum potassium ≥ 6 mEq/L was seen in 70 (3.0%) patients on dapagliflozin 10 mg and 62 (2.7%) patients on placebo. Unlike canagliflozin, with dapagliflozin there was no increase in episodes of hyperkalemia in patients with moderate renal impairment ($\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²). In the dedicated Phase 2b/3 study in this population (MB102029), serum potassium ≥ 6 mEq/L was seen in 3 (3.6%) patients on dapagliflozin 10 mg and 8 (9.6%) patients on placebo.

Phosphorous

Similar to the SGLT2 inhibitor canagliflozin,¹⁹ mean serum phosphorus levels increased at Week 1 in dapagliflozin-treated patients (mean change from baseline of 0.19 mg/dL [dapagliflozin 10 mg] vs. -0.01 mg/dL [placebo]). The increase in serum phosphorus persisted but did not increase in magnitude through Weeks 24 and 102. Serum phosphorus increases are probably due to a subtle increase in renal tubular phosphate reabsorption with dapagliflozin treatment. The levels of increase observed on dapagliflozin treatment do not correspond to any known pathology related to phosphorous changes and do not appear clinically relevant.

Marked abnormalities of increased phosphorus were reported in a small number of patients, with more MAs in patients treated with dapagliflozin 10 mg compared with placebo in both Placebo-controlled Pools (1.7% vs. 0.9% [ST] and 3.0% vs. 1.6% [ST+LT]). Very few of the MAs of increased phosphorus in the 30-MU were reported as AEs of hyperphosphatemia: 1 ($< 0.1\%$) patient treated with dapagliflozin 10 mg and 0 (0%) placebo patients, in both the ST and ST+LT Placebo-controlled Pools.

Magnesium

Similar to the SGLT2 inhibitor canagliflozin,¹⁹ there was a small increase in the mean magnesium concentrations at Week 24 with dapagliflozin 10 mg (0.09 mEq/L) compared with placebo (-0.02 mEq/L), which is consistent with previously reported data and not clinically significant.

Urate

A decrease in serum uric acid concentration was observed consistently across the studies. In the Placebo-controlled ST Pool the change from baseline for the dapagliflozin 10mg group was -0.5 mg/dL vs. 0.0 for the placebo group.

5.1.11.2 Lipids

The mean changes from baseline in fasting lipid levels were small in the dapagliflozin 10 mg and placebo groups in the Placebo-controlled Pools (ST and ST+LT; Table 26), and directionally similar to the changes seen with the SGLT2 inhibitor canagliflozin.¹⁹

Table 26: Mean Change and Mean Percent (%) Change from Baseline in Lipids (30-MU)

	Placebo-controlled Pool (ST)		Placebo-controlled Pool (ST+LT)	
	At Week 24		At Week 102	
	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo
30-MU				
HDL-C (mg/dL)	n = 1851	n = 1748	n = 549	n = 447
Mean Change	2.7	1.3	3.0	1.2
Mean % Change	6.0%	2.7%	6.6%	2.1%
Non-HDL-C (mg/dL)	n = 1851	n = 1747	n = 549	n = 446
Mean Change	1.6	-1.3	0.8	-4.2
Mean % Change	1.3%	-1.1%	0.5%	-3.2%
LDL-C (mg/dL)	n = 1840	n = 1736	n = 542	n = 442
Mean Change	2.8	-0.9	2.6	-2.3
Mean % Change	2.9%	-1.0%	2.9%	-2.2%
Total-C (mg/dL)	n = 1851	n = 1747	n = 550	n = 446
Mean Change	4.3	-0.1	3.8	-3.0
Mean % Change	2.5%	0.0%	2.1%	-1.5%

Source: 30-MU, Appendix 169, Appendix 170, Appendix 275, and Appendix 276

“n” is the number of treated patients with non-missing baseline and Week t values

30-MU = 30-month update; Dapa = dapagliflozin; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol LT = long-term; ST = short-term

In the 30-MU, there are small placebo-adjusted mean percent increases from baseline in high density lipoprotein cholesterol (HDL-C; 3.3% [ST]; 4.5% [ST+LT]), low density lipoprotein cholesterol (LDL-C; 3.9% [ST]; 5.1% [ST+LT]) and total cholesterol (2.5% [ST]; 3.6% [ST+LT]; Table 26). When total non-high density lipoprotein cholesterol (non-HDL-C) was calculated, the mean percent increases were small and reassuring (1.3% [ST]; 0.5% [ST+LT]). Small increases in free fatty acids and small decreases in triglycerides were observed in the

Placebo-controlled Pools (ST and ST+LT) for patients treated with dapagliflozin 10 mg. There was no nonclinical signal showing detrimental effects on lipids and no signal of an increase risk of CV events in humans from the CV meta-analysis (see Section 5.2.1).

The overall distribution of percent change in LDL-C at Week 24 is similar between the dapagliflozin 10 mg and placebo groups with no differences in the proportion of patients with significant increases or reductions in LDL-C.

Additionally, in the Placebo-controlled Pools (ST and ST+LT), changes from baseline LDL to HDL cholesterol ratios were calculated for each patient and then mean percent change in LDL to HDL ratio was calculated for each treatment group. In both treatment groups in the Placebo-controlled Pools (ST and ST+LT), there was a mean decrease in LDL-C/HDL-C ratio. The mean percent change from baseline to Week 24 in LDL-C/HDL-C ratio was -2.93% vs. -3.53% in the dapagliflozin 10 mg and placebo groups, respectively. The mean percent change from baseline to Week 102 in LDL-C/HDL-C ratio was -3.55% vs. -4.05% in the dapagliflozin 10 mg and placebo groups, respectively.

LDL-C/HDL-C ratios provide important information about CV risk. There is growing evidence that this ratio is an independent predictor of heart disease. The complex pattern of changes in various lipids fractions could be the result of complex interactions of weight changes and appetite. However, the decreases in LDL-C/HDL-C are reassuring and suggest that the small changes in cholesterol fractions observed in dapagliflozin-treated patients would have no effect on the overall CV risk.

5.2 Safety Topics of Interest

5.2.1 Hepatic Safety

In the original NDA submission, the FDA noted a single clinical case of potential DILI in a patient receiving dapagliflozin. There had been no other preclinical or clinical signals for liver injury, and no imbalance in liver test abnormalities when comparing dapagliflozin to control.

The case of concern was a patient who experienced a combined elevation of both aminotransferase (greater than 3X ULN) and bilirubin (greater than 2X ULN). Combined elevations of aminotransferase and bilirubin are of particular importance in evaluating drug liver safety, because, if they meet the definition of “Hy’s law,” they constitute a signal for risk of severe DILI resulting in death or transplantation.^{21,22} As noted in the FDA’s 2009 guidance on drug-induced liver injury,²³ Hy’s law cases have 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 control or placebo;
- 2) The cases have concurrent 3-fold elevation above the ULN of ALT or AST and 2-fold elevation above the ULN of bilirubin; and
- 3) No other reason can be found to explain the abnormal liver labs.

Dapagliflozin does not fulfill the first criterion for Hy’s law. Overall, there were no mean increases from baseline or imbalances in liver laboratory tests. In the 30-MU All Phase 2b and 3

Pool, the proportion of patients with elevated laboratory values for ALT, AST, total bilirubin (TBL), and alkaline phosphatase (ALP) was similar in the dapagliflozin and control groups, with no dose-dependence across the doses of dapagliflozin. Overall, 4.3% of dapagliflozin-treated patients and 4.5% of control patients had elevated liver tests (Table 27).

Table 27: Proportion of Patients with Elevated Liver Tests Based on Measured Laboratory Values (30-MU)

Total N (%) Patients with an Event	All Phase 2b and 3 Pool	
	X/N# (Percent)	
	Dapa Total (N = 5936)	All Control (N = 3403)
Total Patients with Elevated Liver Tests	255/5895 (4.3%)	152/3380 (4.5%)
AST or ALT > 3X ULN	92/5895 (1.6%)	64/3380 (1.9%)
AST or ALT > 5X ULN	25/5895 (0.4%)	21/3380 (0.6%)
Total Bilirubin > 2X ULN	22/5894 (0.4%)	11/3379 (0.3%)
AST > 3X ULN or ALT > 3X ULN and TBL > 2X ULN*	7/5894 (0.1%)	4/3379 (0.1%)
ALP > 3X ULN	8/5894 (0.1%)	6/3380 (0.2%)

Source: 30-MU: Appendix 337

N is the number of treated patients.

X is the number of patients with a value meeting the criterion.

N# is the number of patients with at least one non-missing post-baseline value.

* Total bilirubin elevation on or within 14 days after AST or ALT elevation.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ULN = upper limit of normal

Some patients in the dapagliflozin program, both on dapagliflozin and on control, met the second criterion for Hy's law. In the All Phase 2b and 3 Pool, 7/5894 (0.1%) patients in the dapagliflozin total group and 4/3379 (0.1%) patients in the all control group had liver enzyme elevations of AST > 3X ULN or ALT > 3X ULN and TBL > 2X ULN within 14 days on or after AST/ALT elevation that occurred during study treatment or within 30 days of discontinuation of study drug (Table 27). All seven cases on dapagliflozin had probable alternative diagnoses of autoimmune hepatitis, gallstone disease, either alone or in combination with other factors, or pancreatic carcinoma (Table 28).

Table 28: Patients with Elevations of AST > 3X ULN or ALT > 3X ULN and TBL TBL > 2X ULN (30-MU)

Age/Sex	Treatment Group	Alternative Diagnoses
78/M	Dapa 5mg	Autoimmune hepatitis
83/M	Dapa 5mg	Gallstone disease
60/F	Dapa 2.5mg	Gallstone disease
60/M	Dapa 10mg	Gallstone disease
62/M	Dapa 10mg	Pancreatic cancer
70/M	Dapa 10mg	Gallstone disease
70/M	Dapa 10mg	Gallstone disease
67/F	Glipizide	Septic shock
29/M	Placebo	Gallstone disease
62/M	Placebo	Pancreatic cancer
63/M	Placebo	Viral syndrome

* Total bilirubin elevation on or within 14 days after AST or ALT elevation

Source: 30-MU

Dapa = dapagliflozin

Patient D1690C00004-4402-6

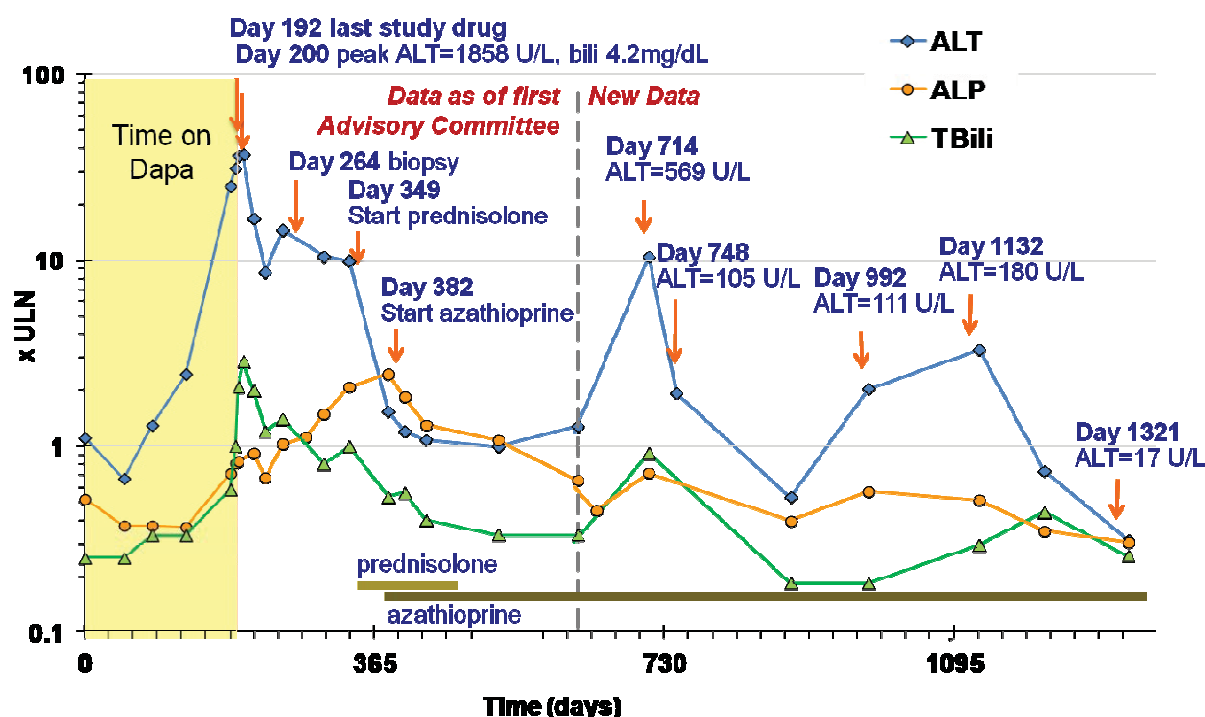
The single clinical case of concern (D1690C00004-4402-6) fulfilled the second criterion for Hy's law, and initially appeared, at the time of the previous Advisory Committee meeting and the CRL, to potentially fulfill the third criterion as well. The case under discussion is one in which the patient experienced biochemical abnormalities consistent with Hy's law (ALT or AST > 3X ULN with serum total bilirubin > 2X ULN). The alternative diagnosis was autoimmune hepatitis. Three expert hepatologists who adjudicated the case in a blinded manner could not agree on the interpretation of this case. In their opinions, the probability of the relationship to drug ranged from *unlikely* to *probably related* (with the consensus being *possibly related*).

Since the CRL, new information was received on this case that makes autoimmune hepatitis the probable diagnosis. Despite the patient's liver tests returning to baseline after drug discontinuation and initiation of immunosuppression, over 3 years later this patient still requires immunosuppression with azathioprine (Figure 28). Even with continued treatment, the patient has had two subsequent episodes of substantial flares in serum aminotransferases after dapagliflozin discontinuation. BMS/AZ consulted with 2 expert hepatologists (Drs. Maddrey and Watkins) about this case. They concluded that this patient has a probable diagnosis of idiopathic autoimmune hepatitis. Thus the third criterion for Hy's law is not fulfilled in this (or any other) case.

Autoimmune hepatitis can be induced or triggered by medicines. Due to the temporal relationship between the onset of the disease and treatment with dapagliflozin, drug-induced autoimmune hepatitis cannot be completely excluded. However, the fact that there is still ongoing active liver disease makes this diagnosis unlikely because drug-induced autoimmune hepatitis, unlike idiopathic autoimmune hepatitis, generally subsides after drug withdrawal.^{24,25} Further, drug-induced autoimmune hepatitis tends to be associated with drugs that increase liver laboratory tests, and thus increase immune exposure to liver antigens; dapagliflozin does not increase liver laboratory tests.

The totality of data indicates that dapagliflozin is not associated with DILI. There were no imbalances in liver enzyme elevations in the clinical program and no nonclinical signal, even at very high exposures (> 3000x human exposures at the maximum recommended human dose [MRHD]). With the new data on the sole clinical case of concern, of the three criteria that must be fulfilled for it to be considered a Hy's law case and thus a possible signal for DILI, neither the first nor the third criterion was fulfilled.

Figure 28: Liver Case of Concern: Time Course of Liver Tests



Source: 30-MU

ALP = alkaline phosphatase; ALT = alanine aminotransferase; bili = bilirubin; Dapa = dapagliflozin; TBili = total bilirubin; ULN = upper limit of normal

5.2.2 Malignancies

5.2.2.1 Introduction

At the time of the original NDA and through the major amendment (Jan-2012), there was no overall imbalance in malignancies in the clinical development program. There were, however,

imbalances in individual tumor types, with some tumor types, such as bladder cancer, more common on dapagliflozin than control, and others, such as renal tract cancer, less common on dapagliflozin than control. None of these imbalances was statistically significant. The preclinical data had shown no evidence of tumor initiation or promotion by dapagliflozin at high multiples of exposure, and there was no identified biologically plausible link between dapagliflozin and bladder cancer. At the time of the 2011 Advisory Committee Meeting, the total number of bladder cancer cases was 9 reported on dapagliflozin (0.06 per 100 patient years) and one on control (0.03 per 100 patient years). All but one of these cases was diagnosed or showed the first clinical sign of bladder cancer (hematuria) within 6 months of starting dapagliflozin therapy, a timeframe indicative of pre-existing tumors. The cases followed the normal epidemiology of bladder cancer, both with respect to risk factors (age, male gender and smoking history), and with respect to tumor grade and invasiveness.

The CRL stated that the NDA resubmission needed to include a safety update with updated information on bladder cancer. In further discussions with the Agency, it was also suggested that additional preclinical data on tumor promotion could help inform the weight-of-evidence regarding potential bladder cancer risk.

In the NDA resubmission, additional clinical data are provided including more overall exposure and more patients with longer follow-up. Also provided in the resubmission is an additional set of preclinical experiments addressing any putative role of dapagliflozin or glucosuria in the promotion or growth enhancement of pre-existing bladder tumors.

5.2.2.2 New Clinical Data

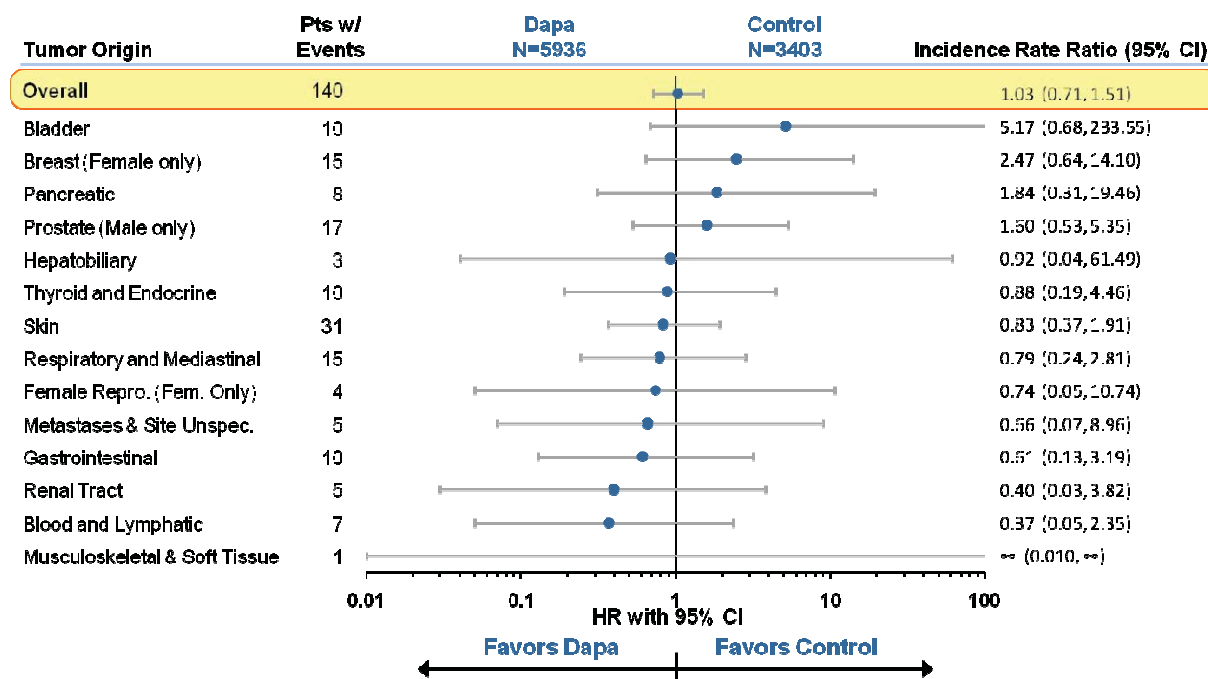
Methodology

As in previous submissions, the malignant and unspecified neoplasm AEs were defined from a pre-specified Standard MedDRA Query (SMQ). The incidence rate ratios of these events were examined based on the All Phase 2b and 3 Pool.

The analyses of incidence rate ratio for malignant and unspecified tumors (overall and by organ) were performed using an exact method described in StatXact, stratified by study. In addition, the incidence rate ratio for overall malignant and unspecified tumors was also analyzed using Cox model, stratified by study.

Overall Malignancies

As with the data previously submitted to the FDA, there continues to be no overall imbalance in malignancies ([Figure 29](#)). As expected for a drug that does not cause cancer, variability in incidence rates across the different types of cancer continues to result in a number of organ systems where the malignancy incidence rate is lower in the control group and a number of organ systems where the incidence rate is lower in the dapagliflozin group. As before, none of the imbalances are statistically significant.

Figure 29: Malignancies by Tumor Type, All Phase 2b and 3 Pool, (30-MU)

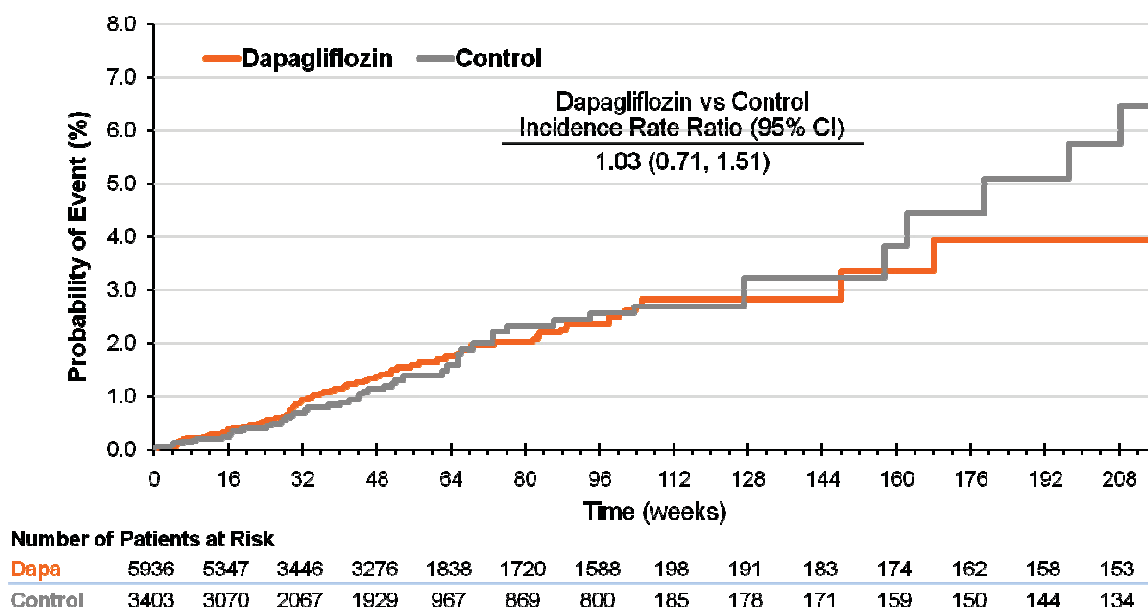
One additional case of bladder cancer was found in study 93-005 which was not finished at the time of data cut for FDA resubmission. The incidence rate ratio with 95% CI including this case is 6.11 (0.827, 272.00).

Source: 30-MU, Figure 2

CI = confidence interval; Dapa = dapagliflozin; Fem. = female; HR = hazard ratio; Pts = patients;

Repro = reproduction; Unspec. = unspecified

The Kaplan-Meier plot of time to malignancy shows matched curves for dapagliflozin and control (Figure 30). There is no upward inflection over time in the dapagliflozin curve, as would be observed with a carcinogen.

Figure 30: Time to First First Event of Malignant and Unspecified Tumors, All Phase 2b and 3 Pool (30-MU)

Does not include one additional case of bladder cancer found in study 93-005 which was not finished at the time of data cut for FDA resubmission.

Source: 30-MU, Figure 1

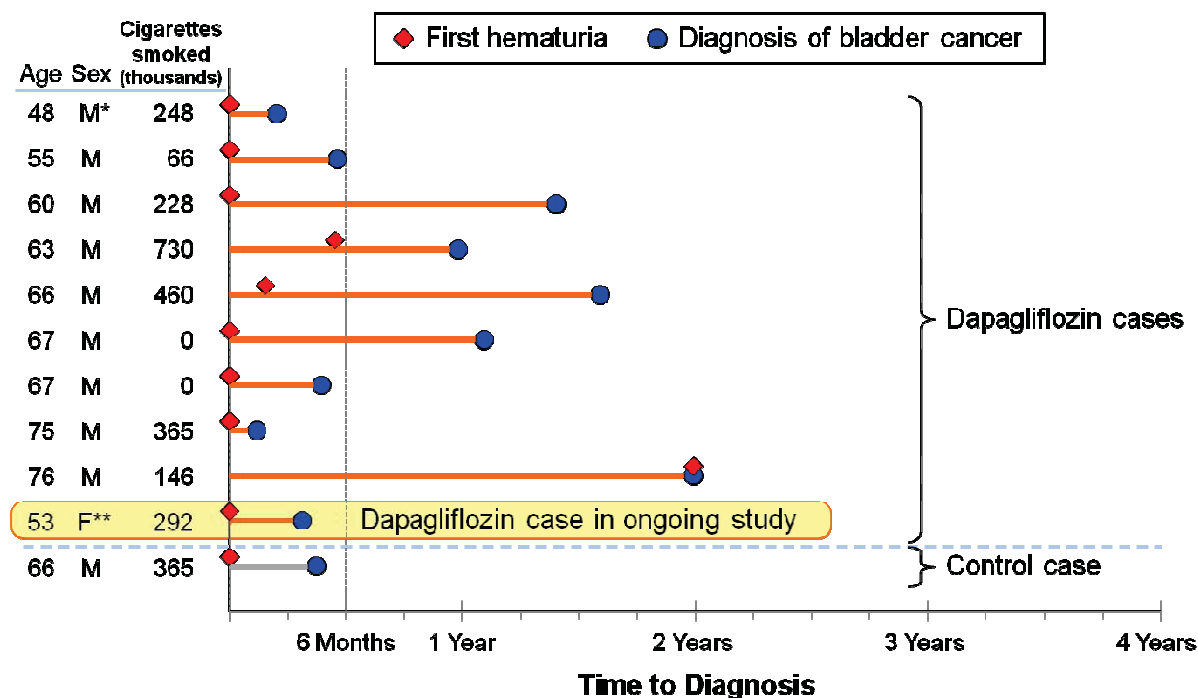
CI = confidence interval; dapa = dapagliflozin

Bladder Cancer

Despite more than 2000 additional patient years of exposure, no additional cases of bladder cancer were identified across the 21 unblinded Phase 2b and 3 studies in the 30-MU. Subsequent to the integrated database lock for the 30-MU, one additional case detected early in the treatment course has been reported in a female patient in the ongoing add-on to SU and metformin study (D1693C00005). This patient was a smoker (50 pack-years), had hematuria at baseline, and her bladder cancer was diagnosed a mere 3.5 months after treatment initiation. Including this newest case, the incidence rate ratio for dapagliflozin vs. control is 6.11 (CI = 0.827, 272.02), similar to that of the original NDA submission.

All 10 cases of bladder cancer in patients on dapagliflozin were reported within 2 years of starting study treatment (range: 43 to 727 days), and all but one were diagnosed or showed the first clinical sign (hematuria) of bladder cancer within 6 months of starting dapagliflozin therapy (Figure 31). In distinct contrast to the pattern expected for a directly causative agent, the incidence rate remained stable over the first 2 years of drug exposure and then fell, with no additional cases between 2 and 4 years exposure, albeit with only 428 patient-years exposure during this time period. The time to bladder cancer diagnosis on dapagliflozin divided into 6 month exposure intervals was: 5 patients (< 6 months); 1 patient (6 to < 12 months), 2 patients (12 to < 18 months), 2 patients (18 to < 24 months), and 0 patients (> 24 months; Table 29).

Figure 31: Characteristics of Diagnosed Cases of Bladder Cancer



*Hematuria in this case was prior to study entry.

**This case was identified in study 93-005 which was not finished at the time of data cut for FDA resubmission and was not included in the resubmission filing.

Source: 30-MU, Table 26

Table 29: Bladder Cancer Events with Incidence Rate Reported by 6-month Intervals, Short-term + Long-term Treatment Period, All Phase 2b and 3 Pool, Treated Patients (30-MU)

Treatment Group		Time Interval in Months					
		Overall	0-6	6-12	12-18	18-24	>24
DAPA TOTAL	# of Subjects with Events	10	5	1	2	2	0
	# Subjects at Risk	6045	6045	4906	2626	1744	1523
	% of Subjects with Events	0.17	0.08	0.02	0.08	0.11	0.00
	95% CI	(0.08,0.30)	(0.03,0.19)	(0.00,0.11)	(0.01,0.27)	(0.01,0.41)	(0.00,0.24)
	Total person years	6744.30	2773.03	1771.10	948.77	822.91	428.48
	Rate per 100 person years	0.15	0.18	0.06	0.21	0.24	0.00
	95% CI	(0.07,0.27)	(0.06,0.42)	(0.00,0.31)	(0.03,0.76)	(0.03,0.88)	(0.00,0.86)
ALL CONTROL	# of Subjects with Events	1	1	0	0	0	0
	# Subjects at Risk	3512	3512	2856	1593	883	755
	% of Subjects with Events	0.03	0.03	0.00	0.00	0.00	0.00
	95% CI	(0.00,0.16)	(0.00,0.16)	(0.00,0.13)	(0.00,0.23)	(0.00,0.42)	(0.00,0.49)
	Total person years	3955.77	1608.25	1062.77	509.14	413.59	362.03
	Rate per 100 person years	0.03	0.06	0.00	0.00	0.00	0.00
	95% CI	(0.00,0.14)	(0.00,0.35)	(0.00,0.35)	(0.00,0.72)	(0.00,0.89)	(0.00,1.02)

MedDRA Version: 15.1; N is the number of treated subjects. Each time window is defined by study days as follows: Month 0-6= Day 1-183; Month 6-12=Day 184-365; Month 12-18=Day 366-548; Month 18-24=Day 549-731; Month >24=>Day 732. Includes serious and non-serious AEs with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment + 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant and Unspecified Tumors; bladder cancer based on clinical review

Does not include 1 mg treatment group from Studies MB102032 and D1692C00005.

The overall exposure (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date + 30 days, end of the interval, death date, follow-up visit, or database snapshot date, whichever is first.

Program Source: /gbs/dev/clin/programs/mb/102/iss/30msuext/rpt/rt-ae-bladinctm005lt23-v01.sas

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The dapagliflozin cases follow the epidemiology of bladder cancer, with advanced age and male gender predominating. Most of the patients had a substantial amount of prior carcinogen exposure; 80% (8 of 10) had a smoking history, tobacco being a recognized potent bladder carcinogen. The heterogeneity of the tumors reflects that seen in the population (reference): 80% were superficial non-muscle invasive, 20% were muscle invasive, and 10% (one case) was metastatic disease.²⁶ Sixty percent (60%) were low grade and the remainders were intermediate or high grade (Table 30).

Table 30: Bladder Cancer: Patient Tumor Characteristics

Age/Sex	Study Tx	Dx Day	Grade/Stage	Treatment**
75/M	2.5mg	43	Grade 2 / T2 N0 MX; muscle invasive	TURBT, cystectomy Chemotherapy
48/M	10mg	74	Low grade / Non-muscle invasive	TURBT, BCG
53/F	10mg	114	Grade 1 / Non-muscle Invasive	TURBT
67/M	5mg	144	High grade / pT2M0; muscle invasive	Cystectomy
55/M	10mg	169	Grade 1 / pT1NOMO; non-muscle invasive	TURBT
63/M	5mg	358	Low grade / pTa : non-muscle invasive	TURBT
67/M	10mg	399	Grade 2 / Non-muscle invasive	TURBT local chemotherapy
60/M	5mg	512	Low grade / pTaNCM0; non-muscle invasive	TURBT
66/M	10mg	581	Low grade / pTa N0 M0; non-muscle invasive	TURBT
76/M	10mg	727	High grade / T1 M0; non-muscle invasive	TURBT, BCG
66/M	Pbo	136	High grade / pT2NOMO; muscle invasive	TURBT, BCG

* Including one case in study -C05 identified after database cut.

** TURBT - transurethral resection of a bladder tumor; BCG – intravesical immunotherapy
30-MU

Dx = date of diagnosis; Tx = treatment

The clinical features of the bladder cancer cases with dapagliflozin treatment indicate that most or all of the cases represent pre-existing tumors. The short time to detection and early hematuria in most of the cases, including the newest case, is not compatible with carcinogenesis. Known human bladder carcinogens require years to decades to cause bladder cancer.²⁷ Furthermore, the biological heterogeneity of the cancers, from low grade to high grade and from non-invasive to widely metastatic, argues against a single short-term trigger causing these cancers.

The fact that most of the bladder cancer cases appear to be pre-existing raises the question not of tumor initiation, for which there is no evidence, but of the possibility that dapagliflozin or its associated glucosuric effect could somehow act to enhance the growth of pre-existing neoplastic lesions or tumors. This concern has been addressed by performing additional nonclinical studies described in [Section 5.2.2.3](#).

Breast Cancer

At the time of the 2011 Advisory Committee Meeting, there was an imbalance in breast cancer cases which was not statistically significant. The total number of breast cancer cases was 9 reported on dapagliflozin (0.37 per 100 patient-years) and one on control (0.09 per 100 patient-years); the incidence rate ratio was 4.41 (95% CI 0.57 to 200.86). All of these cases were diagnosed within 1 year of starting dapagliflozin therapy, a timeframe suggestive of pre-existing tumors. The cases followed the normal epidemiology of breast cancer, both with respect to risk factors (age, female gender), and with respect to tumor marker heterogeneity (estrogen receptor, progesterone receptor, and Her2/Neu positivity).

Since the time of last Advisory Committee meeting, there have been 3 more cases of breast cancer on dapagliflozin and 2 more cases on control. The total number of breast cancer cases on dapagliflozin is 12 (0.45%), with an exposure adjusted incidence rate of 0.40 (95% CI = 0.21, 0.70) vs. 3 cases on control, with an exposure adjusted incidence rate of 0.19 (95% CI = 0.04, 0.56). The incidence rate ratio is 2.47 (95% CI = 0.64, 14.10). The characteristics of the breast cancer cases are shown in [Table 31](#) with the 5 new cases highlighted in yellow.

With the new cases, the characteristics of the breast cancer cases continue to reflect those seen in the general population with respect to patient age and gender and with respect to the tumor heterogeneity, and as before, most of the cases were diagnosed within one year of treatment, a short time frame for carcinogenesis. The decrease in the incidence rate ratio with more patient exposure since the time of the 2011 Advisory Committee meeting shows the instability of the incidence rate ratio due to the small number of cases constituting the original imbalance. The observed imbalance in breast cancer cases has narrowed considerably over time, illustrating the instability of incidence rate ratios with small numbers of cases.

Table 31: Breast Cancer: Patient and Tumor Characteristics*

Age /Race	Study Tx	Dx Day	Weight Change (kg)	Tumor Type	Stage TNM	Progesterone / Estrogen Receptor Status	HER2/neu Status
63 / White	2.5mg	6	0	Invasive ductal carcinoma	T1c, N0, M0	Highly Positive, IRS 12	2+
53 / White	5mg	39	-1.2	Intraductal carcinoma	M0	not performed	not performed
60 / White	10mg	193	0	Ductal carcinoma	T1,N0	Positive, 8/8	Negative
61 / White	10mg	204	-1.5	Invasive lobular, carcinoma	T2, N3a, M0	Positive	Negative
59 / White	10mg	204	-1.9	Invasive, ductal carcinoma	T2, N3, MX	Positive	Negative
64 / White	10mg	211	-1.5	Invasive ductal carcinoma	T1c, N1a, M0	Positive	Negative
64 / White	10mg	285	-10	Infiltrating adenocarcinoma	T2, N2a, MX	Negative	Negative
58 / White	2.5mg	292	1	Unknown	T2, N0, M0	Positive / Negative	Weakly Positive
74 / White	2.5mg	321	-3.8	Invasive ductal carcinoma	T1b, N0	Strongly Positive	Negative
69 / Asian	10mg	334	-2.3	N/A (withdrawn consent)	N/A	N/A	N/A
75 / White	10mg	687	-0.2	Invasive ductal carcinoma	T2N0	Positive	Positive
70 / White	10mg	722	NA	Invasive ductal carcinoma	NA	Negative	Negative
73 / White	Comparator	57	-4.7	Invasive, lobular carcinoma	T3, N3a	Positive, > 80% (IRS 12)	Negative
60 / Asian	Comparator	113	-2.5	Infiltrating ductal breast cancer	T1c, N0, M0	Positive	Negative
60 / White	Comparator	347	-3.1	Ductal carcinoma in situ	T1, N0, M0	Positive, >10%	N/A

Source: 30-MU

*One additional subject had an event of breast cancer after 15-July-2011. Subject D1692C00012-7-6, a 63 year old Japanese female, treated with dapagliflozin 5 mg was diagnosed on Study Day 149 with non-invasive ductal carcinoma (Tis, N0, M0 - estrogen receptor positive, progesterone receptor positive, HER2/Neu negative). This subject and data from Study D1692C00012 (open-label, long-term regional study) is not included in any of the 30-MU integrated safety analysis pools since this was not a controlled study and all subjects were treated with dapagliflozin.

Dx = date of diagnosis; IRS = insulin receptor substrate; N/A = not applicable; TNM = tumor node metastasis; Tx = treatment

5.2.2.3 *Nonclinical Data*

Original NDA Submission

The nonclinical data demonstrated that dapagliflozin lacks carcinogenic potential. This conclusion is based on dapagliflozin's very high specificity for its intended SGLT2 target, which is not expressed in bladder or breast tissues, and on results from in vitro and in vivo genotoxicity studies,²⁸ 2-year rodent carcinogenicity studies,^{29,30} and a 1-year dog toxicology study,³¹ all of which were rigorously conducted in highly validated test systems at exposures upwards of 100 to 3,000 times human exposures at the 10-mg maximum recommended dose. In addition, neither dapagliflozin nor its primary human metabolite showed any significant off-target effects against a panel of over 300 targets, including the estrogen receptor and other steroid receptors, and of the dapagliflozin metabolites present in human plasma and urine were also formed in the animal toxicology and carcinogenicity studies at sufficient quantities to assess their safety in humans. Under these conditions, there was no nonclinical evidence of tumor initiation or promotion (including no dapagliflozin-related tumors or hyperplastic lesions that might suggest a neoplastic process), nor any enhancement of background tumor growth (including no shortening of breast tumor latency, enhancement of growth, nor increase in overall mammary tumor incidence) associated with dapagliflozin administration.

Because, to our knowledge, all known human bladder carcinogens cause some effects in these validated models, the absence of any carcinogenicity signals in the dapagliflozin preclinical program is predictive of there not being any clinical bladder cancer risk. The clean preclinical profile combined with the lack of estrogenic effect also strongly argues against a role for dapagliflozin in breast cancer risk.

New Nonclinical Data

As suggested by the FDA and following the example of another drug (Prasugrel) in which additional preclinical studies were conducted to address tumor imbalances in clinical trials,³² BMS/AZ conducted additional nonclinical studies to assess whether inhibition of SGLT2 in general, or more specifically dapagliflozin administration, can enhance urinary bladder tumor growth.

The potential tumor growth effects of dapagliflozin and its primary human metabolite were tested on human bladder transitional cell carcinoma (TCC) cells in vitro.³³ For these studies, 6 human bladder TCC cell lines were treated with the parent drug or its 3-O-glucuronide metabolite at concentrations up to 20 µg/mL ($\geq 100\times$ human C_{max} at the MRHD). For all 6 TCC cell lines, in vitro exposure to dapagliflozin or dapagliflozin 3-O-glucuronide did not stimulate bladder tumor cell proliferation. The fact that robust proliferation was observed following stimulation with the positive control (10% fetal bovine serum) indicated that the cells were capable of growth stimulation, thus verifying viability of the experimental design.

In a subsequent in vivo xenograft study,³⁴ dapagliflozin was administered daily by oral gavage to male and female nude mice bearing (subcutaneously implanted) human bladder TCC tumors. Comparable to the in vitro results, administration of dapagliflozin (at exposures up to

75x MRHD exposures) did not enhance the growth rate or overall size of the human bladder TCC tumors implanted in these mice.

In addition to the above studies, BMS/AZ conducted an investigation of genetic markers shown to be highly correlated with tumor promotion. Across a panel of tissues in the Zucker Diabetic Fatty (ZDF) rat, dapagliflozin did not cause transcriptional changes characteristic of tumor promoters.³⁵ Although this analysis did not specifically include the bladder because it was part of a pharmacology study intended to further characterize dapagliflozin's MOA, the absence of any parallels to known tumor promoters at a gene transcriptional level provides a useful addition to the weight-of-evidence.

Finally, BMS/AZ conducted two further studies to specifically investigate the role of glucosuria in bladder tumor formation or growth enhancement. In one in vitro study, five human bladder TCC cell lines were exposed to increasing concentrations of glucose up to 50 mM.³⁶ Increases in glucose did not increase in the rate of tumor cell growth; in contrast, glucose became cytostatic at high concentrations (≥ 25 mM). These findings are in line with the toxicology program in general, in which no evidence of dapagliflozin-related proliferative or hyperplastic effects was observed despite glucosuria (up to 400 to 500 mM) that was even greater than urinary glucose levels observed clinically (mean ~ 166 mM at a 10 mg dose). In a second study, 15-month old SGLT2 -/- mice, which were not exposed to any pharmacological interventions and yet had experienced a lifetime of substantial glucosuria, were examined.³⁷ The analysis showed no evidence of proliferative, hyperplastic or pre-neoplastic type changes in the urinary bladder or alterations in renal function.

Since the time of the previous Advisory Committee meeting, preclinical and clinical experience with another SGLT2 inhibitor, canagliflozin, has also become publically available.³⁸ The absence of any bladder cancer signal provides further substantiation for the conclusion that urinary alterations associated with SGLT2 inhibition, including high concentrations of glucose, are not associated with any bladder cancer-related risks.

These additional nonclinical experiments and external data support the conclusion that neither dapagliflozin, nor its metabolites, nor urinary glucose promotes or enhances the growth of pre-existing bladder cancer.

5.2.2.4 Conclusions on Malignancies

The comprehensive nonclinical and clinical data included in the NDA resubmission support the conclusion that dapagliflozin does not present a risk for initiating or promoting cancer. The clinical data show no overall imbalance in malignancies with some tumors being more frequent in control and some being more frequent in dapagliflozin, none of these imbalances being statistically significant. The preclinical data show that dapagliflozin is not genotoxic, and there is no evidence of tumor initiation by dapagliflozin at high multiples of exposure. Further, dapagliflozin is not a tumor promoter. There were no dapagliflozin-related hyperplastic changes in the nonclinical program, and dapagliflozin did not trigger the characteristic gene expression signature of a tumor promoter.

There was a non-statistically significant imbalance in bladder cancer cases in the clinical program. The data do not support a causative role for dapagliflozin.

- No biologically plausible link between dapagliflozin and bladder cancer has been identified. Dapagliflozin is highly selective for its SGLT2 target, and SGLT2 is not expressed in human bladder tissue.
- There is no carcinogenicity signal in the nonclinical program in models that are highly predictive of bladder cancer. All known human bladder carcinogens show signals in these validated models.
- The clinical features of the bladder cancer cases seen with dapagliflozin treatment indicate that most or all of the cases represent pre-existing tumors. All but one of the cases was diagnosed or showed the first clinical sign of bladder cancer (hematuria) within 6 months of starting dapagliflozin therapy. Risk factors of age, male gender, and substantial smoking history are suspected contributors to the etiology of these cases.
- New preclinical data support the conclusion that dapagliflozin also does not enhance growth of pre-existing bladder tumors. There was no growth enhancement of human bladder cancer lines in vitro or in vivo following exposure to dapagliflozin or its major metabolite.
- Finally, the data also support the conclusion that glucosuria per se does not enhance bladder tumor growth. There were no proliferative or hyperplastic effects throughout the preclinical toxicology program in which glucosuria was a consistent finding, no proliferative or hyperplastic effects in SGLT2 -/- mice, and no growth enhancing effect of increased glucose on human bladder cancer cell lines. This is also supported by the absence of any bladder cancer signals, preclinically or clinically, related to glucosuria with another SGLT2 inhibitor (canagliflozin).

There was also a non-statistically significant imbalance in breast cancer cases in the clinical program. The data do not support a causative role for dapagliflozin.

- No biologically plausible link between dapagliflozin and breast cancer has been identified. Dapagliflozin is highly selective for its SGLT2 target; and SGLT2 is not expressed in human breast tissue. There is also no interaction of dapagliflozin or its primary metabolite with estrogen receptors nor any indication of estrogenic effects in rodent or non-rodent species throughout the nonclinical toxicology program.
- There is no carcinogenicity signal in the nonclinical program in models that are sensitive to mammary tumor effects. In the female rat, in particular, where there is a high background incidence of mammary gland tumors, there was no indication of an increase in incidence or a shortened time to onset of mammary tumors. Together with the lack of an increased incidence of hyperplastic lesions, these data indicate that dapagliflozin is not promoting or accelerating breast cancer growth.

- The cases followed the normal epidemiology of breast cancer, both with respect to risk factors (age, female gender), and with respect to tumor marker heterogeneity (estrogen receptor, progesterone receptor, and Her2/Neu positivity).
- The imbalance in the incidence rate ratio is not statistically significant, and has decreased with more patient exposure, a finding that highlights the instability of the incidence rate ratio due to the small number of cases constituting the original imbalance.

In conclusion, the weight-of-evidence strongly argues against a causal relationship of dapagliflozin to bladder or breast cancer. To add assurance, BMS/AZ have designed a rigorous post-marketing plan to continue to follow the potential risk of cancer. This plan includes the ongoing large outcomes trial DECLARE [TIMI-58, Study D1693C00001], that has been considerably increased in scope and modified in design to adequately assess the risk of cancer (see [Section 6.2](#)). The trial includes blinded independent adjudication of all solid tumor events. The trial design also incorporates periodic, pre-defined evaluations of bladder cancer, performed by an independent Data Monitoring Committee (DMC), starting with 8 total bladder cancer events with a plan for ongoing statistical and clinical evaluations at pre-specified timepoints throughout the conduct of the study. This trial will be complemented by a pharmacoepidemiology study evaluating the possible association of dapagliflozin use with cancer in a real world setting. The pharmacoepidemiology study is being undertaken in the European Union (EU), where dapagliflozin is already on the market, and will be expanded to the United States if approved. Additionally, bladder and breast cancer are being assessed by routine and enhanced pharmacovigilance practices in the countries where dapagliflozin is approved (EU, Australia, Mexico, New Zealand, Brazil, and Argentina).

5.2.3 Cardiovascular Safety

In accordance with the FDA Guidance for Industry issued in December 2008: “*Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*”³⁹, a CV meta-analysis was conducted with the original NDA filing. To present, altogether 4 CV meta-analyses have been conducted and submitted to the FDA as follows: the original CV meta-analysis (dated 17-Nov-2010)⁴⁰ submitted with the original NDA, the 4-MSU CV meta-analysis (dated 11-Mar-2011)⁴¹ submitted with the 4-MSU, the supplementary CV meta-analysis (dated 01-Nov-2011)⁴² submitted with the Major Amendment, and an updated CV meta-analysis (dated 16-May-2013),⁴³ based on the dataset for the 30-MU and submitted with the NDA resubmission (July-2013).

The original CV meta-analysis met the FDA criteria for ruling out an unacceptable increase in CV risk by showing that the 98% CI for risk was less than 1.8. The additional CV meta-analyses are provided in accordance with the FDA request, but the alpha-levels are not controlled as part of a pre-specified plan adjusting for multiple meta-analyses.

The summary below focuses on the most recent and comprehensive meta-analysis.

5.2.3.1 Methodology for Cardiovascular Meta-analysis

A Statistical Analysis Plan (SAP) was finalized in advance of the original CV meta-analysis. All subsequent updates to the meta-analysis have used the same methodologies which are described below. The distinction between the original meta-analysis and the updates since then is the level of the CI used to evaluate the primary endpoint. Since the statistical boundary for the 1.8 margin was met with the original meta-analysis, all updates are provided with nominal, two-sided 95% CIs.

Analysis Populations

The main analysis population was the All Phase 2b and 3 Pool (see [Section 2.4](#) for description). There were a number of pre-defined subgroups in the SAP. Of particular interest in the updated CV meta-analysis is the pre-specified subgroup of patients with a history of CV disease. A post-hoc subset of this subgroup comprising pooled studies D1690C00018 and D1690C00019 only (purpose described below) was also analyzed.

Patients with a history of CV disease were defined as those with a history of coronary heart disease, cerebrovascular disease, or peripheral artery disease, specified by any of the following: MI, congestive heart failure (CHF), hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular accident, carotid artery disease, carotid endoarterectomy or stenting, peripheral vascular disease, peripheral vascular surgery, or amputation.

Definition of Endpoints

The definition of the primary composite endpoint, which follows the FDA guideline (*Guidance for Industry, Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, December 2008), was shared and agreed with the FDA. The primary endpoint is a composite endpoint, defined as the time to first event of the following adjudicated events: CV death, MI, stroke, and hospitalization for unstable angina.

The secondary endpoint is a composite endpoint, defined as the time to first event of the following adjudicated events: CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization, and hospitalization for heart failure.

Ad hoc analyses were performed for a third composite endpoint, defined as the time to first event of adjudicated CV death, MI, or stroke (MACE). This classic composite endpoint is not mandatory as the primary endpoint in pre-approval clinical program meta-analyses per FDA guidance,³⁹ as broader composite endpoints including other relevant outcomes such as hospitalizations for unstable angina, unplanned coronary revascularization and heart failure allow more events to be assessed for demonstrating an acceptable HR less than 1.8. Thus, the MACE composite data have been provided here as supportive information. Of note, the three-component MACE composite endpoint is the primary endpoint for the DECLARE study, designed to demonstrate a post-approval hazard ratio CI upper bound less than 1.3 for MACE as further evidence regarding the CV safety of dapagliflozin.

Methods for Analysis

The primary analysis method (Cox proportional hazards model) and secondary analyses methods (Mantel-Haenszel methods, both the asymptotic method and the exact method) were performed for the primary, secondary, and MACE composite endpoints. A supportive Mantel-Haenszel analysis was also performed on the corresponding incidence rate differences. Here, only the results from the Cox proportional hazards model are presented. Results from the Mantel-Haenszel analyses support the results presented here.

5.2.3.2 Cardiovascular Characteristics

In the overall population for the 21 Phase 2b and 3 studies comprising the dataset for the 30-MU of the CV events meta-analysis, the patients on dapagliflozin had a mean age of 57 years and 24% were ≥ 65 years of age. Mean BMI was 31.3 kg/m^2 and the mean duration of T2DM was 7 years. Fifty-five (55) % of the patients had dyslipidemia and 4% had CHF (Table 32).

The total proportions of patients with a history of hypertension (65.7% for dapagliflozin and 71.9% for control) and a prior history of CV disease (31.3% for dapagliflozin and 39.9% for control) appear imbalanced between the treatment groups (Table 32). This imbalance does not impact the results of the CV meta-analysis, however, because the statistical methods are stratified by study, in following with the FDA's guidance.

The imbalance in the population is an artifact resulting from combining studies with different randomization ratios. Specifically, the 2 studies, D1690C00018 and D1690C00019, had a 1:1 ratio of dapagliflozin to control. Patients were required to have a history of CV disease for these 2 studies, and nearly all patients also had a history of hypertension. The remainder of the Phase 2b and 3 studies collectively had a randomization ratio that was roughly 2:1, dapagliflozin to control, and these patients had smaller proportions of patients with histories of hypertension and CV disease, representative of the broader population of patients with T2DM. Proportions of patients with histories of CV disease and hypertension were balanced for each individual study.

Estimated GFR values showed slightly more than 50% of the patients had mild renal impairment ($\text{eGFR} \geq 60$ and $< 90 \text{ mL/min/1.73 m}^2$) and approximately 11% had moderate renal impairment ($\text{eGFR} \geq 30$ and $< 60 \text{ mL/min/1.73 m}^2$; Table 32).

Table 32: Cardiovascular Characteristics, All Phase 2b and 3 Pool (30-MU)

Baseline Characteristics	Dapa Total (N = 5936)	All Control (N = 3403)
Age, mean (years)	56.9	58.1
≥ 65 years (%)	24.0	28.8
BMI, mean (kg/m ²)	31.3	31.6
Duration of T2DM, mean (years)	6.9	7.6
History of CVD (%)	31.3	39.9
History of HTN (%)	65.7	71.9
History of Dyslipidemia (%)	55.2	59.6
History of CHF (%)	4.0	4.8
Smoking history (%)	43.3	46.3
eGFR		
< 30 mL/min/1.73m ² (%)	0.2	0.2
≥ 30 - < 60 mL/min/1.73m ² (%)	11.3	11.4
≥ 60 - < 90 mL/min/1.73m ² (%)	52.4	52.7
≥ 90 mL/min/1.73m ² (%)	36.2	35.7

Source: Source: CV Events 30-MU Meta-Analysis Report

BMI = body mass index; CHF = congestive heart failure; CVD = cardiovascular disease; Dapa = dapagliflozin; HTN = hypertension; T2DM = type 2 diabetes mellitus

5.2.3.3 Summary of Updated Cardiovascular Meta-analysis**Primary results**

The estimated hazard ratio between dapagliflozin and control for the composite primary endpoint of CV death, MI, stroke, and hospitalization for unstable angina, using Cox proportional hazards method, was 0.787 (95% CI: 0.579, 1.070), for the secondary composite endpoint 0.758 (95% CI: 0.581, 0.988) and for the composite endpoint of major adverse cardiovascular events (MACE) was 0.772 (95% CI: 0.543, 1.097; [Table 33](#)). All three composite endpoints give consistent results providing comprehensive assurance of lack of CV risk and the results are consistent with the results of the 3 previously conducted CV meta-analyses with point estimates being below 1, and the upper bound of the 95% CI below 1.8 as required for approval.

Table 33: Summary of Results for Primary Composite Endpoint and MACE Endpoint in CV Analyses of the Dapagliflozin Phase 2b and 3 Clinical Program, All Phase 2b and 3 Pool (30-MU)

	No. of events	HR	95% CI
Overall Phase 2b/3 Population			
Primary endpoint^a	176	0.787	0.579, 1.070
Secondary endpoint^b	236	0.758	0.581, 0.988
MACE^c	134	0.772	0.543, 1.097

^a Composite endpoint of CV death, MI, stroke and hospitalization for unstable angina.

^b Composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization and hospitalization for heart failure.

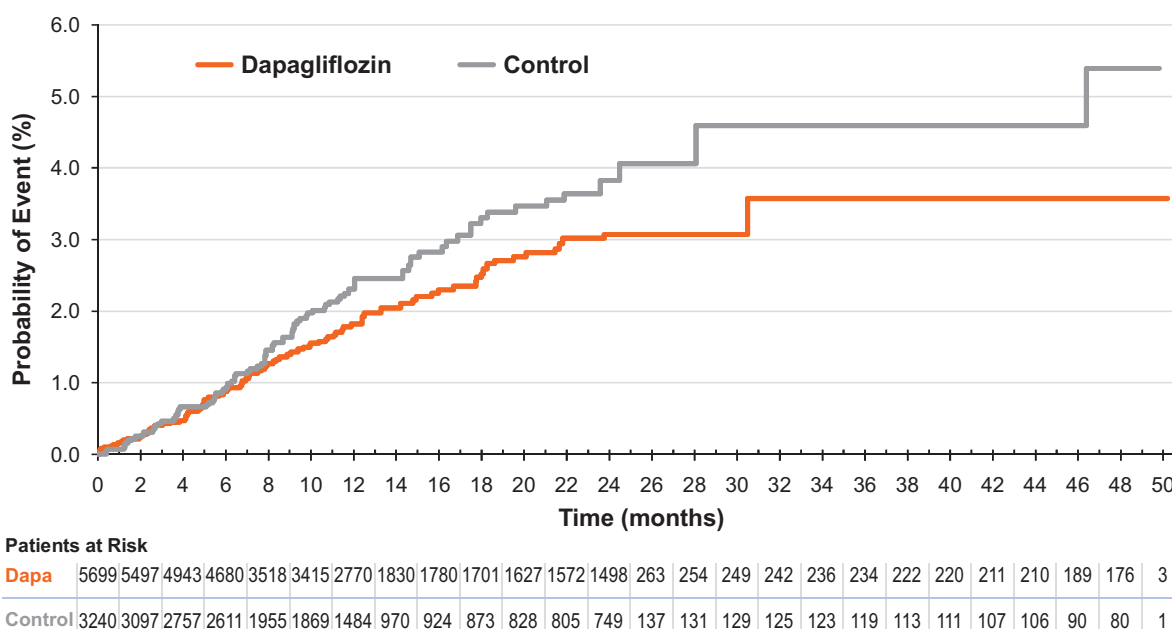
^c Composite endpoint of CV death, MI, and stroke.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events

Source: CV Events 30-MU Meta-Analysis Report

A Kaplan-Meier curve for the cumulative probability of the primary composite endpoint over time is shown in Figure 32. The cumulative probability of the primary endpoint shows a separation of the 2 curves starting at approximately 250 days and then continuously increasing during the treatment period. There was no statistically significant deviation from proportional hazards.

Figure 32: Kaplan-Meier Estimate for Primary Endpoint (MACE+UA), All Phase 2b and 3 Pool (30-MU)



Source: CV Events 30-MU Meta-Analysis Report, Figure 1

Dapa = dapagliflozin

Results in subgroups

In the prospectively-defined subpopulation of patients with CV history, the number of patients was 3214 patients in total, with 1856 exposed to dapagliflozin and 1358 to control. The updated results in this subgroup are consistent with the prior analyses of this prespecified subgroup, as well as with the analysis of the hazard ratio for the composite primary and secondary endpoints and also for the ad hoc composite MACE endpoint (Table 34).

Table 34: Summary of Results for Primary Composite Endpoint and MACE Endpoint in CV Analyses of the Dapagliflozin Phase 2b and 3 Clinical Program, Patients with CV History (30-MU)

	No. of events	HR	95% CI
Primary endpoint^a	128	0.806	0.562, 1.156
Secondary endpoint^b	181	0.772	0.570, 1.047
MACE^c	95	0.802	0.527, 1.221

^a Composite endpoint of CV death, MI, stroke and hospitalization for unstable angina.

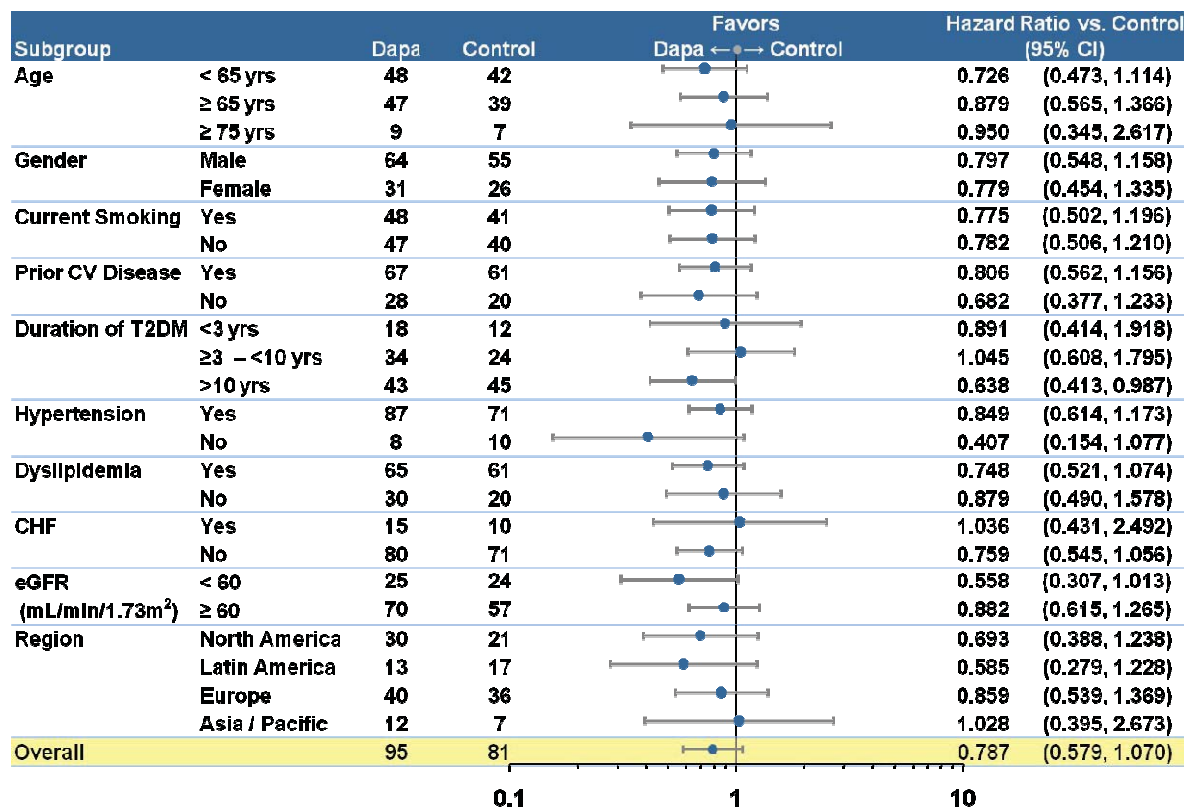
^b Composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization and hospitalization for heart failure.

^c Composite endpoint of CV death, MI, and stroke.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event

Source: CV Events 30-MU Meta-Analysis Report

Analyses were also performed on a number of other subgroups from categories relevant to diabetes (age, gender, BP, dyslipidemia, duration of diabetes, prior CHF history, eGFR, geography) of the entire Phase 2b and 3 population. In general, the results were consistent with the overall results from the primary analysis of the composite primary endpoint. In every evaluable case, the CIs overlap the primary pooled analysis ([Figure 33](#)).

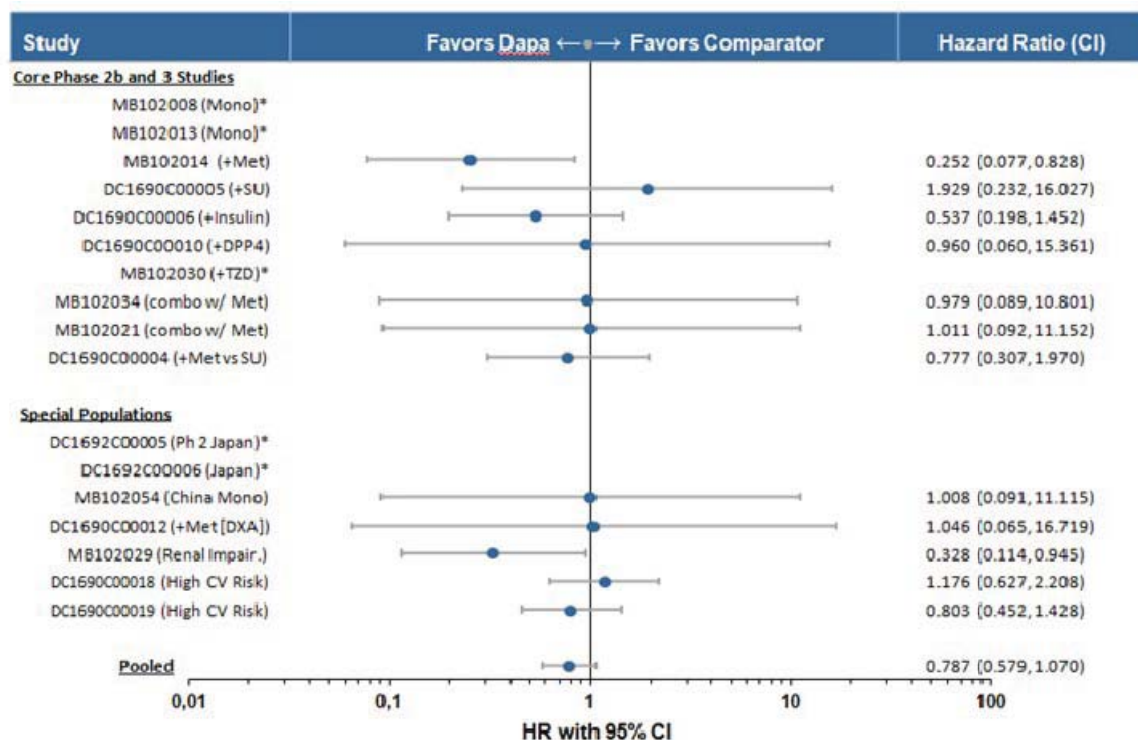
Figure 33: Primary CV Composite Endpoint by Subgroups, All Phase 2b and 3 Pool (30-MU)

Source: CV Events 30-MU Meta-Analysis Report

CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus

Results by study

A forest plot depicting the hazard ratio for the individual studies and the overall stratified analysis is provided in [Figure 34](#). Due to the low number of events in each individual study there was more variability around the hazard ratio estimates than in the meta-analysis.

Figure 34: Individual Study Results - Primary Endpoint, All Phase 2b and 3 Pool (30-MU)

*Studies with events in only one arm and estimated values out of range

Cox Proportional Hazards Model

Source: CV Events 30-MU Meta-Analysis Report

CI = confidence interval; CV = cardiovascular; Dapa = dapagliflozin; DPP4 = dipeptidyl peptidase-4; DXA = dual x-ray absorbiometry; Impair = impairment; Met = metformin; Mono = monotherapy; Ph = phase; SU = sulfonylurea

Based on an FDA request, post hoc analysis of Studies D1690C00018 and D1690C00019 pooled together were performed. Studies D1690C00018 and D1690C00019 were designed to evaluate the effect of dapagliflozin on co-primary endpoints of HbA1c, weight, and SBP. The studies were conducted in a manner similar to the other studies of the Phase 2b and 3 program; these studies were not designed or performed in the manner of CV outcomes studies, and were not intended to provide a standalone assessment of the CV risk. In order to increase experience in high CV risk patients and to fortify the precision of the CV event meta-analysis through the contribution of additional CV events, inclusion criteria required a documented history of CV disease defined as a history coronary heart disease, cerebrovascular disease, or peripheral artery disease, similar to the pre-specified subgroup of patients with history of CV disease. Thus, these two studies comprise an operationally-defined subset of the pre-specified functional subgroup of patients with a history of CV disease.

The baseline characteristics of patients in Studies D1690C00018 and D1690C00019 were similar to those of the pre-specified subgroup of all patients with a history of CV disease (Table 35).

There were more males and patients with hypertension or dyslipidemia in Studies D1690C00018 and D1690C00019.

Table 35: Baseline Characteristics for Patients in All Phase 2b and 3, with History of CV Disease, and in Studies D1690C00018 and D1690C00019 receiving Dapagliflozin (30-MU)

	All Phase 2b & 3 with History of CV Disease N=3214	Studies -018 & -019 N=1887
Age, mean (years)	62.6	63.4
≥ 65 years (%)	41.8	44.8
Gender, (%) Male	62.2	67.5
Female	37.8	32.5
BMI, mean (kg/m²)	32.4	32.8
Duration of T2DM, mean (years)	11.2	12.8
History CV disease (%)	100.0	99.5
History of Hypertension (%)	91.0	96.2
History of <u>Dyslipidemia</u> (%)	77.0	84.2
History of CHF (%)	12.5	14.3
<u>eGFR</u> <60 mL/min/1.73m² (%)	19.0	17.4
≥60 mL/min/1.73m² (%)	81.0	82.6

Source: CV Events 30-MU Meta-Analysis Report

BMI - body mass index; CHF = congestive heart failure; CV = cardiovascular; eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus

Studies: 018 = D1690C00018; 019 = D1690C00019

The rationale for pre-specifying the subgroup of all patients with a history of CV disease in the meta-analysis SAP was to include as many events as possible in the evaluation of dapagliflozin in this patient group to increase the precision of estimates. There was no reason in advance of seeing the results to examine Studies D1690C00018 and D1690C00019 in isolation from the larger pre-specified subgroup. Nevertheless, an analysis of these two studies was requested to be provided in the major amendment provided to FDA in October 2011, and again with the recent NDA resubmission. The analysis provided in 2011 was an interim analysis of the two studies, which were ongoing at the time. In Study D1690C00018, the estimated hazard ratio between dapagliflozin and control was 1.165 (95% CI: 0.555, 2.449) for the primary endpoint, 1.003 (95% CI: 0.522, 1.927) for the secondary endpoint and 1.350 (95% CI: 0.569, 3.205) for MACE. In Study D1690C00019, the corresponding estimated hazard ratios were 0.989 (95% CI: 0.495, 1.978) for the primary endpoint, 0.801 (95% CI: 0.430, 1.494) for the secondary endpoint

and 1.189 (95% CI: 0.514, 2.753) for MACE. The pooled analysis of Studies D1690C00018 and D1690C00019 showed an estimated hazard ratio of 1.068 (95% CI: 0.643, 1.772) for the primary endpoint, 0.891 (95% CI: 0.568, 1.398) for the secondary endpoint and 1.266 (95% CI: 0.693, 2.311) for MACE.

Table 36 presents the updated results now after completion of the two studies for all 3 composite endpoints for Studies D1690C00018 and D1690C00019 individually and for the 2 studies pooled. The pooled analysis show an estimated hazard ratio for the primary endpoint near unity, 0.955 (95% CI: 0.626, 1.458), slightly below unity for the secondary endpoint 0.887 (95% CI: 0.619, 1.271) and slightly above unity for MACE, 1.108 (95% CI: 0.670, 1.831). The results in the individual studies showed estimated hazard ratios below 1 in Study D1690C00019 for the 3 composite endpoints and above 1 in Study D1690C00018. Considering the small sample sizes of either study individually or of the 2 studies pooled, there is considerable variability around the hazard ratios. While not intended by the Sponsor to be taken in isolation, the analyses of Studies D1690C00018 and D1690C00019 altogether (primary, secondary, and MACE) do not suggest an increase in CV risk.

Table 36: Summary of Results for Primary Composite Endpoint and MACE Endpoint in CV Analyses of the Dapagliflozin Phase 2b and 3 Clinical Program, Patients in studies D1690C00018 and D1690C00019 (30-MU)

	No. of events	HR	95% CI
<u>Subgroup of Patients from studies D1690C00018 and D1690C00019 pooled</u>			
Primary endpoint ^a	86	0.955	0.626, 1.458
Secondary endpoint ^b	119	0.887	0.619, 1.271
MACE ^c	61	1.108	0.670, 1.831
<u>Subset of Patients from study D1690C00018 alone</u>			
Primary endpoint ^a	39	1.176	0.627, 2.208
Secondary endpoint ^b	54	1.005	0.590, 1.714
MACE ^c	28	1.344	0.636, 2.841
<u>Subset of Patients from study D1690C00019 alone</u>			
Primary endpoint ^a	47	0.803	0.452, 1.428
Secondary endpoint ^b	65	0.798	0.489, 1.302
MACE ^c	33	0.941	0.476, 1.863

^a Composite endpoint of CV death, MI, stroke and hospitalization for unstable angina.

^b Composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization and hospitalization for heart failure.

^c Composite endpoint of CV death, MI, and stroke.

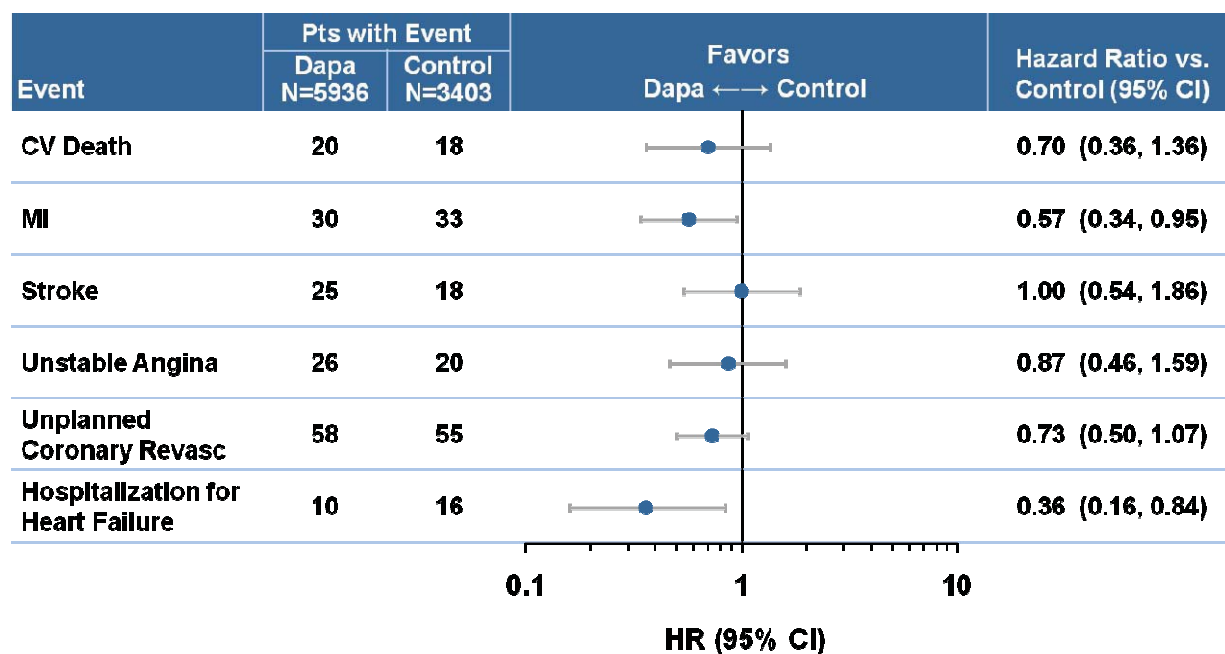
CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event

Source: CV Events 30-MU Meta-Analysis Report

Results for components of the CV composite endpoints

The results of analyzing the components of the three composite endpoints individually are displayed in Figure 35. For all components, the estimated hazard ratio is below 1 or exactly 1 for dapagliflozin versus controls.

Figure 35: Components of Endpoints, Analyzed by Cox Proportional Hazards Methods, All Phase 2b and 3 Pool (30-MU)

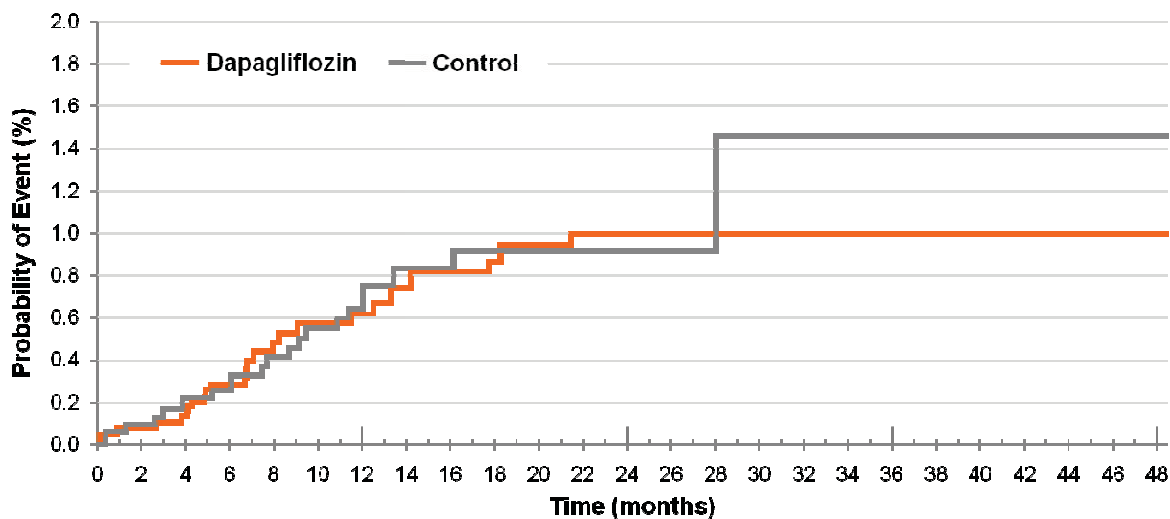


Source: CV Events 30-MU Meta-Analysis Report

CI = confidence interval; CV = cardiovascular; Dapa = dapagliflozin; MI = myocardial infarction; Revasc = revascularization

Stroke

For the approved SGLT2 inhibitor canagliflozin, concern for an elevated stroke hazard was an issue discussed at the Advisory Committee meeting.⁴⁴ In the all Phase 2b and 3 population, there were 44 strokes observed in 43 patients; 41 were ischemic, 1 undetermined and 2 hemorrhagic (Figure 35). Two strokes resulted in death, one on dapagliflozin and one on placebo. Baseline characteristics comparing patients with and without stroke events showed, as expected, that patients experiencing strokes were older, and a higher proportion had a history of CV disease than those not experiencing stroke, both in the dapagliflozin and the control group. None of the patients experiencing stroke had reported AEs of volume depletion prior to the stroke. The Kaplan-Meier curve for the cumulative probability of stroke over time (Figure 36) shows a similar pattern for the dapagliflozin and control arm suggesting no increased risk of stroke with dapagliflozin at any time point after initiation of treatment.

Figure 36: Kaplan-Meier Estimate for Stroke to 4 Years, Overall Stratified Analysis with Weighted Curves, All Phase 2b and 3 Pool (30-MU)**Patients at Risk**

Dapa	4227	4079	3905	3770	2939	2843	2457	1747	1898	1625	1555	1501	1429	264	255	250	244	239	235	223	221	212	211	190	177
Control	2412	2303	2195	2104	1643	1575	1332	924	881	833	790	787	715	139	132	130	128	124	120	113	111	107	107	90	80

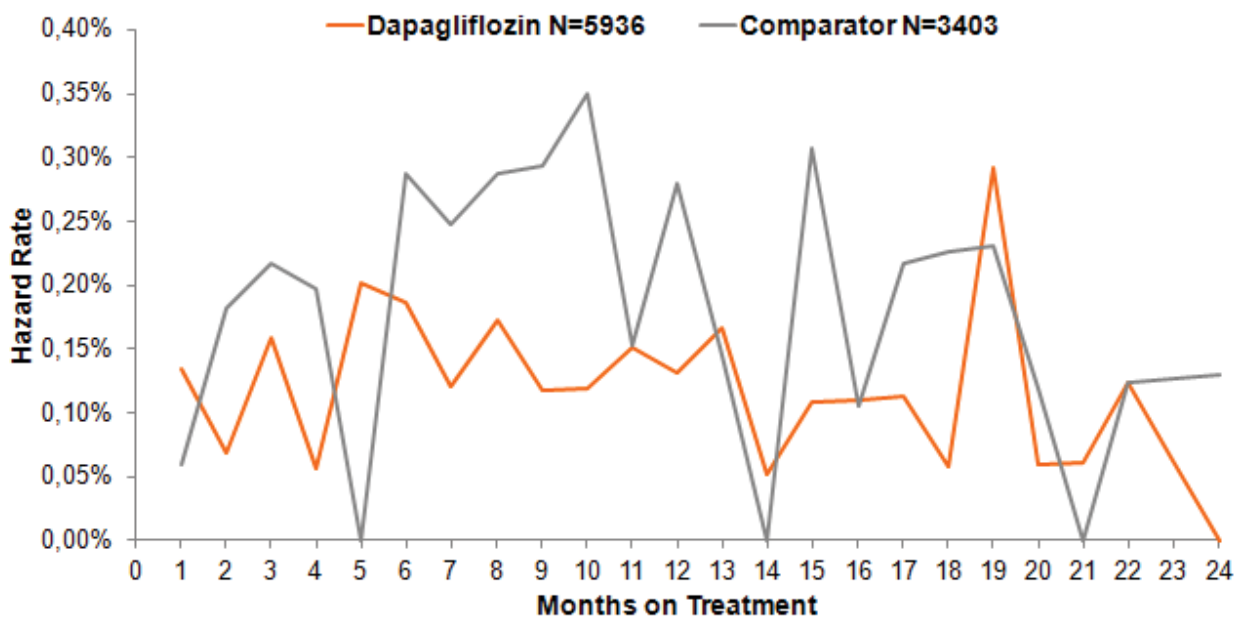
Studies without at least one positively adjudicated event are excluded from the analysis.

Source: ADCOM CV64

Dapa = dapagliflozin

Early CV events

Questions have been raised over a potential class effect of increased risk of early CV events due to the early hemodynamic effect imposed by the MOA of SGLT-2 inhibitors. For the approved SGLT2 inhibitor canagliflozin, an excess of early CV events was a topic of discussion at the Advisory Committee meeting.⁴⁴ For dapagliflozin, in the all Phase 2b and 3 Pool, there were 8 of 5936 patients had primary events on dapagliflozin (1 CV death, 2 MIs, 3 Strokes and 2 hospitalizations for unstable angina) versus 2 of 3403 patients in the control group (1 MI and 1 Stroke) during the first 30-days after randomization. In Figure 37, the estimated hazard rate by 30 day intervals is presented, together with the number of events per time interval. There was a numerically higher hazard rates with dapagliflozin during the first month compared to placebo, but this is reversed during the second month. The observed imbalance in the first 30 days compared to control reflects the variable event rate in both groups. The hazard rate is not notably different at early timepoints compared to later timepoints for dapagliflozin.

Figure 37: Hazard Rate Estimates for Primary Endpoint to Month 24, All Phase 2b and 3 Pool (30-MU)**Patients with Event**

Dapa	8	4	9	3	10	9	5	6	4	4	5	4	4	1	2	2	2	1	5	1	1	2	1	0
Comp	2	6	7	6	0	8	6	6	6	7	3	5	2	0	3	1	2	2	2	1	0	1	1	1

Source: ADCOM CV1 – final

Dapa = dapagliflozin

Finally, looking at the CV events that occurred in the first 30 days in the dapagliflozin group, no predictive factor with respect to baseline characteristics or concomitant medications was identified and in the patients with early CV events there were no prior AEs of hypotension, dehydration or hypovolaemia. However, since dapagliflozin has a mild diuretic effect with lowering of BP, it remains a possibility that hemodynamic effects of diuresis contributed to early CV events. As with any diuretic, caution should be exercised in patients for whom a dapagliflozin-induced drop in BP may pose a risk.

5.2.4 Conclusions on Cardiovascular Risk

In summary, in the updated CV events meta-analysis, estimated hazard ratios for the composite primary, secondary, and MACE endpoints were below 1 with the upper bound of 95% CIs well below 1.8. Additional analyses by study and subgroups support the main results. Specifically, the meta-analysis results in the program-wide subgroup of type 2 diabetes mellitus (T2DM) patients with a history of CV disease, as pre-specified in the SAP, support the main results. The results from this update are similar to the results from the original (17-Nov-2010), 4-MSU (11-Mar-2011), and Supplementary (01-Nov-2011) CV meta-analyses. These additional data show a favorable trend overall, consistent with a potential for CV benefit, with the conclusion that an unacceptable increase in CV risk in patients with T2DM has been ruled out. The analyses of

studies D1690C00018 and D1690C00019, as requested by the FDA, are compatible with this conclusion.

In addition to the evaluation of the CV events observed in the dapagliflozin program, BMS/AZ have also conducted 2 new studies in hypertensive patients with T2DM (MB102073 and MB102077), which are included in the NDA resubmission to the FDA. Treatment with dapagliflozin resulted in a statistically significant placebo-adjusted mean decrease in SBP, both seated (-3.05 and -4.28 mmHg in the 2 studies) and by ambulatory BP monitoring (-2.89 and -4.45 mmHg). Blood pressure is accepted as a surrogate for CV outcome,⁴⁵ with BP reduction leading to a reduction in CV events regardless of pretreatment BP and the presence or absence of existing CV disease.⁴⁶ The observed BP reduction provides support for the hypothesis of CV benefit.

The effect of dapagliflozin on CV outcomes will be definitively evaluated post-approval in DECLARE (TIMI-58, Study D1693C00001) (see [Section 6.2](#) for details).

5.3 Conclusions: Safety Profile of Dapagliflozin in Patients with T2DM

The extensive clinical development program has demonstrated that dapagliflozin, used for treatment of T2DM across a wide range of patient populations and treatment regimens, is safe and well tolerated.

Identified risks with dapagliflozin treatment include genital infection and UTI. Higher proportions of patients treated with dapagliflozin, compared to placebo, experienced events of genital infections and UTIs. These events are manageable within standard clinical practice, as the symptoms are easy to recognize, the vast majority of events are mild or moderate, the events respond to standard treatment without interruption of dapagliflozin, the majority of patients do not have recurrent events, the events did not cause hospitalizations, and no permanent complications were reported. Kidney infections were few and balanced.

Dapagliflozin as a monotherapy has a low overall propensity for hypoglycemia. However, when used with agents with known side effects of hypoglycemia such as insulin and SUs, an increased risk of hypoglycemic events was observed, mainly in minor hypoglycemic events. This risk is manageable and can be addressed by dose reduction of the background therapy.

In the clinical program, although infrequent, there was an increase in non-serious AEs of volume depletion. Dapagliflozin, like all diuretics, may potentially cause volume depletion in susceptible patients. For patients at increased risk for volume depletion due to co-existing conditions or concomitant medications, a 5 mg dose of dapagliflozin, which is associated with reduced diuresis, may be indicated.

Small but consistent mean increases in hematocrit were associated with dapagliflozin treatment. The observed hematocrit increases are likely related to mild plasma volume depletion associated with the diuretic effect of dapagliflozin. There was no imbalance in thromboembolic events between dapagliflozin and control, and no increase in CV events was identified in the meta-analysis of adjudicated CV events.

In dapagliflozin-treated patients, eGFR is stable over long-term follow-up, with an initial physiologic small mean decrease followed by a return to baseline. Renal AEs occurred more frequently in dapagliflozin-treated patients however they were mostly related to reversible, transient, small increases in serum creatinine, which is consistent with a mild diuretic effect. Serious renal events were few and balanced with control. Renal AEs were predominantly reported in patients with eGFR $<60 \text{ mL/min/1.73m}^2$.

The data indicate no evidence of an association of dapagliflozin treatment with liver toxicity and no evidence of severe drug-induced liver injury. Across the Phase 2b and 3 studies, similar proportions of patients with elevations of liver enzymes were observed for dapagliflozin and control patients. These clinical data are aligned with significant nonclinical data showing no indicators of liver toxicity in animals at large exposure margins up to 5000 times the MRHD.

There is no overall imbalance for malignant and unspecified tumors. As expected from an agent that does not cause cancer there were types of tumors more frequent in dapagliflozin and those more frequent in control indicating variability seen with small numbers as a reason for numerical imbalances. Although there are numerical imbalances in bladder and breast cancer, the totality of the clinical and nonclinical data does not support a causal relationship or any contributory role between dapagliflozin treatment and the risk of these cancers.

Dapagliflozin has an acceptable CV, with no evidence for an increased risk of major CV events and with hazard ratios < 1 consistently across various composite CV endpoints and across different subgroups. There is a suggestion of CV benefit which would be consistent with BP and weight reductions.

Patients with moderate renal impairment (eGFR ≥ 30 and $< 60 \text{ mL/min/1.73 m}^2$), a population in whom initiation of dapagliflozin therapy is not recommended, were more sensitive to the adverse effects of diuresis. In this population, patients receiving dapagliflozin had a higher proportion of AEs related to volume depletion and related to renal impairment than patients with greater degrees of renal function. In addition, while the pooled data did not show an increase in fractures in this population, the dedicated Phase 2b/3 study in this population (MB102029) showed more fractures in the dapagliflozin groups than the placebo group. The CV event profile for the composite primary, secondary, and MACE endpoints all showed favorable point estimates in patients with moderate renal impairment, consistent with the findings of the overall study population.

In summary, the dapagliflozin safety profile has been well-characterized, and is acceptable when used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. There is no dose dependency between 5 mg and 10 mg for safety concerns. Potential risks associated with dapagliflozin treatment are mainly related to its MOA and can be handled within standard clinical practice, generally without interruption of dapagliflozin treatment.

6 RISK MANAGEMENT PLAN AND POST-MARKETING PHARMACOVIGILANCE ACTIVITIES

Dapagliflozin has been studied in a broad and comprehensive Phase 2b and 3 clinical program. For additional information in the post-marketing setting the dapagliflozin Risk Management Plan (RMP) will provide for an integrated complementary set of pharmacovigilance activities designed to further identify, characterize, and evaluate potential risks relating to dapagliflozin use. Safety outcomes that will be specifically monitored during the post-marketing period include genital infections, urinary tract infections, hypoglycemia, volume depletion, clinical consequence of increased hematocrit, renal impairment or failure, bone fracture, liver injury, and cancer. Our risk assessment and risk mitigation activities are described in further detail below.

Post-marketing safety surveillance include: 1) routine and enhanced pharmacovigilance; 2) pharmacoepidemiology studies; 3) additional clinical trials in other geographies and adjacent populations; and 4) a large, clinical outcomes study (DECLARE) designed primarily to assess CV safety, but which will also collect data on other AEs.

Routine and enhanced pharmacovigilance activities by BMS and AZ are conducted by a medical surveillance team which is responsible for monthly screening and evaluation of the corporate safety database assessing reported AEs in monthly, quarterly, and annual groupings for all clinical trials, non-interventional studies, and spontaneous AE reports, both serious and non-serious. These AEs are assessed over time and allow for identification of both rates of reporting and of changes in rates over time. BMS and AZ employ targeted questionnaires to gather additional information and enhance the quality of data collected for events of interest in both the post-marketing setting as well as the clinical trials. Additionally, monthly safety assessments evaluate the global medical literature with regards to nonclinical, clinical and marketing reports. Continuously ongoing signal detection activities include review of individual case reports, aggregate analysis of AEs to detect increased frequency trends and potentially log specific product complaints, review of AEs in special populations (e.g. pregnancy, elderly, etc), and particular conditions of use (e.g. drug interactions, overdose, misuse, etc.), and results of disproportionality analysis (e.g. multi-item Gamma-Poisson Shrinker, etc.) as needed. Evaluations of global health authority safety data bases (e.g. FDA AERS) are also conducted.

Additional Pharmacovigilance Activities

BMS and AZ have developed a pharmacoepidemiology program to understand the real-world safety experience of dapagliflozin when used in adult patients with T2DM. This program is described in Section 6.1. In addition, a large, randomized, controlled CV outcomes trial (CVOT; (DECLARE, [TIMI-58, Study D1693C00001]) is currently underway and will characterize the long-term benefit and risk of dapagliflozin for the treatment of T2DM. This study is described in [Section 6.2](#).

6.1 Pharmacoepidemiology Program

The pharmacoepidemiology studies will provide insight on the demographics of patients using dapagliflozin in clinical practice and will estimate the incidence and risk of hospitalization for acute renal injury and acute hepatic injury, severe complications of UTIs, and cancer. For

detection of rare events, such as those being studied, large population studies are needed. The study outcomes will be compared between T2DM patients who are new initiators of dapagliflozin and those who are new initiators of other antidiabetic treatments. These studies are currently underway in EU and will be conducted over a 5 to 10 year period in administrative databases in Europe. With marketing in the US, similar data will be collected over a similar time frame.

6.2 DECLARE

A large, randomized, controlled CVOT (DECLARE, [TIMI 58, Study D1693C00001]) is currently underway and will characterize the long-term benefit and risk of dapagliflozin for the treatment of patients with T2DM. The study will randomize 17,150 patients with T2DM with either established CV disease or at least 2 CV risk factors in addition to T2DM and provides up to 6 years of exposure to dapagliflozin. As of 15-Oct-2013, more than 1400 patients have been randomized. The primary efficacy objective of this study is to determine whether treatment with dapagliflozin added to current glucose-lowering background therapy will result in a reduction in the composite endpoint of adjudicated CV death, MI, or ischemic stroke, compared to placebo. The primary safety objective of this study is to establish whether the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of adjudicated CV death, MI, or ischemic stroke observed with dapagliflozin to that observed in the placebo group is less than 1.3. The study will also provide continued assessment of various safety outcomes of interest including serious UTIs, serious genital infections, hepatic events, renal events, fractures, events related to volume depletion, and malignancies. The study includes blinded adjudication of hepatic events and malignancies as well as pre-specified interim analyses of bladder cancer and is overseen by a DMC.

The interim monitoring for bladder cancers is planned for the purpose of communicating potential signals with regulatory authorities, will be performed by the DMC, and will be firewalled from study personnel. The accumulation of patients with bladder cancer would suggest 4 interim analyses at 8, 16, 24, and 32 events, followed by the final analysis at approximately 43 events. Assuming an annual bladder cancer event rate of 0.06%, the interim analyses will occur after 26, 37, 46 and 55 months, respectively. These interim analyses will be assessed at an alpha-level of 0.10 with a Pocock spending rule. The choice of 8 events for the first analysis is driven by the smallest number of events that could suggest a difference in event rates at the $p < 0.10$ significance level. If an interim analysis is significant, the DMC will initiate communication according to a strict plan. Overall, the estimated relative risk for bladder cancer that can be detected or ruled out with 80% power, using a 1-sided 0.975 CI is 2.34 assuming that the true, underlying relative risk is 1.

6.3 Risk Mitigation

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 its safe use.

6.4 Summary

The BMS and AZ pharmacovigilance activities including post-marketing spontaneous AE reporting and continuous enhanced safety surveillance techniques, pharmacoepidemiology studies, which enable the overall quantitative assessment of risks associated with dapagliflozin in the context of other antidiabetic agents, and complement the risk information derived from the clinical program, additional safety data from ongoing and anticipated clinical trials, and the large CVOT (DECLARE), which will provide evaluations associated with long term exposure, will provide for a continuous comprehensive safety assessment of dapagliflozin in the post approval environment.

7 BENEFITS-RISK CONCLUSIONS

The benefit-risk ratio of dapagliflozin is favorable and warrants approval of the drug.

A substantial proportion of patients with T2DM have difficulty controlling their blood sugar. This is exacerbated by obesity, and by the weight gain caused by many current antidiabetic therapies, such as TZDs, insulin, and SUs. Over 85% of patients with T2DM are overweight or obese, and additional weight gain augments insulin resistance, which exacerbates diabetes disease progression and negatively impacts CV risk factors such as hypertension and dyslipidemia.

Hypertension is a common comorbidity in these patients, with > 70% prevalence. Inadequately controlled hypertension contributes to the increased risk of macro- and microvascular complications of T2DM.⁴⁷ The combination of hypertension and T2DM negatively impacts quality of life of patients with T2DM⁴⁸ and increases diabetes-related healthcare expenditures.⁴⁹

The efficacy of dapagliflozin as a once daily oral therapy for patients with T2DM within the clinical development program has been well demonstrated. Dapagliflozin provides substantial glycemic efficacy, demonstrated in head-to-head clinical trials to be comparable in magnitude to metformin and SUs, with a low intrinsic risk of hypoglycemia. Dapagliflozin brings the additional important benefits of weight loss and modest BP reduction.

The extensive clinical development program showed consistent and clinically important reductions in HbA1c at doses of 5 mg and 10 mg. Both doses are proposed to be made available in the US. The 10 mg dose is our usual recommended dose since it has better efficacy, with no noticeable difference in safety or tolerability when compared to the 5 mg dose.

Dapagliflozin decreases both fasting and post-meal plasma glucose values. The HbA1c reduction from dapagliflozin was shown to be equivalent to metformin, with better reductions than metformin in FPG and weight at Week 24. HbA1c reduction by dapagliflozin was also shown to be non-inferior to SU at Week 52, with one-tenth as many patients experiencing hypoglycemia as on SU. Dapagliflozin treatment led to weight loss, as opposed to weight gain seen with SU.

Dapagliflozin works equally well across a wide range of patient types. Dapagliflozin's MOA leads to direct elimination of glucose in the urine. This makes dapagliflozin complementary to other drug classes and effective regardless of background therapy. Dapagliflozin is also effective regardless of level of insulin resistance or degree of beta cell dysfunction, and thus works at all

stages and durations of T2DM. Dapagliflozin has shown consistent efficacy whether used as monotherapy in drug-naïve patients, as add-on therapy after treatment failure with metformin, SUs, TZDs, or DPP-4 inhibitors, or as add-on therapy in patients on insulin-based regimens. Dapagliflozin also shows substantial added efficacy when used as initial combination therapy with metformin in poorly controlled drug-naïve patients. Dapagliflozin's efficacy is not affected by age, race, gender, or BMI. The mechanism of dapagliflozin is dependent, however, upon renal function, with decreased efficacy in patients with moderate or greater renal impairment. Thus, dapagliflozin is not recommended to be initiated in patients with $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$.

Dapagliflozin has shown little intrinsic propensity to cause hypoglycemia. However, a higher frequency of hypoglycemia was seen when dapagliflozin was used in combination with SUs or insulin, agents which cause hypoglycemia. A lower dose of SU or insulin may be required to minimize the risk of hypoglycemia when dapagliflozin is used in combination with these agents.

Treatment with dapagliflozin leads to clinically meaningful weight loss, a fundamental but difficult to achieve goal for the majority of patients with T2DM. The persistent loss of calories in the urine, and subsequent negative energy balance, causes a slow and steady weight loss over the first 6 to 7 months of treatment in large part accounted by a reduction in total body fat. In hypertensive patients, dapagliflozin also leads to improvements in SBP. This was seen on top of background ACEi/ARB therapy and on top of background dual antihypertensive therapy, including therapy with diuretics.

The clinical PK profile of dapagliflozin makes it convenient for patients to take. Dapagliflozin can be taken once daily without regard to meals, and it has no clinically meaningful drug:drug interactions. Exploratory long-term analyses in both active comparator and placebo-controlled clinical studies support maintenance of glycemic efficacy as well as weight loss over 2 years of dapagliflozin treatment, despite the inherently progressive nature of T2DM.

Adverse effects associated with dapagliflozin treatment are related to its MOA, and generally not related to dose when comparing the 5mg and 10 mg doses. The dapagliflozin clinical development program evaluated safety in a wide range of patients with T2DM. The program comprised 24 Phase 2b and 3 studies with durations ranging from 12 weeks to 4 years. More than 11,000 patients were randomized in these studies, with more than 6,000 receiving dapagliflozin. Patient populations examined covered the range of diabetes progression: drug-naïve patients, patients failing oral therapies, and patients on insulin-based regimens. The program also included a significant experience in elderly patients, patients with a history of CV disease, overweight and obese patients, patients with poorly controlled hypertension, and patients with mild to moderate renal impairment.

Higher proportions of patients treated with dapagliflozin, compared to placebo, experienced urogenital infections. These events are manageable within standard clinical practice, as the symptoms are easy to recognize, and the majority of events are mild or moderate in severity, respond to standard treatment without interruption of dapagliflozin, and do not recur. There was no increase seen in pyelonephritis.

Urinary glucose excretion from dapagliflozin causes a mild osmotic diuresis. The increase in urinary volume is 375 mL/day at the 10 mg dose, the equivalent of one extra void per day. Dapagliflozin, like all diuretics, has the potential to cause volume depletion in susceptible patients. Non-serious AEs of volume depletion were infrequent but more common in patients treated with dapagliflozin than placebo. There were few SAEs of volume depletion, and these were seen at a similar frequency for dapagliflozin and control. While 10 mg is the usual recommended dose because of incrementally better efficacy than 5 mg, for patients susceptible to volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg dose of dapagliflozin, which is associated with less diuresis, may be appropriate.

Renal function is stable over time with dapagliflozin therapy, with up to 4 years of follow-up. There were more non-serious AEs related to renal function on dapagliflozin than placebo, most appearing to be related to the transient changes in volume status that occur with diuretic therapy. This was especially notable in patients with $eGFR < 60 \text{ mL/min/1.73m}^2$, and it should be noted that dapagliflozin is not recommended to be initiated in these patients.

The preclinical and clinical data indicate no evidence of an association of dapagliflozin treatment at any dose with liver toxicity. Liver injury was initially considered to be a potential risk based on a single concerning clinical case for which there was partial information at the time of the CRL. Subsequent additional data from this case, however, show the probable diagnosis to be idiopathic autoimmune hepatitis rather than DILI.

There have been more cases of bladder cancer seen on dapagliflozin than control; however, the weight-of-evidence argues strongly against a causal relationship linking dapagliflozin to bladder cancer. Preclinical models, which are highly predictive of human bladder carcinogens, showed no indications of a bladder cancer risk, nor any evidence of biological plausibility. The original preclinical data and the new preclinical studies together provided substantial weight-of-evidence that dapagliflozin or glucosuria itself are not associated with bladder tumor initiation, promotion, or growth enhancement. The clinical data, including the additional clinical experience in the resubmission, show no overall imbalance in malignancies, with some tumor types, such as bladder cancer, more common on dapagliflozin than control, and others, such as renal cancer, less common on dapagliflozin than control. None of these imbalances was statistically significant. Furthermore, while cumulative patient exposures of between 2 and 4 years are very low, there were no cases of bladder cancer beyond 2 years in the clinical program. The clinical picture of the bladder cancer cases indicates a number of risk factors such as age, male gender, and substantial smoking history that were most likely to have been significant contributors. Further, of the cases of bladder cancer in the program, all but one was diagnosed or showed the first clinical sign of bladder cancer within 6 months of starting dapagliflozin therapy, a timeframe too short to realistically reflect causality, and indicative of pre-existing tumors. Overall, the totality of preclinical and clinical data is inconsistent with drug-induced tumor induction, promotion, or growth enhancement.

There was also a non-statistically significant imbalance in breast cancer cases in the clinical program. The data do not support a causative role for dapagliflozin. No biologically plausible

link between dapagliflozin and breast cancer has been identified. Dapagliflozin is highly selective for its SGLT2 target; and SGLT2 is not expressed in human breast tissue. There is also no interaction of dapagliflozin or its primary metabolite with estrogen receptors nor any indication of estrogenic effects in rodent or non-rodent species throughout the nonclinical toxicology program. There is no carcinogenicity signal in the nonclinical program in models that are sensitive to mammary tumor effects. Together with the lack of an increased incidence of hyperplastic lesions, these data indicate that dapagliflozin is not promoting or accelerating breast cancer growth. The cases followed the normal epidemiology of breast cancer, both with respect to risk factors (age, female gender), and with respect to tumor marker heterogeneity (estrogen receptor, progesterone receptor, and Her2/Neu positivity). The imbalance in the incidence rate ratio is not statistically significant, and has decreased with more patient exposure, a finding that highlights the instability of the incidence rate ratio due to the small number of cases constituting the original imbalance.

Dapagliflozin has an acceptable CV risk profile, with no evidence for increased CV risk. The CV meta-analysis primary, secondary, and MACE endpoints for the overall population and the high CV risk subpopulation show beneficial hazard ratio point estimates, consistent with previous analyses. The upper bound of the CI for the primary endpoint is well within the margin required by FDA guidance to demonstrate no unacceptable CV risk prior to approval.

It is not possible to fully assess all potential rare risks of new drugs prior to approval. For this reason, assessment of certain potential risks that are less likely to be associated with the drug based on available data need to continue post approval. The recently started outcomes study Dapagliflozin Effect on Cardiovascular Events (DECLARE [TIMI-58]), will assess, through a targeted 77,000 total patient-years of exposure, a number of key safety parameters. CV events are being adjudicated, and both CV safety and the hypothesis of CV benefit will be formally statistically tested. In addition, malignancies and liver events are being adjudicated, and the overall safety profile, including urogenital infections, volume-related events, and renal function are being followed. This trial is being monitored by an expert DMC, who periodically evaluate the evolving benefit-risk profile demonstrated in the trial. Complementing the large outcomes trial is a series of pharmacoepidemiology studies underway in Europe, where dapagliflozin is already on the market, and to be expanded to the US upon approval. These studies gather real-world evidence on the frequency of selected events in patients receiving dapagliflozin compared to patients on other antidiabetic therapies. The pharmacoepidemiology studies are examining malignancies, acute liver injury, acute renal injury, and severe complications of urinary tract infections. The safety profile of dapagliflozin is further being assessed by routine and enhanced pharmacovigilance practices in ongoing trials, and in the countries where dapagliflozin is already approved (EU, Australia, New Zealand, Mexico, Brazil, and Argentina).

Dapagliflozin has a well-defined profile supporting its use. For patients with T2DM, it is an easy to use once daily oral medication with early and sustained demonstrable benefits and good tolerability. The efficacy and safety profile of dapagliflozin are clearly described in the proposed prescribing information, with appropriate guidance provided to ensure safe and appropriate use

post approval. In addition, a robust post-approval plan is in place for monitoring issues related to patient safety.

Patients are struggling to improve glycemia, while maintaining control of weight and BP. The data, including the addition of new data since the time of the CRL, show that the benefit-risk ratio of dapagliflozin for the treatment of T2DM is positive and warrants approval of drug to help address these unmet medical needs. More choices are needed for treating T2DM; dapagliflozin represents an important new treatment option for patients and health care providers.

8 LIST OF ABBREVIATIONS

Term	Definition
30-MU	30-Month Update
ACEi	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AZ	AstraZeneca
BA	bioavailability
BE	bioequivalence
BMD	bone mineral density
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	confidence interval
CrCl	creatinine clearance
CRL	complete response letter
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DECLARE	Dapagliflozin Effect on Cardiovascular Events Study
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
DPP-4i	dipeptidyl peptidase-4 inhibitor
DXA	dual x-ray absorbiometry
eGFR	estimated glomerular filtration rate
Emax	maximum effect
EMDAC	Endocrinology and Metabolic Drug Advisory Committee
EU	European Union

Term	Definition
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HEC	hyperinsulinemic euglycemic clamp
HOMA-2	homeostasis model assessment 2
LDL-C	low density lipoprotein cholesterol
LOCF	last observation carried forward
LT	long-term
MA	marked laboratory abnormality
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MOA	mechanism of action
MRHD	maximum recommended human dose
NDA	New Drug Application
non-HDL-C	non-high density lipoprotein cholesterol
NYHA	New York Heart Association
OAD	oral antidiabetic
PD	pharmacodynamic
PK	pharmacokinetic
PPG	post prandial glucose
PT	preferred term
RMP	risk management plan
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SBP	systolic blood pressure
SCS	Summary of Clinical Safety
SGLT1	sodium-dependent glucose transporter 1
SGLT2	sodium-dependent glucose transporter 2
SMQ	Standard MedDRA Query
SOC	system organ class
ST	short-term

Term	Definition
ST+LT	short-term plus long-term
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TCC	transitional cell carcinomas
TmG	tubular glucose transport
TZD	thiazolidinedione
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit normal
US	United States
UTI	urinary tract infection
XR	extended release
ZDF	Zucker Diabetic Fatty

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