



BACKGROUND DOCUMENT

**DAPAGLIFLOZIN
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US FOOD & DRUG ADMINISTRATION ENDOCRINOLOGIC & METABOLIC ADVISORY COMMITTEE

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SUMMARY

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) are seeking approval for dapagliflozin (also known as BMS-512148) for treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin is a rationally designed, stable, competitive, reversible, highly selective and orally active inhibitor of the sodium glucose co-transporter 2 (SGLT2), which is the major transporter responsible for renal glucose re-absorption. Dapagliflozin's mechanism of action (MOA) is different from currently available anti-diabetic medicines, resulting in the direct elimination of glucose by the kidney. Glucosuria serves as a fundamental pharmacodynamic (PD) marker of the action of dapagliflozin, with the controlled elimination of glucose into the urine by dapagliflozin foreshadowing improvements in hyperglycemia. Its effect is independent of the action of insulin and therefore, complementary to the mechanisms of existing medications for T2DM.

BMS and AZ designed and executed an extensive non-clinical and clinical program to evaluate this new mechanism of action as a unique treatment for T2DM. The comprehensive development program was designed to both estimate the efficacy and evaluate potential safety concerns related to the consequences of dapagliflozin's direct elimination of glucose via the kidney.

The basis for the clinical potential of inhibiting SGLT2-mediated transport as a means to facilitate glucose elimination derives from the observation that patients with rare familial renal glucosuria (FRG) have mutations in the SGLT2 gene.^{1,2} These patients often first present with unexplained glucosuria during routine medical assessment. The lack of functional SGLT2 transporters in FRG patients is otherwise associated with mostly benign phenotypes, with no relevant off-target effects or symptoms of chronic glucosuria. FRG patients generally have a good prognosis with normal life expectancies.

The sections that follow describe the overall results of the dapagliflozin development program. The presentation focuses on those safety and efficacy topics most relevant to the use of dapagliflozin as a treatment for T2DM through direct elimination of glucose by the kidney. This implies that the efficacy of dapagliflozin will be a function of both circulating plasma glucose levels and the underlying glomerular filtration rate (GFR). Similarly, the safety profile is expected to include effects related to glucosuria and

osmotic diuresis. These topics include 1) hypoglycemia, both alone and in combination with other anti-diabetic agents; 2) the impact of glomerular filtration rate on the safety and efficacy profile of dapagliflozin, 3) the impact of the diuretic effect on volume and electrolyte status, as well as potential symptoms and side effects due to glucosuria, including polyuria and nocturia; 4) the risk and characterization of renal events, urinary tract infections (UTIs), and vulvovaginitis, balanitis and related genital infections associated with glucosuria; 5) the impact of treatment on bone health; and 6) other possible long-term adverse effects of chronic treatment with dapagliflozin and/or chronic glucosuria, including a comprehensive cardiovascular event meta-analysis.

As may be expected in development programs at this stage, there were also some unexpected findings. Although the incidence rates between dapagliflozin and control patients were similar for overall malignancies, imbalances were observed in breast and bladder cancers. Based on a thorough nonclinical and clinical assessment, the data do not suggest that dapagliflozin is associated with a risk for either of these cancers; however, the data are limited, and further assessment and follow-up of these observations are planned.

The proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed recommended dose is 10 mg once daily, at any time of the day, regardless of meals. A 5-mg starting dose may be appropriate for patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics.

Because dapagliflozin depends on adequate renal function to eliminate glucose through unopposed urinary excretion, it should not be used in patients with $\text{eGFR} < 45 \text{ mL/min/1.73m}^2$ due to the lack of clinical efficacy. This renal threshold for use of dapagliflozin corresponds to the creatinine clearance and/or gender-specific serum creatinine thresholds guiding the recommended use of metformin in patients with T2DM.

Overview of Clinical Development Program

The overall clinical development program consisted of 27 pharmacology studies, and a total of fourteen Phase 2b and 3 studies (three Phase 2b and eleven Phase 3 studies). The clinical pharmacology evaluation took place across a broad range of doses, ranging from 0.001 to 500 mg. The clinical program in patients with T2DM focused mostly on 3 doses

of dapagliflozin: 2.5, 5, and 10 mg, after assessment in a 12-week multi-group dose-ranging study, which demonstrated that higher doses of 20 and 50 mg led to additional increases in hematocrit measurements, as well as vulvovaginitis, balanitis and related genital infections and UTIs, but did not provide further improvements in glycemic efficacy. More than twice as many patients were randomized to treatment with dapagliflozin (n = 4287) as to control treatment with a placebo or other anti-diabetic drug (n = 1941) in the initial New Drug Application (NDA).

A broad population with overall clinical characteristics representative of patients with T2DM in real-world practice were enrolled in the dapagliflozin clinical program. This broad population was comprised of treatment-naïve patients as well as patients with T2DM of long duration who were already receiving metformin, sulfonylureas (SUs), insulin and thiazolidinediones (TZDs), and elderly patients. Patients with T2DM who had a history of CV disease, hypertension, and chronic complications of T2DM (mild and moderate renal impairment, retinopathy, neuropathy) were included to assess the impact of dapagliflozin and its unique MOA on CV morbidity and mortality, and address efficacy and safety questions related to underlying renal function.

More than half of the 4287 patients treated with dapagliflozin 2.5 mg or higher were treated for > 1 year and 441 patients were treated for at least 2 years. The 10-mg dose of dapagliflozin was used in approximately 2000 patients in the Phase 2b and 3 clinical program, with 461 patients treated with the 10-mg dose for at least 77 weeks. Cumulative treatment with dapagliflozin in the Phase 2b and 3 studies was 4009 patient-years while cumulative treatment with a control was 1682 patient-years. One additional Phase 2b study and longer treatment periods were included in the 4-month safety update to the initial NDA.

Summary of Clinical Pharmacology and Dosing Evaluations

The Clinical Pharmacology program profiled the safety, tolerability, pharmacokinetics (PK), PD, population PK, exposure-response, and biopharmaceutic characteristics of dapagliflozin. The Clinical Pharmacology program compiled data from 27 pharmacology studies in 704 subjects, 651 treated with dapagliflozin over a dose range of 0.001 to 500 mg. Studies included healthy subjects as well as patients with T2DM (118 patients

total, 101 treated with dapagliflozin) and subjects without T2DM but with renal or hepatic impairment (20 and 18 patients respectively, all receiving dapagliflozin).

Overall, these early Phase 1 and Phase 2a studies of dapagliflozin established that it was possible to use dapagliflozin to harness the capacity of the kidneys to eliminate glucose in the urine in a controlled way, offering a useful and novel approach to reduce the hyperglycemia of diabetes with minimal impact on volume and salt balance. In fact, glucosuria is a fundamental PD marker of activity of dapagliflozin, with amounts equal to approximately 80 grams of glucose excreted daily.

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

Dapagliflozin had no clinically-meaningful effect on the QTc interval or cardiac rhythm based on results of a study to specifically evaluate the risk of any change in the QTc interval, which included a positive control. This study did not show any dapagliflozin dose or plasma concentration-related effect on QTc interval at doses up to 150 mg once daily, providing a wide safety margin relative to the proposed dose of 10 mg. No drug-drug interactions were identified, confirming that dapagliflozin can be co-administered with a wide variety of other common medications. PK are not meaningfully affected by age, T2DM, body weight, gender, race, UGT1A9 polymorphism, mild or moderate hepatic impairment, or mild renal impairment.

Summary of Efficacy

Dapagliflozin was effective in reducing hemoglobin A1c (HbA1c) in a broad range of patients regardless of disease progression/duration or concomitant use of anti-diabetic therapies. Significant improvements in glycemic control were observed when dapagliflozin was given as monotherapy; as add-on combination therapy to metformin, a

SU (glimepiride), a TZD (pioglitazone) or insulin (\pm oral anti-diabetics [OAD]); and as initial combination therapy with metformin. In addition, the mean reduction from baseline in HbA1c achieved with dapagliflozin 10 mg plus metformin was non-inferior when directly compared to the glipizide (SU) plus metformin with a significantly smaller proportion of patients with hypoglycemic events in the dapagliflozin group vs glipizide ($p < 0.0001$). The mean reduction from baseline in HbA1c achieved with dapagliflozin 10 mg was non-inferior when directly compared to the metformin. Effects on secondary glycemic efficacy parameters, including fasting plasma glucose (FPG) and post-prandial glucose (PPG), support the primary HbA1c efficacy findings. Overall, dapagliflozin 10 mg provided better glycemic efficacy for treatment of patients with T2DM than the 2.5- or 5-mg doses.

Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass as a consequence of caloric loss from urinary excretion of glucose. Placebo-controlled data for up to 2 years on similar background and rescue therapies indicate that the beneficial effects of dapagliflozin on glycemic and body weight parameters were maintained during long-term treatment. Finally, treatment with dapagliflozin across several studies was associated with small but potentially meaningful reductions in blood pressure (BP), particularly systolic BP, which are likely due to the mild diuretic effect and sodium loss occurring along with glucosuria, the fundamental PD marker for use of dapagliflozin.

As expected, the glucose-lowering effect of dapagliflozin in patients with moderate renal impairment was less than in those with normal renal function. In patients with moderate renal impairment consisting of eGFR values ≥ 45 and < 60 mL/min/1.73m², the reductions in mean HbA1c, FPG, and body weight were less than results achieved in patients with better renal function. Although the threshold cutoff for effective and appropriate use of dapagliflozin represents an informed judgment, BMS and AZ recommend allowing the use of dapagliflozin in patients with T2DM and moderate renal impairment (eGFR values ≥ 45 and < 60 mL/min/1.73m²). Coupled with routine clinical practice to monitor renal status over time through standard laboratory chemistry testing, this recommendation will allow patients and health care providers to assess glycemic reduction effects in individual patients based on their individual benefit-risk profile.

Summary of Safety

The safety of dapagliflozin was evaluated at doses of 2.5, 5, and 10 mg, administered as monotherapy or in combination with another anti-diabetic agent. Its safety profile is consistent with glucosuria and diuresis resulting from the inhibition of SGLT2.

Mechanism-related Safety

- Dapagliflozin treatment was associated with a low intrinsic propensity to cause hypoglycemia with similar rates to placebo when used as monotherapy or combined with metformin or pioglitazone. Higher rates of hypoglycemia were evident when dapagliflozin was combined with glipizide or insulin.
- A small increase in UTIs (4.8% for dapagliflozin 10 mg vs 3.7% for placebo) and an increase in genital infection (5.1% for dapagliflozin 10 mg vs 0.9% for placebo) were identified, likely due, in part, to increased levels of urinary glucose. The term genital infection is used to refer to vulvovaginitis, balanitis and related infections, and does not include sexually-transmitted infections.
 - Most were mild to moderate in intensity (98% for UTI and 99% for genital infections) and did not recur (84% for UTI and 73% for genital infections).
 - These infections generally responded to conventional antibiotic therapy, without interrupting treatment with dapagliflozin.
 - Discontinuations due to UTI and vulvovaginitis, balanitis and related genital infections were rare (0.2% and 0.1%, respectively) as were infections classified as serious; pyelonephritis was reported in 0.1% of dapagliflozin-treated patients vs 0.2% of control
 - Organisms identified in patients with UTI were generally those commonly associated with UTIs in the general population, such as *Escherichia coli* and *Klebsiella* species.
- Hemodynamic effects were consistent with diuresis.
 - Modest mean reductions in systolic blood pressure (BP) in dapagliflozin-treated patients were observed and there was no increase in measured orthostatic hypotension.
 - Events related to volume depletion were more common in patients treated with dapagliflozin compared with placebo; the most common event was hypotension.
- There was no evidence of any impact on estimated glomerular filtration rate (eGFR) in patients with normal or mildly impaired renal function. There was a small initial decrease in eGFR that was stable and did not appear to progress in a special study of patients with T2DM and moderate renal impairment

- Treatment with dapagliflozin has no overall impact on bone health when used as recommended.
 - Fracture adverse event rates across the entire clinical program, including all patients with varying degrees of renal impairment, were balanced between dapagliflozin and comparators.
 - Results from a 1-year bone densitometry assessment demonstrated no differences in bone mineral density between dapagliflozin and placebo patients.
 - There was a potential risk of fracture in the special study in patients with T2DM and moderate renal impairment, particularly in patients with more advanced, stage 3B renal impairment ($\text{eGFR} \geq 30$ and < 45 mL/min/1.73m²), but such patients are not recommended to receive treatment with dapagliflozin.

Other Safety Findings

- The proportion of patients with events of malignant and unspecified tumors was similar between treatment groups, up to an extended treatment period 7 months after the cut-off date for the 4-month safety update: 1.4% for dapagliflozin-treated patients vs 1.3% for control. However, imbalances in the proportion of patients with breast and bladder cancer were observed.
 - Nine (0.4%) patients treated with dapagliflozin vs 1 (0.09%) with placebo were reported with breast cancer. One additional case was reported in a patient who remains blinded in an ongoing study. Nine (0.3%) patients treated with dapagliflozin vs 1 (0.05%) with placebo were reported with bladder cancer.
 - Risk factors and clinical characteristics for the observed cases of breast and bladder cancer were typical of these types of cancers in the general population, including age at onset and gender.
 - The duration of exposure to dapagliflozin prior to the identification of cases of breast and bladder cancer was short compared to the extended latency periods usually associated with breast and bladder cancers induced by known carcinogens.
 - The small number of events of breast and bladder cancer in dapagliflozin-treated vs control patients and the wide CIs for incidence risk ratios limit the ability to assess causality based on statistical analyses.
- Overall, there was no clear association of dapagliflozin treatment at any dose with liver toxicity and no evidence of severe drug-induced liver injury.
 - No imbalance in liver AEs or liver laboratory test abnormalities was observed.
 - Eight patients met the laboratory criteria of ALT or AST $> 3 \times$ ULN and concomitant or subsequent TBL $> 2 \times$ ULN: 5 (0.1%) treated with dapagliflozin and 3 (0.2%) with a placebo or active drug comparator.

- All 8 patients had possible underlying causes of these elevations; 2 of the five patients treated with dapagliflozin were independently adjudicated to have a possible relationship to study drug.
- Of these 2, the case on dapagliflozin with an initial diagnosis drug-induced hepatitis and a subsequent alternative diagnosis of autoimmune hepatitis remains of concern because of the difficulty differentiating between a drug-induced event and autoimmune hepatitis.
- There was no increase in cardiovascular (CV) events associated with dapagliflozin treatment. The hazard ratio (HR) for the primary composite endpoint of CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina was 0.674 (98% CI: 0.385, 1.178), after a meta-analysis across the Phase 2b and 3 clinical program. These results met the requirement of an upper bound < 1.8 for the 95% CI for the HR in the FDA CV guidance.⁶³

Ongoing Safety Assessment

Proactive safety surveillance and evaluation in the post-marketing period is planned to enable the continued assessment of the benefit-risk profile of dapagliflozin. BMS and AZ propose a program of continued safety monitoring in clinical studies, a pharmacoepidemiology (PE) program, and a randomized, clinical outcome trial. Prospective, observational database studies of adult patients with T2DM are also planned as part of the post-launch, as well as enhanced surveillance activities to assess the safety profile of dapagliflozin in the T2DM population under conditions of usual care. Based on the current safety profile, these studies will further evaluate the risk of cancer, bone fractures, severe complications of urinary tract infections, acute renal failure and acute liver failure.

In addition to prospective observational PE studies, 9 clinical studies are ongoing as of the date of this document and any data from these studies will complement data from the proposed post-marketing observational studies.

BMS and AZ are committed to conducting a large, randomized, controlled clinical outcomes study to characterize the long-term benefit and risk of dapagliflozin for the treatment of T2DM. 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, non-fatal

myocardial infarction, or non-fatal ischemic stroke, compared to placebo. This study will also provide continued assessment of various safety outcomes of interest including bladder cancers, breast cancers, bone fractures, urinary tract infections, and liver safety with long-term treatment and follow-up. The study will enable prospective adjudication of endpoints and other outcomes of interest and will complement the real-world evaluations from the epidemiologic, observational database studies. BMS and AZ are currently working with the FDA in planning the design and execution of this study.

Conclusions

Dapagliflozin, with its novel yet straightforward mechanism of action, represents an unexpected yet effective choice for treating T2DM patients. By acting directly and specifically at the SGLT2 target in the kidney to eliminate glucose via an insulin-independent mechanism, dapagliflozin provides a unique treatment option. In essence, the capacity of the kidneys to eliminate glucose in the urine is harnessed in a controlled way, offering a useful and novel approach to reduce the hyperglycemia of T2DM with minimal impact on volume and salt balance.

Dapagliflozin provides clinically meaningful glycemic benefits on par with commonly used agents (metformin, SUs), with weight loss that is mostly from fat. These benefits are seen across the spectrum of T2DM — in drug-naïve patients early in their course of diabetes; in patients who have failed to achieve treatment goals with metformin, SUs, or pioglitazone; and finally in patients at later stages who are treated with insulin-based regimens.

With its unique MOA, dapagliflozin can play an important treatment role in these various clinical settings, dapagliflozin can help to relieve the cycle of increased insulin resistance, which contributes to the propensity for T2DM to developing and/or deteriorating, while weight gain and other metabolic and/or cardiovascular co-morbidities, such as hyperlipidemia and hypertension, worsen. Clinical studies demonstrate that glucosuria persists over time and remains stable during long-term treatment, resulting in maintenance of the reductions in HbA1c and FPG. This maintenance of effect is an important benefit due to the progressive nature of T2DM, particularly with respect to beta-cell dysfunction and insulin resistance due to glucotoxicity, which limits the efficacy of several of the existing anti-diabetic medications over time.

Dapagliflozin has a positive benefit-risk profile in a broad range of patients. Specific risks highlighted for assessment due to dapagliflozin's MOA have been thoroughly evaluated and are better understood. Most findings were either found not to be relevant, such as minimally increased urine volumes or negligible symptoms of polyuria or nocturia, or represent manageable issues. For example, increased UTIs and vulvovaginitis, balanitis and related genital infections in the presence of glucosuria were identified in the dapagliflozin clinical program, but individual cases were similar to those commonly encountered in patients with T2DM and were managed with treatment approaches used in routine clinical practice. Theoretical possibilities in patients with declining renal function, such as hyperphosphatemia, secondary hyperparathyroidism, and a possible increased risk of fractures, have been noted. The lack of an imbalance in fractures in the rest of the dapagliflozin clinical program and the bone mineral density results from the body weight and composition study suggest that these risks can be avoided by limiting the use of dapagliflozin to patients with T2DM with eGFR values ≥ 45 mL/min/1.73m².

Based on exploratory safety assessments, selected uncommon or rare clinical events have emerged as potential safety issues, including bladder and breast cancer, fractures in moderate renal impairment, and rare hepatic events. These potential safety risks will be better understood with additional clinical and/or observational population data. Results from a CV safety meta-analysis across the dapagliflozin program suggest that there is no evidence for increased CV risk with dapagliflozin treatment, and raises the hypothesis of possible CV benefit. The commitment by BMS and AZ to conduct a large, randomized clinical study to understand hypothesized CV benefits and concurrently evaluate cancer, fractures, and liver safety will further elucidate these preliminary findings.

Overall, dapagliflozin can provide value to the patient and the health care provider alike, contributing in a useful and complementary fashion toward more effective management of T2DM, one of the most progressive, challenging, and widely prevalent disorders we face.

1 BACKGROUND

1.1 Development Rationale

T2DM is a chronic disease characterized by hyperglycemia and an increased risk of microvascular and macrovascular complications. Despite the fact that there are many medications approved for the treatment of T2DM, achieving and maintaining treatment goals are challenging. The glycemic-lowering effect of most available anti-hyperglycemic agents is dependent on the presence of insulin and is limited by a loss of efficacy over time, in part due to progressive worsening of insulin resistance and beta-cell function.^{3,4} Most patients eventually require more than a single agent to achieve and maintain glycemic targets.⁵

Available anti-diabetic agents are associated with undesirable side effects that can necessitate a change in medication or exacerbate co-morbidities associated with diabetes. Weight gain and hypoglycemia are among the most common treatment-associated adverse effects that complicate the management of T2DM.⁶ Hypoglycemia is a clinically important barrier to optimizing treatment with insulin and sulfonylureas (SUs), both of which are preferred second-line treatment options in the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) diabetes treatment algorithm.⁵ Efforts by patients to lose weight as part of a therapeutic lifestyle 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 exacerbates disease progression and negatively impacts CV risk factors such as hypertension and dyslipidemia.

There is a clear need for innovation in the treatment of T2DM due to the progressive nature of the disease and limitations of available therapies, as patients struggle to achieve glycemic and weight reduction goals. A new paradigm has emerged for the development of these innovative therapies for T2DM, lasting in many cases for approximately 12 to 15 years when pre-approval and post-approval evaluations are all considered. The initial compound selection and evaluation in toxicology and early clinical studies, as for all new drug assessments, typically entails over 5 years of study by sponsors. Subsequently, Phase 3 clinical programs in T2DM have become more extensive, providing a more

complete picture of safety, particularly for a thorough cardiovascular safety assessment in accordance with recent FDA Guidelines. Even larger registrational clinical programs in T2DM cannot completely answer all safety considerations, especially for any rare events or other safety signals that emerge. In this new paradigm, a Phase 3 clinical program receiving regulatory approval for a new medicine will be followed by a number of post-marketing assessments lasting another 4 or more years, including a CV outcomes study, to confirm and refine the profile of the drug. As will be described later, BMS and AZ are planning to conduct a specific CV outcome study to test the hypothesis of the superiority of dapagliflozin relative to standard-of-care therapies for T2DM, while also evaluating other safety concerns. Complementary observational studies and post-marketing surveillance will also be conducted to evaluate potential safety signals.

1.2 Mechanism of Action

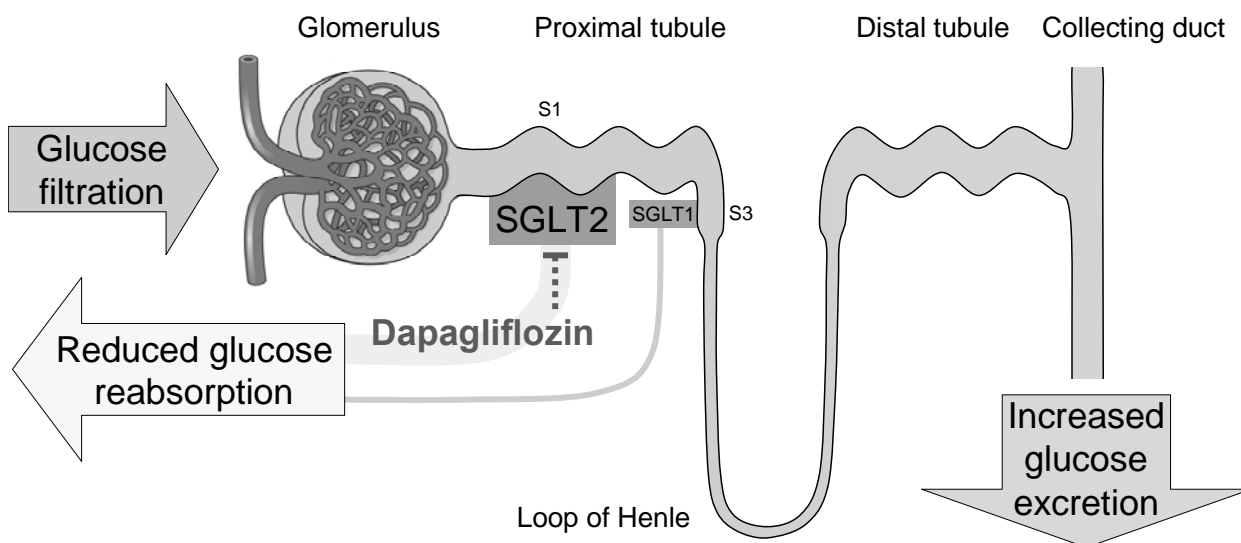
Dapagliflozin is a rationally designed, stable, competitive, reversible, highly selective, and orally active inhibitor of SGLT2, the major transporter responsible for renal glucose re-absorption. Dapagliflozin selectively inhibits human SGLT2 ($K_i = 0.55 \pm 0.16$ nM) vs human SGLT1 ($K_i = 0.81 + 0.2$ μ M) and is more than 1400-fold more potent at inhibiting SGLT2. While SGLT1 is the major glucose transporter responsible for the absorption of glucose in the small intestine, it has a smaller role in the kidney. Normally, essentially all of the glucose filtered in the glomerulus is subsequently re-absorbed in the tubule by this co-transporter system, predominantly by SGLT2 and to a lesser extent, SGLT1.

Dapagliflozin lowers plasma glucose levels in patients with T2DM by inhibiting renal glucose re-absorption and inducing increased urinary glucose excretion, which depends primarily on the amount of glucose filtered by the kidney (Figure 1). Overall, the amount of filtered glucose serves as an intrinsic PD marker and is determined by the patient's baseline glycemic control and underlying renal function. As SGLT2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target effects.

Dapagliflozin's MOA is different from and complementary to the mechanisms of currently available medicines to treat T2DM, resulting in the direct elimination of glucose by the kidney, independent of any action of insulin. Thus, glycemic efficacy with dapagliflozin does not require any contribution from the patient's existing beta-cell

function or insulin sensitivity, which are already deteriorating as a result of their T2DM. Although dapagliflozin's activity does not depend on insulin, dapagliflozin actually improves beta-cell function and insulin sensitivity by lowering hyperglycemia via the kidney, thereby limiting the negative effects of hyperglycemia on these parameters. This improvement has been demonstrated in both animal (Section 1.4) and human clinical studies (Section 4.3). The steady excretion of glucose due to SGLT2 inhibition also results in a continual loss of calories that contributes to a modest decrease in body weight and adiposity, a supplemental benefit that addresses some of the underlying problems in the pathogenesis of T2DM, over-nutrition and caloric excess.

Figure 1: How Dapagliflozin Works (Mechanism of Action)



1.3 Proposed Indications and Use

The proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The proposed recommended dose is 10 mg once daily at any time of the day regardless of meals. Dapagliflozin is not indicated for use in patients with type 1 diabetes and should not be used for the treatment of diabetic ketoacidosis. The efficacy of dapagliflozin is dependent on renal function. Thus, dapagliflozin should not be used in patients with moderate to severe renal impairment.

(defined as $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ using the estimating equation from the Modification in Diet in Renal Disease study (MDRD)¹⁸ or estimated creatinine clearance (eCrCl) $< 60 \text{ mL/min}$, using the Cockcroft-Gault estimating equation⁸). A 5-mg starting dose may be appropriate for patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics.

1.4 Nonclinical Development

The nonclinical profile of dapagliflozin was characterized in a comprehensive testing program that included *in vitro* and *in vivo* studies of PD, safety pharmacology, PK and metabolism, and toxicokinetics and toxicity.

Nonclinical pharmacology studies demonstrated that dapagliflozin improved both fasting and post-prandial plasma glucose levels (FPG and PPG) in diabetic rats by reducing renal glucose re-absorption and subsequent excretion of glucose in the urine. Once daily treatment with dapagliflozin over 4 weeks reduced hyperglycemia and improved insulin secretion as a function of insulin resistance compared to vehicle treatment. The observed effects were associated with histological improvements in islet morphology, including increased insulin staining in dapagliflozin-treated rats vs vehicle-treated rats.⁷

The toxicity profile of dapagliflozin was well characterized in selected nonclinical species and is consistent with the intended pharmacology to reduce glucose re-absorption in the kidney. No nonclinical findings raised concern about long-term clinical use.

Most of the effects observed in repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose, and included decreases in body weight, increased food consumption, and increases in urine volumes. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of $\leq 25 \text{ mg/kg/day}$ ($\geq 346\times$ the human exposures at the maximal recommended human dose (MRHD) of 10 mg), and in dogs for up to 12 months at doses of $\leq 120 \text{ mg/kg/day}$ ($\geq 3200\times$ the human exposures at the MRHD). Despite achieving exposure multiples of $\geq 3200\times$ the human exposure at the MRHD, there was no dose-limiting or target organ toxicities identified in the 12-month dog study.

In the rat, increased tissue mineralization was associated with increased serum calcium and mineralization of trabecular bone. This was observed only at high-exposure multiples ($\geq 2100\times$ based on human exposures at the MRHD) and is hypothesized to be related to off-target SGLT1 inhibition at high exposures. Other dapagliflozin-induced target-organ mineralization in the rat occurred in the kidney and stomach also at very high exposure multiples ($\geq 2116\times$ and $\geq 942\times$, respectively). Increased serum calcium with bone formation and tissue mineralization in the kidney and stomach were not observed in the mouse or dog following dapagliflozin administration. The high multiples associated with these findings indicate that they are not relevant to humans.

Dapagliflozin was not genotoxic nor carcinogenic. No dapagliflozin-related neoplasms were observed in studies of short- or long-term duration, including 2-year bioassays, in rodent species at doses up to $186\times$ the MRHD. Importantly, the doses of dapagliflozin evaluated in the carcinogenicity studies were well above pharmacologically active levels associated with robust glucosuria and diuresis in the species tested. Dapagliflozin did not cause transcriptional changes that are predictive of tumor promoters.^{59,60} nor was it associated with immunosuppression, alteration of urinary pH, local irritation or direct toxicity to the urothelium, estrogen effects, or cell proliferation. Additional details about nonclinical carcinogenicity findings are provided in Section 5.5.1.4.

Conventional reproductive toxicity studies indicated that dapagliflozin was not teratogenic at doses below those associated with profound maternal toxicity ($\geq 675\times$ MRHD) nor did it impair fertility. In juvenile toxicity assessments in rats, however, dapagliflozin was associated with renal tubular and pelvic dilatation at $15\times$ human exposures at the MRHD (i.e., the lowest exposure tested) suggesting an increased sensitivity of the developing kidney. It is hypothesized that dapagliflozin-induced glucosuria and the associated osmotic diuresis in juvenile rats leads to increases in urinary flow in the developing renal system, thereby resulting in the observed dilations in the kidneys.

In conclusion, the nonclinical program supported use in humans.

2 CLINICAL PHARMACOLOGY AND DOSING EVALUATIONS

The Clinical Pharmacology program profiled the safety, tolerability, PK, PD, population PK, exposure-response, and biopharmaceutic characteristics of dapagliflozin. The Clinical Pharmacology program compiled data from 27 pharmacology studies in 704 subjects, 651 treated with dapagliflozin over a dose range of 0.001 to 500 mg. Studies included healthy subjects in addition to patients with T2DM (118 patients, 101 treated with dapagliflozin) and subjects with renal or hepatic impairment (20 and 18 patients respectively, all receiving dapagliflozin). Overall, these early Phase 1 and Phase 2a studies of dapagliflozin established that it was possible to use dapagliflozin to harness the capacity of the kidneys to eliminate glucose in the urine in a controlled way, offering a useful and novel approach to reduce the hyperglycemia of diabetes with minimal impact on volume and salt balance.

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 patients with T2DM administered daily doses of 100 mg for 2 weeks. Glucose was detectable in the urine in both healthy volunteers and T2DM patients for a dose-related period of time, with no events of dehydration, hypotension or electrolyte imbalance. Daily urine volumes increased up to an additional 400 ml per day, starting from a baseline total urine volume range between 2.0 to 2.4 liters/day, with no distinguishable signs or symptoms of polyuria, polydipsia, or nocturia. The additional volume is equivalent to approximately one additional void per day.

Dapagliflozin also had no clinically-meaningful effect on the QTc interval or cardiac rhythm based on the results of a study to specifically evaluate the risk of any change in the QTc interval, which included a positive control. This study did not show any dapagliflozin dose or plasma concentration-related effect on QTc interval at doses up to 150 mg once daily, providing a wide safety margin relative to the proposed dose of 10 mg.

Dapagliflozin is rapidly absorbed, with a high absolute bioavailability (78%) and dose-proportional systemic exposures across a broad range of doses (0.1 to 500 mg) after oral administration. Renal excretion of dapagliflozin is minimal (< 2%), but renal excretion of

dapagliflozin metabolites is extensive (73% of dose). Dapagliflozin is approximately 91% bound to human plasma proteins.

In humans, 75% of the dose of dapagliflozin is primarily metabolized to dapagliflozin 3-O-glucuronide, through the uridine diphosphate glucuronosyltransferase (UGT)1A9 pathway. There have been reports of several low-frequency allelic variants of UGT1A9, which may lead to reduced function or enzyme expression, and which could potentially be a basis for patient-to-patient variability in exposure. However, pharmacogenetic analyses showed no conclusive evidence of this. The profile of metabolites in human urine vs nonclinical species is qualitatively similar, but differs in quantitative aspects, with the 3-O-glucuronide metabolite representing a major fraction of the administered dose in human ($\approx 60\%$) and a smaller fraction in mouse, rat, and dog (0.4 – 5%). The *in vitro* pharmacological potency of the glucuronidated metabolite is low and is not a meaningful inhibitor of SGLT2 at clinically relevant concentrations. Considering the high multiples of exposure to dapagliflozin in the toxicology compared to humans taking the 10-mg dose, the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies, including and rodent carcinogenicity studies, at exposure levels that are greater than or approximately equal to the anticipated human exposures to the 3-O-glucuronide metabolite.

Dapagliflozin is suitable for once-daily dosing, illustrated by a terminal phase half-life of 12.9 hours at the proposed clinical dose of 10 mg and sustained inhibition of urinary glucose re-absorption over 24 hours after treatment.

In healthy subjects and in subjects with T2DM, the PD increase in the amount of glucose excreted in the urine was observed following the administration of dapagliflozin doses ≥ 0.3 mg. The change from baseline in the amount of glucose excreted over 24 hours after dosing was higher for a given dapagliflozin dose in patients with T2DM compared to healthy subjects (mean E_{max} values of 83.1 g and 66.2 g, respectively) (see [Figure 2](#)). This finding was expected because patients with T2DM have a higher amount of glucose filtered by the kidney, and glucosuria is an intrinsic PD marker of the activity of dapagliflozin.

Regardless of the population (healthy or T2DM), the proposed dose of dapagliflozin (10 mg) is near the upper inflection point of the sigmoid E_{max} urinary glucose excretion

Dapagliflozin's effect on urinary glucose excretion results in osmotic diuresis, with small increases in urinary volume amounting to approximately 400 mL daily added to baseline urine outputs between 2 to 2.5 L. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion of 2 to 3 days that was not associated with changes in serum sodium concentrations.

Figure 1 is a log-log plot showing the relationship between Dapagliflozin Dose (mg) on the x-axis and CFB in 24-Hr Urinary Glucose (g) on the y-axis. The x-axis ranges from 0.0001 to 1000 mg, and the y-axis ranges from -10 to 160 g. Data points for Healthy Subjects (open circles) and Subjects with T2DM (asterisks) are plotted. Fitted lines are shown for both groups: a solid line for Healthy Subjects and a dashed line for Subjects with T2DM. Both groups show an increase in urinary glucose excretion with increasing dose, with Healthy Subjects generally having higher excretion values at higher doses.

Legend:

- ○ ○ ○ Observed Values for Healthy Subjects
- * * * * Observed Values for Subjects with T2DM
- Fitted Line for Healthy Subjects
- - - Fitted Line for Subjects with T2DM

CFB = Change from baseline; hr = Hour; T2DM = Type 2 diabetes

The steady-state 24-hour urinary glucose excretion due to dapagliflozin was highly dependent on renal function. Renal function was assessed using the Cockcroft-Gault⁸ equation for estimated creatinine clearance (eCrCl) for the purpose of PK analyses, consistent with the FDA Guidance on Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling.⁹ The amount of glucose excreted per day after a daily dose of dapagliflozin 20 mg in patients with T2DM decreased with reduced renal function based on eCrCl, in a focused, Phase 1 renal function study (MB102007; Table 1).

Table 1: Amount of Excreted Glucose (g/day) by Renal Function Category (Cockcroft-Gault⁸) after a Daily Dose of Dapagliflozin 20 mg in Patients with T2DM

Renal Function Category ⁹	Estimated Creatinine Clearance Values	Number of Patients	g (mean) of Glucose/Day
Normal	> 80 mL/min	4	85
Mild	> 50 to ≤ 80 mL/min	4	52
Moderate	≥ 30 to ≤ 50 mL/min	4	18
Severe	< 30 mL/min	3	11

PK are not meaningfully affected by age, T2DM, body weight, gender, race, UGT1A9 polymorphism, mild or moderate hepatic impairment, or mild renal impairment. The mean systemic exposure to dapagliflozin in patients with moderate or severe renal impairment and T2DM was less than 2× higher compared to patients with T2DM and normal renal function. Likewise, the mean systemic exposure to dapagliflozin in non-diabetic subjects with severe hepatic impairment was less than 2× higher compared non-diabetic subjects with normal hepatic function.

Pharmacogenetic analysis showed no evidence for a meaningful difference in dapagliflozin clearance across UGT1A9 genotypes for any single nucleotide polymorphisms. Thus, in patients who are suitable for dapagliflozin therapy, there are no identified intrinsic factors that will result in extremely high or extremely low drug exposure from the recommended daily 10-mg dose, and dose adjustments would not be needed based on dapagliflozin PK data.

There are no identified extrinsic factors that will markedly alter dapagliflozin drug exposure in patients with T2DM treated with the proposed recommended daily 10-mg dose. *In vitro* metabolism (cytochrome P450 (CYP) CYP3A4, CYP2C9, CYP2C8 and CYP2C19) along with transporter (organic anion transporters (OCT) OCT1, OCT2, OAT3, and P-glycoprotein (P-gp) studies and clinical drug-drug interaction studies with common concomitant medication used by the T2DM population (metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, simvastatin, mefenamic acid, and rifampin) demonstrated that dapagliflozin has little potential to either affect their metabolism or have its metabolism meaningfully affected by co-administration of other drugs. In healthy subjects, dapagliflozin's diuretic properties did not meaningfully interfere with the PD activity of a loop diuretic (bumetanide) and vice versa. Based on the PK and PD, and supported by efficacy results in the clinical program, dapagliflozin can be given without regard to food or time of day.

3 CLINICAL DEVELOPMENT PROGRAM

3.1 Overview

The dapagliflozin clinical development program was designed to assess the safety and efficacy of dapagliflozin in a wide range of patients with T2DM. The program included a comprehensive package of placebo-controlled and standard-of-care direct comparison studies in 1) drug-naïve patients at an early stage of disease; 2) in patients who required additional therapy after failure to reach adequate glycemic control with their current regimen of OADs; and 3) in patients with later stage disease who failed to reach glycemic goals with insulin therapy ([Table 2](#)). A study making a direct comparison with the sulfonylurea, glipizide, was also conducted. A blood-pressure-lowering effect was anticipated due to the mild diuretic effect resulting from inhibition of renal tubular glucose and sodium re-absorption, and assessments of dapagliflozin's effect on blood pressure were included in the clinical development program.

In recognition of anticipated consequences of dapagliflozin's novel MOA, BMS and AZ designed and executed an extensive clinical program to evaluate potential efficacy and safety concerns relating to underlying renal function, volume and electrolyte status, symptoms of glucosuria, and possible long-term consequences of chronic glucosuria. Because dapagliflozin is active even at normoglycemic plasma glucose concentrations, it

was also important that counter-regulatory responses to defend against hypoglycemia were active when dapagliflozin was used as monotherapy, or in combination with SUs or insulin. It was also critical that any accompanying volume and salt losses occurring with dapagliflozin treatment were negligible.

Three dapagliflozin doses, 2.5, 5 and 10 mg daily, were studied in various settings across the Phase 3 program, while the dapagliflozin 1 mg daily dose was studied in a 24-week low-dose monotherapy Phase 3 study (MB102032) as well as a 12-week dose-ranging Phase 2b study in Japanese patients (D1692C00005).

A separate study was conducted to specifically evaluate the effect of dapagliflozin treatment in patients with T2DM and moderate renal impairment ($\text{eGFR} \geq 30$ to $< 60 \text{ mL/min/1.73m}^2$; MB102029). Patients with severe renal impairment were not studied in large controlled studies, as glycemic efficacy was not expected in the absence of adequate renal function.

The Phase 2b and 3 dapagliflozin clinical development program consisted of three Phase 2b studies and eleven Phase 3 studies that supported the NDA. This included a total of 4287 patients treated with dapagliflozin 2.5 mg or higher in the fourteen completed Phase 2b and 3 studies (Table 2). More than twice as many patients were treated with dapagliflozin (4287) as control (1941).

The primary objective in all Phase 2b and 3 studies was change in HbA1c from baseline. The exception was in study D1690C00012, in which the primary objective was change in weight from baseline at Week 24. Body composition was also measured in this study using dual-energy X-ray absorptiometry (DXA). All placebo-controlled Phase 3 studies had a short-term, double-blind period for the primary endpoint of 24 weeks. In the direct comparison to glipizide study (D1690C00004), the primary efficacy and safety endpoints were assessed at 52 weeks.

Eight studies had long-term extension treatment periods up to 156 additional weeks in duration. The long-term periods from 5 studies were ongoing as of data cut-off date for the NDA: monotherapy (MB102013); patients with T2DM and moderate renal impairment (MB102029), direct comparison with glipizide (D1690C00004), add-on to insulin (D1690C00006), and evaluation of body weight and composition

(D1690C00012). This controlled, long-term, clinical information was important for assessing durability of effect and long-term safety. Bone mineral density (BMD) was evaluated in the body weight and composition study (D1690C00012) using dual-energy X-ray absorptiometry (DXA) as part of the long-term safety assessment. Patients who failed to meet pre-specified glycemic targets, which became more stringent as studies progressed, were maintained within initial randomized dapagliflozin or control groups, and received rescue medication or were discontinued from the study. Whenever possible, patients continued to be followed after rescue therapy was initiated.

Other clinical studies with dapagliflozin that recently concluded or are currently still ongoing are presented in [Table 3](#).

Table 2: Summary of Completed Clinical Studies with Dapagliflozin

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

Table 2: Summary of Completed Clinical Studies with Dapagliflozin

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

* MB denotes studies sponsored by BMS

**D denotes studies sponsored by AZ

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

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

Table 3: Summary of Recently Concluded or Ongoing Clinical Studies with Dapagliflozin as of the 12-May-2011

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

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

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

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

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

3.2 Analysis Populations

The primary data establishing the clinical efficacy and safety of dapagliflozin originate from three Phase 2b studies and eleven Phase 3 studies evaluating dapagliflozin as monotherapy, add-on combination therapy, and initial combination therapy (Table 2). Additional information about analysis methods for efficacy is described in Section 4.2.

3.2.1 Populations Supporting Efficacy

Most of the efficacy data in this document is presented by study. However, some pooling of efficacy data was conducted to assess the impact of intrinsic and extrinsic factors on efficacy, including different levels of renal function.

3.2.1.1 *Monotherapy/Combination Therapy Pool*

The Monotherapy/Combination Therapy Pool was used to assess the effect of dapagliflozin on HbA1c lowering for 10 important clinical baseline variables related to demographic and disease characteristics: age, gender, race, female age, ethnicity, geographical region, baseline HbA1c, baseline BMI, baseline eGFR, and duration of T2DM. This pool combined data from nine, placebo-controlled Phase 3 studies to increase the statistical power for detecting interactions between subgroups and treatment at Week 24. A total of 4047 patients from treated with placebo or dapagliflozin 2.5, 5, or 10 mg were in this pool; not all patients had valid values for each variable.

The specific studies in this pool were the monotherapy (MB102013), low-dose monotherapy (MB102032), add-on to metformin (MB102014), add-on to pioglitazone (MB102030), add-on to glimepiride (D1690C00005), add-on to insulin (D1690C00006), body weight and composition (D1690C00012), and the 2 (dapagliflozin 5 [MB102021] and 10 mg [MB102034]) initial combination with metformin studies. Patients from the following studies or groups were excluded from this pool: 1) the direct comparison to glipizide study (D1690C00004) because it did not have a placebo comparator; 2) special study of patients with T2DM and moderate renal impairment because it represents a population of special risk; 2) the uncontrolled group (Group2) from the monotherapy study MB102013 and the dapagliflozin only groups from the initial combination with metformin studies because there were no placebo groups to compare to; and the 1-mg

dose from the low-dose monotherapy study because it was only evaluated in that single Phase 3 study.

The same Monotherapy/Combination Therapy Pool was used to assess glycemic efficacy by eGFR category. Patients in this analysis with eGFR values consistent either normal renal function and mild or moderate renal impairment. The number of patients categorized with mild renal impairment was 2226 of the 4047 patients in this pool.

3.2.1.2 Monotherapy/Combination Therapy Subset

A subset of 5 studies from the Monotherapy/Combination Therapy Pool was used to assess overall efficacy for the primary endpoint and key secondary endpoints at Week 24 presented in Section 8. The Pool includes 1379 patients treated with dapagliflozin 10 mg or placebo. The pool is comprised of patients treated in the morning from the monotherapy study MB102013, and those from the add-on to metformin (MB102014), add-on to glimepiride (D1690C00005), add-on to pioglitazone (MB102030), and add-on to insulin (D1690C00006) studies. This pool facilitates comparisons of efficacy variables because number of patients in each treatment group in each study was approximately equal through randomization and therefore, baseline characteristics were expected to be balanced. Patients treated in the evening in study MB102013 were excluded because only those treated in the morning were used to evaluate the primary endpoint in this study.

3.2.2 Populations Supporting Safety

Most of the data that support the safety of dapagliflozin in the initial NDA come from the 2 large pooled analyses: the Placebo-controlled Pool and the All Phase 2b and 3 Pool. The data cut-off date for these Pools in the initial NDA was on or before 25-Jun-2010.

3.2.2.1 Placebo-controlled Pools in the Initial NDA

The short-term Placebo-controlled Pool (NDA) is the most robust and best-controlled data available for interpretation of safety and was the primary pool for safety analyses of most events. This pool includes a total of 12 studies: 12-week data from three Phase 2b studies and 24-week data from nine Phase 3 studies (Figure 3; Table 4). Five treatment groups are included in this pool: dapagliflozin 2.5 mg, 5 mg, 10 mg, total dapagliflozin (2.5, 5, 10, and 20 and/or 50 mg), and placebo.

Figure 3: Pooling Strategy for the Short-term and Short-term plus Long-term Placebo-controlled Pool and the All Phase 2b and 3 Pool (NDA)

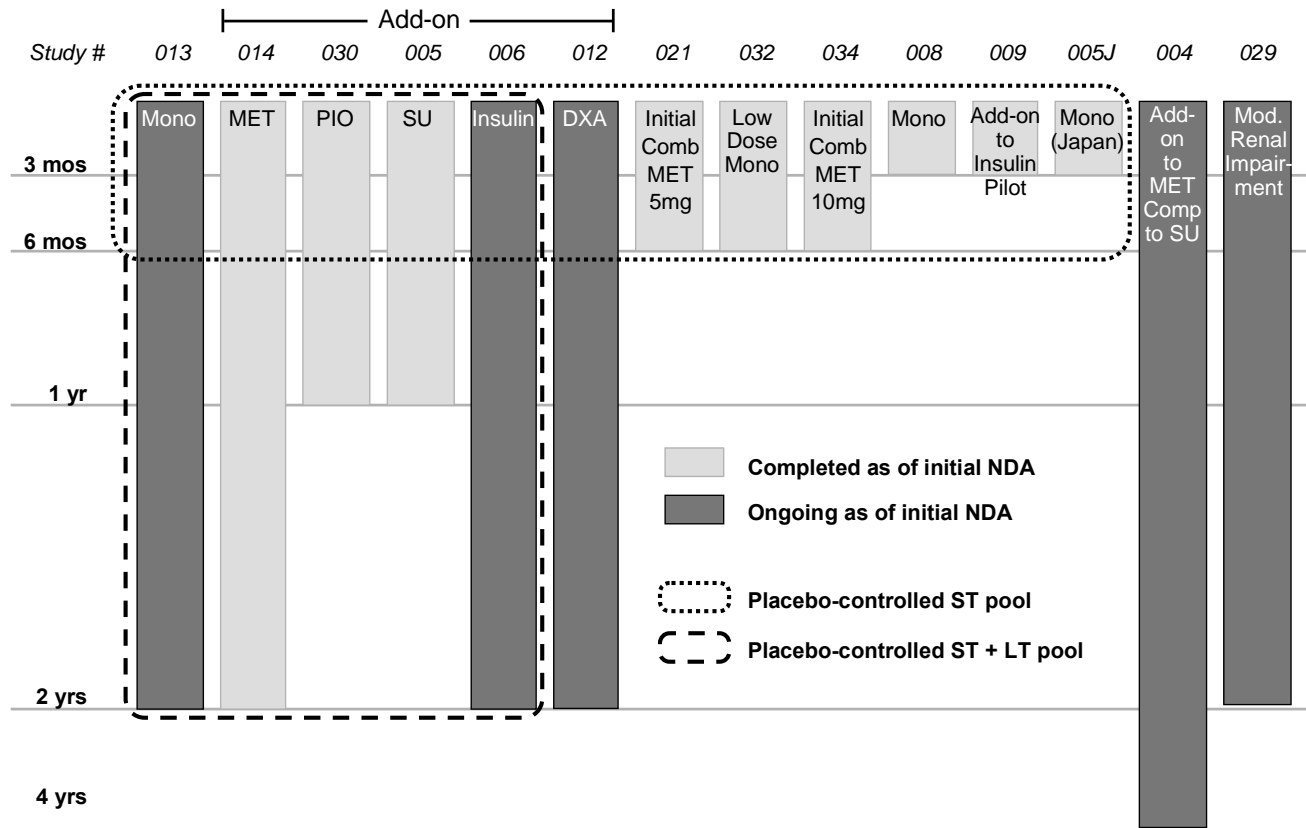


Table 4: Doses and Studies Included in the Short-term and Short-term plus Long-term Placebo-controlled Pools (NDA Dataset)

	Trtm Period		Study	Dapagliflozin Dose				PBO
	ST + LT			Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa 20 and/or 50 mg	
	ST	LT						
Monotherapy	X		MB102008	X	X	X	X	X
	X		D1692C00005	X	X	X		X
	X	X	MB102013	X	X	X		X
	X		MB102032 (low dose)	X	X			X
Dapa Plus Metformin	X	X	MB102014	X	X	X		X
	X		D1690C00012			X		X
Dapa Plus Insulin (pilot)	X		MB102009			X	X	X
Dapa Plus Glimepiride	X	X	D1690C00005	X	X	X		X
Dapa Plus Pioglitazone	X	X	MB102030		X	X		X
Dapa Plus Insulin	X	X	D1690C00006	X	X	X		X
Initial Combination Dapa 5mg	X		MB102021		X			X*
Initial Combination Dapa 5mg	X		MB102034			X		X*

Dapa - dapagliflozin, LT - long-term, PBO - placebo, ST - short-term, Trtm - treatment

* MB102021 and MB102034 were active (metformin) controlled studies; For the purposes of the Placebo-controlled Pool only 2 groups were included and the the metformin group was designated as placebo + metformin.

The short-term Placebo-controlled Pool excludes 1) data from long-term treatment periods to avoid confounding results due to rescue medications and to give a relatively uniform duration of exposure across studies; 2) the special study in patients with T2DM

and moderate renal impairment (MB102029) because of differences in background safety and anticipated decreased PD effect in these patients; 3) the direct comparison to glipizide study (D1690C00004) to avoid confounding safety from the active control drug, glipizide; 4) dapagliflozin-only group from the initial combination with metformin studies (MB102021 and MB102034) to enable a direct comparison between dapagliflozin and metformin, and placebo and metformin; 5) Cohort 1 from the pilot 2b add-on to insulin study (MB102009) and Group 2 from the monotherapy study MB102013, because these 2 populations do not have concurrent control groups; and lastly, the 1mg treatment group from the Phase 3 low-dose monotherapy (MB102032) and Phase 2b dose-ranging study in Japanese patients (D1692C00005) because this dose was considered to be sub-therapeutic.

The short-term plus long-term Placebo-controlled Pool in the initial NDA is the most complete pool for the comparison of the long-term safety profile of dapagliflozin with placebo and includes five of 12 studies from the short-term Placebo-controlled Pool that had long-term data at the time of the initial NDA (Figure 3; Table 4). Five treatment groups are included in this pool: dapagliflozin 2.5 mg, 5 mg, 10 mg, total dapagliflozin (2.5, 5, 10, and 20 and/or 50 mg), and placebo.

3.2.2.2 All Phase 2b and 3 Pool in the Initial NDA

The All Phase 2b and 3 Pool in the initial NDA is the total clinical data from the Phase 2b and 3 program, and includes data from all short-term and short-term plus long-term treatment periods from the twelve Phase 2b and 3 in the short-term Placebo-controlled Pool, plus the direct comparison to glipizide study as well as the special study in patients with T2DM and moderate renal impairment. This Pool has the largest number of patients in the initial NDA, the most exposure (treatment) to study drug, and was used to detect imbalances in uncommon events such as deaths, pyelonephritis, events of fracture, hepatic safety, and CV safety. Two treatment groups are included in this pool: total dapagliflozin (2.5, 5, 10, and 20 and/or 50 mg), and placebo. The data cutoff date for most assessments in the initial NDA occurred on or before 25-Jun-2010. A cutoff date of 30-Jul-2010 was chosen for the CV safety meta-analysis to increase the precision of the estimate of CV risk.

3.2.2.3 *Special Assessments to Evaluate Safety in Patients with T2DM and Moderate Renal Impairment Population in the Initial NDA*

Two populations from the initial NDA were used to examine safety of profile of dapagliflozin in patients with T2DM and moderate renal impairment, defined as patients with eGFR values ≥ 30 and < 60 mL/min/1.73². Three treatment groups are included in these population: dapagliflozin 5 and 10 mg, and placebo.

The first consists of a single study, which includes all patients from the special study of moderate renal impairment (MB102029) up to Week 24.

The second population pools data from all patients from the special moderate renal impairment (MB102029) up to Week 24 and all patients in the short-term (24-week) Placebo-controlled Pool with eGFR values consistent with moderate renal impairment.

Both populations were used to assess AEs related to volume depletion and general renal safety, as a function of eGFR values ≥ 30 and < 60 mL/min/1.73². Analyses from the second (pooled) population were performed for 2 subgroups of moderate renal impairment based on eGFR values: a 3A Subgroup with eGFR values ≥ 45 and < 60 mL/min/1.73² and a 3B Subgroup with eGFR values ≥ 30 and < 45 mL/min/1.73².

3.2.2.4 *Placebo-controlled and All Phase 2b and 3 Pools in the 4-Month Safety Update*

The purpose of the 4-month safety update (4MSU) is to identify possible new safety signals that might have emerged after the data cut-off date for the initial NDA, which was on or before 25-Jun-2010. The data cutoff date for the 4MSU was 15-Oct-2010. The 4MSU includes approximately 9% additional patient-years of treatment, or exposure to dapagliflozin than in the initial NDA. The extent of exposure is presented in more detail in Section 3.3.2.

The 4MSU includes updated data in 2 ways: the short-term plus long-term the Placebo-controlled Pool (4MSU dataset) and an All Phase 2b and 3 Pool, both of which included additional short-term plus long-term data, from studies with long-term treatment periods of 1 to 2 years.

The All Phase 2b and 3 Pool for the 4MSU included all 14 studies from the initial NDA plus data from a 12-week short-term an insulin sensitivity study (MB102045), for a total of 15 studies ([Table 5](#)). This updated pool provides safety for the largest number of patients in the program and the longest treatment with study drug.

The short-term plus long-term Placebo-controlled Pool in the 4MSU was comprised of 6 studies that with long-term treatment periods at the time of the initial NDA: monotherapy (MB102013), add-on to metformin (MB102014), add-on to glimepiride (D1690C00005), add-on to pioglitazone (MB102030), add-on to insulin (D1690C00006), and body weight and composition studies (D1690C00012).

Short-term plus long-term data from the body weight and composition study was included in the datasets for the initial NDA, but not included in any analyses because of insufficient exposure at the time of submission.

This updated pool provides the most comprehensive placebo-controlled dataset to characterize the long-term safety profile of dapagliflozin.

Table 5: Doses and Studies Included in the All Phase 2b and 3 Pool, Short-term and Short-term plus Long-term Treatment (4MSU Database)

		Trtm Period		Study	Dapagliflozin Dose				PBO
		ST	ST + LT		Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa 20 and/or 50 mg	
Placebo-controlled	Monotherapy	X		MB102008	X	X	X	X	X
		X		D1692C00005	X	X	X		X
		X	X	MB102013	X	X	X		X
		X		MB102032 (low-dose)	X	X			X
	Dapagliflozin Plus Metformin	X	X	MB102014	X	X	X		X
		X	X	D1690C00012			X		X
	Dapa Plus Insulin (pilot)	X		MB102009			X	X	X
	Dapa Plus Glimepiride	X	X	D1690C00005	X	X	X		X
	Dapa Plus Pioglitazone	X	X	MB102030		X	X		X
	Dapa Plus Insulin	X	X	D1690C00006	X	X	X		X
	Initial Combination Dapa 5mg	X		MB102021		X			X
	Initial Combination Dapa 5mg	X		MB102034			X		X†
	Dapa Plus Metformin ± Insulin, Insulin Sensitivity	X		MB102045*		X			X†
	Moderate Renal Impairment	X	X	MB102029**		X	X		X
Direct comparison	Dapagliflozin vs Glipizide	X	X	D1690C00004**	X	X	X		

Dapa - dapagliflozin, LT - long-term, PBO - placebo, ST - short-term, Trtm - treatment

* Unblinded within 4 months of the NDA submission and safety assessment included in the 4MSU.

** Not included in the Placebo-controlled Pool, only in the Phase 2b and 3 Pool.

† MB102021 and MB102034 were active (metformin) controlled studies; For the purposes of the Placebo-controlled Pool only 2 groups were included and the the metformin group was designated as placebo + metformin.

In study D1690C00004, patients were randomized 1:1 to glipizide 5 mg plus metformin or dapagliflozin 2.5 mg plus metformin, and were titrated up over 18 weeks in a step-wise fashion in 3-dose intervals to achieve a clinical glycemic effect (FPG <110 mg/dL), or to the highest tolerated dose (glipizide 20 mg or dapagliflozin 10 mg).

Short-term plus long-term data from the body weight and composition study was it was included in the datasets for the initial NDA but not included in any analyses. This updated pool provides the most comprehensive placebo-controlled dataset to characterize the long-term safety profile of dapagliflozin.

3.2.2.5 Special Assessments to Evaluate Safety in Patients with T2DM and Moderate Renal Impairment Population in the 4MSU

Two populations were constructed from the 4MSU database to examine the safety profile of dapagliflozin in patients with renal impairment up to the end of this time period. The first consists of a single study of all patients from the special moderate renal impairment study (MB102029) with up to 104 weeks of treatment.

The second population pools patients from the special moderate renal impairment (MB102029) and the patients from the short-term plus long-term Placebo-controlled Pool updated through the 4MSU. Three treatment groups are included in this population: dapagliflozin 5 and 10 mg, and placebo.

Both populations were used to assess AEs of fracture as a function of eGFR values ≥ 30 and < 60 mL/min/1.73². Analyses from the second (pooled) population were performed for 2 subgroups of moderate renal impairment based on eGFR values: a 3A Subgroup with eGFR values ≥ 45 and < 60 mL/min/1.73² and a 3B Subgroup with eGFR values ≥ 30 and < 45 mL/min/1.73².

3.2.2.6 Integrated Cancer Summary as of 12-May-2011

Additional analyses were performed to evaluate the most current data for malignancies using the most recent information from all unblinded studies. The data cutoff date for these analyses was 12-May-2011. This is called the 12-May Integrated Cancer Summary

(ICS). This additional information was used to determine the exposure and incidence rate for patients with malignant or unspecified tumors.

The 12-May ICS includes updated information for all unblinded studies that were ongoing at the time of the 4MSU (direct comparison to glimepiride [D1690C00004], body weight and composition [D1690C00012, and patients with T2DM and moderate renal impairment [MB102029]), and data from final database lock for the add-on to insulin [D1690C00006]. It also includes data from 2 studies that were completed after the 4MSU data cut-off date (a Phase 2b study of the effects of treatment on the GFR of patients with inadequate control of glycemia and blood pressure [MB102035] and the short-term database lock of a Phase 3 study of add-on combination treatment with sitagliptin [D1690C00010]). Three patients with bladder cancer were identified in 2 ongoing blinded studies: one study with patients with T2DM and CV disease plus hypertension (D1690C00018) and one with patients with T2DM and CV disease alone (D1690C00019). These 3 patients were unblinded to provide the most complete assessment possible at this time for bladder cancer.

3.3 Extent of Exposure to Dapagliflozin

3.3.1 Extent of Exposure in Initial NDA

More than twice as many patients were randomized to treatment with dapagliflozin (n = 4287) than to control (n = 1941) by design in the initial NDA(All Phase 2b and 3 Pool; [Table 6](#)). More than half of the 4287 patients treated with dapagliflozin 2.5 mg or higher were treated for > 1 year, and 441 patients were treated for at least 2 years ([Table 7](#)). About 2000 patients were treated with dapagliflozin 10 mg in the Phase 2b and 3 studies, with 461 patients treated with this dose for at least 77 weeks. Cumulative treatment with dapagliflozin in the Phase 2b and 3 studies was 4009 patient-years, while cumulative control treatment was 1682 patient-years ([Table 8](#); highlighted in grey).

Table 6: Number of Patients per Treatment Group by Population, Short-Term Treatment Period (NDA Dataset)

Population	Placebo/control	Dapagliflozin Dose			Total Dapa
		2.5 mg	5 mg	10 mg	
All Phase 2b and 3 Pool	1941				4287*
Placebo-controlled Pool ST	1393	814	1145	1193	3291*
Placebo-controlled Pool ST + LT	694	625	767	768	2160

Dapa = dapagliflozin, LT = long-term, ST = short-term,

* Total Dapa includes dapagliflozin 2.5, 5, 10, 20, and 50 mg

Does not include Group 2 from MB102013 and Cohort 1 from MB102009 because these were uncontrolled populations, and does not include the 1-mg treatment group from MB102032 and D1692C00005 because this dose was considered to be sub-therapeutic

Table 7: Clinical Exposure to Dapagliflozin 2.5 mg or Higher, Short-term plus Long-term Treatment Period, Including Data after Rescue, Treated Patients (NDA Dataset)

Population	Total Number of Patients Exposed				
	Total	6 months	12 months	18 months	24 months
All Phase 2b and 3 Pool	4287	3333	2232	1317	441
Placebo-controlled Pool	3291	2481	1769	1017	429

 This table includes all treated patients with at least one dose of dapagliflozin 2.5 mg or higher.
 24 weeks, 48 weeks, 76 weeks and 102 weeks are used for 6 months, 12 months, 18 months and 24 months respectively.
 Includes all studies in each population/pool regardless of length.
 Does not include Group 2 from Study MB102013 or Cohort 1 from Study MB102009 because these were uncontrolled populations.
 Does not include 1 mg treatment group from Studies MB102032 and D1692C00005 because this dose was considered to be sub-therapeutic.

Table 8: Extent of Exposure Summary, Short-term Plus Long-term Treatment Period, Including Data After Rescue, All Phase 2b and 3 Pool, Treated Patients (NDA Dataset)

DAPA TOTAL N = 4287				ALL CONTROL N = 1941		
Duration of Exposure (Weeks)	# of Patients Entering Interval	Patient-years Within Interval (a)	Cumulative Patient-years (0-End of Interval) (b)	# of Patients Entering Interval	Patient-years Within Interval (a)	Cumulative Patient-years (0-End of Interval) (b)
0 - 10	4287	792.8	792.8	1941	355.7	355.7
>10 - 22	4014	817.4	1610.2	1786	368.6	724.3
>22 - 35	3370	633.0	2243.2	1530	269.4	993.7
>35 - 48	2345	573.7	2817.0	973	234.5	1228.2
>48 - 61	2018	387.4	3204.4	814	160.9	1389.1
>61 - 74	1502	355.2	3559.6	621	142.9	1532.0
>74 - 87	1347	264.0	3823.6	505	96.7	1628.7
>87 - 100	809	163.0	3986.7	261	47.5	1676.2
>100	532	22.4	4009.1	125	5.7	1681.9
Number (%) of Patients						
		DAPA 2.5MG N = 1220	DAPA 5MG N = 1810	DAPA 10MG N = 2000	DAPA TOTAL N = 4287	ALL CONTROL N = 1941
SUMMARY STATISTICS						
MEAN		273.4	247.8	335.4	341.6	316.5
MEDIAN		168.5	169.5	330.0	335.0	249.0
MIN , MAX		5, 752	1, 758	1, 751	1, 758	1, 748
STANDARD DEVIATION		261.25	213.05	213.55	229.58	217.21

This table includes all treated patients. Percentages reported are based on the total number of patients in each treatment group. The extent of exposure to study medication during the short-term plus long-term treatment period is defined as the difference between the last dose of short-term and long-term study medication and the first dose of study medication of the short-term double-blind treatment period plus 1 day. (a) Patient-years Within Interval is the sum over the patients exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval- First dosing date in interval plus 1 day; (b) Cumulative Patient-years: 0 - End of Interval is the sum over the patients exposure from day 1 of dosing through the end of the interval to study medication expressed in years where cumulative subject exposure to end of interval is last dosing date in interval- first dosing date plus 1 day. All Phase 2b and 3 Pool includes Studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, D1692C00005, D1690C00004, D1690C00005, D1690C00006 and D1690C00012. Does not include 1 mg treatment group from Studies MB102032 and D1692C00005, as this dose was considered to be sub-therapeutic.

3.3.2 Exposure Extent of Exposure in the 4-Month Safety Update

As a result of the accumulation of additional study data, the 4MSU includes approximately 9% additional patient-years than in the initial NDA. Cumulative patient-years of treatment at this update were about 2.3× greater with dapagliflozin (4354 patient-years) than with control (1899 patient-years) ([Table 9](#); highlighted in grey).

Table 9: Extent of Exposure Summary, Short-term Plus Long-term Treatment Period, Including Data After Rescue, All Phase 2b and 3 Pool, Treated Patients (4MSU Dataset)

	Number (%) of Patients				
	DAPA 2.5MG N = 1220	DAPA 5MG N = 1833	DAPA 10MG N = 2003	DAPA TOTAL N = 4310	ALL CONTROL N = 1962
CUMULATIVE EXPOSURE (PATIENT - YEARS)	967.1	1252.5	2103.7	4354.4	1898.9
DURATION (DAYS)					
1 - 90	544 (44.6)	575 (31.4)	254 (12.7)	746 (17.3)	356 (18.1)
91 - 180	115 (9.4)	486 (26.5)	470 (23.5)	1075 (24.9)	502 (25.6)
181 - 270	15 (1.2)	32 (1.7)	40 (2.0)	85 (2.0)	63 (3.2)
271 - 360	180 (14.8)	437 (23.8)	336 (16.8)	789 (18.3)	328 (16.7)
361 - 450	17 (1.4)	21 (1.1)	208 (10.4)	108 (2.5)	58 (3.0)
451 - 540	10 (0.8)	12 (0.7)	64 (3.2)	111 (2.6)	100 (5.1)
541 - 630	22 (1.8)	36 (2.0)	76 (3.8)	128 (3.0)	69 (3.5)
631 - 720	216 (17.7)	179 (9.8)	357 (17.8)	745 (17.3)	224 (11.4)
721 - 810	101 (8.3)	55 (3.0)	182 (9.1)	478 (11.1)	214 (10.9)
811 - 900	0	0	16 (0.8)	42 (1.0)	45 (2.3)
> 900	0	0	0	3 (<0.1)	3 (0.2)
Number (%) of Patients					
	DAPA 2.5MG N = 1220	DAPA 5MG N = 1833	DAPA 10MG N = 2003	DAPA TOTAL N = 4310	ALL CONTROL N = 1962
SUMMARY STATISTICS					
MEAN	289.5	249.6	383.6	369.0	353.5
MEDIAN	168.5	169.0	339.0	336.0	329.0
MIN , MAX	5, 786	1, 792	1, 859	1, 908	1, 908
STANDARD DEVIATION	282.61	219.33	243.26	257.95	255.21

This table includes all treated patients with at least one dose of dapagliflozin 2.5 mg or higher. Percentages reported are based on the total number of patients in each treatment group. The extent of exposure to study medication during the short-term plus long-term treatment period is defined as the difference between the last dose of short-term plus long-term study medication and the first dose of study medication of the short-term double-blind treatment period plus 1 day. Cumulative exposure is calculated as the sum of the exposure to study medication of all patients (in years) in a treatment group. Does not include 1 mg treatment group from Studies MB102032 and D1692C00005, as this dose was considered to be sub-therapeutic. Patients from studies D1690C00004 and D1690C00006 may be included in more than one dapagliflozin dose group due to titration. The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, and D1690C00012.

A comparison of the exposure of patients treated with dapagliflozin in the All Phase 2b and 3 Pool between the initial NDA and the 4MSU is presented in Table 10.

Table 10: Number of Patients Treated with Dapagliflozin in the Phase 2b and 3 Pooled Population (NDA and 4MSU Datasets)

Exposure	Dapagliflozin ST + LT NDA Dataset	Dapagliflozin ST+ LT 4MSU Update Dataset
Total	4287	4310
≥ 1 year (1)	2232	2302
≥ 18 months (2)	1317	1424
≥ 2 years (3)	441	956

(1) ≥ 50 weeks; (2) ≥ 76 weeks; (3) ≥ 102 weeks

The number of patients in Table 10 treated with dapagliflozin met or exceeded ICH and FDA guidelines^{10,11} for development of new drugs to treat diabetes.

3.3.3 Extent of Exposure in the Integrated Cancer Summary as of 12-May-2011

The number of patients, overall exposure of, and duration of follow-up for patients with a malignancy or unspecified tumor (excluding initial NDA) for both dapagliflozin and control for the initial NDA, 4MSU, and the 12-May ICS is presented in [Table 11](#).

Table 11: Comparison of the Total Number of Patients, Overall Exposure, and Follow-up Time for Events of Malignant and Unspecified Tumors between the Initial NDA, 4MSU and the 12-May ICS

	<u>Initial NDA</u>		<u>4MSU</u>		<u>12-MAY ICS</u>		<u>Update for Bladder Cancer†</u>	
	Dapagliflozin	Control	Dapagliflozin	Control	Dapagliflozin	Control	Dapagliflozin	Control
Total Number of Patients	4287	1941	4310	1962	4559	2239	5478**	3156**
Overall Exposure (patient-years)	4009	1682	4354	1899	Not calculated††	Not calculated††	Not calculated††	Not calculated††
Follow-up time for malignancies (patient-years) ^	Not calculated*	Not calculated*	4621	2024	4977	2348	5624**	2975**

†Includes additional unblinded 3 patients from 2 ongoing blinded studies

††Not calculated because no other analyses were performed with the 12-May ICS.

* Not calculated for initial NDA

**These values are estimated because 2 studies (D1690C00018 and D1690C00019) were ongoing and blinded. The total sample size and follow-up time for D1690C00018 and D1690C00019 were equally divided into dapagliflozin and control groups.

^ Includes 30 days of follow-up after the end of treatment. Follow-up time after an event is not included in the total.

4MSU = 4-month safety update; ICS = integrated cancer summary (for malignant and unspecified tumors)

3.4 Patient Demographics and Baseline Disease Characteristics

A wide range of patients with overall clinical characteristics representative of patients with T2DM in real-world practice were enrolled in the Phase 3 program.

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

Demographic and baseline disease characteristics of patients from all fourteen Phase 2b and 3 placebo-controlled or direct comparison studies in the NDA are presented in [Table 12](#) (All Phase 2b and 3 Pool). Patient age ranged from 19 to 92 years, with a mean age 56 years. Most patients were white; black patients comprised approximately 3.5% of the dapagliflozin and control patients. The proportion of males and females was similar. Approximately 30% of patients were from the United States or Canada. The majority of patients in the Phase 3 program had a BMI ≥ 27 kg/m² at baseline.

Relevant sub-populations included the elderly, patients with mild and moderate renal impairment, patients with long disease duration, and patients with common comorbidities such as CV disease and hypertension.

Table 12: Demographic and Baseline Characteristics Summary, All Phase 2b and 3 Pool^a (NDA Dataset)

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

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

* CV meta-analysis, (Table 50)

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

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

4 CLINICAL EFFICACY

4.1 Introduction

Dapagliflozin was effective in reducing HbA1c in a broad range of patients regardless of disease progression/duration or concomitant use of anti-diabetic therapies. Improvements in glycemic control were seen when dapagliflozin was given as monotherapy or as add-on combination therapy to metformin, a SU (glimepiride), a TZD (pioglitazone) or insulin (\pm oral anti-diabetics [OAD]); or as initial combination therapy with metformin. In addition, the mean reduction from baseline in HbA1c achieved with dapagliflozin 10 mg plus metformin was non-inferior when directly compared to glipizide plus metformin at Week 52, with a significantly smaller proportion of patients with hypoglycemic events in the dapagliflozin group vs glipizide ($p < 0.0001$). The mean reduction from baseline in HbA1c achieved with dapagliflozin 10 mg was non-inferior when directly compared to the metformin. Dapagliflozin 10 mg consistently demonstrated statistically and clinically significant mean reductions in HbA1c vs placebo among the 3 doses typically studied (2.5, 5, and 10 mg) in the general study population. Effects on secondary glycemic efficacy parameters, including FPG and PPG, support the primary HbA1c efficacy findings. Overall, dapagliflozin 10 mg provided better glycemic efficacy for treatment of patients with T2DM than the 2.5- or 5-mg doses. Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass due to a loss of calories from urinary excretion of glucose. Placebo-controlled data for up to 2 years on similar background and rescue therapies indicate that the beneficial effects of dapagliflozin on glycemic and non-glycemic parameters were maintained during long-term treatment.

4.2 Analysis Methods

Data establishing the clinical efficacy of dapagliflozin originate from three Phase 2b studies and eleven Phase 3 studies evaluating dapagliflozin as monotherapy, add-on combination therapy, and initial combination therapy ([Table 2](#)). The primary efficacy variable for 10 of the eleven studies in the Phase 3 program was change from baseline in HbA1c. Measurements obtained after the start of rescue therapy were excluded from analysis. Last observation carried forward (LOCF) methodology was used when

measurements were not available or when they were excluded. These methods are consistent with FDA's guidance on the development of new drugs to T2DM.¹¹ Secondary assessments included complementary glycemic parameters (change from baseline in FPG and PPG), body weight, and the proportion of patients achieving a therapeutic response of HbA1c < 7.0%. The proportion of patients with hypoglycemia was also a secondary endpoint in the direct comparison to glipizide study.

Analysis of Covariance (ANCOVA) was used to analyze the primary and all continuous secondary endpoints. A modified logistic regression was used for dichotomous secondary endpoints (e.g., proportion of responders). All models included adjustments for treatment group effects, baseline value, and stratification factor at randomization (other than site) if applicable. The primary endpoint in each study was evaluated by comparing the difference in 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 $\alpha = 0.05$ tests only for treatment groups found to be statistically significant in the primary efficacy analysis. An exception to this rule was the body weight and composition study, where Hochberg's method was used. Sequential testing of secondary endpoints was performed independently within each dapagliflozin arm, with statistical inference stopping at the first endpoint that failed to reject the null hypothesis.

In the direct comparison glipizide study, 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 the initial combination of dapagliflozin 10 mg plus metformin study, in which a comparison between the dapagliflozin and metformin monotherapy groups was pre-specified.

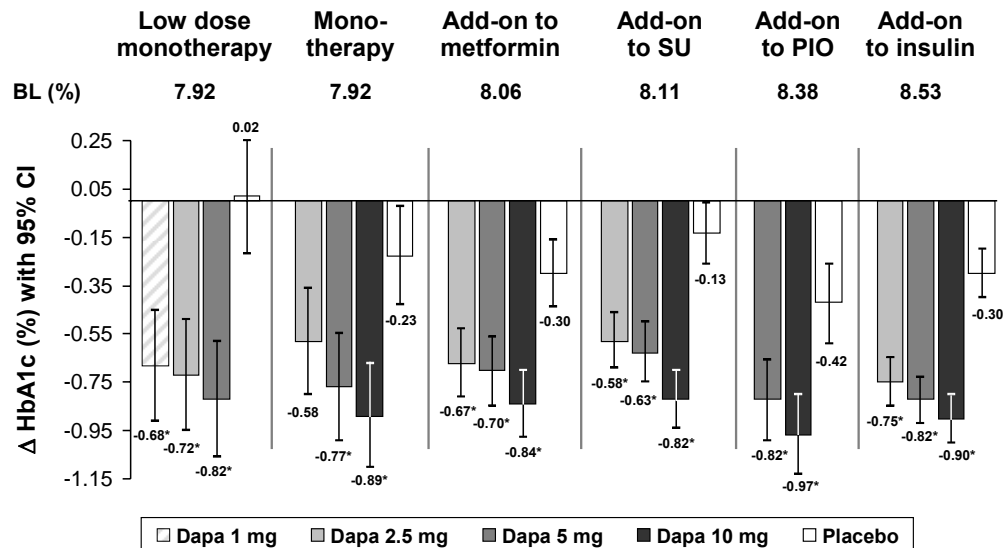
Due to the increasing number of patients who discontinued from the study or received rescue during the long-term treatment periods, as well as the lengthening interval of time between last observation and the analysis timepoint, a repeated measures mixed model analysis using observed cases was utilized, in contrast to the LOCF approach employed in the confirmatory analyses of short term data. Analyses were performed both excluding

as well as including data after rescue to help evaluate the impact of missing data and the use of rescue treatment on conclusions during the long-term period. Both analyses have limitations: when data are excluded, treatment estimates are derived from a selected subset of the randomized study population; when data after rescue or insulin up-titration are included, HbA1c values are affected directly, resulting in estimates that reflect the combined effects of investigational product and rescue.

Subgroup analyses were performed within individual studies and in the pooled study population comprised of data from 9 of eleven Phase 3 studies (Monotherapy/Combination Therapy Pool) described in Section 3.2.1.1. ANCOVA was used to assess the interaction between subgroup and treatment, which was evaluated as a focused test for heterogeneity across subgroups of the average effect of dapagliflozin over doses versus placebo. ANCOVA was also used to estimate the effect of each dapagliflozin dose within subgroup categories with respect to mean change in HbA1c at Week 24. Baseline HbA1c and eGFR were evaluated as continuous covariates in this test. This same pool was used to explore differences in efficacy by age group, controlling for degree of renal impairment. The focused interaction test compared the average dapagliflozin effect versus placebo between age groups across 3 categories of baseline eGFR. Focused interaction tests with p-values < 0.10 were considered to be suggestive of differential efficacy among subgroups.

4.3 Change in Glycemic Parameters after Monotherapy or Add-on Combination Treatment

Treatment with dapagliflozin 5 and 10 mg consistently resulted in statistically significant mean reductions in HbA1c compared to placebo ([Figure 4](#)). Dapagliflozin 10 mg consistently resulted in numerically greater HbA1c mean reductions compared to the 5-mg dose in each of 5 placebo-controlled Phase 3 studies that evaluated both doses (monotherapy [MB102013], add-on to metformin, add-on to pioglitazone, add-on to glimepiride, and add-on to insulin). Only treatment with the 10-mg dose also consistently resulted in clinically meaningful, placebo-corrected mean reductions of at least 0.5% in HbA1c values.

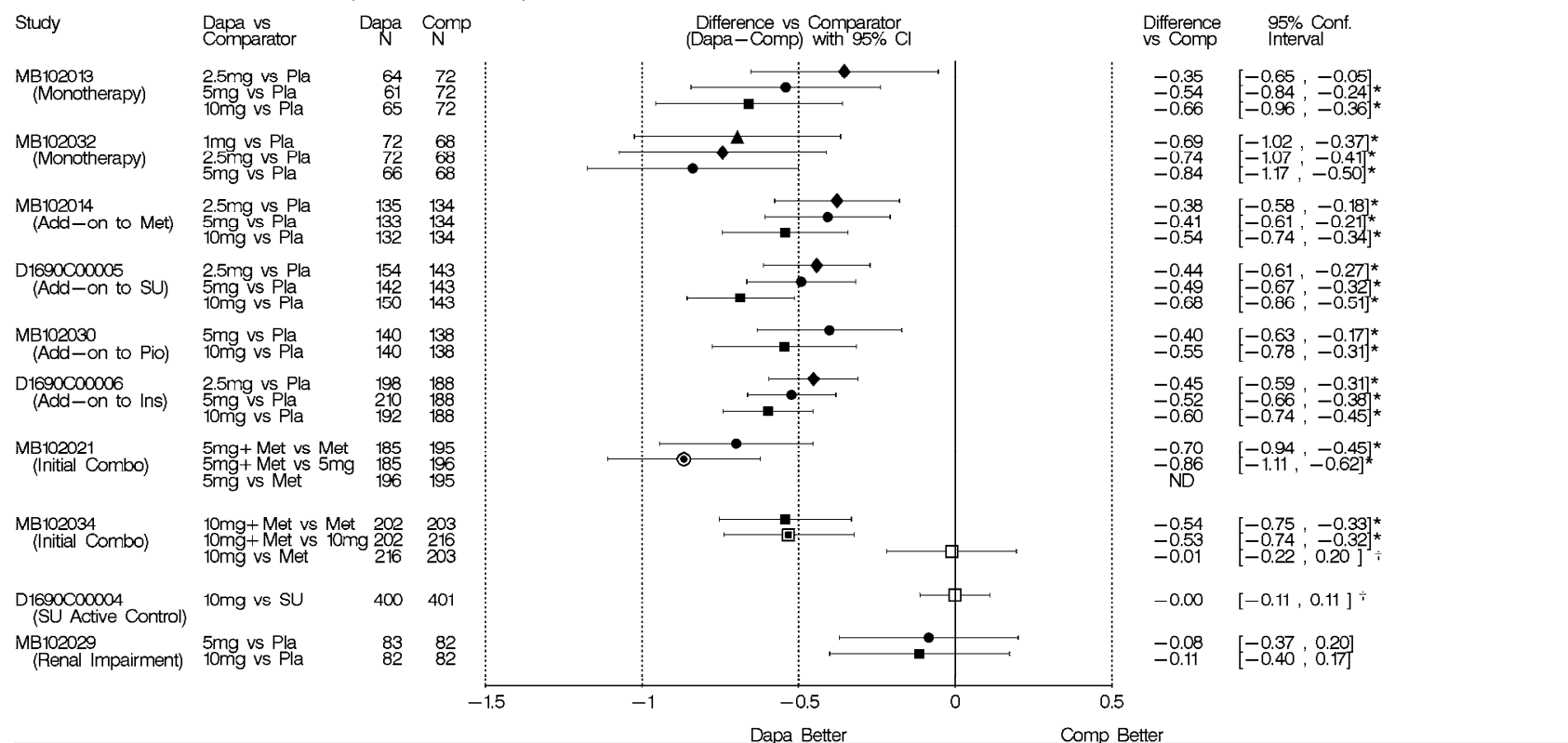
Figure 4: Adjusted Mean Change from Baseline in HbA1c (%) at Week 24

* Statistically significant vs. placebo using Dunnett's correction
 Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)
 Randomized Patients Dataset/Full Analysis Set; BL = baseline

Doses of 2.5 mg and lower did not demonstrate a consistent clinical benefit for the treatment of T2DM. In 4 of 5 studies in which the 2.5-mg dose was evaluated (monotherapy [MB102013], low-dose monotherapy, add-on to metformin, add-on to glimepiride, and add-on to insulin), the 2.5-mg dose provided mean HbA1c reductions less than 0.5% in magnitude.

A summary of mean change from baseline in HbA1c for Phase 3 studies where mean change in HbA1c was the primary efficacy endpoint is shown in [Figure 5](#). The HbA1c-lowering effect of dapagliflozin administered with either morning or evening meals was explored in the monotherapy study MB102013. An HbA1c-lowering effect was observed when dapagliflozin was given in the morning or evening in this study. Monotherapy study MB102013 also included an exploratory cohort of patients with baseline HbA1c $\geq 10.1\%$ to $\leq 12.0\%$ (Group 2); there was no placebo control for this group. Treatment with dapagliflozin 5 mg and 10 mg in this group resulted in numerical HbA1c reductions from baseline of 2.88% and 2.66%, respectively, at Week 24.

Figure 5: Adjusted Mean Change from Baseline in HbA1c (%) at end of Short-Term Period,^a Full Analysis Data Set,^b (NDA Dataset)



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

^b Efficacy Analysis Data Set refers to the Randomized Patients Data Set [BMS] or Full Analysis Set [AZ].

N is the number of patients with non-missing baseline and Week 24 (LOCF) values (or Week 52 (LOCF) values in study D1690C00004).

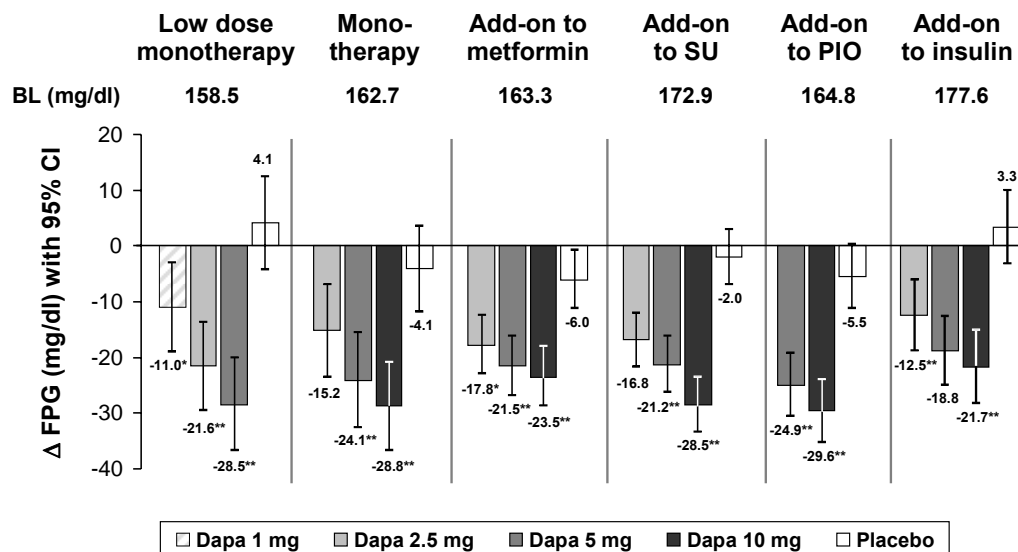
* denotes significantly different from comparator. Dagger (†) denotes statistical criterion for non-inferiority met with 95% confidence

NI boundary = 0.35%. MB102032 is the low-dose monotherapy study

Pla=placebo, Met=metformin, SU=sulfonylurea, Pio=pioglitazone, Ins=insulin, Comp=comparator, CI=confidence interval, ND=not done.'

FPG was evaluated as a secondary efficacy parameter in six Phase 3 placebo-controlled studies (Figure 6). The effect on FPG was dose-dependent with the greatest placebo-corrected mean reductions in FPG seen with the 10-mg dose, ranging from –17.5 to –26.5 mg/dL across the monotherapy and add-on combination studies. Mean decreases from baseline in FPG were seen as early as 1 week following the initiation of therapy due to the rapid effect of glucosuria as the initial PD marker of dapagliflozin's action, with superiority vs placebo apparent across all dapagliflozin treatment groups. Treatment with the 2.5 mg dose was not significantly different from placebo for the change from baseline in FPG in 2 of the 5 studies (monotherapy [MB102013] and add-on to glimepiride) (Figure 6).

Figure 6: Adjusted Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) at Week 24



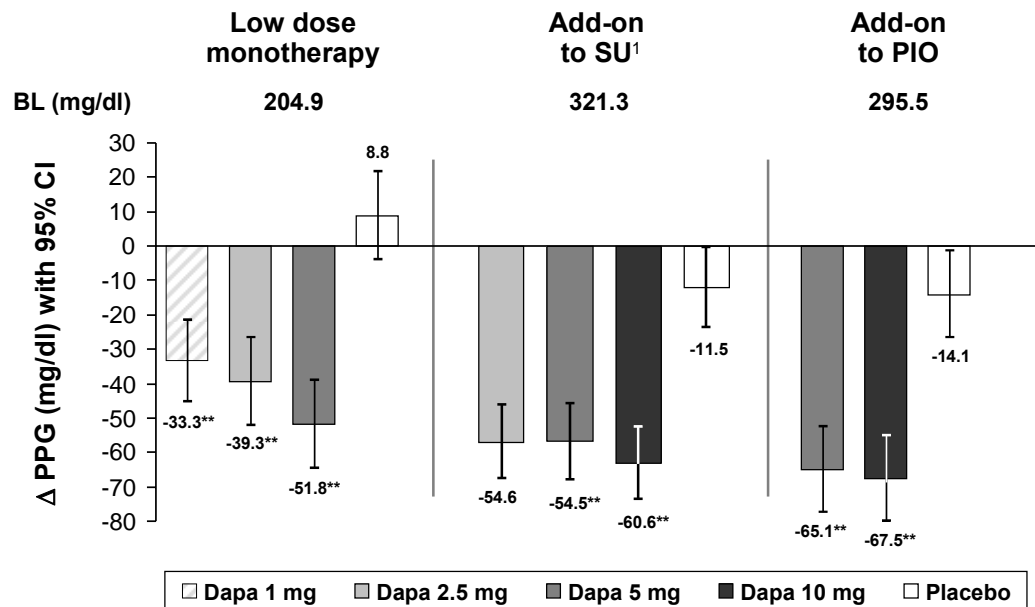
Statistically significant vs. placebo by hierarchical testing rule: * = p<0.05; ** = p<0.001

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

Randomized Patients Dataset/Full Analysis Set; excludes data after rescue (LOCF); BL = baseline

Significant mean reductions in 2-hour PPG values were also seen in those studies where this variable was assessed (low-dose monotherapy, add-on to glimepiride, and add-on to pioglitazone studies) (Figure 7).

Figure 7: Adjusted Mean Change from Baseline in 2-hour Post-prandial Glucose (mg/dL) at Week 24



Statistically significant vs. placebo by hierarchical testing rule: ** = $p < 0.001$

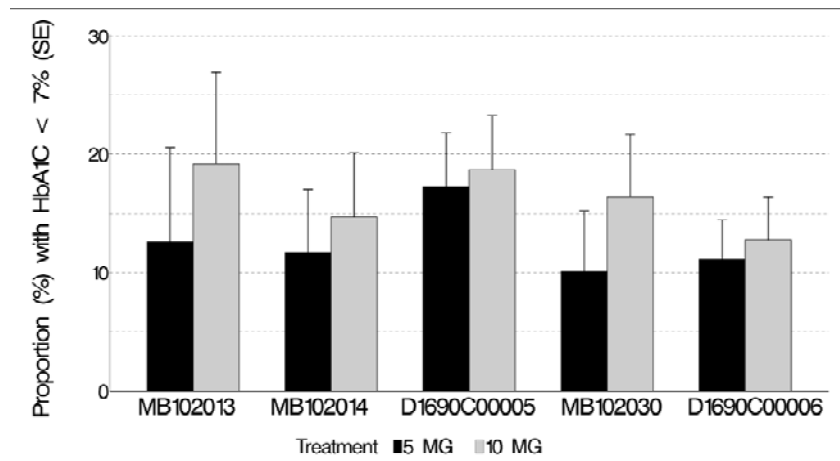
¹ In the add-on to SU study CSR, PPG results are displayed as the difference between time 0 and 2 hours

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

Randomized Patients Dataset/Full Analysis Set; excludes data after rescue (LOCF); BL = baseline; CSR = clinical study report; PPG = post-prandial glucose

Categorical glycemic target responses were consistent with mean changes in HbA1c. 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, add-on to pioglitazone, and add-on to glimepiride studies ($p < 0.05$) (Figure 8). The proportion of patients was numerically lower and dose-ordered in both monotherapy studies (MB102013 and MB102032) for the 5- and 10-mg doses. 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 familywise type I error.

Figure 8: Comparison of Dapagliflozin 5 mg and 10 mg in Placebo-corrected, Adjusted Mean Change from Baseline in Proportion of Patients with HbA1c < 7% at Week 24 (LOCF),



MB102013 = monotherapy; MB102014 = add-on to metformin; D1690C00005 = add-on to glimepiride; MB102030 = add-on to pioglitazone; D1690C00006 = add-on to insulin.

Bars denote difference versus placebo in mean change from baseline in the proportion of patients with HbA1c < 7% at Week 24 (LOCF), adjusted for baseline HbA1c value and stratification factor if used. Error bars denote standard errors for the difference versus placebo in adjusted mean or proportion (approximated for proportions as the difference in the upper and lower 95% confidence limit divided by 2×1.96). QAM doses only shown for Study MB102013.

4.3.1 Subgroup Analyses

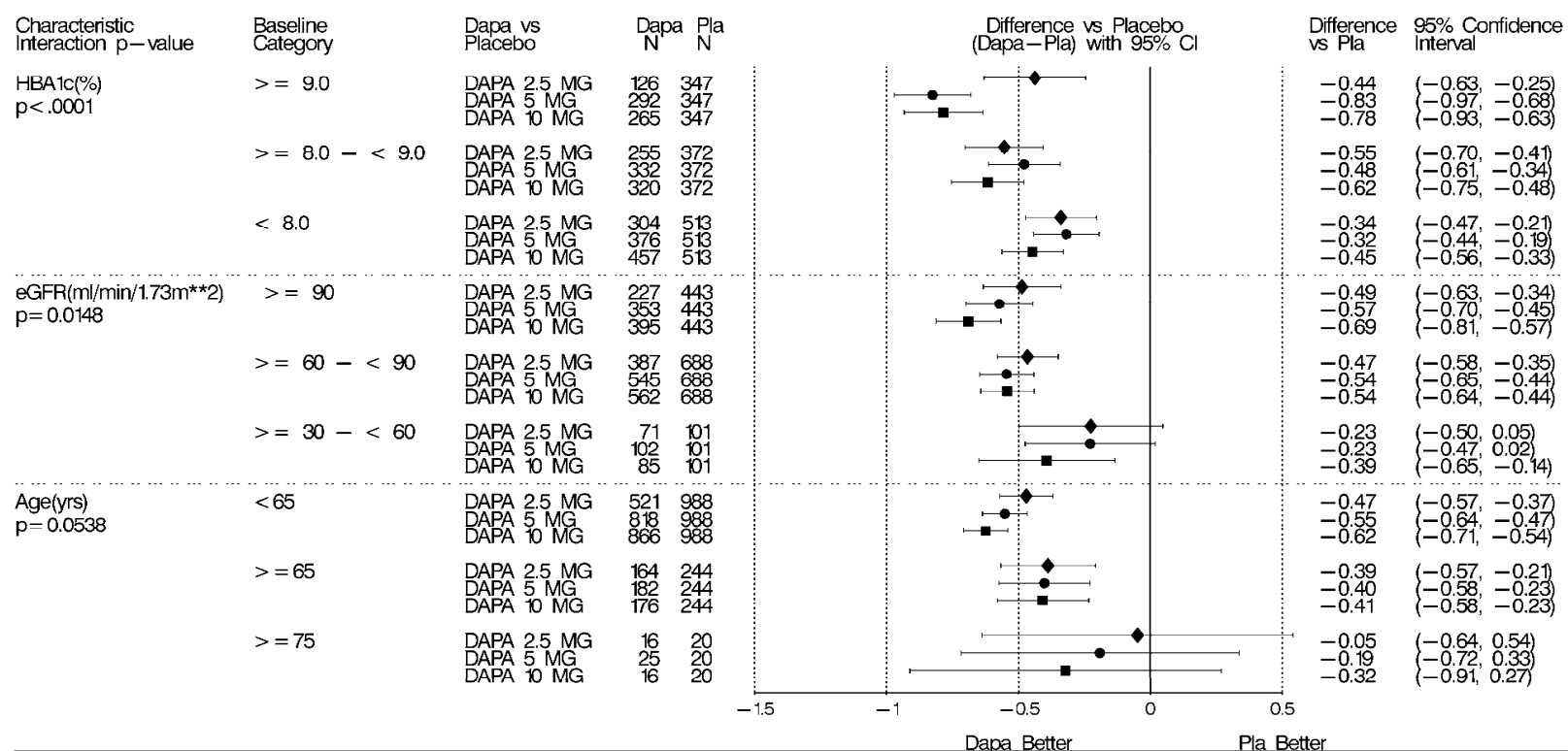
The effect of dapagliflozin on HbA1c lowering was assessed for 10 important clinical baseline variables related to demographic and disease characteristics. The primary goal of these investigations was to identify factors that might impact efficacy of dapagliflozin in the overall population compared to placebo.

Data were combined from nine of the Phase 3 studies to increase the statistical power for detecting interactions between subgroups and treatment at Week 24. The studies combined for these analyses were the monotherapy, low-dose monotherapy, add-on to metformin, add-on to pioglitazone, add-on to glimepiride, add-on to insulin, body weight and composition and the 2 initial add-on to metformin studies (dapagliflozin 5 and 10 mg). No differential efficacy was seen with respect to gender, race, ethnicity, region, baseline BMI, or duration of T2DM.

Dapagliflozin produced greater mean reductions from baseline (p value for interaction test < 0.1) for patients with higher baseline HbA1c values (Figure 9). Dapagliflozin also demonstrated greater mean HbA1c reductions from baseline for patients with higher baseline eGFR and younger age compared to placebo (Figure 9).

The impact on renal function was anticipated based on dapagliflozin's MOA. With a low filtered load of glucose, inhibition of SGLT2 cannot cause enough glucose to be excreted to produce a clinically meaningful effect. In other words, adequate renal function is required for dapagliflozin to cause direct elimination of glucose via the kidneys and a glycemic-lowering effect.

Figure 9: Subgroup Analyses — Difference versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 (LOCF), Excluding Data after Rescue, Pooled Monotherapy/Combination Therapy Group, Efficacy Analysis Data Set



Efficacy Analysis Data Set refers to the Randomized Patients Data Set [BMS] or Full Analysis Set [AZ]. Number of patients is the number with non-missing baseline and Week 24 values. P-value for treatment-by-subgroup interaction based on average dapagliflozin effect relative to placebo using continuous HbA1c, continuous eGFR, and categories <65 versus ≥ 65 for age.

The age-related decline in renal function was expected to confound the interpretation of the age-related findings. Analyses based on age suggested that a reduction in HbA1c-lowering may be present in older patients, although conclusions are difficult to make for patients 75 years of age or older due to the small numbers involved. However, since older age is associated with reduced renal function, a preplanned analysis of age, controlling for the amount of renal function, was also conducted resulting in a p-value of 0.29 for the interaction test. In short, after controlling for changes in eGFR, there was no conclusive evidence to suggest that age is an independent factor affecting the efficacy of dapagliflozin.

Additionally, in the Phase 3 studies that included the greatest numbers of patients in the ≥ 65 subgroup (add-on to glimepiride, add-on to insulin, and direct comparison to glipizide, in which n=36 to 120 per treatment group), p-values from focused interaction tests failed to indicate differences between age groups among the dapagliflozin doses, and 95% CIs for the placebo-corrected adjusted mean HbA1c reductions did not cross zero for either age subgroup within any of the dapagliflozin treatment groups.

No clinically meaningful differences in dapagliflozin PK due to age after controlling for renal function, gender, and body weight were evident.

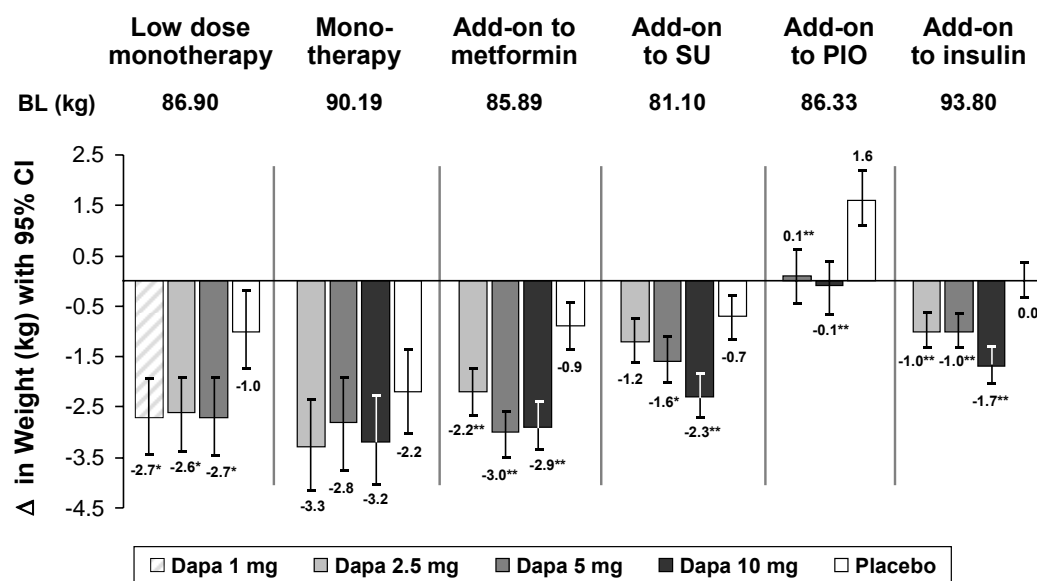
4.4 Change in Body Weight and Composition after Monotherapy or Add-on Combination Treatment

Weight loss is a fundamental goal for the majority of patients with T2DM. Weight loss has been shown to improve glycemic control as well as co-morbid conditions,¹² but it is difficult to achieve. More than 85% of patients with T2DM are overweight or obese¹³ and many anti-diabetic therapies are commonly associated with an increase in body weight. Dapagliflozin has the potential to achieve a slow and steady, modest weight loss with a reduction in total body fat due to its unique MOA, which results in persistent loss of calories in the urine.

The placebo-corrected mean weight reductions over 24 weeks ranged from -0.46 to -2.16 kg in six placebo-controlled Phase 3 studies and, with the exception of the monotherapy study MB102013, were statistically significant for the 5- and 10-mg doses of dapagliflozin (Figure 10). Weight loss in the placebo group in monotherapy study MB102013 was greater than is typical for clinical studies in patients with T2DM.

Meaningful weight loss from baseline is often easier to achieve in a monotherapy treatment setting, even for patients randomized to placebo, due to the uniform diet and exercise measures that are implemented for all patients in clinical studies. A dose-dependent effect was observed in three of the 4 add-on combination therapy studies (add-on to glimepiride, add-on to pioglitazone, and add-on to insulin), while there was no dose relationship observed in the 2 monotherapy studies.

Figure 10: Adjusted Mean Change from Baseline in Total Body Weight (kg) at Week 24



Statistically significant vs. placebo by hierarchical testing rule: * = $p < 0.05$; ** = $p < 0.001$
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Randomized Patients Dataset/Full Analysis Set; includes data after rescue (LOCF); BL = baseline

As expected, mean weight changes observed in placebo-treated patients varied depending on background therapy. Patients with inadequate glycemic control on stable background treatment with metformin or glimepiride lost weight over the 24-week study period. However, the weight loss observed in patients treated with dapagliflozin 5 and 10 mg was statistically significantly greater vs placebo in both studies at Week 24.

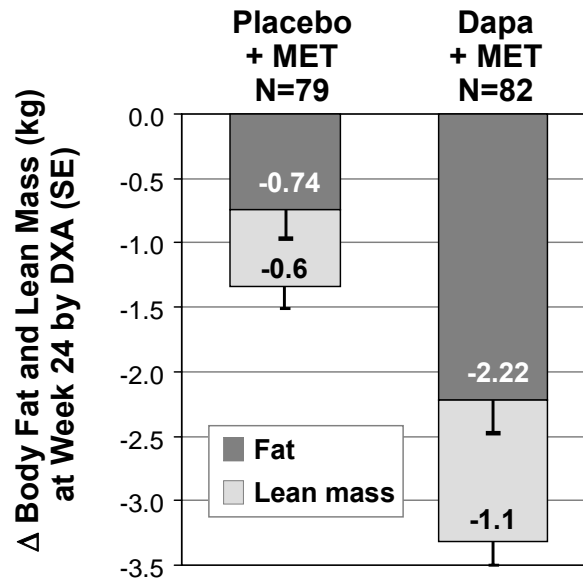
Weight gain with pioglitazone is often progressive, even in the presence of inadequate glycemic control at baseline and after many months of treatment,¹⁴ and patients treated

with pioglitazone and placebo in the add-on to pioglitazone study continued to gain weight (1.64 kg) during the 24-week study period. Conversely, body weight remained close to baseline values over 24 weeks among patients treated with pioglitazone and dapagliflozin. Thus, dapagliflozin mitigated the weight gain associated with pioglitazone treatment. Finally, placebo-treated patients in the add-on to insulin study did not lose weight, but dapagliflozin added to insulin resulted in significant weight loss even in this difficult-to-treat population.

Weight loss associated with dapagliflozin treatment were evaluated further with a special study (D1690C00012) to evaluate change in body weight and body composition, including adipose and lean mass changes, using dual energy X-ray absorptiometry (DXA). The primary endpoint in this study was reduction in total body weight. Patients enrolled in this study had previously failed to achieve glycemic control after treatment with metformin alone. The adjusted mean change in body weight for patients treated with dapagliflozin 10 mg plus metformin and placebo plus metformin was -2.96 kg and -0.88 kg, respectively. This difference amounted to a statistically significant, placebo-corrected mean weight change of -2.08 kg ($p < 0.0001$) in patients treated with dapagliflozin plus metformin. These data are consistent with the weight loss observed in the main add-on to metformin study, MB102014.

Changes in body composition in the body weight and composition study were measured by dual-energy X-ray absorptiometry (DXA). Reduction in total body fat mass accounted for most of the weight loss in this study. Thus, the fundamental PD action of dapagliflozin to induce the caloric loss through glucosuria initiated the expected whole-body metabolic response, enhancing fatty acid oxidation and decreasing body adipose stores, including visceral fat. Weight loss from reduction in lean body mass was small, indicating that the effect of treatment on weight was not due primarily to fluid loss over 24 weeks. The reduction in total body fat mass was approximately 3× larger in the dapagliflozin group (-2.22 kg) than in the placebo group (-0.74 kg) (p -value < 0.0001 , for the comparison between the two treatment groups) (Figure 11). Total body fat correlates directly with CV risk factors as well as with measures of insulin resistance.¹⁵

Figure 11: Adjusted Mean Change from Baseline in Total Body Fat Mass (kg) at Week 24, Body Weight and Composition Study



Full Analysis Set; includes data after rescue (LOCF); BL = baseline; MET = metformin; DXA = dual-energy X-ray absorptiometry

A statistically significant, placebo-corrected, mean reduction of 1.5 cm in waist circumference was also observed in the dapagliflozin group in this body weight and composition study, which is consistent with the reduction in body weight and estimated loss of body fat mass. 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 placebo (4.3%). In an exploratory sub-study using magnetic resonance imaging, mean visceral adipose tissue (VAT) volume was reduced from baseline to Week 24 by approximately 10% in the dapagliflozin group (–322.6 cm³), whereas there was no meaningful change in the placebo group (–8.7 cm³) (nominal p value = 0.0063).

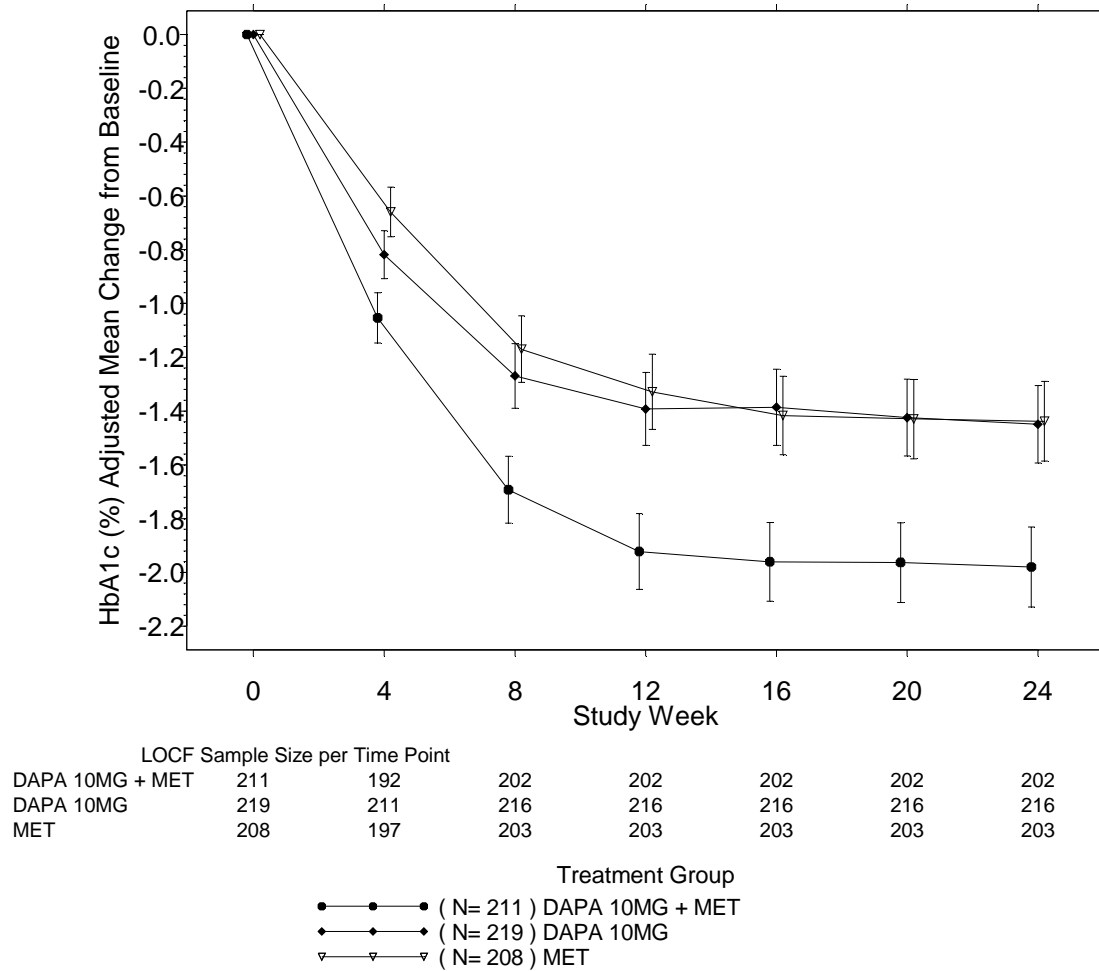
4.5 Results of Initial Combination Studies

Two initial combination studies were performed in drug-naïve patients who were poorly controlled on diet and exercise alone: one study with dapagliflozin 5 mg plus metformin XR (extended release) and one with dapagliflozin 10 mg plus metformin XR. Metformin is the standard of care for T2DM.

Initial combination therapy, with either dapagliflozin 5 or 10 mg plus metformin XR (up to 2000 mg), was superior to metformin monotherapy and superior to either dapagliflozin 5 mg or 10 mg monotherapy in reducing HbA1c values ([Figure 12](#)). Treatment with dapagliflozin 10 mg (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA1c.

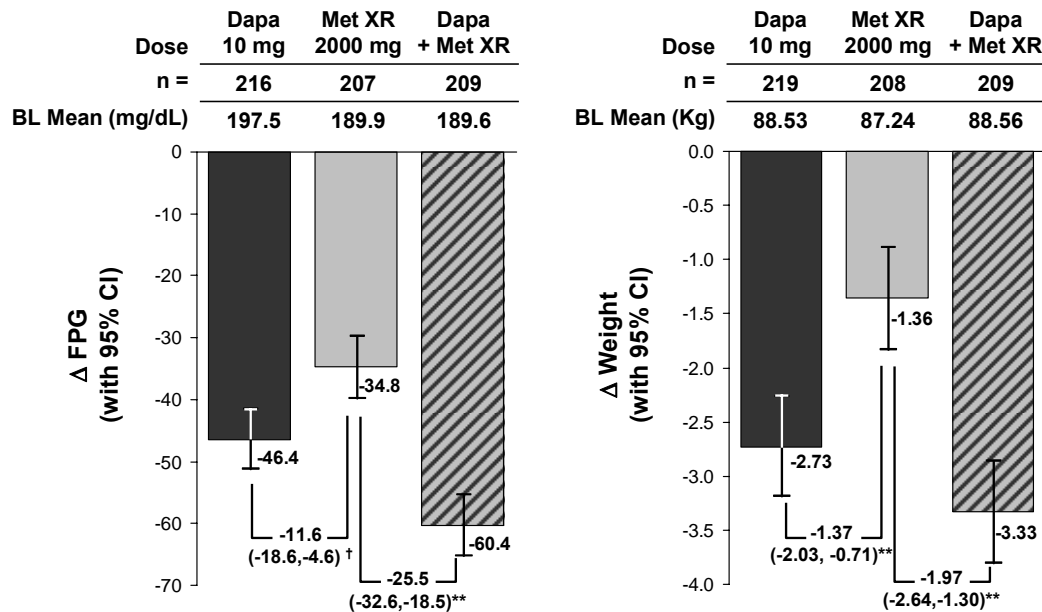
Treatment with dapagliflozin 10 mg was superior to metformin for reduction of FPG and body weight ([Figure 13](#)).

Figure 12: Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 (LOCF), Initial Combination with Dapagliflozin 10 mg plus Metformin XR, Double-blind Treatment Period



Randomized subjects who took at least one dose of double-blind study medication
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping
Excludes data after rescue; XR = extended release

Figure 13: Adjusted Mean Change from Baseline in Fasting Plasma Glucose (mg/dL) and Body Weight (kg) at Week 24, Initial Combination with Dapagliflozin 10 mg plus Metformin XR up to 2000 mg



4.6 Direct Comparison with Glipizide

Dapagliflozin plus metformin was directly compared to glipizide plus metformin over 52 weeks, based on the hypothesis that there would be comparable glycemic efficacy with less risk of hypoglycemia and favorable effects on weight. In this active drug-controlled study, patients with baseline HbA1c of > 6.5% to ≤ 10% and who failed treatment with metformin (mean dose of metformin 1900 mg/day) were randomized 1:1 to glipizide 5 mg plus metformin or dapagliflozin 2.5 mg plus metformin. Subsequently, patients were titrated up in dose of masked active treatments in 3 intervals over 18 weeks to achieve a clinical glycemic effect (FPG <110 mg/dL) or to the highest tolerated dose. The maximum target dose for titration was glipizide 20 mg or dapagliflozin 10 mg. Thereafter, doses achieved during this initial dose titration period were kept constant over the next 34 weeks, with down-titration allowed only in cases of hypoglycemia. Mean

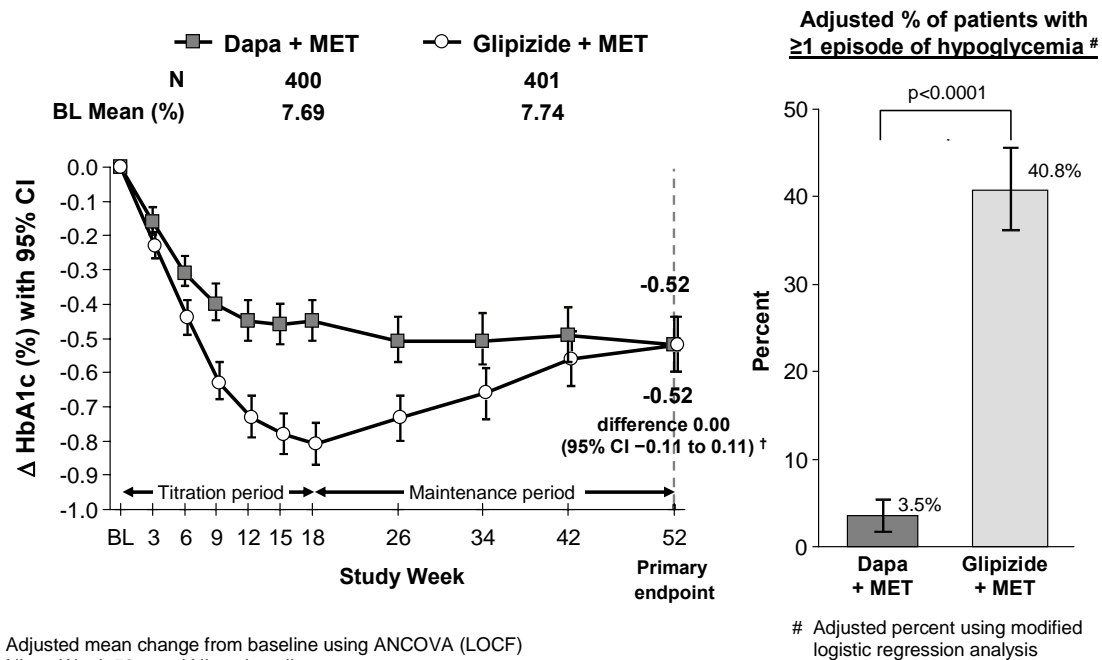
doses for dapagliflozin and glipizide were 9.2 mg and 16.4 mg, respectively, at the end of the up-titration period, and 9.2 mg and 15.9 mg, respectively, at the end of the 52-week treatment period. Seventy seven percent (77%) of patients in the glipizide plus metformin group and 79.3% of patients in the dapagliflozin group completed the 52-week treatment period.

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 subsequently required down-titration due to hypoglycemia vs 5.1% of patients in the glipizide group. The mean reduction from baseline in HbA1c achieved with dapagliflozin plus metformin was non-inferior to that seen with glipizide plus metformin (-0.52% mean reduction in HbA1c from baseline to Week 52 in both treatment groups) (Figure 14).

A comparison of hypoglycemic events between dapagliflozin and glipizide was a secondary efficacy endpoint in this study. Hypoglycemia was more than 10-fold more common in patients treated with glipizide plus metformin (40.8%) than those treated with dapagliflozin plus metformin (3.5%) over 52 weeks of treatment ($p < 0.0001$). More than 90% of these patients had at least 1 episode of confirmed hypoglycemia based on a finger stick FPG value < 63 mg/dl. Six patients in the glipizide plus metformin group and no (0) patients in the dapagliflozin plus metformin group were discontinued due to hypoglycemia.

Treatment with dapagliflozin plus metformin in this study resulted in an estimated weight change of -3.2 kg vs a weight gain of 1.4 kg with glipizide plus metformin. A significantly greater proportion of patients in the dapagliflozin plus metformin group (33.3%), compared to glipizide plus metformin (2.5%), had a body weight loss of at least 5% from baseline to Week 52 ($p < 0.0001$). In exploratory analyses, 55.6% and 6.0% of patients in the dapagliflozin and glipizide groups, respectively, had body weight reductions of at least 3% from baseline to Week 52, and there was a mean decrease in waist circumference of -2.33 cm in the dapagliflozin group compared to a mean increase of 1.09 cm in the glipizide group (for both analyses, the nominal p-value for the difference between dapagliflozin and glipizide was < 0.0001).

Figure 14: Adjusted Mean Change from Baseline in HbA1c (%) to Week 52 and Adjusted Proportion of Patients with Hypoglycemic Events



Adjusted mean change from baseline using ANCOVA (LOCF)
 N's at Week 52 equal N's at baseline
 † Non-inferior compared to limit of 0.35%

Full Analysis Set; error bars represent 95% confidence intervals.; BL = baseline; Met = metformin; Dapa = dapagliflozin; HbA1c = hemoglobin A1c

4.7 Effects on Insulin Use, Insulin Sensitivity, and Beta-cell Function

Changes in insulin requirements were evaluated as supportive measures of glycemic efficacy and were secondary endpoints in the add-on to insulin study. There were minimal reductions in mean total daily insulin dose in all 3 dapagliflozin treatment groups at Week 24 (0.6 – 1.8 international units; IU) vs an increase in mean insulin dose by 5.1 IU for placebo. A statistically significantly higher proportion of patients treated with dapagliflozin 2.5 and 10 mg had mean daily insulin dose reductions of at least 10% (18.2% and 19.6%, respectively) vs placebo (11.0%) ($p < 0.05$). The difference between the 5-mg and placebo groups was not statistically significant.

Exploratory analyses of insulin sensitivity and beta-cell function using HOMA-2 were included in the monotherapy study MB102013, the add-on to metformin study, the direct comparison with glipizide study, and the body weight and composition study. Adjusted mean percent change in insulin sensitivity based on HOMA-2 increased in the dapagliflozin 10 mg groups versus comparator (2.95% to 28.21%) in the 4 studies. Numerical mean increases in beta cell function (0.45 % to 17.27%) were also observed for dapagliflozin 10 mg versus placebo in the monotherapy study MB102013, the add-on to metformin study, and the body weight and composition study. Adjusted mean percent change in beta cell function increased in both treatment groups in direct comparison with glipizide study, though to a greater extent in the glipizide group compared to the dapagliflozin group (26.58% versus 14.23%), as anticipated due to the mechanism of action of glipizide, which directly stimulates insulin release from beta cells.

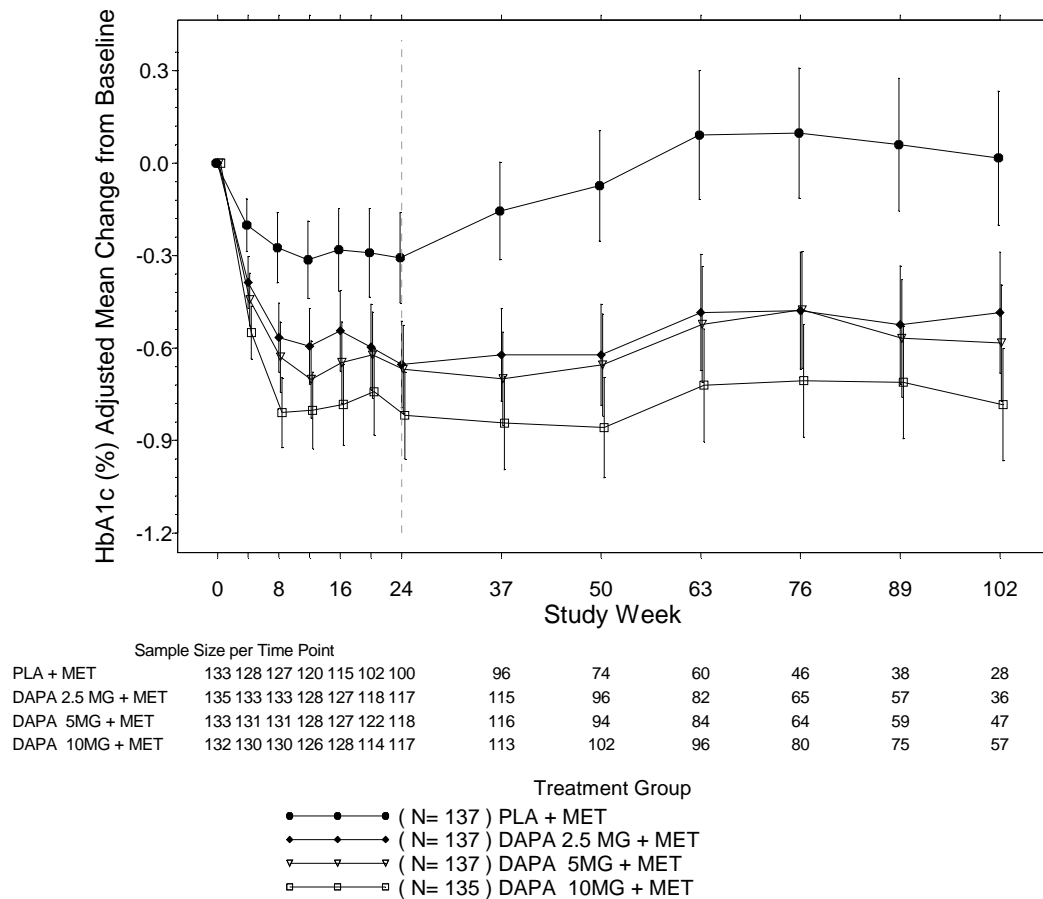
4.8 Maintenance of Effect

While the primary purpose of the long-term extension treatment periods for Phase 3 studies was to assess safety according to initial randomization, exploratory efficacy analyses were also performed to assess the durability of treatment effects on HbA1c, other glycemic endpoints, and body weight. Long-term extension treatment periods were completed for add-on to pioglitazone, add-on to glimepiride, and add-on to insulin studies, all with 48 weeks of treatment from randomization, and the add-on to metformin study, through 102 weeks of treatment from randomization, and a supplemental (interim) statistical analysis for efficacy and safety of the monotherapy study MB102013 was conducted for the NDA among patients with 99 to 102 weeks of treatment from randomization. Long-term extension treatment periods of 36 and 18 months, respectively, are presently ongoing for the direct comparison with glipizide and the body weight and composition studies.

The add-on to metformin study demonstrated that mean reduction in HbA1c observed at Week 24 were maintained through Week 102 in all dapagliflozin groups vs placebo (Figure 15). This finding is consistent with continued glucosuric PD effects observed during long-term treatment (Figure 16). Larger numerical mean reductions in HbA1c at 102 weeks were observed in the dapagliflozin groups compared to the placebo groups in this study (0.02, -0.48, -0.58 and -0.78% in the placebo and dapagliflozin 2.5, 5 and 10 mg groups, respectively), excluding data after rescue. Sensitivity analyses of the

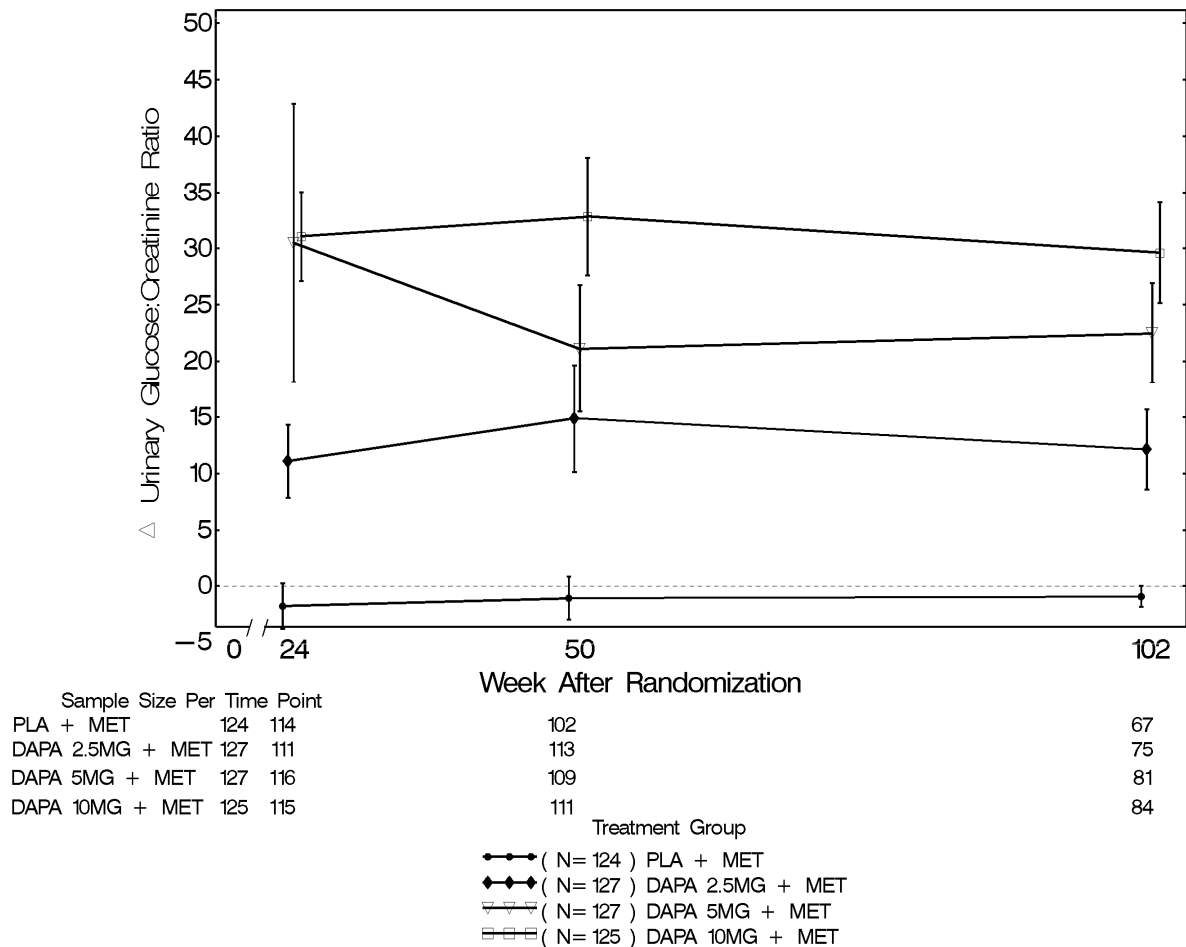
adjusted mean change from baseline in HbA1c and FPG, including data after rescue, were consistent in showing that dapagliflozin's treatment effect in reducing HbA1c and FPG is maintained through Week 102.

Figure 15: Adjusted Mean Change from Baseline in HbA1c (%), Up to Week 102, Add-on to Metformin



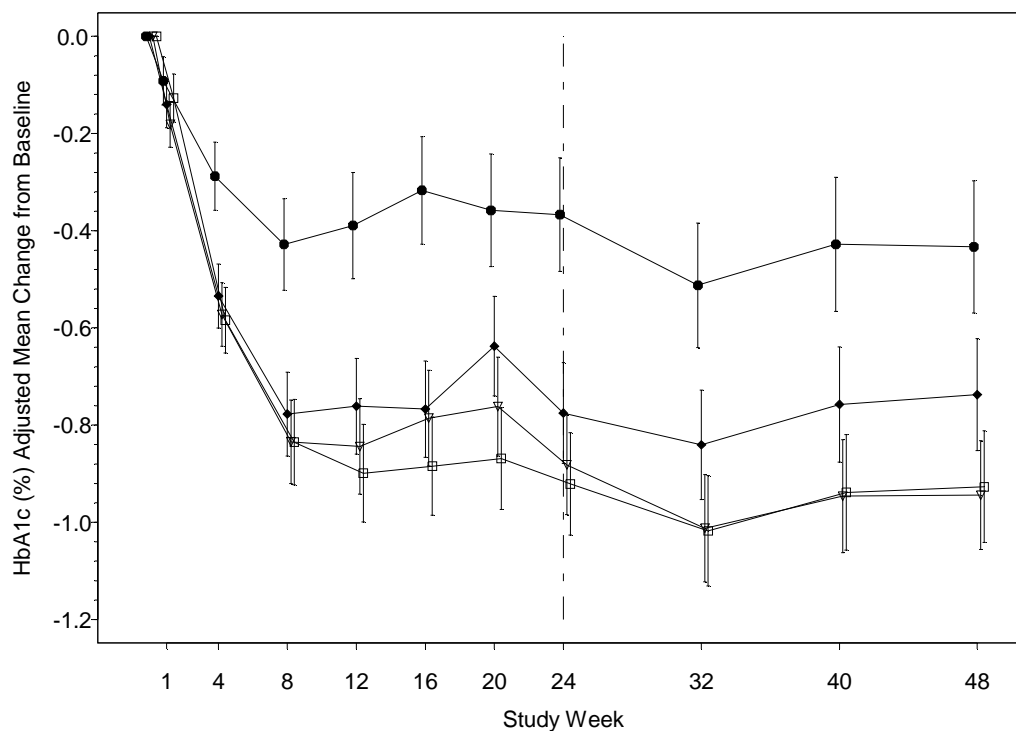
Randomized subjects who took at least one dose of double-blind study medication
Mean value based on a longitudinal repeated measures model with fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping
Excludes data after rescue

Figure 16: Adjusted Mean Change from Baseline Urinary Glucose:Creatinine Ratio, up to Week 102, Add-on to Metformin Study, Including Data After Rescue, Randomized Patients



Similarly, mean reductions in HbA1c compared to baseline were observed in all treatment groups in the add-on to insulin study at Week 48 (Figure 17). These reductions were clinically meaningful (differences compared to placebo approximately -0.5%) in the dapagliflozin 5 and 10 mg groups, with similar results whether data after insulin up-titration were excluded or included.

Figure 17: Adjusted Mean Change from Baseline HbA1c (%) up to Week 48, Add-on to Insulin



Sample Size per Time Point										
PLA + INS	184	168	142	135	128	120	122	111	100	89
DAPA 2.5MG + INS	199	195	183	176	172	168	162	151	145	135
DAPA 5MG + INS	209	197	182	178	175	171	165	163	153	147
DAPA 10MG + INS	188	185	176	171	166	160	158	153	148	139

Treatment Group

- (N= 193) PLA + INS
- ◆ (N= 202) DAPA 2.5MG + INS
- ▽ (N= 211) DAPA 5MG + INS
- (N= 194) DAPA 10MG + INS

Subjects in the full analysis set.

Mean value based on repeated measures analysis model:

post-baseline = baseline treatment stratum week week*treatment week*baseline.

Treatment symbols shifted horizontally to prevent error bar overlapping.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Excludes data after insulin up-titration

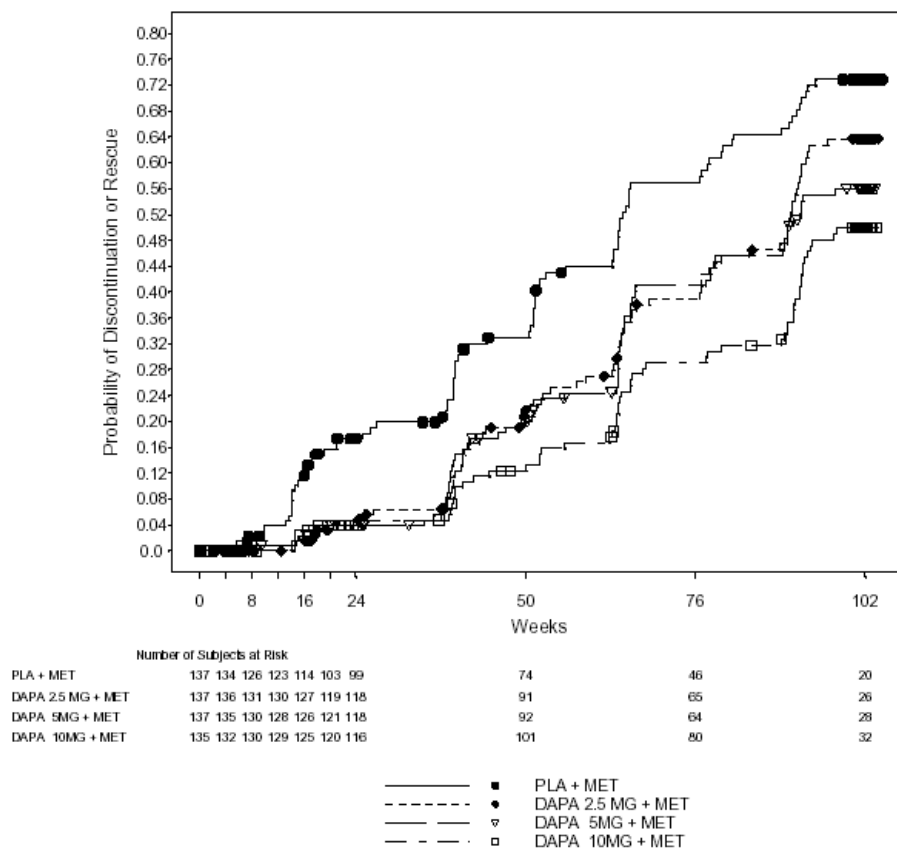
Dapagliflozin treatment resulted in continuing, undiminished urinary glucose excretion consistent with its MOA for up to 2 years. Dose-ordered, placebo-corrected, sustained mean increases from baseline in urinary glucose (add-on to insulin study) or urinary glucose:creatinine ratio were observed through Week 48 in the add-on to insulin study and in the add-on to pioglitazone study, and through Week 102 in the monotherapy

(MB102013) and add-on to metformin studies. This maintained PD effect in the add-on to metformin study is illustrated in [Figure 16](#).

Long-term efficacy is further supported in the analyses assessing rescue or discontinuation for failing to achieve glycemic targets and the proportion of patients achieving $\text{HbA1c} < 7.0\%$. The adjusted proportion of patients in the add-on to metformin study who were discontinued or rescued for failing to achieve glycemic targets, based on pres-specified criteria, was numerically lower in the dapagliflozin 5 mg (43.9%) and 10 mg (44.0%) groups than in the dapagliflozin 2.5 mg (53.0%) or placebo (60.1%) groups at Week 102. Data from long-term extension periods from other Phase 3 studies also consistently demonstrated that fewer dapagliflozin-treated patients required rescue treatment or discontinuation due to lack of glycemic control compared to placebo. Overall, the probability of either discontinuation or rescue for failing to achieve glycemic targets over time was numerically lower for the dapagliflozin treatment groups than the placebo group at all time points after Week 4 ([Figure 18](#)).

The proportion of patients achieving a glycemic response, defined as $\text{HbA1c} < 7.0\%$, was higher in the dapagliflozin groups than in the placebo group at Week 102, and the proportion at Week 24 was maintained until Week 102 in the dapagliflozin treatment groups. The placebo-corrected proportions of patients achieving $\text{HbA1c} < 7.0\%$ in the dapagliflozin 2.5 mg, 5 mg, and 10 mg groups were 5.3%, 11.0%, and 16.1% at Week 102 in the add-on to metformin study, respectively.

Figure 18: Time to Rescue or Discontinuation for Failing to Achieve Pre-Specified Glycemic Targets, up to Week 102, Add-on to Metformin



Symbols represent censored observations.

Week is not the scheduled visit week but the actual number of days from the first dose of double-blind study medication divided by 7.

Number of subjects at risk is the number of subjects at risk at the beginning of the period. The results beyond Week 102 should be interpreted with caution as the number of subjects at risk might be limited.

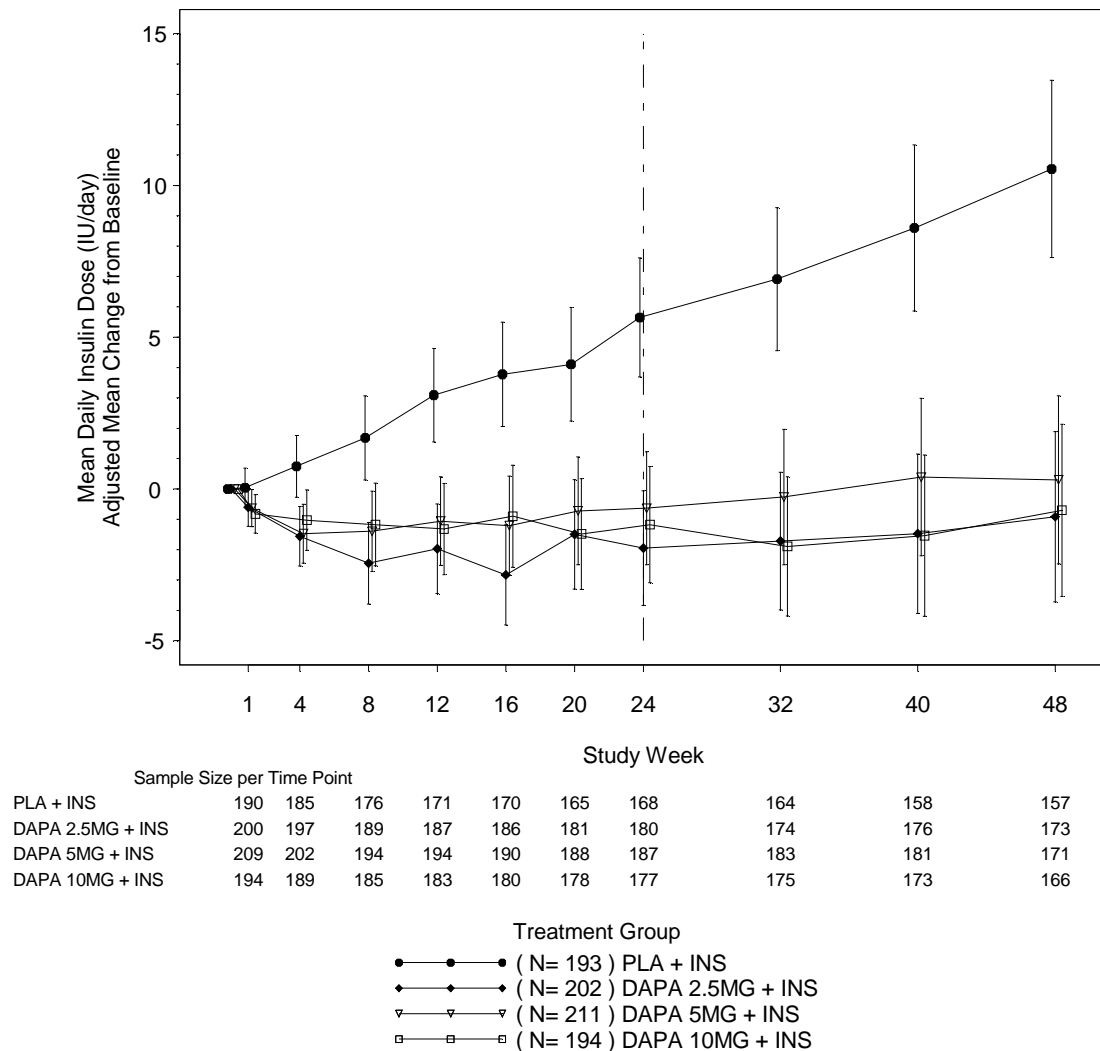
Randomized patients

Relative mean reductions in total body weight observed at Week 24 in the dapagliflozin treatment groups were maintained through Week 102, consistent with the continued loss of calories due to glucosuria and subsequent metabolic responses to enhance fat oxidation. Mean weight reductions were larger at Week 102 in the 3 dapagliflozin treatment groups compared to the placebo group and were dose ordered (1.36, -1.10, -1.70, and -1.74 kg in the placebo and dapagliflozin 2.5, 5 and 10 mg groups, respectively), including data after rescue, in the add-on to metformin study.

The findings from the add-on to pioglitazone, add-on to glimepiride, and add-on to insulin studies also suggest that effects on HbA1c, FPG, and weight were maintained during the long-term period, whether data after rescue were included or excluded.

As described in Section 4.7, daily insulin use was also impacted as expected in the add-on to insulin study. There was no meaningful change in mean daily insulin dose at Week 24 or 48 in the dapagliflozin treatment groups compared to baseline (less than 1 IU/day mean change in the dapagliflozin groups), including data after rescue ([Figure 19](#)). A mean numerical increase of 10.54 IU/day was observed in the placebo group. The increase in the daily insulin dose in the placebo group observed at Week 24 nearly doubled at Week 48, whereas there was no further change in the dapagliflozin groups from Week 24 to Week 48. Importantly, there was evidence of continuing increases from baseline in body weight in the placebo group, a finding that coincided with the increase in daily insulin. Given that escalating insulin therapy is often associated with weight gain, this finding may be related to the insulin-sparing effect of dapagliflozin, in addition to its direct effects on urinary glucose caloric loss.

Figure 19: Adjusted Mean Change from Baseline Over Time in Calculated Mean Daily Insulin Dose (IU/day) over 48 Weeks, Add-on to Insulin Study, including Data after Insulin Up-Titration (Full Analysis Set)



Subjects in the full analysis set.

Mean value based on repeated measures analysis model:

post-baseline = baseline treatment stratum week week*treatment week*baseline.

Treatment symbols shifted horizontally to prevent error bar overlapping.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

4.9 Efficacy as a Function of Dose

Comprehensive data available from the entire clinical development program support dapagliflozin 10 mg as the dose providing better efficacy for the treatment of patients with T2DM than the 2.5- or 5-mg doses. Clinical pharmacology studies demonstrated that glucosuria, the primary PD measure, increased with dose, up to a range of 20 to 25 mg. The 10-mg dose provided ~80% of maximum glucosuria.

Several studies provided data to evaluate the impact of dose on the efficacy of dapagliflozin. The doses evaluated for efficacy ranged from 1 mg to 10 mg.

Evaluation of efficacy at the lower end of this dose range (1 – 2.5 mg) was based on results of several studies. Dapagliflozin 1 mg was studied in a Phase 2b dose-ranging study in Japanese patients (D1692C00005) and a Phase 3 low-dose monotherapy study (MB102032). The 2.5 mg dose was studied in two Phase 2b monotherapy dose-ranging studies (D1692C00005 and MB102008) and two Phase 3 monotherapy studies (MB102013 and MB102032 [low-dose]). This dose was also included in three Phase 3 add-on combination therapy studies. Collectively, efficacy for the 1 mg and 2.5 mg doses was inconsistent and variable, and statistically significant and clinically significant efficacy was not reliably demonstrated for either of these doses. Based on these data, doses of 2.5 mg or lower are not considered to have sufficient efficacy in lowering HbA1c to be a recommended dose.

Evaluation of efficacy at the upper end of this dose range (5 mg and 10 mg) was primarily based on studies in the Phase 3 program. In these studies, the 10-mg dose was consistently associated with statistically and clinically significant mean reductions compared to placebo in studies with mean reduction in HbA1c from baseline as the primary endpoint, (Figure 4). The 10-mg dose also provided numerically superior results for lowering of HbA1c and FPG compared to the 5-mg dose in each of five placebo-controlled Phase 3 studies that included both doses (monotherapy (MB102013), add-on to metformin, add-on to pioglitazone, add-on to glimepiride, and add-on to insulin studies).

Dapagliflozin 10 mg also consistently resulted in clinically meaningful reductions of HbA1c of at least 0.5% vs placebo. A larger proportion of patients treated with 10-mg achieved glycemic control (HbA1c < 7.0%) vs dapagliflozin 5 mg (Figure 8). Likewise, dapagliflozin 10 mg was non-inferior in mean change from baseline HbA1c when

directly compared to glipizide (Figure 14) or metformin XR (Figure 12). Finally, statistically greater mean reductions from baseline in FPG were observed in 4 of the five Phase 3 studies that included dapagliflozin 10 mg (Figure 6.)

Based on these data, dapagliflozin 10-mg provided more consistent and larger overall effects for numerous assessments of glycemic control than did the 5-mg dose. Based on this more consistent efficacy, the 10-mg dose is therefore the recommended dose for most patients, with 5 mg as a potential starting dose for patients at risk of hypotension or volume depletion.

5 SAFETY

5.1 Introduction

The safety of dapagliflozin was evaluated at doses of 2.5, 5 and 10 mg, administered as monotherapy or in combination with another anti-diabetic agent. Its safety profile is consistent with glucosuria and diuresis resulting from the inhibition of SGLT2. Events considered as potentially related to dapagliflozin's MOA at the beginning of the clinical development program, and studied in depth throughout the program were: hypoglycemia; UTIs; vulvovaginitis, balanitis and related genital infections; hemodynamic effects, such as blood pressure, volume depletion, and changes in hematology; effects on renal function, such as glomerular filtration rate, associated AEs, serum sodium, serum potassium, and urate; and effects on bone, such as laboratory tests associated with bone health, bone mineral density, and fractures. Extensive safety assessments were also conducted on events of malignancy and hepatic safety, which are always important when considering a novel oral treatment. Evaluation of CV safety included a meta-analysis of independently confirmed, blindly adjudicated, CV events among fourteen Phase 2b and 3 studies as well as measurements of blood pressure and serum lipids. Safety in special groups of people, such as the elderly, was also assessed.

5.2 Methods

5.2.1 Safety Data Collection and Monitoring

Safety was extensively evaluated based on standard safety assessments that included collection of AEs, deaths, SAEs, AEs leading to discontinuation, clinical laboratory tests, and vital signs, such as blood pressure and electrocardiograms, at every visit.

Additional clinical information was collected for certain events of interest based on the MOA or of general interest for drug development in diabetes. These areas of interest were hypoglycemia, UTIs, vulvovaginitis, balanitis and related genital infections, renal safety, malignancies and other tumors, hepatic safety, cardiovascular safety, and bone metabolism. Patients were proactively questioned at every visit for signs and symptoms of UTIs and genital infections, and when infections were reported, additional information was collected on special case report forms (CRFs). If the patient's response to proactive questioning by the investigator suggested a UTI, a urinary culture was to be performed, with a second follow-up culture performed within 7 days of the resolution of clinical symptoms. Special CRFs were also used to capture detailed additional information about hypoglycemic events. Additional follow-up of laboratory abnormalities was mandated according to protocol algorithms for relevant variables (serum creatinine, sodium, creatine kinase, liver enzymes, total bilirubin, and glucose).

Analyses were performed based on customized Medical Dictionary for Regulatory Activities (MedDRA) queries based on expansive predefined lists of events (preferred terms or PTs) for UTIs, vulvovaginitis, balanitis and related genital infections, renal impairment or failure, volume depletion, and urinary stones. A standardized MedDRA query (SMQ) was used to identify events of hepatic disorder.

A blinded independent Clinical Event Committee (CEC) was established to adjudicate cardiovascular events and a similar Hepatic Adjudication Committee was established to evaluate liver abnormalities. Additional information about the assessment of hepatic safety is provided in Section 5.5.2 and for CV safety, in Section 5.5.3.

5.2.2 Datasets

Treatment with other diabetes medications (rescue treatment) was permitted based on pre-specified criteria for lack of glycemic control to ensure patient health. The primary safety analyses were performed on data including treatment with rescue therapy. Select analyses were also performed on data excluding treatment with rescue therapy to assess whether results were similar, regardless of the presence of rescue. Because rescue treatment can cause hypoglycemia, the primary analyses for hypoglycemia were performed excluding data after rescue. The analysis populations are described in detail in Section 3.2.

5.3 Overall Adverse Events

Death was an infrequent event across the program. A total of 34 deaths were reported in the All Phase 2b and 3 Pool up to the 4MSU. Of these 12 (0.6%) were reported in control patients and 22 (0.5%) in patients treated with varying doses of dapagliflozin. The most common cause of death was related to cardiac disorders, a common co-morbidity among patients with T2DM. No increase in the incidence rate of adjudicated CV death was associated with dapagliflozin treatment.

Serious adverse events (SAEs) were balanced between treatment groups and reported for small proportions of patients (Table 13). The most commonly reported SAEs were categorized as infections and infestations; musculoskeletal and connective tissue disorders; and cardiac disorders. The most commonly reported SAEs were pneumonia, angina pectoris, and acute myocardial infarction. SAEs did not appear to be related to dose.

Overall, a small proportion of patients experienced an AE that led to discontinuation, with similar proportions of patients across the treatment groups (Table 13). The category with the greatest proportion of discontinuations was the investigations category (0.2 to 0.6% in the dapagliflozin groups vs 0.5% in the placebo group). Within this category, the most frequent reason for discontinuation in the placebo group was increased weight, while in the dapagliflozin groups, the most common reason was increased blood creatinine (0.1 to 0.4% for dapagliflozin vs 0.1% for placebo). All protocols had criteria for discontinuation due to elevated serum creatinine values, in many cases based on metformin labeling, which was used as a background or rescue medication in many

studies. The next most frequent reasons for discontinuation were due to gastrointestinal disorders (0.3 to 0.4% for dapagliflozin vs 0.6% for placebo), followed by infections and infestations (0.4% for all dapagliflozin groups vs 0.1%), and renal and urinary disorders (0.2 to 0.4% vs 0.1%). In the renal and urinary disorders category, no events were reported by more than 1 patient in any treatment group, and most were related to urinary output (e.g., dysuria, polyuria) rather than renal function.

The proportion of patients with at least 1 AE was higher in each of the dapagliflozin groups relative to placebo during the short-term treatment period ([Table 13](#)). The proportions were similar by the end of the long-term extension treatment periods. The largest contributors to this difference were events of hypoglycemia, vulvovaginitis, balanitis and related genital infections, and UTI. These events will be discussed in greater detail in Sections 5.4.1, 5.4.2, and 5.4.3.

5.4 Mechanism-related Safety

Certain risks could reasonably be expected based on dapagliflozin's targeted MOA in the kidney, and generally associated with urinary glucose excretion and mild diuresis. Specific mechanism-related safety risks are hypoglycemia, UTIs, vulvovaginitis, balanitis and related genital tract infections, changes in blood pressure, and volume depletion. Adverse events and changes in laboratory values related to renal function, and effect on electrolytes and other laboratory parameters were also examined, as was the effect on calcium homeostasis and bone health.

This section focuses on the results from the short-term Placebo-controlled Pool, except where otherwise stated. This dataset was the best-controlled pool available for assessment of safety and was used for the primary analysis of safety.

Table 13: Overall Adverse Events Summary, Short-term Double-blind Treatment Period including Data after Rescue - Placebo-controlled Pool, Treated Patients (NDA Dataset)

	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.

5.4.1 Hypoglycemia

Dapagliflozin alone showed a low intrinsic propensity to cause hypoglycemia, but, as expected with any blood sugar lowering drug, the risk of hypoglycemia increased when given in combination with agents such as SUs and insulin. The frequency of hypoglycemia depended on the type of background therapy used in each study. Total hypoglycemia included minor hypoglycemia, defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode. A major episode was defined as a symptomatic episode requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 54 mg/dL and prompt recovery after glucose or glucagon administration.

There were no major episodes of hypoglycemia with dapagliflozin in studies of dapagliflozin used as monotherapy, add-on to metformin, add-on to pioglitazone, and initial combination with metformin (dapagliflozin 5 and 10 mg) up to 24 weeks ([Table 14](#)). Studies with add-on sulfonylurea and add-on insulin combination therapy had higher rates of hypoglycemia, but major events were rare.

In the add-on to glimepiride study, no episode of major hypoglycemia was reported in the dapagliflozin 5 or 10 mg groups up to 24 weeks. In the add-on to insulin study up to 24 weeks, episodes of major hypoglycemia were reported in 0.5% and 0.5% patient in dapagliflozin 10 mg plus insulin and placebo plus insulin groups, respectively.

Hypoglycemia was more than 10-fold more common in patients treated with glipizide plus metformin (40.8%) than those treated with dapagliflozin plus metformin (3.5%) over 52 weeks of treatment ($p < 0.0001$).

Table 14: Hypoglycemia in Placebo-controlled Studies Short-term Treatment Period (NDA Dataset)

Population		DAPA 2.5 mg	DAPA 5 mg	DAPA 10 mg	PBO†
		n = 814	n = 1145	n = 1193	n = 1393
Placebo-controlled Pool ^a	Total*	15.5%	10.9%	10.2%	7.0%
	Major**	0.4%	0.1%	0.1%	0.1%
		n = 321	n = 316	n = 245	n = 251
Monotherapy Pool	Total*	2.5%	2.2%	2.9%	2.0%
	Major**	0	0	0	0
Add-on Combination Treatment					
				n = 226	n = 228
+ Metformin (Pool)	Total*	—	—	3.1%	3.1%
	Major**	—	—	0	0
			n = 141	n = 140	n = 139
+ Pioglitazone	Total*	—	2.1%	0	0.7%
	Major**	—	0	0	0
		n = 154	n = 145	n = 151	n = 146
+ Glimepiride	Total*	7.1%	6.9%	7.3%	4.8%
	Major*	0.6%	0	0	0
		n = 202	n = 212	n = 196	n = 197
+ Insulin	Total*	51.5%	45.3%	42.3%	35%
	Major**	1.0%	0.5%	0.5%	0.5%

* Total hypoglycemia included minor hypoglycemia, which was defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode.

** Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.

DAPA = dapagliflozin; PBO = placebo

Rescue medication with other oral anti-diabetic drugs was permitted in most studies.

† For add-on combination studies, placebo treatment includes placebo plus the additional anti-diabetic drug.

^a In the Placebo-controlled Pool, the All Dapa includes 20 mg and 50 mg in addition to dapagliflozin 2.5 mg, 5 mg, and 10 mg. Includes studies shown as well as the dapagliflozin plus metformin and placebo plus metformin groups from the initial combination studies (MB102021 and MB102034), and the pilot add-on to insulin study (MB102009).

5.4.2 Urinary Tract Infection

Adverse events of UTI were reported spontaneously as well as in response to questions related to the signs and symptoms of these infections proactively posed to patients during all study visits. A pre-specified list of events based on MedDRA PTs that indicated a diagnosis of UTI was used to identify these infections.

UTIs were reported more often among patients treated with dapagliflozin than placebo: 4.3% and 3.7% of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-term Placebo-controlled Pool (Table 15). All UTIs reported in patients treated with dapagliflozin 10 mg were considered by the investigator to be mild (patient was aware of the event but easily tolerated it) to moderate (discomfort was enough to cause some interference with the patient's usual activity). Most patients responded to an initial course of standard treatment (93.1% in the dapagliflozin-treated patients overall and 85.7% in placebo) without interrupting treatment with dapagliflozin. UTIs rarely caused discontinuation from the study: 0.3% dapagliflozin 10 mg vs 0.1% placebo. UTIs were more frequently reported in females than in males (Table 15). Organisms identified in study patients with UTI were generally those commonly associated with UTIs in the general population, such as *Escherichia coli* and *Klebsiella* species.

Patients in the short-term Placebo-controlled Pool who had a history of recurrent UTI were more likely to have this type of event (17.6% of patients with history of UTI treated with dapagliflozin 10 mg and 17.1% of patients with history of UTI on placebo) during the study than those without such a history (3.7% on dapagliflozin 10 mg and 3.4% on placebo). Pyelonephritis was rare and balanced between treatment groups across the entire program (0.1% for dapagliflozin and 0.2% for control).

During long-term follow-up (the short-term plus long-term Placebo-controlled Pool), the proportions of patients with UTIs were 7.7% (59/768) in dapagliflozin 10 mg and 6.3% (44/694) in placebo. Of the 59 patients treated with dapagliflozin 10 mg who experienced

a UTI, 74.6% had only one and 5.1% had three or more. Of the 44 patients treated with placebo who experienced a UTI, 86.4% had only one and 6.8% had three or more.

There was no dose relationship in the frequency or intensity of UTIs between 5 mg and 10 mg. Overall, the proportion of patients with events of UTI after treatment with dapagliflozin 5 mg was similar to dapagliflozin 10 mg treatment. Post-marketing surveillance plans for safety assessment of patients hospitalized for severe UTIs are described in Section 7.

Table 15: Adverse Events of Urinary Tract Infection, Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

	Percent of Patients			
	Dapa 2.5 mg N=814	Dapa 5 mg N=1145	Dapa 10 mg N=1193	Placebo N=1393
Total	3.6%	5.7%	4.3%	3.7%
	n=400	n=581	n=598	n=677
Female	5.8%	9.6%	7.7%	6.6%
	n=414	n=564	n=595	n=716
Male	1.4%	1.6%	0.8%	1.0%

MedDRA Version: 13.0

Dapa = dapagliflozin; N or n is the number of treated patients.

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.

Percentages are based on the number of treated patients per treatment group.

Events of urinary tract infections are based on a limited predefined list of events.

5.4.3 Vulvovaginitis, Balanitis and Related Genital Infection

The term genital infection in this section refers to vulvovaginitis, balanitis and related infections, and does not include sexually-transmitted infections. These infections were reported spontaneously as well as in response to questions related to the signs and

symptoms of these infections proactively posed to patients during all study visits. A pre-specified list of events based on MedDRA PTs that indicated a diagnosis of genital infection was used to identify these infections.

Events of non-sexually transmitted genital infections were reported more often among patients treated with dapagliflozin than placebo (Table 16). The most frequently reported types of genital infections were vulvovaginal mycotic infections and vaginal infection in females, and balanitis and fungal genital infection in males. These events were reported in 4.8% and 0.9% of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-term Placebo-controlled Pool. These infections did not require interruption of treatment with dapagliflozin. All events of genital infections reported in patients treated with dapagliflozin 10 mg were considered by the investigator to be mild (patient was aware of the event but easily tolerated it) to moderate (discomfort was enough to cause some interference with the patient's usual activity).

Most events of vulvovaginitis, balanitis and related infections responded to an initial standard course of treatment (71.2% dapagliflozin 10 mg vs 92.3% in placebo), and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg vs 0% in placebo). Additional treatment was given because of inadequate response to the initial course of treatment in a small proportion of the events: 0%, 6.5%, and 4.5% of events in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 0 events in the placebo group. Genital infections were more frequently reported in females than in males (Table 16).

Patients in the short-term Placebo-controlled Pool who had a history of recurrent vulvovaginitis, balanitis and related infections were more likely to have a genital infection (25.0% of patients with history of genital infection treated with dapagliflozin 10 mg and 10.0% of patients with history of genital infection on placebo) during the study than those without such a history (5.0% on dapagliflozin 10 mg and 0.8% on placebo).

During long-term follow-up (the short-term plus long-term Placebo-controlled Pool), the proportions of patients with vulvovaginitis, balanitis and related infections were 8.2% in dapagliflozin 10 mg and 1.3% in placebo. Of the 63 patients treated with dapagliflozin 10 mg who experienced a genital infection, 74.6% had only one and 15.8% had three or

more. Of the 9 patients treated with placebo who experienced a genital infection, 77.8% had only one and none had three or more.

There was no dose relationship in the frequency or intensity of vulvovaginitis, balanitis and related infections between 5 mg and 10 mg. Overall, the proportion of patients with events of genital infection after treatment with dapagliflozin 5 mg was similar to dapagliflozin 10 mg treatment.

Table 16: Adverse Events of Vulvovaginitis, Balanitis and Related Infections, Short-term Treatment Period, Including Data After Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

	Percent of Patients			
	Dapa 2.5 mg N=814	Dapa 5 mg N=1145	Dapa 10 mg N=1193	Placebo N=1393
Total	4.1%	5.7%	4.8%	0.9%
	n=400	n=581	n=598	n=677
Female	5.8%	8.4%	6.9%	1.5%
	n=414	n=564	n=595	n=716
Male	2.4%	2.8%	2.7%	0.3%

MedDRA Version: 13.0; Dapa = dapagliflozin; N or n is the number of treated patients.

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.

Adverse events of genital infections are based upon a limited predefined list of events.

5.4.4 Effects of Osmotic Diuresis

5.4.4.1 Hemodynamic Effects (Blood Pressure and Volume Depletion)

Potential hemodynamic effects due to dapagliflozin's MOA were changes in blood pressure and volume depletion. In general, any observed effects on blood pressure and

volume depletion were consistent with mild diuresis, and had little to no effect on the overall safety profile of dapagliflozin.

Blood Pressure

A decrease in measured blood pressure was observed with dapagliflozin, likely related to diuresis and to weight loss. Systolic blood pressure (SBP) mean change from baseline at Week 24 was -4.4 mmHg and diastolic blood pressure (DBP) mean change was -2.1 mmHg for the dapagliflozin 10 mg group vs changes of -0.9 mmHg systolic and -0.5 mmHg diastolic for placebo (Table 17 and Table 18). These changes occurred without any increased incidence of measured orthostatic hypotension (3.7% for both dapagliflozin 10 mg and placebo at Week 24; Table 19).

Table 17: Summary Statistics for Seated Systolic Blood Pressure (mmHg), 24-Week Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

----- Change From Baseline Period -----								
Visit	Treatment Group	N#	Mean	SD	Min , Max	Mean	SD	Min, Max
ST TREAT WEEK 24	PLA	1096	129.2	14.33	88 , 178	-0.9	13.13	-54 , 36
	DAPA 2.5MG	621	128.4	15.60	89 , 198	-4.0	14.16	-58 , 43
	DAPA 5MG	908	125.5	15.02	83 , 211	-3.5	13.36	-56 , 58
	DAPA 10MG	949	126.0	14.44	89 , 185	-4.4	13.92	-55 , 42
	DAPA TOTAL	2478	126.4	14.99	83 , 211	-4.0	13.78	-58 , 58

N# is the number of treated patients with non-missing baseline and Week t values. DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Table 18: Summary Statistics for Seated Diastolic Blood Pressure (mmHg), 24-Week Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool Treated Patients (NDA Dataset)

Change From Baseline Period								
Visit	Treatment Group	N#	Mean	SD	Min , Max	Mean	SD	Min , Max
ST TREAT WEEK 24	PLA	1096	79.2	8.44	53 , 111	-0.5	8.31	-35 , 33
	DAPA 2.5MG	621	77.8	9.06	50 , 113	-1.8	8.45	-31 , 32
	DAPA 5MG	908	77.2	8.36	50 , 106	-2.1	7.92	-34 , 29
	DAPA 10MG	949	77.1	8.35	47 , 104	-2.1	8.44	-39 , 30
	DAPA TOTAL	2478	77.3	8.54	47 , 113	-2.0	8.25	-39 , 32

N# is the number of treated patients with non-missing baseline and Week t values.

Table 19: Measured Orthostatic Hypotension Short-term, Double-blind Treatment Period including Data After Rescue Placebo-controlled Pool Treated Patients (NDA Dataset)

X/N# (Percent)					
Week	PLA (N = 1393)	DAPA 2.5MG (N = 814)	DAPA 5MG (N = 1145)	DAPA 10MG (N = 1193)	DAPA TOTAL (N = 3291)
BASELINE	40/1245 (3.2)	37/ 771 (4.8)	40/1097 (3.6)	46/1056 (4.4)	125/3048 (4.1)
24-WEEK DOUBLE-BLIND PERIOD	118/1283 (9.2)	101/ 811 (12.5)	115/1127 (10.2)	109/1085 (10.0)	337/3154 (10.7)
WEEK 1	47/1254 (3.7)	41/ 799 (5.1)	48/1103 (4.4)	44/1059 (4.2)	136/3082 (4.4)
WEEK 12	46/1032 (4.5)	31/ 753 (4.1)	39/ 922 (4.2)	38/ 871 (4.4)	114/2668 (4.3)
WEEK 24	37/1003 (3.7)	27/ 615 (4.4)	34/ 899 (3.8)	32/ 861 (3.7)	93/2375 (3.9)

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

X is the number of patients with orthostatic hypotension at Week t defined as decrease from supine to standing of > 20 mmHg in systolic blood pressure or > 10 mmHg in diastolic blood pressure.

N# is the number of treated patients with non-missing Week t values.

24-WEEK DOUBLE-BLIND PERIOD presents the number of patients with at least one event during the treatment period.

Changes in SBP and DBP were analyzed as exploratory efficacy endpoints to characterize blood pressure change in the subgroups of patients with baseline SBP > 140 mmHg and SBP ≤ 140 mmHg in the Monotherapy/Combination Therapy Pool (nine Phase 3 studies: (monotherapy, low-dose monotherapy, add-on to metformin, add-on to pioglitazone, add-on to glimepiride, add-on to insulin, direct comparison to glipizide, and both initial combination with metformin studies). No test for interaction between treatment and subgroup was performed. Background antihypertensive medications were not controlled.

Reductions in both SBP and DBP were observed in all of the dapagliflozin treatment groups in both subgroups but were greater in the hypertensive subgroup with baseline SBP > 140 mmHg. These reductions are highlighted in grey in [Table 20](#) and [Table 21](#).

Table 20: Seated Systolic Blood Pressure (mmHg) Adjusted Mean Change from Baseline at Week 24 (LOCF) by Baseline Blood Pressure Category, Excluding Data after Rescue, Monotherapy/Combination Therapy Pool, Randomized Patients/Full Analysis Set (NDA Dataset)

SUBGROUP STATISTIC	POOLED PLACEBO N=1257	POOLED DAPA 2.5 MG N=699	POOLED DAPA 5 MG N=1025	POOLED DAPA 10 MG N=1066
BASELINE SEATED SYSTOLIC BLOOD PRESSURE: ≤140 mmHg				
N#	934	491	787	781
BASELINE MEAN (SD)	123.5 (10.53)	123.9 (10.61)	123.0 (10.63)	123.2 (10.91)
WEEK 24 MEAN (SD)	125.1 (12.62)	123.5 (13.18)	122.2 (13.14)	122.0 (12.51)
MEAN CHANGE FROM BASELINE (SD)	1.6 (11.30)	-0.4 (12.15)	-0.8 (11.48)	-1.2 (11.61)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	1.6 (0.413)	0.3 (0.597)	-0.4 (0.467)	-1.2 (0.467)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[0.8, 2.4]	[-0.9, 1.4]	[-1.3, 0.5]	[-2.2, -0.3]
DIFFERENCE VS PLACEBO (SE)		-1.3 (0.729)	-1.9 (0.614)	-2.8 (0.617)
95% CI OF DIFFERENCE VS PLACEBO		[-2.7, 0.1]	[-3.2, -0.7]	[-4.0, -1.6]
BASELINE SEATED SYSTOLIC BLOOD PRESSURE: >140 mmHg				
N#	314	203	228	274
BASELINE MEAN (SD)	149.5 (9.75)	153.0 (10.17)	151.2 (10.11)	151.0 (10.40)
WEEK 24 MEAN (SD)	140.7 (13.49)	139.5 (15.14)	138.5 (14.57)	137.3 (14.50)
MEAN CHANGE FROM BASELINE (SD)	-8.8 (13.31)	-13.4 (15.12)	-12.7 (15.02)	-13.7 (15.17)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-8.9 (0.710)	-12.9 (0.902)	-12.3 (0.842)	-13.8 (0.769)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[-10.3, -7.5]	[-14.7, -11.1]	[-14.0, -10.7]	[-15.3, -12.3]
DIFFERENCE VS PLACEBO (SE)		-4.0 (1.143)	-3.4 (1.095)	-4.9 (1.033)
95% CI OF DIFFERENCE VS PLACEBO		[-6.2, -1.8]	[-5.6, -1.3]	[-6.9, -2.9]

N is the number of patients in the Randomized Patients (BMS studies) or Full Analysis Set (AZ studies).

N# is the number of patients with non-missing baseline and Week 24 (LOCF) values in the Randomized Patients/Full Analysis Set.

Studies in Pooled Mono/Combo Group: MB102013 (monotherapy, QAM and QPM doses combined, excluding Group 2), MB102032 (monotherapy, excluding 1 mg), MB102014 (add-on to metformin), MB102030 (add-on to TZD), D1690C00005 (add-on to SU), D1690C00006 (add-on to insulin), D1690C00012 (add-on to metformin), MB102021, MB102034 (initial combination with metformin, excluding dapagliflozin arm). Based on an ANCOVA model with treatment group, subgroup, and study as categorical factors and interaction between treatment group and subgroup.

Table 21: Seated Diasystolic Blood Pressure (mmHg) Adjusted Mean Change from Baseline at Week 24 (LOCF) by Baseline Blood Pressure Category, Excluding Data after Rescue, Monotherapy/Combination Therapy Pool, Randomized Patients/Full Analysis Set (NDA Dataset)

SUBGROUP STATISTIC	POOLED PLACEBO N=1257	POOLED DAPA 2.5 MG N=699	POOLED DAPA 5 MG N=1025	POOLED DAPA 10 MG N=1066
BASELINE SEATED SYSTOLIC BLOOD PRESSURE: ≤140 mmHg				
N#	934	491	787	781
BASELINE MEAN (SD)	77.7 (7.56)	77.2 (7.94)	77.3 (8.04)	77.1 (7.93)
WEEK 24 MEAN (SD)	78.0 (8.23)	76.3 (8.49)	76.5 (8.28)	76.2 (8.03)
MEAN CHANGE FROM BASELINE (SD)	0.3 (7.77)	-0.9 (8.04)	-0.8 (7.52)	-0.9 (7.60)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	0.4 (0.265)	-0.5 (0.383)	-0.5 (0.300)	-0.9 (0.300)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[-0.2, 0.9]	[-1.3, 0.2]	[-1.1, 0.0]	[-1.5, -0.3]
DIFFERENCE VS PLACEBO (SE)		-0.9 (0.468)	-0.9 (0.394)	-1.3 (0.396)
95% CI OF DIFFERENCE VS PLACEBO		[-1.8, 0.0]	[-1.7, -0.1]	[-2.0, -0.5]
BASELINE SEATED SYSTOLIC BLOOD PRESSURE: >140 mmHg				
N#	314	203	228	274
BASELINE MEAN (SD)	86.6 (8.63)	85.9 (8.88)	86.5 (7.89)	85.4 (9.37)
WEEK 24 MEAN (SD)	82.9 (8.43)	81.0 (9.28)	80.5 (8.25)	80.0 (9.12)
MEAN CHANGE FROM BASELINE (SD)	-3.7 (8.28)	-4.9 (9.35)	-6.1 (7.75)	-5.4 (9.28)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-3.8 (0.456)	-4.7 (0.579)	-5.8 (0.540)	-5.5 (0.494)
95% CI OF ADJUSTED MEAN CHANGE FROM BASELINE	[-4.7, -2.9]	[-5.8, -3.5]	[-6.9, -4.8]	[-6.4, -4.5]
DIFFERENCE VS PLACEBO (SE)		-0.9 (0.734)	-2.0 (0.703)	-1.7 (0.663)
95% CI OF DIFFERENCE VS PLACEBO		[-2.3, 0.6]	[-3.4, -0.7]	[-3.0, -0.4]

N is the number of patients in the Randomized Patients (BMS studies) or Full Analysis Set (AZ studies).

N# is the number of patients with non-missing baseline and Week 24 (LOCF) values in the Randomized Patients/Full Analysis Set.

Studies in Pooled Mono/Combo Group: MB102013 (monotherapy, QAM and QPM doses combined, excluding Group 2), MB102032 (monotherapy, excluding 1 mg), MB102014 (add-on to metformin), MB102030 (add-on to TZD), D1690C00005 (add-on to SU), D1690C00006 (add-on to insulin), D1690C00012 (add-on to metformin), MB102021, MB102034 (initial combination with metformin, excluding dapagliflozin arm). Based on an ANCOVA model with treatment group, subgroup, and study as categorical factors and interaction between treatment group

Volume Depletion

Events related to volume depletion, captured under PTs of hypovolemia, dehydration or hypotension, were reported in 0.8% and 0.4% of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-term Placebo-controlled Pool ([Table 22](#)). The most commonly reported event was hypotension, probably related to the reductions in blood pressure described in the previous section. None of these events were classified as a SAE. One patient was discontinued because of an event of dehydration and pre-renal azotemia. This patient was on a loop diuretic in the dapagliflozin 10 mg plus insulin group in a pilot Phase 2b add-on to insulin study (MB102009). This patient was the only patient in the entire dapagliflozin clinical program who was discontinued due to an event related to volume depletion. Most (20/27) of these events were mild in intensity in patients treated with dapagliflozin. There was no pattern to the day of onset for these events, with no evidence of a first-dose effect. In general, the duration of these events varied from 1 to 6 days.

Adverse events related to volume depletion (hypotension/dehydration/hypovolemia) were reported for a greater proportion of patients taking loop diuretics at any time after randomization than those not taking loop diuretics at any time ([Table 23](#) and [Table 24](#)). The difference in event rates between dapagliflozin and placebo patients taking loop diuretics was not dose-ordered: 1.8% in the placebo group, and 8.1%, 0%, and 9.7%, for the dapagliflozin 2.5, 5, 10 mg groups, respectively. This difference was driven by a higher proportion of dapagliflozin-treated patients with clinical signs of hypotension compared to the placebo group. Most events of volume depletion in patients treated with concomitant loop diuretics were mild. Time to event and duration of the events were distributed across treatment groups with no pattern.

Table 22: Adverse Events of Volume Depletion (Hypotension/Dehydration/Hypovolemia), Short-term, Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL PATIENTS WITH AN EVENT	5 (0.4)	10 (1.2)	7 (0.6)	9 (0.8)	27 (0.8)
HYPOTENSION	2 (0.1)	6 (0.7)	5 (0.4)	5 (0.4)	16 (0.5)
SYNCOPE	1 (<0.1)	0	0	2 (0.2)	2 (<0.1)
DEHYDRATION	0	3 (0.4)	0	1 (<0.1)	4 (0.1)
URINE FLOW DECREASED	0	0	0	1 (<0.1)	1 (<0.1)
BLOOD PRESSURE DECREASED	1 (<0.1)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	1 (0.1)	2 (0.2)	0	4 (0.1)
URINE OUTPUT DECREASED	1 (<0.1)	1 (0.1)	0	0	1 (<0.1)

MedDRA Version: 13.0

N is the number of treated patients.

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.

Based on a predefined list of events of hypotension/dehydration/hypovolemia.

Table 23: Adverse Events of Volume Depletion (Hypotension/Dehydration/Hypovolemia), Subgroup of Patients Taking Loop Diuretics at Any Time After Randomization, Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Preferred Term (%)	PLA N = 55	DAPA 2.5MG N = 37	DAPA 5MG N = 40	DAPA 10MG N = 31	DAPA TOTAL N = 114
TOTAL PATIENTS WITH AN EVENT	1 (1.8)	3 (8.1)	0	3 (9.7)	7 (6.1)
DEHYDRATION	0	0	0	1 (3.2)	1 (0.9)
HYPOTENSION	0	3 (8.1)	0	1 (3.2)	4 (3.5)
SYNCOPE	0	0	0	1 (3.2)	1 (0.9)
BLOOD PRESSURE DECREASED	1 (1.8)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	0	0	0	1 (0.9)

MedDRA Version: 13.0

N is the number of treated Patients Taking Loop Diuretics at Any Time After Randomization.

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.

Percentages are based on the number of treated patients taking loop diuretics at any time after randomization per treatment group. Based on a predefined list of events of hypotension/dehydration/hypovolemia.

Table 24: Adverse Events of Volume Depletion (Hypotension/Dehydration/Hypovolemia), Subgroup of Patients Not Taking Loop Diuretics at Any Time After Randomization, Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients, (NDA Dataset)

Preferred Term (%)	PLA N = 1338	DAPA 2.5MG N = 777	DAPA 5MG N = 1105	DAPA 10MG N = 1162	DAPA TOTAL N = 3177
TOTAL PATIENTS WITH AN EVENT	4 (0.3)	7 (0.9)	7 (0.6)	6 (0.5)	20 (0.6)
HYPOTENSION	2 (0.1)	3 (0.4)	5 (0.5)	4 (0.3)	12 (0.4)
SYNCOPE	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
URINE FLOW DECREASED	0	0	0	1 (0.1)	1 (<0.1)
DEHYDRATION	0	3 (0.4)	0	0	3 (0.1)
ORTHOSTATIC HYPOTENSION	0	1 (0.1)	2 (0.2)	0	3 (0.1)
URINE OUTPUT DECREASED	1 (0.1)	1 (0.1)	0	0	1 (<0.1)

MedDRA Version: 13.0

N is the number of treated Patients Not Taking Loop Diuretics at Any Time After Randomization.

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.

Percentages are based on the number of treated patients not taking loop diuretics at any time after randomization per treatment group.

Based on a predefined list of events of hypotension/dehydration/hypovolemia.

Adverse events related to volume depletion (hypotension/dehydration/hypovolemia) by age (< 65 years vs ≥ 65 years) (Table 25 and Table 26) were reported in similar proportions of patients as in the overall population (Table 22). The proportion of patients with these events was higher for patients ≥ 65 -years-old and treated with dapagliflozin than for placebo patients ≥ 65 -years-old (Table 26). The difference in event rates between dapagliflozin and placebo patients ≥ 65 -years-old was not dose-ordered: 0.4% in the placebo group, 3.1% in the 2.5-mg group, 0.5% in the 5-mg group, and 1.5% in the 10-mg group. Most events were mild in intensity in both age subgroups. Events of volume depletion in the elderly were infrequent but in patients ≥ 65 , these events occurred early in treatment at a high frequency (4/10 within approximately 2 weeks from the first dose).

Table 25: Adverse Events of Volume Depletion (Hypotension/Dehydration/Hypovolemia), Subgroup of Patients Less Than 65 Years of Age, Short-term Double-blind Treatment Period, Including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Preferred Term (%)	PLA N = 1117	DAPA 2.5MG N = 621	DAPA 5MG N = 929	DAPA 10MG N = 989	DAPA TOTAL N = 2660
TOTAL PATIENTS WITH AN EVENT	4 (0.4)	4 (0.6)	6 (0.6)	6 (0.6)	17 (0.6)
HYPOTENSION	1 (0.1)	1 (0.2)	5 (0.5)	5 (0.5)	11 (0.4)
SYNCOPE	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
BLOOD PRESSURE DECREASED	1 (0.1)	0	0	0	0
DEHYDRATION	0	2 (0.3)	0	0	2 (0.1)
ORTHOSTATIC HYPOTENSION	0	1 (0.2)	1 (0.1)	0	3 (0.1)
URINE OUTPUT DECREASED	1 (0.1)	1 (0.2)	0	0	1 (<0.1)

MedDRA Version: 13.0

N is the number of treated Patients Less Than 65 Years of Age.

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.

Percentages are based on the number of treated Patients Less Than 65 Years of Age per treatment group.

Based on a predefined list of events of hypotension/dehydration/hypovolemia.

Table 26: Adverse Events of Volume Depletion (Hypotension/Dehydration/Hypovolemia), Subgroup of Patients Greater Than or Equal to 65 Years of Age, Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Preferred Term (%)	PLA N = 276	DAPA 2.5MG N = 193	DAPA 5MG N = 216	DAPA 10MG N = 204	DAPA TOTAL N = 631
TOTAL PATIENTS WITH AN EVENT	1 (0.4)	6 (3.1)	1 (0.5)	3 (1.5)	10 (1.6)
DEHYDRATION	0	1 (0.5)	0	1 (0.5)	2 (0.3)
SYNCOPE	0	0	0	1 (0.5)	1 (0.2)
URINE FLOW DECREASED	0	0	0	1 (0.5)	1 (0.2)
HYPOTENSION	1 (0.4)	5 (2.6)	0	0	5 (0.8)
ORTHOSTATIC HYPOTENSION	0	0	1 (0.5)	0	1 (0.2)

MedDRA Version: 13.0

N is the number of treated Patients Greater Than or Equal to 65 Years of Age.

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.

Percentages are based on the number of treated Patients Greater Than or Equal to 65 Years of Age per treatment group.

Based on a predefined list of events of hypotension/dehydration/hypovolemia.

5.4.4.2 Renal Safety

Renal safety was of special interest in the clinical program because dapagliflozin exerts its MOA by inhibiting glucose re-absorption in the kidneys. Renal function can be divided into 5 categories based on an estimate of glomerular filtration rate (eGFR), calculated using the Modification in Diet in Renal Disease Study (MDRD) estimating equation.¹⁸

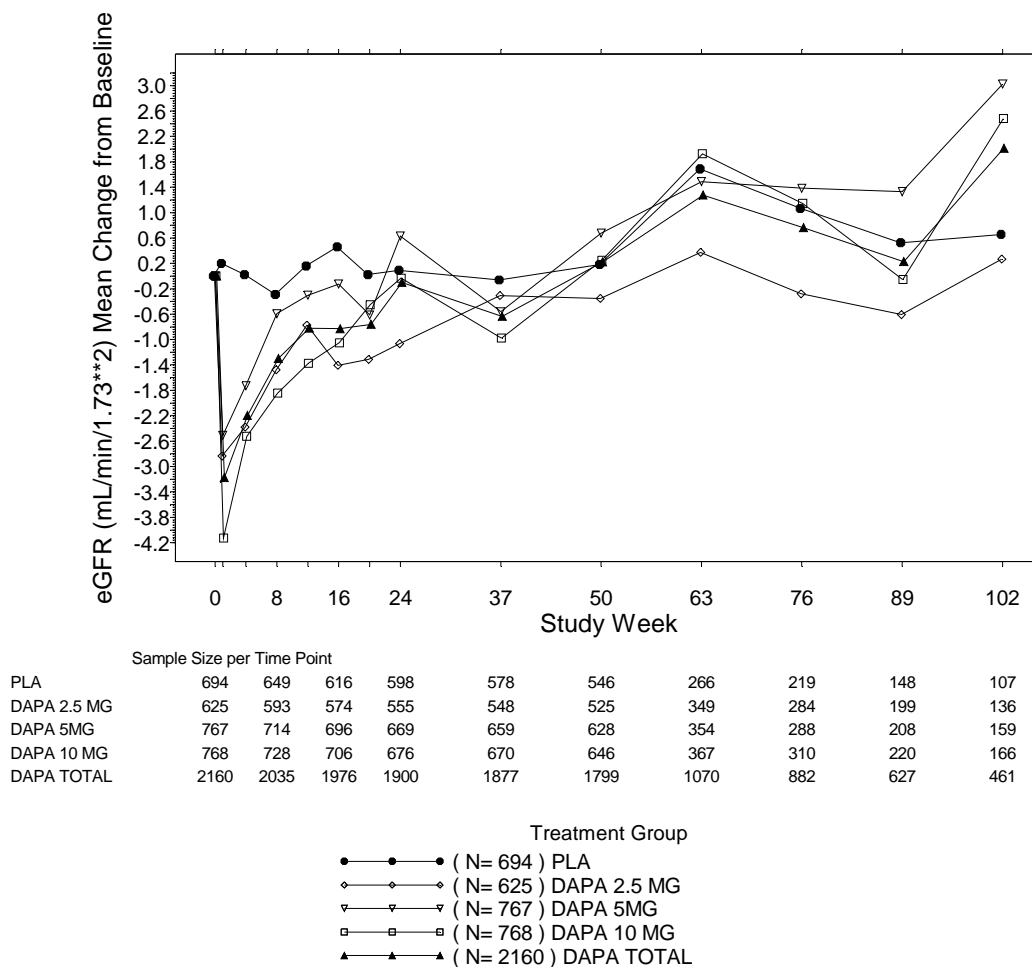
The categories of renal function by eGFR are as follows^{16,17}:

- Normal: $\geq 90 \text{ mL/min/1.73m}^2$
- Mild renal impairment: $\geq 60 \text{ to } < 90 \text{ mL/min/1.73m}^2$
- Moderate renal impairment: $\geq 30 \text{ to } < 60 \text{ mL/min/1.73m}^2$
- Severe renal impairment: $\geq 15 \text{ to } < 30 \text{ mL/min/1.73m}^2$
- Kidney failure: $\leq 15 \text{ mL/min/1.73m}^2$

This section describes the impact of dapagliflozin treatment on various indicators of renal function in the overall clinical program. Dapagliflozin was not studied in patients with severe renal impairment or kidney failure in large controlled studies because a treatment effect was not expected, and use in this population is not recommended.

Small mean decreases in eGFR (estimated by the MDRD equation¹⁸) from baseline were observed in dapagliflozin-treated patients at Week 1 (Figure 20) in the short-term plus long-term Placebo-controlled Pool. Following this initial drop in eGFR, there was a gradual return to baseline without evidence of progressive renal dysfunction. These early decreases in renal function assessments, though small, were dose ordered, and may reflect early, dynamic, auto-regulatory changes related to the mild proximal tubular diuretic effect of dapagliflozin.

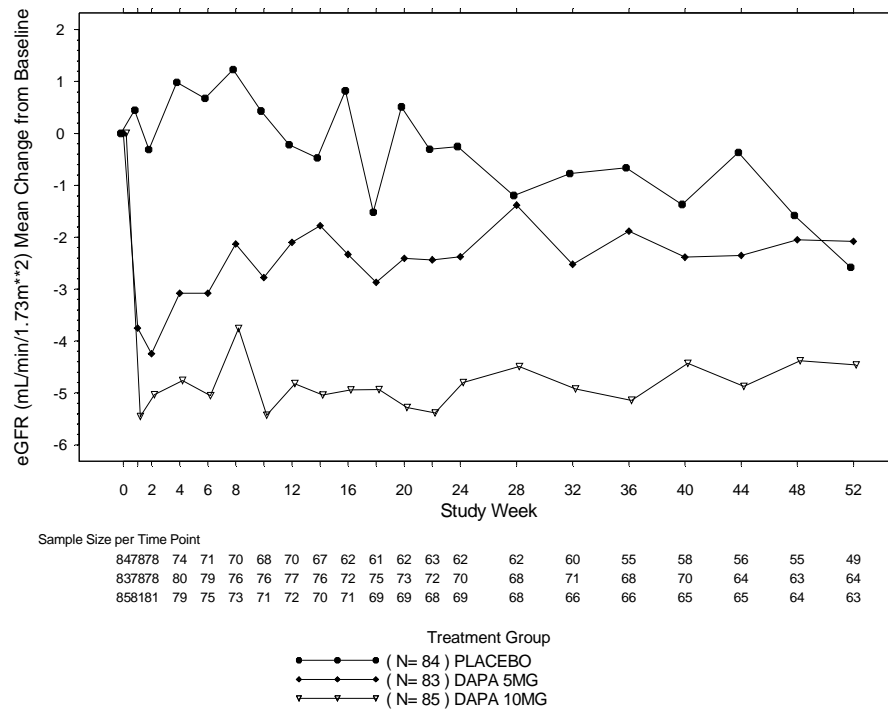
Figure 20: Estimated GFR Mean Change from Baseline Over Time Short-term Plus Long-term Treatment Period including Data after Rescue Placebo-controlled Pool Treated Patients (NDA Dataset)



Treated subjects who took at least one dose of double-blind study medication
Treatment symbols shifted horizontally to prevent overlapping

In the special study of patients with T2DM and moderate renal impairment ($\text{eGFR} \geq 30$ and $< 60 \text{ mL/min/1.73 m}^2$), mean eGFR decreased from baseline to Week 1 in the dapagliflozin 5 and 10 mg groups then stabilized, with mean reductions from baseline at Week 52 that were slightly less than those seen at Week 1 (Figure 21). Patients treated with placebo had a progressive decline in eGFR over 52 weeks.

Figure 21: Estimated GFR (mL/min/1.73m²) Change from Baseline over Time in Special Study of Patients with Moderate Renal Impairment (MB102029), 52-Week Short-term plus Long-term Double-blind Treatment Period, Including Data after Rescue



Treated subjects who took at least one dose of double-blind study medication
Treatment symbols shifted horizontally to prevent overlapping

There was minimal change from baseline in serum creatinine, and changes in blood urea nitrogen (BUN) during the short-term double-blind treatment period were not clinically relevant ([Table 27](#)).

Table 27: Summary Statistics for Serum Creatinine (mg/dL) and Blood Urea Nitrogen (mg/dL), Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients, Week 24 (NDA Dataset)

SERUM CREATININE (MG/DL)						
Period Visit	Treatment Group	N#	Change From Baseline			
			Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1087	-0.005	0.00326	-0.010	0.120
	DAPA 2.5MG	619	0.010	0.00419	0.010	0.130
	DAPA 5MG	899	-0.001	0.00358	0.000	0.120
	DAPA 10MG	935	0.001	0.00344	0.000	0.120
	DAPA TOTAL	2453	0.003	0.00214	0.000	0.120
BLOOD UREA NITROGEN (mg/dL)						
Period Visit	Treatment Group	N#	Change From Baseline			
			Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1087	0.3	0.115	0.0	5.0
	DAPA 2.5MG	619	1.5	0.157	2.0	5.0
	DAPA 5MG	899	1.4	0.136	1.0	5.0
	DAPA 10MG	935	1.6	0.133	1.0	5.0
	DAPA TOTAL	2453	1.5	0.081	1.0	5.0
N# is the number of treated patients with non-missing baseline and Week 24 values.						
DAPA TOTAL includes DAPA 20MG and DAPA 50MG.						

Marked laboratory abnormalities for renal variables were reported by similar proportions of patients in all treatment groups. Variables for assessment of renal function included BUN (≥ 60 mg/dL or Urea > 21.4 mmol/L) and serum creatinine ($\geq 1.5\times$ baseline or ≥ 2.5 mg/dL). Similar proportions of patients in each dapagliflozin group and the placebo group had elevated renal test results based on laboratory values for BUN and creatinine.

Dapagliflozin was not associated with an increased risk of renal impairment. Assessment of AEs associated with renal failure or impairment was based on a pre-specified list of MedDRA preferred terms. AEs of renal impairment or failure were infrequent and balanced across treatment groups during the short-term double-blind treatment period (Table 28). Most of the reported events were small and reversible increases in creatinine, consistent with transient changes in fluid balance. No events of acute tubular necrosis or acute nephritis, suggestive of toxic or allergic nephropathy, were reported for any dapagliflozin-treated patient, and there was no evidence of renal impairment or

progression of diabetic nephropathy. Similar proportions of patients in each dapagliflozin group and the placebo group had elevated renal test results based on laboratory values and/or AEs of renal impairment or failure (Table 29). Similar findings were seen during the long-term treatment periods.

Table 28: Overall Adverse Events of Renal Impairment/Failure, Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool Treated Patients

NUMBER OF PATIENTS WITH AN EVENT (%)

PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
12 (0.9)	11 (1.4)	15 (1.3)	11 (0.9)	38 (1.2)

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.

Based on a predefined list of events of renal impairment/failure.

Table 29: Proportion of Patients with Elevated Renal Tests Based on Measured Laboratory Values and/or Reported Adverse Events of Renal Impairment Short-term Double-blind Treatment Period, including Data after Rescue Placebo-controlled Pool Treated Patients (NDA Dataset)

	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
PATIENTS WITH EITHER REPORTED AE (A) OR MEASURED LABORATORY VALUE (B)	30 (2.2)	21 (2.6)	30 (2.6)	29 (2.4)	83 (2.5)
REPORTED AE ONLY (A)	8 (0.6)	10 (1.2)	8 (0.7)	8 (0.7)	27 (0.8)
MEASURED LABORATORY VALUE ONLY (B)	18 (1.3)	10 (1.2)	15 (1.3)	18 (1.5)	45 (1.4)
BOTH REPORTED AE (A) AND MEASURED LABORATORY VALUE (B)	4 (0.3)	1 (0.1)	7 (0.6)	3 (0.3)	11 (0.3)

(A) Based on SMQ for renal disorders.

(B) Criteria based on either creatinine ≥ 1.5 X PreRx creatinine or creatinine ≥ 2.5 mg/dL

Includes serious and nonserious adverse events with onset on or after the first date/time of short-term double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 30 days or 4 days respectively or on or prior to the first day of long-term treatment if earlier (if appropriate).

Includes lab values measured on/after the first date/time of short-term double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or on or prior to the first day of long-term treatment if earlier (if appropriate). Patients can only be included in one category.

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

5.4.4.3 *Electrolytes and Related Laboratory Findings*

Because of dapagliflozin's mild diuretic effect, changes in serum electrolytes are of clinical interest. No mean changes in sodium, potassium, bicarbonate, or chloride were observed.

Serum uric acid levels consistently decreased in all dapagliflozin groups across the program. Placebo-corrected mean change from baseline ranged from -0.45 mg/dL to -0.8 mg/dL in the monotherapy, low-dose monotherapy, and add-on to metformin studies. In the initial combination with metformin therapy studies, mean changes from baseline were also observed for the combination therapy groups vs the metformin monotherapy groups (-0.75 mg/dL [dapagliflozin 5 mg plus metformin] and -0.72 mg/dL [dapagliflozin 10 mg plus metformin]). Serum uric acid levels were also reduced in the add-on to insulin study, but the changes were of less magnitude than in the other Phase 3 studies. Placebo-corrected mean changes in serum uric acid in this study ranged from -0.19 to -0.24. The clinical relevance of these reductions is not known and the mechanism for the effect is unclear, although an association between glucosuria and increased renal uric acid clearance has been reported in some studies.¹⁹ Summary statistics for serum uric acid for the Placebo-controlled Pool during the short-term double-blind treatment period are presented in [Table 30](#). Mean change from baseline at Week 24 ranged from -0.51 to -0.57 mg/dL in the dapagliflozin-treated groups, with no relationship to dose, compared to 0.11 for placebo.

Table 30: Summary Statistics for Serum Uric Acid (mg/dL), Short-term Double-blind Treatment Period, Including Data After Rescue, Placebo-controlled Pool, Treated Patients

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Max	Change From Baseline				
						25	Median	75	N#		Mean	SE	Median	IQR	
ST TREAT SCS WK 24	PLA	1087	5.39	1.429	1.5	4.40	5.30	6.30	13.2	1087	0.11	0.0277	0.10	1.00	
	DAPA 2.5MG	618	4.87	1.278	2.1	4.00	4.70	5.60	9.6	618	-0.55	0.0390	-0.50	1.20	
	DAPA 5MG	899	4.66	1.348	1.2	3.70	4.50	5.40	10.0	899	-0.51	0.0340	-0.50	1.10	
	DAPA 10MG	935	4.66	1.267	1.2	3.80	4.50	5.40	10.0	935	-0.57	0.0334	-0.50	1.30	
	DAPA TOTAL	2452	4.72	1.302	1.2	3.80	4.60	5.50	10.0	2452	-0.54	0.0204	-0.50	1.20	

N# is the number of treated patients with non-missing baseline and Week t values.
DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Dapagliflozin treatment was associated with small increases in hematocrit with no imbalance in thromboembolic events. These small increases in hematocrit are consistent with a limited reduction in plasma volume and mild diuretic activity, particularly up to 16 weeks of treatment.

Increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed (short-term Placebo-controlled Pool). At Week 24, the mean changes from baseline in hematocrit were 2.15% in the dapagliflozin 10 mg group vs -0.40% in the placebo group. At the same time, hematocrit values > 55% were reported in 1.3% of dapagliflozin 10 mg treated patients vs 0.3% of placebo patients. During short-term plus long-term treatment up to Week 50, the mean changes were 2.51% vs -0.29%, respectively.

Reticulocyte counts were measured in four Phase 3 studies (add-on to glimepiride, add-on to insulin, direct comparison with glipizide, and the body weight and composition). Small transient increases from baseline to Week 1 or 4 in mean reticulocyte counts were observed with dapagliflozin treatment. After Week 4, mean reticulocyte counts began to decrease and at the end of the short-term period, were slightly below baseline levels for all dapagliflozin doses studied.

5.4.5 Bone Health

Because of its renal mechanism of action and potential effects on tubular handling of bone minerals, the effect of dapagliflozin on bone was investigated. Based on nonclinical bone-related findings, evaluation of bone biomarkers, bone mineral density, and events of fracture, dapagliflozin treatment had no overall impact on bone health. There was a potential risk of fracture in the special study in patients with T2DM and moderate renal impairment, particularly in patients with more advanced, stage 3B renal impairment ($\text{eGFR} \geq 30$ and < 45 mL/min/1.73m²). Dapagliflozin is not recommended in patients with stage 3B renal impairment, where the fracture risk appeared to be greatest. Post-marketing surveillance plans for safety assessment of bone health are described in Section 7.

5.4.5.1 Nonclinical Bone-related Findings

Increased trabecular bone accretion was seen in rats in chronic toxicology studies at very high exposures ($\geq 2100\times$ the MRHD [maximum recommended human dose]) in nonclinical studies. No such effects were observed in dogs at $> 3000\times$ the MRHD. As previously discussed in Section 1.4, dapagliflozin has greater selectivity for sodium SGLT2 than SGLT1 in humans (1 vs 1391 nM) compared with rats (3 vs 620 nM). Administration of high doses of dapagliflozin would be expected to lead to off-target inhibition of SGLT1 in the intestines of rats and inhibition of SGLT1 would increase calcium absorption due to fermentation of intestinal glucose subsequent to bacterial growth. The finding of increased trabecular bone accretion in rats only, and at high exposure multiples, indicate that this finding is not relevant to humans.

5.4.5.2 Bone Mineral Density

The effects of dapagliflozin on bone mineral density (BMD) were measured by dual-energy X-ray absorptiometry (DXA) in the body weight and composition study (D1690C00012). The effects of dapagliflozin 10 mg plus metformin on body weight and composition at Week 24 in this study were described previously in Section 4.4. The effects of dapagliflozin 10 mg plus metformin on BMD in this study at Week 50 are reported in this section.

Patients enrolled in this study were post-menopausal women, 55 to 75 years old, and men, 30 to 75 years old. The proportions of men and women were similar in both groups. The endpoint for the effect on BMD was percent change at the lumbar spine, femoral neck, or total hip from baseline to Week 50. A 2% difference in BMD change at Week 50 was selected as an accepted, clinically relevant difference for this endpoint. Three standard locations for BMD measurements were included to evaluate effects on both trabecular (lumbar spine) and cortical (femoral neck and total hip) bone.

Dapagliflozin 10 mg plus metformin treatment at 50 weeks was not associated with any clinically relevant or statistically significant changes in BMD at lumbar spine (L1 – L4), femoral neck, or total hip sites ([Table 31](#)).

Table 31: Adjusted Percent Change in BMD at Lumbar Spine (L1-4), Femoral Neck, and Total Hip from Baseline to Week 50, Safety Analysis Set, Body Weight and Composition Study (03-Feb-2011)

	<u>Lumbar spine (L1-4)</u>		<u>Femoral neck</u>		<u>Total hip</u>	
	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91
Summary statistics						
N#	83	81	83	81	83	81
Baseline mean (SD) [g/cm ²]	1.19 (0.191)	1.18 (0.200)	0.94 (0.137)	0.97 (0.141)	1.06 (0.113)	1.10 (0.136)
Week 50 mean (SD) [g/cm ²]	1.19 (0.198)	1.19 (0.214)	0.94 (0.135)	0.97 (0.147)	1.05 (0.119)	1.10 (0.144)
Mean percent change from baseline (SE)	0.19 (0.3273)	0.29 (0.3518)	0.15 (0.3479)	-0.47 (0.3105)	-0.25 (0.2255)	0.03 (0.4530)
Adjusted percent change from baseline						
Mean (SE)	0.15 (0.3327)	0.25 (0.3377)	0.15 (0.3333)	-0.47 (0.3346)	-0.23 (0.3578)	-0.02 (0.3614)
95% two-sided CI	[-0.50, 0.81]	[-0.41, 0.92]	[-0.51, 0.81]	[-1.13, 0.19]	[-0.94, 0.48]	[-0.73, 0.70]
Difference in adjusted percent change from baseline vs PLA + MET						
Mean (SE)		0.10 (0.4725)		-0.62 (0.4703)		0.22 (0.5130)
95% two-sided CI		[-0.83, 1.04]		[-1.54, 0.32]		[-0.79, 1.24]
p-value vs. PLA + MET		0.8318		0.1926		0.6713

N is the number of patients in the safety analysis set.

N# is the number of patients in the safety analysis set with non-missing baseline and Week 50 values.

Based on ANCOVA model with treatment group and stratum as effect and baseline value as a covariate.

A larger decrease in BMD in the femoral neck location was noted in women treated with dapagliflozin compared to placebo. The femoral neck is a difficult region to measure BMD, with high variability due to the narrow anatomical target area. Overall, the placebo-corrected difference was small and within the expected examination variability, with a 95% CI that included zero.

5.4.5.3 Laboratory Evaluation of Bone Health

No clinically important changes were observed for mean serum concentrations of calcium. Changes in mean urinary calcium levels were inconsistent and not dose ordered.

Small mean increases from baseline in mean serum phosphorus levels were observed with dapagliflozin. The mean increase in the 10-mg group was 0.17 mg/dL compared to 0.03 mg/dL for placebo at Week 24 ([Table 32](#)). Similar results were seen at Week 50. These results were compatible with agents inhibiting the family of SGLT transporters, such as phlorizin, which have been reported to enhance tubular phosphate transport.²⁰

Small mean increases in magnesium plasma levels were observed in some studies; however, the difference between dapagliflozin treatment groups and placebo was minimal (0.05 to 0.07 mEq/L in the dapagliflozin groups and -0.04 mEq/L in the placebo groups at Week 24) and was not considered to be clinically relevant ([Table 33](#)).

Mean changes from baseline in parathyroid (PTH) levels tended to be slightly higher in the dapagliflozin groups compared to placebo at Week 24, but were still within the normal range (-0.6 pg/mL in the placebo group, and 1.8 to 2.6 pg/mL in each dapagliflozin group) ([Table 34](#)). These changes were not dose-ordered.

No clinically important changes were observed for mean serum concentrations 25-hydroxyvitamin D (25[OH]VitD) or 1,25-dihydroxyvitamin D (1,25[OH]VitD).

Table 32: Summary Statistics for Inorganic Phosphorus (mg/dL), Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Period Visit	Treatment Group	N#	Mean	SD	Percentiles					Change From Baseline				
					Min	25	Median	75	Max	N#	Mean	SE	Median	IQR
PRE ST TREAT BASELINE	PLA	1393	3.59	0.506	1.9	3.30	3.60	3.90	5.1		0			
	DAPA 2.5MG	814	3.55	0.538	1.7	3.20	3.50	3.90	5.3		0			
	DAPA 5MG	1145	3.58	0.499	1.7	3.20	3.60	3.90	5.9		0			
	DAPA 10MG	1193	3.58	0.517	2.0	3.20	3.60	3.90	5.7		0			
	DAPA TOTAL	3291	3.58	0.519	1.7	3.20	3.60	3.90	5.9		0			
ST TREAT SCS WK 24	PLA	1087	3.62	0.524	2.0	3.30	3.60	4.00	5.4	1087	0.03	0.0155	0.00	0.60
	DAPA 2.5MG	618	3.63	0.510	2.4	3.30	3.60	3.90	5.9	618	0.10	0.0201	0.10	0.60
	DAPA 5MG	898	3.74	0.516	2.1	3.40	3.70	4.10	5.3	898	0.16	0.0174	0.10	0.70
	DAPA 10MG	935	3.74	0.513	2.1	3.40	3.70	4.10	5.5	935	0.17	0.0161	0.20	0.60
	DAPA TOTAL	2451	3.71	0.515	2.1	3.40	3.70	4.10	5.9	2451	0.15	0.0102	0.10	0.70

N# is the number of treated patients with non-missing baseline and Week t values.
DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Table 33: Summary Statistics for Magnesium (mEq/L), Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Period Visit	Treatment Group	N#	Mean	SD	Percentiles					Change From Baseline				
					Min	25	Median	75	Max	N#	Mean	SE	Median	IQR
PRE ST TREAT BASELINE	PLA	1393	1.71	0.227	1.1	1.60	1.70	1.80	3.2	0				
	DAPA 2.5MG	814	1.73	0.233	0.9	1.60	1.70	1.80	2.7	0				
	DAPA 5MG	1145	1.72	0.239	0.8	1.60	1.70	1.80	2.8	0				
	DAPA 10MG	1193	1.71	0.245	1.0	1.60	1.70	1.80	3.3	0				
	DAPA TOTAL	3291	1.71	0.237	0.8	1.60	1.70	1.80	3.3	0				
ST TREAT SCS WK 24	PLA	1087	1.65	0.179	0.9	1.50	1.60	1.80	2.6	1087	-0.04	0.0058	0.00	0.20
	DAPA 2.5MG	619	1.75	0.196	1.2	1.60	1.70	1.80	2.8	619	0.05	0.0091	0.10	0.20
	DAPA 5MG	898	1.75	0.204	1.0	1.60	1.70	1.80	3.3	898	0.07	0.0074	0.10	0.20
	DAPA 10MG	936	1.75	0.178	1.0	1.70	1.70	1.80	2.7	936	0.07	0.0076	0.10	0.20
	DAPA TOTAL	2453	1.75	0.192	1.0	1.60	1.70	1.80	3.3	2453	0.06	0.0046	0.10	0.20

N# is the number of treated patients with non-missing baseline and Week t values.
DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Table 34: Summary Statistics for Parathyroid Hormone (pg/mL), Short-term Double-blind Treatment Period, including Data after Rescue, Placebo-controlled Pool, Treated Patients (NDA Dataset)

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Change From Baseline				
						25	Median	75	Max	N#	Mean	SE	Median	IQR
PRE ST TREAT BASELINE	PLA	1373	36.6	18.95	3	24.0	33.0	46.0	265		0			
	DAPA 2.5MG	797	38.9	18.48	3	26.0	35.0	48.0	137		0			
	DAPA 5MG	1123	37.2	19.36	3	24.0	34.0	46.0	196		0			
	DAPA 10MG	1169	37.7	19.36	3	24.0	34.0	47.0	145		0			
	DAPA TOTAL	3227	37.6	19.01	3	24.0	34.0	47.0	196		0			
ST TREAT SCS WK 24	PLA	1069	35.8	20.00	3	23.0	32.0	44.0	243	1069	-0.6	0.502	-1.0	16.0
	DAPA 2.5MG	598	40.7	21.32	3	26.0	36.0	49.0	155	598	2.6	0.681	2.0	19.0
	DAPA 5MG	879	38.2	18.11	5	25.0	35.0	48.0	127	879	1.9	0.516	2.0	16.0
	DAPA 10MG	914	39.5	21.86	3	25.0	36.0	49.0	271	914	1.8	0.583	1.0	17.0
	DAPA TOTAL	2391	39.3	20.43	3	25.0	35.0	49.0	271	2391	2.0	0.339	2.0	17.0

N# is the number of treated patients with non-missing baseline and Week t values.
DAPA TOTAL includes DAPA 20MG and DAPA 50MG.

Biomarkers of bone formation and resorption were evaluated in five Phase 3 studies (monotherapy, add-on to metformin, add-on to pioglitazone, low-dose monotherapy, body weight and composition studies; Table 35).

Table 35: Overview of Bone Marker Assessments in Dapagliflozin Phase 3 Studies

Study/Table Number	<u>Markers of Bone Resorption</u>				<u>Markers of Bone Formation</u>		
	Serum CTX	Urine CTX	Serum NTX	Urine NTX	Serum OC	Serum P1NP	Serum BAP
Monotherapy	X	–	X	–	X	X	–
Add-on to metformin	X	–	X	–	X	X	–
Add-on to pioglitazone	X	–	X	–	X	X	–
Low-dose monotherapy	X	–	X	–	X	X	–
Body weight & composition	X	X	X	X	X	X	X

BAP = bone alkaline phosphatase, CTX = type I collagen crosslinked C-telopeptide, NTX = type I collagen crosslinked N-telopeptide, OC = osteocalcin, P1NP = Procollagen type 1 propeptide

Mean changes from baseline in the markers of bone resorption were found to be slightly higher in dapagliflozin-treated patients compared to placebo-treated patients in some but not all studies. The most complete results for evaluation of bone markers are from the body weight and composition study (D1690C00012), presented in [Table 36](#) and [Table 37](#). No meaningful mean changes from baseline to Week 50 in osteocalcin, bone-specific alkaline phosphatase, or procollagen type-1 N-terminal propeptide were demonstrated in dapagliflozin-treated patients, while in the placebo group a mean decrease of all bone formation markers was observed (Table 36).

Table 36: Adjusted Mean Change in Bone Formation Markers from Baseline to Week 50, Safety Analysis Set, Body Weight and Composition Study (03-Feb-2011)

	Osteocalcin [ng/mL]		Bone-specific ALP [U/L]		P1NP [µg/L]	
	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91
Summary statistics						
N#	76	78	80	78	77	78
Baseline mean (SD)	15.20 (5.598)	14.07 (4.944)	17.03 (6.261)	17.06 (5.330)	28.19 (13.471)	26.72 (10.480)
Week 50 mean (SD)	13.21 (4.932)	13.67 (4.276)	15.42 (4.798)	16.26 (6.513)	24.45 (10.608)	25.93 (10.366)
Mean change from baseline (SE)	-1.99 (4.132)	-0.40 (3.329)	-1.61 (3.803)	-0.80 (4.841)	-3.74 (11.128)	-0.79 (8.282)
Adjusted change from baseline						
Mean (SE)	-1.77 (0.3716)	-0.61 (0.3657)	-1.60 (0.4488)	-0.78 (0.4545)	-3.38 (0.9371)	-1.11 (0.9299)
95% two-sided CI	[-2.51, -1.04]	[-1.33, 0.12]	[-2.49, -0.72]	[-1.68, 0.11]	[-5.24, -1.53]	[-2.94, 0.73]
Difference in adjusted change from baseline vs. PLA + MET						
Mean (SE)		1.17 (0.5219)		0.82 (0.6378)		2.28 (1.3191)
95% two-sided CI		[0.13, 2.20]		[-0.44, 2.08]		[-0.33, 4.88]
p-value vs. PLA + MET		0.0269		0.2001		0.0862

N is the number of patients in the safety analysis set; N# is the number of patients in the safety analysis set with non-missing baseline and Week 50 values.

Based on ANCOVA model with treatment group and stratum as effect and baseline value as a covariate.

PLA = placebo; DAPA = dapagliflozin; MET = metformin; ALP = alkaline phosphatase; P1NP = Procollagen type-1 N-terminal propeptide

Patients in the dapagliflozin group also showed a mean increase in C-terminal cross-linking telopeptides of type I collagen (CTX) in serum (0.04 [95% CI: 0.02, 0.07] ng/mL) and a mean decrease in N-terminal cross-linking telopeptides of type I collagen (NTX) in urine (−41.7 [95% CI: −71.8, −11.7] nmol BCE) from baseline to Week 50 ([Table 37](#)). Patients in the placebo group showed mean changes of both variables in the same direction but of smaller magnitude compared to patients in the dapagliflozin group, but were not clinically relevant change from baseline to Week 50 in both treatment groups. Overall, no clinically relevant changes in markers of bone formation and resorption were observed ([Table 36](#) and Table 37).

Table 37: Adjusted Mean Change in Bone Resorption Markers from Baseline to Week 50, Safety Analysis Set, Body Weight and Composition Study (03-Feb-2011)

	Serum CTX [ng/mL]		Serum NTX [nm/BCE]		Urine CTX (µg/L)		Urine NTX [nmol BCE]	
	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91	PLA + MET N = 91	DAPA 10MG + MET N = 91
Summary statistics								
N#	76	78	80	80	78	79	78	80
Baseline mean (SD)	0.24 (0.132)	0.22 (0.123)	8.91 (2.404)	9.00 (2.396)	10.49 (9.891)	8.76 (5.613)	314.4 (185.44)	275.2 (136.76)
Week 50 mean (SD)	0.26 (0.154)	0.26 (0.113)	8.34 (2.709)	8.64 (3.685)	10.21 (7.511)	9.86 (5.672)	271.4 (166.58)	243.4 (129.43)
Mean change from baseline (SE)	0.02 (0.140)	0.04 (0.106)	-0.57 (2.948)	-0.36 (4.063)	-0.27 (9.204)	1.10 (6.258)	-43.0 (174.39)	-31.8 (161.42)
Adjusted change from baseline								
Mean (SE)	0.02 (0.0128)	0.04 (0.0126)	-0.55 (0.3530)	-0.29 (0.3527)	0.31 (0.6843)	0.58 (0.6802)	-29.1 (15.389)	-41.7 (15.209)
95% two-sided CI	[-0.00, 0.05]	[0.02, 0.07]	[-1.25, 0.14]	[-0.99, 0.41]	[-1.04, 1.66]	[-0.76, 1.92]	[-59.5, 1.3]	[-71.8, -11.7]
Difference in adjusted change from baseline vs PLA + MET								
Mean (SE)		0.02 (0.0179)		0.26 (0.4973)		0.27 (0.9646)		-12.6 (21.643)
95% two-sided CI		[-0.02, 0.05]		[-0.72, 1.25]		[-1.63, 2.18]		[-55.4, 30.1]
p-value vs PLA + MET		0.3338		0.5958		0.7771		0.5599

N is the number of patients in the safety analysis set. N# is the number of patients in the safety analysis set with non-missing baseline and week 50 values.

Based on ANCOVA model with treatment group and stratum as effect and baseline value as a covariate.

CTX = C-terminal cross-linking telopeptides of type I collagen; NTX = N-terminal cross-linking telopeptides of type I collagen; PLA = placebo; DAPA = dapagliflozin; MET = metformin

5.4.5.4 Events of Fracture in the Overall Study Population

There was no increase in events of fractures in patients treated with dapagliflozin in the overall clinical development program (Table 38). The proportions of patients with fractures in the All Phase 2b and 3 Pool and in the short-term plus long-term Placebo-controlled Pool up to the 4MSU were small and balanced between the dapagliflozin and placebo/comparator groups. There was no relationship to dose. Few of these events led to discontinuation of study drug.

Table 38: Number and Percent of Patients with Events of Fracture in the Phase 2b and 3 Clinical Program, Short-term plus Long-term Treatment, Treated Patients (4MSU Dataset)

	N	n (%) Events of Fracture
All Phase 2b and 3 Pool		
Dapagliflozin Total	4310	56 (1.3)
All Control	1962	25 (1.3)
Placebo-controlled Pool^a		
2.5 mg Dapagliflozin	625	9 (1.4)
5 mg Dapagliflozin	767	12 (1.6)
10 mg Dapagliflozin	859	11 (1.3)
Placebo	785	12 (1.5)

a 6-study pool from the 4MSU described in Section 3.2.2.4: monotherapy, add-on to metformin, add-on to glimepiride, add-on to pioglitazone, add-on to insulin, and body weight and composition.

There was no specific pattern in the anatomical site of fracture; the most common anatomical locations of fractures were the foot and ankle (Table 39).

Table 39: Adverse Events of Fracture, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (4MSU Dataset)

	DAPA TOTAL	ALL CONTROL
Preferred Term (%)	N = 4310	N = 1962
TOTAL PATIENTS WITH AN EVENT	56 (1.3)	25 (1.3)
FOOT FRACTURE	10 (0.2)	2 (0.1)
ANKLE FRACTURE	8 (0.2)	4 (0.2)
TRAUMATIC FRACTURE	7 (0.2)	0
HAND FRACTURE	4 (<0.1)	2 (0.1)
UPPER LIMB FRACTURE	4 (<0.1)	1 (<0.1)
WRIST FRACTURE	4 (<0.1)	1 (<0.1)
FACIAL BONES FRACTURE	3 (<0.1)	0
HUMERUS FRACTURE	3 (<0.1)	2 (0.1)
RADIUS FRACTURE	3 (<0.1)	3 (0.2)
BONE FISSURE	2 (<0.1)	0
HIP FRACTURE	2 (<0.1)	1 (<0.1)
JAW FRACTURE	1 (<0.1)	0
LOWER LIMB FRACTURE	1 (<0.1)	0
LUMBAR VERTEBRAL FRACTURE	1 (<0.1)	2 (0.1)
MULTIPLE FRACTURES	1 (<0.1)	0

MedDRA Version: 13.1

N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on a predefined list of events of fracture.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, and D1690C00012.

5.4.5.5 Events of Fracture in Patients with Moderate Renal Impairment

Events of fracture were reported for 12 patients treated with dapagliflozin and none treated with placebo in the special study in patients with T2DM and moderate renal impairment (Table 40). Four of the patients with events of fracture in the special study (4.8%) were classified as stage 3A (2 in the 5 mg group, 2 in the 10 mg group) and 8 (9.4%) as stage 3B (2 in the 5 mg group, 6 in the 10 mg group) renal impairment. One of the 12 patients in the moderate renal impairment study had a hip fracture (Table 40). Four of these patients had foot fractures and one had a patellar fracture, anatomical locations not usually associated with osteoporotic fractures.

When patients with moderate renal impairment from the Placebo-controlled Pool and from the study in diabetic patients with moderate renal impairment from the 4MSU were combined, as described in Section 3.2.2.5, the number of patients with fractures in the 3A Subgroup was small and similar for patients on dapagliflozin and placebo ([Table 41](#)). The anatomical location of fractures in the special study in patients with T2DM and moderate renal impairment ([Table 40](#)) was similar to those in the combined stage 3A ([Table 41](#)) and 3B subgroups ([Table 42](#)).

Table 40: Adverse Events of Fracture, Short-term Plus Long-term Plus Long-term Treatment, Special Study in Patients with Moderate Renal Impairment. Including Data after Rescue, Treated Patients (4MSU)

Preferred Term (%)	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL PATIENTS WITH AN EVENT	0	4 (4.8)	8 (9.4)
FOOT FRACTURE	0	3 (3.6)	1 (1.2)
HIP FRACTURE	0	0	1 (1.2)
LUMBAR VERTEBRAL FRACTURE	0	0	1 (1.2)
PATELLA FRACTURE	0	0	1 (1.2)
RADIUS FRACTURE	0	0	1 (1.2)
TRAUMATIC FRACTURE	0	0	1 (1.2)
UPPER LIMB FRACTURE	0	0	1 (1.2)
WRIST FRACTURE	0	0	1 (1.2)
HUMERUS FRACTURE	0	1 (1.2)	0

MedDRA Version: 13.1

N is the number of treated patients.

Includes non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term plus long-term extension treatment plus 4 days, or before the data cutoff if earlier.

Includes serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term plus long-term extension treatment plus 30 days, or before the data cutoff if earlier.

Based on a predefined list of events of fracture.

Table 41: Adverse Events of Fracture, Short-term Plus Long-term Treatment, Including Data After Rescue, Placebo-controlled Pool plus the Special Study in Patients with Moderate Renal Impairment, Treated Patients with Baseline eGFR ≥ 45 and < 60 mL/min/1.73m² (3A Subgroup) (4MSU)

Preferred Term (%)	PLA N = 109	DAPA 2.5MG N = 65	DAPA 5MG N = 110	DAPA 10MG N = 93	DAPA TOTAL N = 268
TOTAL PATIENTS WITH AN EVENT	2 (1.8)	1 (1.5)	4 (3.6)	2 (2.2)	7 (2.6)
LUMBAR VERTEBRAL FRACTURE	0	0	0	1 (1.1)	1 (0.4)
RADIUS FRACTURE	0	0	0	1 (1.1)	1 (0.4)
FOOT FRACTURE	1 (0.9)	0	3 (2.7)	0	3 (1.1)
HUMERUS FRACTURE	1 (0.9)	0	0	0	0
MULTIPLE FRACTURES	0	1 (1.5)	0	0	1 (0.4)
TRAUMATIC FRACTURE	0	0	1 (0.9)	0	1 (0.4)

MedDRA Version: 13.1

N is the number of treated patients with baseline eGFR ≥ 45 and < 60 mL/min/1.73m².

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment

and on or prior to the last day of short-term plus long-term treatment plus 30 days

(or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on a predefined list of events of fracture.

Table 42: Adverse Events of Fracture, Short-term Plus Long-term Treatment, Including Data After Rescue, Placebo-controlled Pool plus the Special Study in Patients with Moderate Renal Impairment, Treated Patients with Baseline eGFR ≥ 30 and < 45 mL/min/1.73m² (3B Subgroup) (4MSU)

Preferred Term (%)	PLA N = 43	DAPA 2.5MG N = 7	DAPA 5MG N = 54	DAPA 10MG N = 62	DAPA TOTAL N = 123
TOTAL PATIENTS WITH AN EVENT	0	0	2 (3.7)	6 (9.7)	8 (6.5)
FOOT FRACTURE	0	0	1 (1.9)	1 (1.6)	2 (1.6)
HIP FRACTURE	0	0	0	1 (1.6)	1 (0.8)
PATELLA FRACTURE	0	0	0	1 (1.6)	1 (0.8)
TRAUMATIC FRACTURE	0	0	0	1 (1.6)	1 (0.8)
UPPER LIMB FRACTURE	0	0	0	1 (1.6)	1 (0.8)
WRIST FRACTURE	0	0	0	1 (1.6)	1 (0.8)
HUMERUS FRACTURE	0	0	1 (1.9)	0	1 (0.8)

MedDRA Version: 13.1

N is the number of treated patients with baseline eGFR ≥ 30 and < 45 mL/min/1.73 m².

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment.

and on or prior to the last day of short-term plus long-term treatment plus 30 days or 4 days, respectively

Based on a predefined list of events of fracture.

5.4.5.6 Summary of Bone Health

Treatment with dapagliflozin had no overall impact on bone health. Fracture adverse event rates across the entire clinical program, including all patients with varying degrees of renal impairment, were balanced between dapagliflozin and comparators. Results from a 1-year bone densitometry assessment demonstrated no differences in bone mineral density between dapagliflozin and placebo patients. There was a potential risk of fracture in the special study in patients with T2DM and moderate renal impairment, particularly in patients with more advanced, stage 3B renal impairment ($\text{eGFR} \geq 30$ and $< 45 \text{ mL/min/1.73m}^2$). Dapagliflozin is not recommended in patients with stage 3B renal impairment, where the fracture risk appeared to be greatest.

5.5 Other Safety Findings

5.5.1 Malignancies

This section provides an analysis of the overall incidences of unspecified and malignant neoplasm in the Pooled All Phase 2b and Phase 3 data using the initial NDA and 4MSU datasets as well as relevant nonclinical information. As part of the ongoing assessment of these events, additional integrated data through 12-May-2011 (Integrated Cancer Summary [ICS] dataset) described in Section 3.2.2.6, are also included in this section. Based on the 12-May-2011 ICS dataset, the overall incidence rates of unspecified and malignant neoplasms are similar between dapagliflozin and control. Some individual cancer types were more common with comparator than with dapagliflozin, while others were more common for dapagliflozin than comparator. Two types of cancer—breast and bladder cancer—will be discussed in detail in this section.

In the NDA dataset, bladder cancer was reported in 7 patients treated with dapagliflozin and 0 in the control group. Breast cancer was also reported more frequently with dapagliflozin than control (9 and 1, respectively). In addition to these data based on analysis of the 12-May-2011 ICS dataset cut, several clinical studies of dapagliflozin (amounting to approximately 1800 additional patients) are ongoing. Three recently diagnosed cases of bladder cancer have been recorded during the first 6 months of these studies, and these cases have been characterized and unblinded in order to provide the most up-to-date assessment of bladder cancer cases as is feasible for this evolving safety

assessment. Two of these cases were in patients treated with dapagliflozin and the other, with control. These cases and estimated exposure from the ongoing studies were included in the analysis of bladder cancer.

With the inclusion of these most recent and up-to-date data, both breast cancer and bladder cancer occurred in 10 patients, with 9 patients treated with dapagliflozin per each tumor type. For breast cancer, this 9:1 distribution compares to an expected distribution of about 6.9:3.1, if allocation of the 10 cases had occurred purely due to chance, since 69% of patient follow-up was in the dapagliflozin group. For bladder cancer, this 9:1 is compares to an expected distribution of 6.5:3.5, since 65% of patient follow-up was in the dapagliflozin group. The observed distributions of 9:1 are consistent with a wide range of incremental risk estimates, including some that favor dapagliflozin, making it difficult to draw a conclusion based on statistical grounds alone.

This section also addresses many important considerations regarding malignancy and the observed current imbalances in breast and bladder cancer. An examination of these individual malignancy cases revealed typical clinical features, with many cases occurring early in the course of treatment. A biologic hypothesis for a potential association between dapagliflozin and either tumor type has not been identified. Both breast and bladder cancer are readily detectable in animal models of carcinogenesis, but neither were observed in the 2-year carcinogenicity studies with dapagliflozin. Dapagliflozin is not genotoxic, and rigorous 2-year carcinogenicity studies in mice and rats did not demonstrate preneoplastic or neoplastic changes. The direct pharmacologic effect of dapagliflozin, glucosuria, would not be expected to increase the risk of cancer, and no indirect effects that could increase the risk of cancer have been identified. Thus, these data suggest that dapagliflozin is not carcinogenic.

For 2 tumor types—breast and bladder cancer—further evaluation is indicated based on limited observations to date. More definitive information using approaches to identify additional data, consisting of future clinical trials (including a large post-marketing CV outcomes trial) and pharmacoepidemiology surveillance studies utilizing administrative claims databases, will be conducted. The ability of these studies to rule out excess risk is discussed further in Section 7.1.

5.5.1.1 Overall Malignant or Unspecified Tumors

[Table 43](#) shows an overview of malignant and unspecified tumors by safety dataset, the data cutoff date for the each dataset, the cumulative follow-up time for patients with an event in patient-years, and the proportion of patients with an event of malignant and unspecified tumors up to that time point.

Events of malignant or unspecified tumors were identified from the Standardized MedDRA Query (SMQ), Malignant or Unspecified Tumors, and included tumors of the skin, breast, bladder, prostate, gastrointestinal tract, thyroid gland and other endocrine organs, respiratory system and mediastinum, pancreas, blood and lymphatic system, liver and bile ducts, female reproductive system, and renal tract, and metastatic or unspecified tumors.

Malignant and unspecified tumors were observed more frequently in patients treated with dapagliflozin than control in the All Phase 2b and 3 Pool for both the initial NDA and the 4MSU. With additional data collected since the 4MSU, these differences are smaller, and the overall incidence rates were similar between dapagliflozin and control.

In each analysis, an imbalance in overall malignancies was largely driven by events attributable to breast cancer and to bladder cancer. In the 12-May-2011 ICS dataset, this imbalance was offset by more frequent reports of other types of malignancy in the control group.

Comparative incidence rates for specific cancer types varied. Lower absolute incidence rates in dapagliflozin-treated patients compared to control were observed for some cancer types: skin, respiratory and mediastinal, blood and lymphatic, female reproductive cancers, metastases and unspecified sites, and renal tract cancers. Lower absolute incidence rates in control patients compared to dapagliflozin were observed in breast and bladder cancer, prostate, thyroid and endocrine, gastrointestinal, pancreatic, hepatobiliary, and musculoskeletal cancers.

In the 12-May-2011 ICS dataset, reports of events of malignant and unspecified tumors were 1.4% of dapagliflozin-treated patients vs 1.3% of control patients, corresponding to an estimated incidence rate of 1310 per 100,000 patient-years for dapagliflozin treated patients and 1240 per 100,000 patient-years for control. These data are highlighted in grey in [Table 44](#).

Table 43: Overview of Events of Malignant and Unspecified Tumors by Organ Category by Dataset (NDA, 4MSU, 12-May-2011)**Initial NDA (DATA CUT-OFF DATE: 25-June-2011)**

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4287					ALL CONTROL N = 1941				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
PATIENTS WITH EVENTS	60 (1.4)	NA*	NA*	NA*	NA*	19 (1.0)	NA*	NA*	NA*	NA*

*These additional analyses were not performed for the initial NDA.

4MSU (DATA CUT-OFF DATE: 15-Oct-2011)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4310					ALL CONTROL N = 1962				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
PATIENTS WITH EVENTS	64 (1.48)	(1.15, 1.89)	4620.68	1.39	(1.07, 1.77)	21 (1.07)	(0.66, 1.63)	2023.88	1.04	(0.64, 1.59)

Table 43: Overview of Events of Malignant and Unspecified Tumors by Organ Category by Dataset (NDA, 4MSU, 12-May-2011)**May 12 ICS DATABASE (DATA CUT-OFF DATE: 12-May-2011)**

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
PATIENTS WITH EVENTS	65 (1.43)	(1.10, 1.81)	4976.80	1.31	(1.01, 1.66)	29 (1.30)	(0.87, 1.85)	2348.02	1.24	(0.83, 1.77)

MedDRA Version: 13.0 for NDA; 13.1 for 4MSU; and 14.0 for 12-MAY; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or Dataset snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
PATIENTS WITH EVENTS	65 (1.43)	(1.10, 1.81)	4976.80	1.31	(1.01, 1.66)	29 (1.30)	(0.87, 1.85)	2348.02	1.24	(0.83, 1.77)
SKIN	12 (0.26)	(0.14, 0.46)	5005.81	0.24	(0.12, 0.42)	8 (0.36)	(0.15, 0.70)	2358.06	0.34	(0.15, 0.67)
BASAL CELL CARCINOMA	7 (0.15)					6 (0.27)				
MALIGNANT MELANOMA	2 (0.04)					1 (0.04)				
KERATOACANTHOMA	1 (0.02)					0 (0.00)				
NEOPLASM SKIN	1 (0.02)					0 (0.00)				
SQUAMOUS CELL CARCINOMA OF SKIN	1 (0.02)					0 (0.00)				
BOWEN'S DISEASE	0 (0.00)					2 (0.09)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
BREAST (FEMALES ONLY)	9 (0.40)	(0.19, 0.77)	2416.28	0.37	(0.17, 0.71)	1 (0.09)	(0.00, 0.53)	1084.53	0.09	(0.00, 0.51)
BREAST CANCER	9 (0.40)					1 (0.09)				
PROSTATE (MALES ONLY)	8 (0.34)	(0.15, 0.67)	2587.97	0.31	(0.13, 0.61)	2 (0.17)	(0.02, 0.61)	1277.54	0.16	(0.02, 0.57)
PROSTATE CANCER	6 (0.26)					2 (0.17)				
NEOPLASM PROSTATE	1 (0.04)					0 (0.00)				
PROSTATE CANCER RECURRENT	1 (0.04)					0 (0.00)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
BLADDER	7 (0.15)	(0.06, 0.32)	5012.28	0.14	(0.06, 0.29)	0 (0.00)	(0.00, 0.16)	2363.01	0.00	(0.00, 0.16)
BLADDER TRANSITIONAL CELL CARCINOMA	3 (0.07)					0 (0.00)				
BLADDER CANCER	2 (0.04)					0 (0.00)				
BLADDER NEOPLASM	1 (0.02)					0 (0.00)				
BLADDER TRANSITIONAL CELL CARCINOMA STAGE II	1 (0.02)					0 (0.00)				
TRANSITIONAL CELL CARCINOMA	1 (0.02)					0 (0.00)				
THYROID AND ENDOCRINE	7 (0.15)	(0.06, 0.32)	5009.67	0.14	(0.06, 0.29)	3 (0.13)	(0.03, 0.39)	2360.73	0.13	(0.03, 0.37)
THYROID NEOPLASM	7 (0.15)					3 (0.13)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
THYROID CANCER	0 (0.00)					1 (0.04)				
GASTROINTESTINAL	6 (0.13)	(0.05, 0.29)	5012.11	0.12 (0.04, 0.26)		2 (0.09)	(0.01, 0.32)	2361.95	0.08 (0.01, 0.31)	
COLON CANCER	2 (0.04)					2 (0.09)				
GASTRIC CANCER	2 (0.04)					0 (0.00)				
COLON NEOPLASM	1 (0.02)					0 (0.00)				
RECTOSIGMOID CANCER	1 (0.02)					0 (0.00)				
RESPIRATORY AND MEDIASTINAL	5 (0.11)	(0.04, 0.26)	5014.86	0.10 (0.03, 0.23)		5 (0.22)	(0.07, 0.52)	2361.27	0.21 (0.07, 0.49)	
LUNG NEOPLASM	2 (0.04)					3 (0.13)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
LUNG NEOPLASM MALIGNANT	2 (0.04)					1 (0.04)				
MEDIASTINUM NEOPLASM	1 (0.02)					0 (0.00)				
BRONCHIAL CARCINOMA	0 (0.00)					1 (0.04)				
LARYNGEAL CANCER	0 (0.00)					1 (0.04)				
PANCREATIC	4 (0.09)	(0.02, 0.22)	5015.47	0.08	(0.02, 0.20)	1 (0.04)	(0.00, 0.25)	2362.96	0.04	(0.00, 0.24)
PANCREATIC CARCINOMA	2 (0.04)					1 (0.04)				
PANCREATIC CARCINOMA METASTATIC	1 (0.02)					0 (0.00)				
PANCREATIC NEOPLASM	1 (0.02)					0 (0.00)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
BLOOD AND LYMPHATIC CHRONIC LYMPHOCYTIC LEUKAEMIA	2 (0.04) 1 (0.02)	(0.01, 0.16)	5015.37	0.04 (0.00, 0.14)		2 (0.09) 1 (0.04)	(0.01, 0.32)	2360.85	0.08 (0.01, 0.31)	
HODGKIN'S DISEASE LYMPHOCYTIC LEUKAEMIA	1 (0.02) 0 (0.00)					0 (0.00) 1 (0.04)				
HEPATOBIILIARY BILE DUCT CANCER HEPATIC NEOPLASM MALIGNANT	2 (0.04) 1 (0.02) 1 (0.02)	(0.01, 0.16)	5015.72	0.04 (0.00, 0.14)		0 (0.00) 0 (0.00) 0 (0.00)	(0.00, 0.16)	2363.01	0.00 (0.00, 0.16)	

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
FEMALE REPRODUCTIVE (FEMALES ONLY)	1 (0.04)	(0.00, 0.25)	2422.75	0.04	(0.00, 0.23)	1 (0.09)	(0.00, 0.53)	1084.14	0.09	(0.00, 0.51)
ENDOMETRIAL CANCER	1 (0.04)					1 (0.09)				
METASTASES AND SITE UNSPECIFIED	1 (0.02)	(0.00, 0.12)	5015.70	0.02	(0.00, 0.11)	2 (0.09)	(0.01, 0.32)	2362.09	0.08	(0.01, 0.31)
METASTASES TO CENTRAL NERVOUS SYSTEM	1 (0.02)					0 (0.00)				
METASTATIC SQUAMOUS CELL CARCINOMA	0 (0.00)					1 (0.04)				
NEOPLASM MALIGNANT	0 (0.00)					1 (0.04)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

Table 44: Summary and Incidence Rates of Adverse Events of Malignant and Unspecified Tumors, By Organ Category, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (12-May2011 ICS)

CATEGORY PREFERRED TERM (PT)	Treatment Group									
	DAPA TOTAL N = 4559					ALL CONTROL N = 2239				
	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)	Patients with Event (%)	95% (CI)	Follow-up (Patient -Years)	Incidence Rate*	95% (CI)
MUSCULOSKELETAL OR SOFT TISSUE	1 (0.02)	(0.00, 0.12)	5013.77	0.02	(0.00, 0.11)	0 (0.00)	(0.00, 0.16)	2363.01	0.00	(0.00, 0.16)
MALIGNANT FIBROUS HISTIOCYTOMA	1 (0.02)					0 (0.00)				
RENAL TRACT	0 (0.00)	(0.00, 0.08)	5015.79	0.00	(0.00, 0.07)	2 (0.09)	(0.01, 0.32)	2362.61	0.08	(0.01, 0.31)
RENAL CANCER	0 (0.00)					1 (0.04)				
RENAL CELL CARCINOMA	0 (0.00)					1 (0.04)				
RENAL NEOPLASM	0 (0.00)					1 (0.04)				

MedDRA Version: 14.0; N is the number of treated patients.

Includes serious and non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days (or up to follow-up visit whichever comes first) or 4 days, respectively.

Based on the SMQ of Malignant or Unspecified Tumors; organ categories based on clinical review of preferred terms.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010 and D1690C00012.

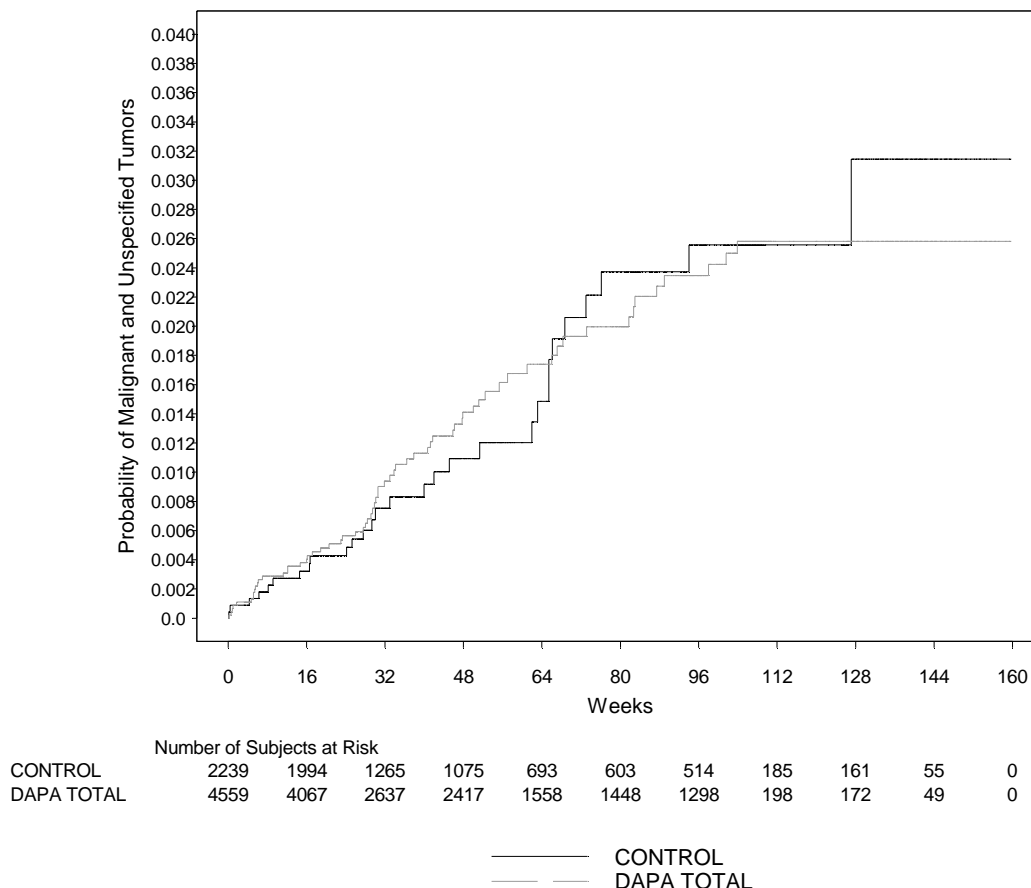
The overall follow-up time (patient-years) of a subject is calculated from first dose date to the event date, or the end of study date+30, follow-up visit, or database snapshot date, whichever is the earliest. *Incidence Rate = Per 100 person-years.

The dapagliflozin clinical program includes a wide range of studies with differences in the proportion of patients randomized to dapagliflozin across studies, ranging from 50% to 85%. A number of *post hoc* statistical analyses for events of malignant and unspecified tumors were performed to explore this imbalance, adjusting for these differences in allocation.

The difference in incidence rates of malignant and unspecified tumors was calculated using Mantel-Haenszel exposure weights, stratified by study, with CIs based on a normal approximation. The estimated difference between dapagliflozin-treated and control patients was 10 per 100,000 patient-years (95% CI: -580, 590) and was not statistically significant ($p > 0.10$), indicating that the estimated risk of malignant and unspecified tumors between patients treated with dapagliflozin or control was similar. This is supported by an incidence rate ratio vs control of 1.004 (95% CI: 0.627, 1.644). The Cox proportional hazards ratio (HR), stratified by study, was 1.016 (95% CI: 0.645, 1.601), with a p value of 0.944.

Likewise, time to first event analyses of malignant and unspecified tumors (Kaplan-Meier estimates) using the most recent 12-May-2011 dataset were similar between patients treated with dapagliflozin and those treated with control ([Figure 22](#)).

Figure 22: Time to First Event of Malignant and Unspecified Tumors, Short-term Plus Long-term Treatment Period, including Data after Rescue, Phase 2b and 3 Pool, Treated Patients (Integrated Dataset as of 12-May2010)



Week is not scheduled visit week but actual days from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.
MedDRA Version: 14.0, Based on SMQ of Malignant and Unspecified Tumors.

5.5.1.2 Breast Cancer

Breast cancer was reported in 10 female patients (9 on dapagliflozin and 1 on control) across seventeen completed Phase 2b and 3 studies in the clinical program up to 12-May-2011 (Table 44). The proportion of female dapagliflozin-treated patients with breast cancer vs control is 0.4% and 0.1%, respectively (Table 44). The estimated incidence rate

is 370 per 100,000 female patient-years for dapagliflozin-treated patients and 90 per 100,000 female patient-years for control, based on a cumulative follow-up time of 2416 female patient-years for dapagliflozin and 1085 female patient-years for control. One additional case was identified in a patient who remains blinded in an ongoing study; available information for this patient is included in [Table 45](#).

Table 45 provides a clinical summary of patients with events of breast cancer, ordered by study day of diagnosis within treatment group, which includes a recently identified subject from a blinded ongoing study as noted above. This patient is not included in the analyses in [Table 43](#) or [Table 44](#). In the dapagliflozin clinical program, all patients with breast cancer were female and > 50 years old (Table 45). These clinical attributes are typical of breast cancer in the general population. Eight of the 11 patients were > 60 years old. Seven patients were treated with background anti-diabetic medications: insulin (3), metformin (3), and glimepiride (1) (Table 45). All except the 53-year-old subject were post-menopausal.

All cases were detected < 1 year after exposure to dapagliflozin and 2 were reported within the first 8 weeks of treatment (Table 45). This short duration of exposure is inconsistent with the latency period for the development of chemically-induced human breast cancers, which is typically several years to decades.²¹ Patients came from 9 different countries across 3 continents, indicating no geographic clustering of the events.

Table 45: Summaries of Confirmed Breast Cancer Cases, Short-term plus Long-term Period Up to 13-June-2011, Ordered by Study Day within Treatment Group

Age/Sex	Dapa Dose ± Treatment	Tumor type	Grade	TNM*	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Diagnosis (Study Day)
63/F	2.5 mg + Ins	Invasive ductal carcinoma.	Grade 2	T1c, N0, M0	Highly positive, IRS 12	Highly positive, IRS 12	2+	6
53/F	5 mg	Intraductal carcinoma	Grade 3	M0	NA†	NA†	NA†	39
60/F	10 mg + Met**	Ductal carcinoma	Grade 1	T1,N0	Positive, 8/8	Positive, 8/8	Negative	193
61/F	10 mg + Ins	Invasive lobular, carcinoma	Grade 2	T2, N3a, M0	Strongly positive	Mildly positive	Negative	204
64/F	10 mg + Met	Invasive ductal carcinoma	Grade 2 – 3	T1c, N1, M0	40% – 50%	85 – 90%	NA^	211
64/F	10 mg + Met	Infiltrating adenocarcinoma	High grade	T2, N2a, MX	Negative	Negative	Negative	285
58/F	2.5 mg + Ins	Breast cancer	Grade 2	T2, N0, M0	Moderately positive (25% – 50%)	Negative	Weakly positive	292
74/F	2.5 mg	Ductal carcinoma	Grade 2	T1b, N0	Strongly positive	Strongly positive	Negative	321
69/F	10 mg + Glip	NA§	NA§	NA§	NA§	NA§	NA§	334
73/F	Placebo	Invasive, lobular	Grade 2	T3, N3a	> 80% (IRS 12)	> 80% (IRS 12)	Negative	57

Table 45: Summaries of Confirmed Breast Cancer Cases, Short-term plus Long-term Period Up to 13-June-2011, Ordered by Study Day within Treatment Group

Age/Sex	Dapa Dose ± Treatment	Tumor type	Grade	TNM*	Estrogen Receptor Status	Progesterone Receptor Status	HER2/neu Status	Diagnosis (Study Day)
		carcinoma						
59/F	Blinded	Invasive, ductal carcinoma	NA [^]	NA [^]	NA [^]	NA [^]	NA [^]	230

* TNM Classification of Malignant Tumors

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

†Tests not performed

[^] Information requested, but not yet received

§ Patient withdrew consent

Dapa = dapagliflozin ER = estrogen receptor; Ins = insulin; Met = metformin; Glip = glipizide; NA = not available

The estimated incidence rate difference for breast cancer was calculated as part of the *post hoc* statistical analyses up to 12-May-2011 ICS dataset, using exact methods stratified by study.^{27,28} The estimated incidence rate difference vs control was 339 events per 100,000 patient-years (95% CI: -381, 899), corresponding to detection of 1 excess case per 295 patient-years. Given the wideness of the CI, this range could suggest 1 excess case per 111 patient-years caused by treatment with dapagliflozin as a worst case scenario, and at best, 1 case per 262 patient-years prevented by treatment with dapagliflozin. The estimated lower limit is below 0 and the p value did not indicate statistical significance ($p > 0.10$), suggesting that this imbalance may have occurred by chance. However, the small number of events of breast cancer for dapagliflozin-treated vs control patients currently limits the ability to assess causality based on statistical analyses.

The age-adjusted annual female incidence rate of breast cancer is 122.9 cases per 100,000 person-years for all women and 291.8 per 100,000 person-years for women between the ages of 45 and 79, based on data from the Surveillance Epidemiology and End Results (SEER) program, which is a US registry of cancer for the general population (non-diabetic and diabetic).²² Similarly, the 2008 US female age-adjusted breast cancer incidence rate reported from GLOBOCAN is 240 per 100,000 person-years.²³ The results of a meta-analysis showed that women with diabetes have approximately a 20% increased risk of breast cancer (summary RR = 1.20; 95% CI: 1.12, 1.28) compared to women without diabetes.⁴⁶ A direct comparison between the dapagliflozin breast cancer incidence rate and background rates reported above should be made with caution as the dapagliflozin clinical development program was not designed or large enough to assess the risk of breast cancer (as noted by the wide 95% CIs), and the background incidence rates do not fully represent the population studied in these trials. The estimated incidence rate for breast cancer and its 95% CI observed in the dapagliflozin program (370 per 100,000 patient-years, 95% CI: 170, 710; Table 44) includes the incidence rate reported among women aged 45 to 79 in the general population (diabetic and non-diabetic) from SEER (290 cases per 100,000 patient-years. The numerical imbalance between the dapagliflozin treatment group and the control group warrant additional follow up. Proposed pharmacovigilance activities are discussed in Section 7.

5.5.1.3 *Bladder Cancer*

Bladder cancer was reported for 7 dapagliflozin-treated patients (0.15 %) vs 0 control patients (0%) across seventeen completed Phase 2b and 3 studies up to 12-May-2011 (Table 44). The estimated incidence rate is 140 per 100,000 patient-years for dapagliflozin-treated patients and 0 per 100,000 patient-years for control, based on a cumulative follow-up time of 5012 patient-years for dapagliflozin and 2363 patient years for control.

Blinded studies are still ongoing in the dapagliflozin program. Three cases with bladder cancer have been reported in such blinded studies. When these 3 additional cases were unblinded and included in the integrated analysis for bladder cancer, bladder cancer was reported in 10 male patients (9 on dapagliflozin and 1 on control) across nineteen Phase 2b and 3 studies (Table 46). The proportion of patients with bladder cancer for dapagliflozin-treated patients vs control is 0.3% vs 0.05%, respectively, based on this most current analysis.

Table 46 shows a clinical summary of patients with events of bladder cancer, ordered by study day of diagnosis, within treatment group. In the dapagliflozin clinical program, all patients with bladder cancer were male and most were ≥ 60 -years-old. These clinical attributes are typical of bladder cancer in the general population. Microscopic or trace hematuria was reported for 6 patients prior to study treatment with dapagliflozin or placebo, which may indicate the presence of pre-existing bladder cancer.²⁴ Hematuria was present at baseline in 9.0% of both dapagliflozin and control patients in the overall study population. In addition, baseline hematuria was present in 3.7% of dapagliflozin-treated males and 4.2% of control males. In contrast, hematuria was present at baseline in 14.4% of dapagliflozin-treated females and 14.3% of control females.

Table 46: Summaries of Confirmed Malignant Bladder Cancer Cases, Short-term plus Long-term Period as of 7-June-2011, Ordered by Study Day within Treatment Group

Age/Sex	Dapa Dose ± Treatment	Tumor type	Grade	TNM*	Diagnosis Study Day	Smoking Status	Baseline Hematuria	Presence of Hematuria within 6 m of Randomization
75/M	2.5 mg	Transitional cell	Grade 2	T2, N0, MX	43	Former	2+	YES
48/M	Dapa 10	Transitional cell	Low grade Non-invasive	NA	74	Former	Negative	NO
67/M	5 mg + Pio	Squamous cell carcinoma	Grade 3	T2	144	Never	Trace	YES
55/M	10 mg	Transitional cell	Grade 1 Non-invasive	NA	169	Current	Trace	TRACE
63/M	5 mg + Ins	Transitional cell	Grade 2 Non-invasive	Ta	393	Current	Negative	NO
67/M	10 mg + Ins	Transitional cell	Grade 2	NA	399	Never	3+	YES
60/M	5 mg+ Met	Transitional cell	Low Grade Non-invasive	Ta, N0, M0	512	Former	2+	YES
66/M	10 mg + Ins	Transitional cell	Low Grade Non-invasive	NA	581	Former	Negative	YES
76/M	10 mg +	Transitional cell, partial squamous	High Grade	T1	727	Never	Negative	NO

Table 46: Summaries of Confirmed Malignant Bladder Cancer Cases, Short-term plus Long-term Period as of 7-June-2011, Ordered by Study Day within Treatment Group

Age/Sex	Dapa Dose ± Treatment	Tumor type	Grade	TNM*	Diagnosis Study Day	Smoking Status	Baseline Hematuria	Presence of Hematuria within 6 m of Randomization
	Met**	differentiation	Invasive					
67/M	Placebo	Transitional cell	High grade Micro-invasive	NA	136	Current	3+	YES

* TNM Classification of Malignant Tumors

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

m = months; Pio = pioglitazone; Ins = insulin; Met = metformin; NA = not available

Eight patients with bladder cancer were current or former smokers, a risk factor for bladder cancer.²⁵ Overall, 40% of patients were current or former smokers in the Phase 2b and 3 program; and the proportions of patients were balanced between the dapagliflozin and control groups. Six patients were treated with background anti-diabetic medications: insulin (3), metformin (2), and pioglitazone (1).

All 10 cases were reported within 2 years of starting study treatment, with a median time to event of 393 days, and a range of 43 to 727 days. Three patients were diagnosed between 0 and 6 months, one between 7 and 12 months, 2 between 13 and 18 months, 3 between 19 and 24 months, and none at more than 24 months. The long latency period (18 – 44 years) associated with carcinogen-induced bladder cancer²⁶ suggests that the possibility of dapagliflozin treatment leading to de novo cases of bladder cancer is unlikely. Patients came from 8 different countries across 4 continents, indicating no geographic clustering of the events.

The estimated incidence rate difference for bladder cancer was calculated as part of the *post hoc* statistical analyses up to 12-May-2011, including the 3 additional cases from the blinded studies, using exact methods stratified by study.^{27,28} The estimated total number of patients, with or without an event, used in the calculation the estimated incidence rate difference was 5478 dapagliflozin-treated patients vs 3156 on control. The corresponding estimates of cumulative follow-up time were 5624 patient-years dapagliflozin vs 2975 patient-years with control. The pooled event rates were 160 and 34 events per 100,000 patient-years. For these calculations, the total sample size and the follow-up time for the 2 on-going blinded studies (D1690C00018 and D1690C00019) were equally divided into dapagliflozin and control groups.

The estimated incidence rate difference vs control was 125 events per 100,000 patient-years (95% CI: –180, 376), corresponding to detection of 1 excess case per 800 patient-years. Given the width of the CI, this range could suggest 1 excess case per 266 patient-years caused by treatment with dapagliflozin as a worst case scenario, and at best, 1 case per 556 patient-years prevented by treatment with dapagliflozin. The estimated lower limit is below 0 and the p value did not indicate statistical significance ($p > 0.10$), suggesting that this imbalance may have occurred by chance. However, the small number of events of bladder cancer in dapagliflozin-treated vs control patients currently limits the ability to assess causality based on statistical analyses.

Overall, differences in clinical trial monitoring (e.g., repeated assessments for hematuria) vs general practice, as well as the global variability in medical practice, make it difficult to develop applicable epidemiologic bladder cancer background rates in this worldwide clinical program. This assessment for bladder cancer is different from assessments for more common cancers, such as breast cancer, which are subject globally to periodic standard screening practices in the general population.

Bladder cancer has an age-adjusted incidence rate in the general US population (non-diabetic and diabetic) of 21.1 cases per 100,000 persons per year.²⁹ The incidence rate among patients between the ages of 45 and 79 in the general population was 43.6 per 100,000 patient-years for men and women between the ages of 45 and 79, based on SEER data from 2003 to 2007.²⁹

Bladder cancer appears to be approximately 20 to 40% more common among diabetics than in the general population.^{47,49} Bladder cancer incidence rates among patients with T2DM have been reported to be between 55.1 per 100,000 person-years (95% CI: 48.1, 64.6), based on data from the PharMetrics[®] Integrated Dataset, and 68.8 per 100,000 patient-years, based on an observational, longitudinal, cohort study using data from a diabetes registry and excluding patients that were never treated with pioglitazone.⁴³

A direct comparison between the dapagliflozin bladder cancer incidence rate and background rates reported above should be made with caution as the dapagliflozin clinical trial program was not designed or large enough to assess the risk of bladder cancer (as noted by the wide 95% CIs), and the background incidence rates do not fully represent the population studied in these trials. The estimated incidence rate for bladder cancer and its 95% CI observed in the dapagliflozin program, (160 per 100,000 patient-years, 95% CI: 73, 304; including the 3 patients from D1690C00018 and D1690C00019) excludes the incidence rate reported among men and women, aged 45 to 79 from SEER (43.6 cases per 100,000 person-years) in the general population; however, the 95% CI from the dapagliflozin program does overlap the point estimate (68.8 per 100,000 patient-years) for patients with T2DM, excluding those that had never been treated with pioglitazone in the observational, longitudinal, cohort study.⁴³ The numerical imbalance between the dapagliflozin treatment group and the control group warrant additional follow up. Proposed pharmacovigilance activities are discussed in Section 7.

5.5.1.4 Nonclinical Carcinogenicity Findings

An integrated review of the nonclinical data from the dapagliflozin program, with additional perspective from the literature, was conducted to assess the biological plausibility and/or potential linkages between dapagliflozin and malignant tumors.

Target Selectivity and Genotoxicity

Dapagliflozin is a potent, highly selective inhibitor of SGLT2. Dapagliflozin and its primary 3-O-glucuronide metabolite were tested in an expanded panel of liability assays at 10 μ M (> 300 distinct targets consisting of enzymes, transporters, and receptors, including estrogen and androgen receptors). There were no off-target interactions. Moreover, dapagliflozin and its 3-O-glucuronide metabolite had no structural alerts for mutagenicity or carcinogenicity in *in silico* assessments. Formal evaluations via *in vitro* Ames mutagenicity assays and an *in vivo* clastogenicity study in rats at C_{max} and AUC multiples >550 \times and 2100 \times , respectively, also supported the conclusion that dapagliflozin is not genotoxic.

General Toxicology Assessments

Evidence suggests that histopathologic results from standard repeat-dose toxicity studies can reliably predict carcinogenicity risk.³⁰ Specifically, preneoplastic effects (such as hyperplasia, hypertrophy, and atypical cellular foci observed in chronic toxicology studies) can be considered to be premonitory to carcinogenicity findings. Conversely, absence of these findings at clinically relevant exposures, generally suggests an absence of carcinogenic risk.³⁹

Dapagliflozin was not associated with preneoplastic-type effects at clinically relevant exposure. There was no histological evidence of progressive cellular proliferative changes, increased cell proliferation as characterized by excessive mitotic figures, or atypical cellular foci above background control levels in dapagliflozin-treated animals, across a battery of nonclinical studies in mice, rats and dogs. There was slight exacerbation of hypertrophy/vacuolation of the zona glomerulosa of the adrenal cortex in a 6-month toxicity study in rats, but this finding was considered to be a physiologic response to increased urinary glucose excretion and secondary increases in sodium excretion and osmotic diuresis. Urothelial hyperplasia was observed in concert with other

histological changes in the kidney of rats at treatment multiples $> 2000\times$ the MRHD of 10 mg (rat doses of 150 mg/kg/day). These were background effects and not related to treatment with dapagliflozin. In the 12-month dog study, there were no direct dapagliflozin-related hyperplastic changes at doses up to 120 mg/kg/day and exposure multiples $> 3000\times$ the MRHD. Minimal to slight sub-urothelial inflammation was present in the renal pelvis and/or papilla of 4 of 33 dapagliflozin-treated females, which was accompanied in 2 of these instances by urothelial hyperplasia of the bladder and/or the lining of the renal pelvis or papilla. However, these findings were not dose-dependent and only occurred in dogs associated with urinary tract infections; therefore, they were considered to be secondary to a likely infection and not related to treatment with dapagliflozin. These studies did not suggest a risk for neoplastic effects associated with dapagliflozin, despite the high exposure multiples relative to the MRHD of 10 mg.

Rodent Carcinogenicity Studies: Relevance, Predictive Value for Humans, and Results

The carcinogenic potential of dapagliflozin was specifically assessed in 24-month studies in mice and rats. These 2-year studies are essentially lifetime studies in rodents and are considered to be the gold standard for assessment of carcinogenicity, particularly for less potent and/or non-genotoxic carcinogens.

Rodent carcinogenicity models have been widely studied and validated for evaluation of breast and bladder carcinogenesis. Both mice and rats are uniquely susceptible to the development of spontaneous and chemically-induced mammary gland neoplasms. Potent carcinogens typically induce a preneoplastic or neoplastic response with a latency period of a few weeks.³¹ In contrast, several months to years are necessary for adequate assessment of the latency resulting from exposure to less potent or non-genotoxic carcinogens.³¹ In rodent models of urinary bladder carcinogenesis, 6 to 12 month experimental periods are typically required for a potent carcinogen to produce a high incidence of bladder tumors.

Rodent carcinogenicity models are directly relevant to human risk assessment, as histological classifications used for human mammary and urinary bladder neoplasms are directly applicable to rodent neoplasms. For example, rodents and humans similarly develop both benign and malignant mammary neoplasms, which demonstrate glandular, stromal, or mixed glandular and stromal differentiation^{31, 32} The most significant malignant neoplasm in the human breast is the adenocarcinoma, which is derived from

glandular epithelial cells.^{31,32} Chemically-induced rodent mammary tumors are also generally adenocarcinomas³² and are histologically comparable to the adenocarcinoma observed in humans.³¹ Furthermore, both spontaneous and experimentally-induced rodent mammary neoplasms are hormone-dependent, a factor considered key to the use of models of human breast cancer.³¹ As is the case for mammary neoplasms, urinary bladder neoplasms in rodents bear numerous similarities to the humans, including low-grade papillary tumors and high-grade lesions that progress from flat dysplastic and carcinoma *in situ* changes to invasive carcinomas.^{33,34}

While the 2-year rodent assay does have some limitations in accurately predicting human carcinogenicity,^{35,36,37,38} errors in prediction favor a higher rate of false positives, particularly when a risk-avoidance interpretation is used. Any positive result in a sex/species combination is considered a positive prediction of human carcinogenicity based on these criteria, with a sensitivity of 90% and a 10% false negative rate.²² The potential for false negative results was addressed. False negatives most often occur in inadequately designed studies in which: 1) high-dose exposures do not meet ICH S1C guidelines of 25× AUC multiples for the primary compound or ~1× for metabolites; 2) statistical power has not been reached due to inadequate number of animals (the standard is 50/sex/group); and 3) insufficient numbers of dose groups are assigned to characterize a dose-response relationship.^{36,37}

The rodent carcinogenicity studies for dapagliflozin met and exceeded these criteria by using the following to assess dose-response relationships: 1) treatment multiples were up to 105× in mice and 186× in rats for dapagliflozin, with acceptable coverage for the glucuronide metabolite (up to 1.3×); 2) 60 mice/sex/dose group and 70 rats/sex/group were used; and 3) 2 control groups and 3 dapagliflozin groups were tested for each rodent species. Therefore, the carcinogenicity studies conducted with dapagliflozin were adequately designed to provide an accurate assessment of carcinogenic potential, while minimizing the possibility of false negative results. In addition, glucosuria and diuresis were common features of all dapagliflozin toxicity and carcinogenicity studies with no impact on study outcomes.

Under the aforementioned stringent testing conditions, dapagliflozin did not induce tumors in either species at any of the doses evaluated with treatment multiples > 100× the

MHRD of 10 mg. Specific to risk assessment for humans, there were no increases above the control level in the incidence of breast or urinary bladder tumors in either species at any dose in these studies.

Urinary bladder tumors in both rodent species and mammary tumors in mice are relatively low-incidence background neoplasms.^{39,40} Therefore, dapagliflozin-related increases above background levels would have been detected if present; there were no such trends for increased bladder tumor development. There were also no indications of dapagliflozin-related hyperplastic changes in either species. Transitional epithelial hyperplasia in rats and urothelial hyperplasia in male mice were observed, but the incidence was neither dose related nor substantially different from controls, and therefore, not related to dapagliflozin treatment. Moreover, in no case did these changes transform to neoplasms in the bladder.

Conversely, mammary tumors are a common background tumor in rats and were seen at high numbers in the rat carcinogenicity study in both control rats and animals treated with dapagliflozin by the end of the study. Despite the high incidence in control rats, however, there was no evidence of either an earlier onset or an increase in the overall incidence of mammary tumors following dapagliflozin administration to rats. These data suggest that dapagliflozin is neither an initiator of tumorigenesis nor a promoter of tumor development in these well-established rodent models.

The lack of any nonclinical signal with dapagliflozin contrasts with the experience the PPAR γ agonist, pioglitazone, which caused urinary bladder tumors in rats in 2-year carcinogenicity studies.^{41,42} The precise relationship of these effects to human risk assessment, however, is still not completely defined because there is only a weak association between pioglitazone and an increased risk of bladder cancer in patients with T2DM.⁴³

Additional Mechanistic Perspectives

A variety of other possible risk factors for biological plausibility were evaluated to identify whether there is any other underappreciated mechanistic linkage or biologic association between dapagliflozin and an increased risk for tumors. These included target expression in the tissues of interest, potential relevance of mechanism-related effects to

tumorigenesis, and whether dapagliflozin impacts any risk factors previously linked to breast or bladder tumor promotion.

SGLT2 is not expressed in breast and urinary bladder tissue

Human SGLT2 expression was assessed in 72 normal tissues using quantitative RT-PCR methodology employing several probes across the length of the gene.⁴⁴ The results of these experiments indicated that SGLT2 mRNA is highly expressed in human kidney, but is not detected in breast or urinary bladder tissue. Expression of other SGLT isoforms and family members was also evaluated, and very little to no expression was detectable in either human breast or urinary bladder tissues. A modest level of expression of the sodium-myoinositol cotransporter, SMIT, was detected in these and many other tissues, but still at far lower levels than in the kidney.⁵³ These data demonstrate a lack of expression of SGLT2 or other closely related proteins, and suggest that there is a low likelihood for target-related effects in breast and bladder tissues. Notably, SGLT2 is almost exclusively expressed in the kidney. There is no suggestion of renal carcinoma, in either the nonclinical or clinical program, in the organ where target expression is abundant and MOA is in effect.

Epidemiology studies have demonstrated that patients with T2DM have an increased risk for a variety of cancers, including breast and bladder cancer.^{45,46,47,48,49} The mechanism responsible for this increased risk in T2DM is unknown. One proposed mechanism is through an increase in insulin levels secondary to insulin resistance. Insulin functions as a mitogen and could promote tumor cell growth,⁵⁰ but a review of the literature suggests that the association between insulin and cancer is far from clear, and several lines of evidence argue against the carcinogenic potential of insulin.^{50,51} These include: 1) circulating levels of insulin in patients receiving insulin analogues are quite low in comparison to those levels of insulin that act as a mitogen *in vitro*⁵⁰; 2) increased mitogenicity does not in itself translate to increased carcinogenicity⁵⁰; 3) therapeutic experience with insulin therapy in type 1 and type 2 diabetics does not suggest an increase in tumor proliferation in patients with established or diagnosed cancers or an increase in tumor incidence based on pharmacovigilance and periodic safety updates⁵¹; 4) insulin does not act as a co-carcinogen in special rat toxicity studies conducted with the carcinogen methyl-nitroso-urea⁵²; and 5) the European Medicines Agency concluded that

both human insulin and an insulin analogue have the capability of producing mammary tumors in Sprague-Dawley rats, but only after prolonged treatment at supra-physiological concentrations.⁵¹ Dapagliflozin does not induce such insulin levels in rodents at the doses studied.

Substantial increases in urine output, secondary to repeated bladder over-expansion and/or increased exposure to metabolic by-products excreted in urine, have also been suggested to be a risk factor for bladder cancer. However, chronic toxicology and carcinogenicity assessments of the diuretic, furosemide,⁵³ do not support a linkage between diuresis and bladder tumor risk.

One other theoretical possibility, particularly for bladder tumors, is that dapagliflozin-related glucosuria may provide an optimized nutrient-rich microenvironment for tumor growth. Data from nonclinical toxicology studies with dapagliflozin, in which glucosuria was a common feature, suggest that the presence of glucosuria does not lead to bladder tumors even in the face of a background incidence of hyperplastic changes. The amount of glucose in cell culture formulations ranges from 1 g/L (5.5 mM) to as high as 10 g/L (55 mM). Many classical media are supplemented with approximately 5.5 mM D-glucose, which approximates normal blood sugar levels *in vivo*. In tissue culture experiments, increasing glucose concentrations from 5 mM to 22 mM did not increase proliferation in the T24 bladder-tumor cell line, although a 15% increase was observed in the MCF-7 tumor cell line.⁵⁴ In another study, increasing tissue culture concentrations of glucose in the medium from 5 mM to 25 mM did not significantly increase the proliferation of MCF-7 cells.⁵⁵ Consistent with these data, preliminary results from recent BMS experiments examining growth rate of 6 bladder transitional cell tumor cell lines cultured in 11, 25, 35, and 50 mM glucose concentrations demonstrated no cell growth enhancement beyond 11 mM glucose in the medium, and clear growth inhibition at 50 mM glucose. Thus, there is no clear evidence that increasing glucose concentrations in the growth medium of bladder or breast tumor cell lines promote cell growth.

Lack of effect on suggested mechanisms of tumor promotion

Risk factors for tumor promotion particularly for bladder tumors include, but are not limited to, immunosuppression, perturbations of hormonal balance, alterations in urinary pH and/or urinary composition leading to crystalluria and bladder irritation, cytotoxicity, local infection, inflammation, and/or cell proliferation. The common theme is

interruption of intercellular communication and/or induction of cell proliferation acts as a stimulus for tumor promotion.⁵⁶ Dapagliflozin was not associated with any of the above, except for a low incidence of inflammatory effects in chronic studies in rats and dogs, which did not translate to neoplastic changes. Finally, some literature has suggested a common mechanistic link between teratogenesis and tumor promotion as conditions of increased cell mitosis.^{57,58} Dapagliflozin was not associated with any embryo-fetal development effects at treatment multiples > 1400× the MRHD.

Dapagliflozin did not cause transcriptional changes that are predictive of tumor promoters.^{59,60} This set of 22 genetic markers was found to be 96% to 97% accurate, sensitive, and specific (based upon test set of 63 chemicals) for positive results in a 2-stage cell transformation assay in Balb/c 3T3 cells and highly correlated with published reports of in vivo tumor promoting activities and/or rodent carcinogenicity results.⁶⁰ Eighteen of these 22 markers from microarray datasets collected from the kidney, liver, adipose tissue, and skeletal muscle of ZDF diabetic rats treated daily with dapagliflozin for 5 weeks (C_{max} ~ 640 ng/mL, which is 4 to 5× the C_{max} at the MRHD of 10 mg) were evaluated. These organs were specifically selected as they represent target organs in the treatment of diabetes. At the time of the experiment, the currently observed imbalance in bladder and breast cancer was not known, and these organs were selected independent of the current clinical data. The findings for these nonclinical markers suggest that dapagliflozin treatment did not induce transcriptional changes characteristic of known tumor promoters. These data provide further evidence, this time in a rodent model of diabetes, that dapagliflozin is not a tumor promoter. In conclusion, there is no overall evidence that dapagliflozin possesses any tumor promotor activity.

Overall, the biologic plausibility for dapagliflozin to be causally related to breast or bladder cancer is not supported by nonclinical data.

5.5.1.5 Summary of Malignant or Unspecified Tumors

Overall, available data suggest that the likelihood of a causal association between dapagliflozin and control for breast or bladder cancer is small. The overall proportion of patients with malignant or unspecified tumors was similar between those treated with dapagliflozin (1.4%) and control (1.3%) and the estimated difference in incidence rate between the 2 groups did not indicate statistical significance. Imbalances were observed

for breast (9 cases on dapagliflozin vs 1 on control) and bladder (9 cases on dapagliflozin vs 1 on control) cancers. This corresponds to an estimated incidence rate for breast cancer of 370 per 100,000 female patient-years for dapagliflozin-treated patients and 92 per 100,000 female patient-years for control and for bladder cancer, approximately 160 events per 100,000 patient-years for dapagliflozin-treated patients and control group an incidence rate of 34 events per 100,000 patient years.

The breast and bladder cancer cases reported in clinical studies with dapagliflozin were typical in terms of the presence of risk factors, including age at onset and gender. The duration of exposure to dapagliflozin prior to the reports of cancer was relatively short. In light of the lengthy latency period associated with carcinogen-induced breast and bladder cancers, it is unlikely that treatment with dapagliflozin causes bladder cancer.

Nonclinical studies suggest that dapagliflozin is very unlikely to cause cancer. Dapagliflozin is not genotoxic, and rigorous 2 year carcinogenicity studies in mice and rats did not demonstrate preneoplastic or neoplastic changes. Additionally, the direct pharmacologic effect of dapagliflozin, glycosuria, would not be expected to increase the risk of cancer, and no indirect effects which could increase the risk of cancer have been identified.

The small number of events of breast and bladder cancer in dapagliflozin-treated vs control patients currently limits the ability to assess causality based on statistical analyses. Additional safety studies are planned, which are designed to rule out a level of increased risk of breast or bladder cancer that would be clinically unacceptable in the context of the level of benefit that is provided by the treatment with dapagliflozin. These studies utilizing administrative claims databases and through a large post-marketing outcomes studies are described in greater detail in Section 7.

5.5.2 Hepatic Safety

Hepatic function was monitored during the Phase 3 program in alignment with FDA's Guidance for Industry: Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009).⁶¹ Investigators were asked to complete supplemental CRFs for events of increased liver tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3× upper limit of normal [ULN]). Patients with clinical liver disease and elevated hepatic parameters were excluded from the clinical studies.

There were no meaningful, consistent changes from baseline in mean liver function test values across studies and there were no clinically meaningful differences between the dapagliflozin and placebo groups. There were also no cases of severe drug-induced liver injury, defined as fatal or requiring liver transplantation.⁶¹ In both dapagliflozin and control groups, 5.7% of patients had elevated liver tests based on laboratory values and/or reported AEs of hepatic disorder in the All Phase 2b and 3 Pool. There was no imbalance in the proportion of patients with laboratory values for ALT or AST $> 3 \times$ ULN and concomitant or subsequent TBL $> 2 \times$ ULN up to the 4MSU (Table 47).

Five (0.1%) patients treated with dapagliflozin had ALT or AST values $> 3 \times$ ULN and concomitant or subsequent TBL $> 2 \times$ ULN vs 3 (0.2%) treated with the comparator (2 with placebo and 1 with glipizide). All had possible underlying causes of these elevations and are discussed later in this section.

Table 47: Summary of Proportion of Patients with Elevated Liver Tests, Based on Measured Laboratory Values, Short-term Plus Long-term Treatment Period, including Data after Rescue, All Phase 2b and 3 Pool, Treated Patients (4MSU)

	X/N# (Percent)	
	DAPA TOTAL N = 4310	ALL CONTROL N = 1962
TOTAL PATIENTS WITH ELEVATED LIVER TESTS	207/4281 (4.8)	92/1943 (4.7)
ALT ELEVATION		
> 3X ULN	62/4281 (1.4)	31/1943 (1.6)
> 5X ULN	17/4281 (0.4)	11/1943 (0.6)
> 10X ULN	4/4281 (0.1)	3/1943 (0.2)
> 20X ULN	2/4281 (<0.1)	1/1943 (0.1)
AST OR ALT ELEVATION		
> 3X ULN	74/4281 (1.7)	37/1943 (1.9)
TOTAL BILIRUBIN ELEVATION		
> 2X ULN	18/4281 (0.4)	5/1942 (0.3)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION (AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	5/4281 (0.1)	3/1942 (0.2)

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.

Includes laboratory values measured on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days.

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

The All Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, and D1690C00012.

The following criteria were used to identify potential liver-injury cases for adjudication:

- AST and/or ALT $> 3 \times$ ULN and TB $> 1.5 \times$ ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT $> 5 \times$ ULN
- Hepatic disorders SMQ AEs/SAEs in patients who prematurely discontinued study treatment due to any AE/SAE
- Hepatic disorders SMQ AEs/SAEs in any patients who died

Fourteen Phase 2 and 3 studies with completed short-term, placebo-controlled treatment periods (4 with ongoing long-term extension treatment periods), and 7 ongoing blinded studies up to the 4MSU (15-Oct-2010) were screened for liver-related abnormalities. Based on the above criteria, 54 cases from these studies were evaluated by an independent, blinded Hepatic Adjudication Committee (HAC), using consensus causality assessment. Of these 54 cases, 35 were treated with dapagliflozin, 17 with placebo or a comparator drug, and 2 from blinded ongoing studies. The distribution of cases between dapagliflozin and control (35:17) is what would be expected given the difference in exposure between the 2 groups.

Only one causality assessment was provided for each case, regardless of how many liver-related events were reported for an individual patient. Cases were adjudicated in a blinded, independent manner by the HAC members to assess the probability of drug-induced liver injury using the 5-point likelihood causality scale displayed in [Table 48](#).⁶² This assessment included both numerical and descriptive terms to grade cases as definitely, highly likely, probably, possibly, or unlikely related to drug-induced liver injury.

Table 48: Clinical Assessment of Causality Scale: Definitions

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

When cases did not meet any of the above description, 2 additional likelihood causality scale terms were used, as described below:

- **Excluded:** Cases should be ranked as excluded if there is a definite and documented alternative cause for the abnormality.
- **Not Assessable:** Cases should be ranked as not assessable if critical data are missing that interferes with a fair assessment.

No case was assessed to be definitely or highly likely related to blinded study drug. Liver-related abnormalities in 2 patients treated with control were assessed by the HAC as probably related to study treatment, are highlighted in grey in [Table 49](#), and will not be discussed further. Fifteen of the 54 cases were assessed to be possibly related to study treatment (7 patients treated with dapagliflozin, 7 patients in a control group, and 1 patient in an ongoing blinded study).

Two of the 5 cases identified in [Table 47](#) and [Table 49](#), with AST >3× ULN or ALT > 3× ULN and TBL > 2× ULN within 14 days on or after AST/ALT elevation, were among the 15 adjudicated cases the Committee considered to be possibly related to treatment.

One patient treated with dapagliflozin in the study evaluating dapagliflozin (added to metformin) in direct comparison to glipizide had severe concomitant elevations of both AST/ALT (> 20× ULN) and TBL (> 2× ULN) values while treated with dapagliflozin 5 mg and metformin XR. The patient was diagnosed with drug-induced acute hepatitis,

based on liver biopsy results, with a subsequent additional diagnosis of probable autoimmune hepatitis. The second diagnosis of probable autoimmune hepatitis was based on biopsy results and response to immunosuppressive treatment. Liver enzymes and bilirubin improved slightly when study drug was suspended on study Day 193, and improved further, returning to baseline levels on study Day 349, after immunosuppressive treatment. The patient was living up to 1 year ago. He has voluntarily withdrawn from the study.

The other patient was treated with dapagliflozin 5 mg plus glimepiride in the add-on to glimepiride study. This patient had history of obstructive jaundice due to stones in the common bile duct, 9 months before enrollment in the study. He had 1 episode of an elevated liver test (ALT > 3× ULN; 178 U/L) Day 85. Study drug was temporarily stopped from Day 113 to Day 119. On Day 113, normal liver function tests were recorded while the patient was still being treated with dapagliflozin. On Day 141, when dapagliflozin had been restarted, a new episode of elevated liver tests was recorded. The patient was discontinued from the study on Day 141. The maximal increase to ALT > 5× ULN (271 U/L) and TBL > 2× ULN (2.7 mg/dL) was reported on Day 148, 7 days after discontinuation of dapagliflozin. Liver test values returned toward normal and were almost normalized on Day 176 (ALT: 63 U/L; TLB: 1.2 mg/dL).

The causality assessment across treatment groups is summarized in [Table 49](#). Cases that met multiple identification criteria are included in each applicable category in the table.

Table 49: Summary of HAC Blinded Assessment of Causal Relationship to Study Drug per Category

Category ¹	Number of Patients (Percent)		
	DAPAGLIFLOZIN N=4310 ²	CONTROL N=1962 ²	BLINDED N=1943 ³
AT > 3XULN and TB > 2XULN	5 (0.12%)	3 (0.15%)	0
Definite	0	0	0
Highly Likely	0	0	0
Probable	0	0	0
Possible	2 (0.05%)	0	0
Unlikely	2 (0.05%)	2 (0.1%)	0
Excluded	1 (0.02%)	1 (0.05%)	0
Not Assessable	0	0	0
AT > 3XULN and TB> 1.5XULN and ≤ 2XULN	3 (0.07%)	1 (0.05%)	0
Definite	0	0	0
Highly Likely	0	0	0
Probable	0	1 (0.05%)	0
Possible	1 (0.02%)	0	0
Unlikely	1 (0.02%)	0	0
Excluded	1 (0.02%)	0	0
Not Assessable	0	0	0
AT > 5X ULN	19 (0.44%)	14 (0.71%)	2 (0.10%)
Definite	0	0	0
Highly Likely	0	0	0
Probable	0	1 (0.05%)	0
Possible	7 (0.16%)	5 (0.25%)	1 (0.05 %)
Unlikely	8 (0.19%)	5 (0.25%)	0
Excluded	4 (0.09 %)	3 (0.15%)	1 (0.05%)
Not Assessable	0	0	0

Table 49: Summary of HAC Blinded Assessment of Causal Relationship to Study Drug per Category

Category ¹	Number of Patients (Percent)		
	DAPAGLIFLOZIN N=4310 ²	CONTROL N=1962 ²	BLINDED N=1943 ³
HEPATIC DISORDER AE/SAE IN PATIENTS WHO DIED	2 (0.05%)	0	0
Definite	0	0	0
Highly Likely	0	0	0
Probable	0	0	0
Possible	0	0	0
Unlikely	0	0	0
Excluded	2 (0.05%)	0	0
Not Assessable	0	0	0
HEPATIC DISORDER AEs/SAEs IN DAE PATIENTS	17 (0.39%)	4 (0.20%)	0
Definite	0	0	0
Highly Likely	0	0	0
Probable	0	0	0
Possible	3 (0.07%)	1 (0.05%)	0
Unlikely	6 (0.14 %)	1 (0.05%)	0
Excluded	8 (0.19%)	2 (0.10%)	0
Not Assessable	0	0	0

AT = AST and/or ALT, DAE = prematurely discontinued study treatment due to any AE/SAE, TB = total bilirubin, ULN = upper limit of normal.

The adjudication results from patients D1690C00004-3104-4 and D1690C00004-3408-9 (occurred > 30 days after discontinuation of blinded study drug) and subject MB102032-67-399 (the subject received dapagliflozin 1 mg) are not included in the table.

¹ Cases meeting multiple identification criteria included in each applicable category.

² N is the number of treated patients from the 15 completed/ST sponsor unblinded studies. Does not include the 1 mg treatment group from Studies MB102032 and D1692C00005 and does not include Group 2 from Study MB102013 or Cohort 1 from Study MB102009.

³ N is the number of randomized patients from the 7 blinded studies.

There was no clear association of dapagliflozin treatment at any dose with liver toxicity and no evidence of severe drug-induced liver injury. One of the cases on dapagliflozin case with an initial diagnosis drug-induced hepatitis and a subsequent alternative diagnosis of autoimmune hepatitis remains of concern because of the difficulty differentiating between a drug-induced event and autoimmune hepatitis.

BMS and AZ will conduct pharmacoepidemiology studies that include evaluation of acute liver failure. The incidence and relative risk of hospitalization for acute liver failure in patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated as the primary outcome in this study. As part of the secondary outcomes, death due to acute liver failure, and composite hospitalizations for acute liver failure and/or death due to acute liver failure will also be estimated. A subset of potential cases will also be adjudicated based on review of the medical records. Additional information about post-marketing assessments of hepatic safety is described in Section 7.

5.5.3 Cardiovascular Safety

A pre-specified assessment of CV safety was conducted using a meta-analysis of independently confirmed, blindly adjudicated, CV events among fourteen Phase 2b and 3 studies. In a meta-analysis, the hazard ratio (HR) for the primary composite endpoint of CV death, MI, stroke, and hospitalization for unstable angina was 0.674 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078). These results are consistent with the conclusion that dapagliflozin is not associated with a CV risk, and met the requirement of an upper bound < 1.8 for the 98% CI for the HR in the FDA CV guidance.⁶³ Analyses conducted as part of the 4MSU confirmed the results in the initial NDA. Evaluations of lipids (Section 5.5.3.4) and blood pressure (Section 5.4.4.1) were also performed. Post-marketing surveillance plans for ongoing assessment of CV safety are described in Section 7.

5.5.3.1 Overview of Meta-analyses for Cardiovascular Safety

The primary objective of the meta-analysis was to assess the CV safety of all dapagliflozin relative to all comparators, pooled across all doses over the total exposure (short-term plus long-term treatment periods) of the Phase 2b and 3 program. An independent, blinded adjudication process was used for all CV events.

To limit the probability of falsely concluding that dapagliflozin was non-inferior to the control groups, sequential analysis was instituted. The first analysis was scheduled to occur when the primary time points in the 14 studies were reached. During this analysis, the primary endpoint was evaluated using a nominal one-sided significance level of 0.01, corresponding to a 98% CI. If the upper bound of the 98% CI for the HR of dapagliflozin relative to placebo was < 1.8 , the results would be considered to be sufficiently strong to fulfill the requirements of the 2008 FDA Guidance.⁶³ If not, a second planned analysis would be performed after a second set of studies had reached their primary time point. At the time of the first analysis, dapagliflozin met the < 1.8 criterion. The analyses presented in this section are the results of this first analysis.

The relative risk ratio for the primary composite endpoint of adjudicated CV death, MI, stroke, and hospitalization for unstable angina was calculated, as agreed with the FDA. A secondary endpoint consisting of time-to-first event that included events of the primary composite endpoint plus unplanned coronary revascularization and hospitalization for heart failure was included. Additional analyses of major adverse CV events (MACE) were also conducted for CV death, MI, and stroke.

The primary methodology for these variables was the Cox proportional hazards model with a term for treatment, stratified by study. Estimation of the risk difference for the primary endpoint was performed using Mantel-Haenszel methodology and a normal approximation.

5.5.3.2 Exposure and Cardiovascular Risk Factors

The meta-analysis study population included 6228 patients from the All Phase 2b and 3 Pool in the initial NDA (Section 3.2.2.2): 4287 in the dapagliflozin group and 1941 in the comparator group. The cutoff date of 30-Jul-2010 was chosen for the CV safety meta-analysis to increase the precision of the estimate of CV risk. The observed population was representative of the intended T2DM population. On average, the amount of exposure was 1 year per patient. CV risk factors in addition to T2DM from the meta-analysis for CV safety for dapagliflozin are summarized in [Table 50](#).

Table 50: Cardiovascular Risk Factors in Addition to T2DM from the Meta-Analysis for CV Safety for Dapagliflozin (NDA Dataset)

	Number (%) of Patients	
	All DAPA n = 4287	Control n = 1941
Patients with at least one CV Risk Factor in addition to T2DM ^a	3772 (88.0)	1708 (88.0)
Patients with at least two CV Risk Factor in addition to T2DM	2750 (64.1)	1266 (65.2)
Hypertension	2635 (61.5)	1248 (64.3)
Hypercholesterolemia ^b	2116 (49.4)	947 (48.8)
Smoking History	1703 (39.7)	782 (40.3)
History of heart failure ^c	93 (2.2)	33 (1.7)
Family history of premature CVD ^d	641 (15)	293 (15.1)
Age ≥ 65 years	879 (20.5)	456 (23.5)
Prior CV Disease ^e	841 (19.6)	353 (18.2)
eGFR < 60 ml/min/1.73 ²	485 (11.3)	212 (10.9)

^a Includes all factors in table^b Includes dyslipidemia^c Also included in Prior CV disease, counted once only^d First degree relative with premature coronary heart disease, male < 55 years of age, female < 65 years of age^e Prior CV Disease defined as previous myocardial infarction, congestive heart failure, hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular accident, carotid artery disease, carotid endoarterectomy or stenting, peripheral vascular disease, peripheral vascular surgery, amputation

5.5.3.3 Results of Meta-analyses for Cardiovascular Safety

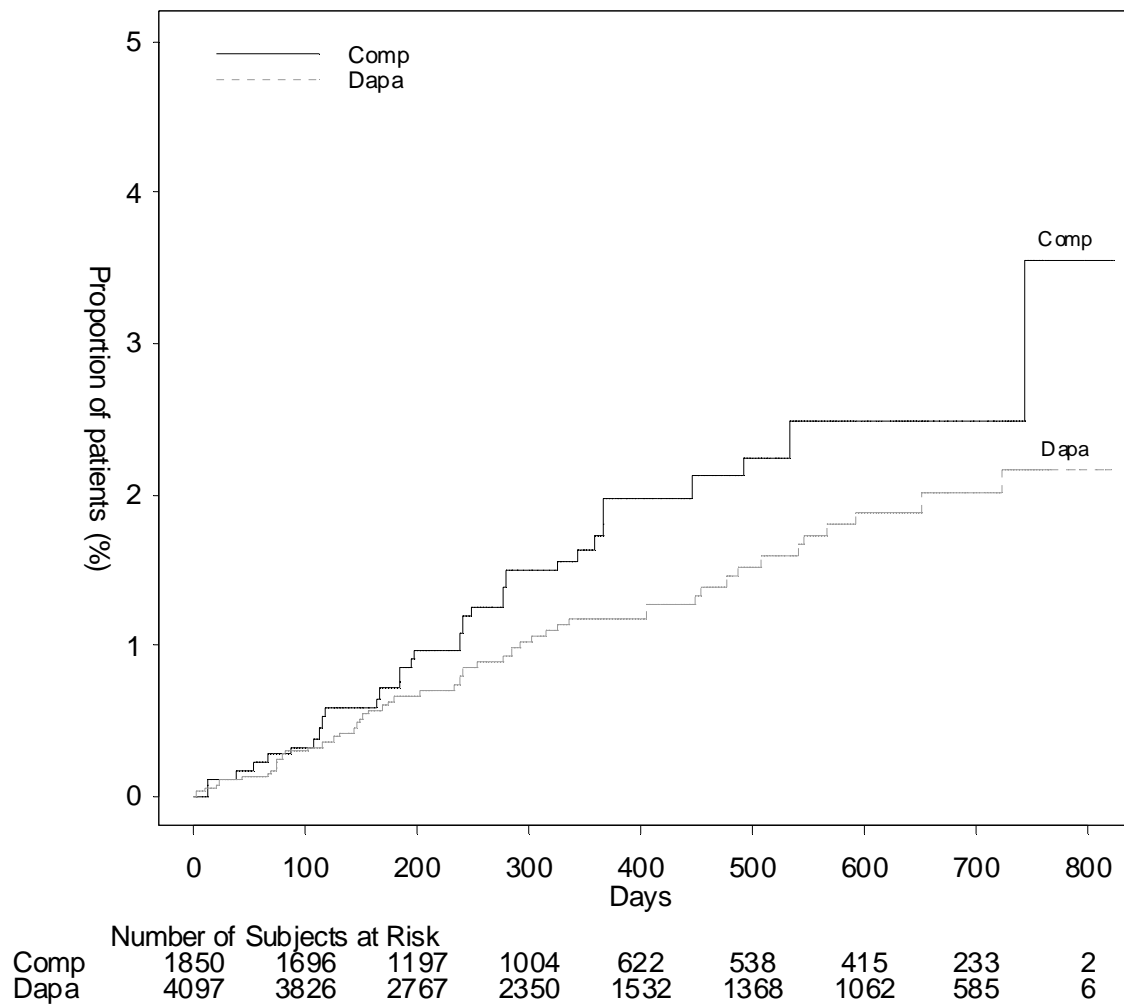
In total, 78 patients had a confirmed adjudicated event contributing to the primary endpoint and 98 patients had confirmed adjudicated events contributing to the secondary endpoint during the short-term plus long-term treatment period. The stratified event rate (patients with events/1000 patient-years) was 11.1 and 16.4 for the dapagliflozin and comparator groups, respectively for the primary composite endpoint, and 13.7 and 21.7, respectively, for the secondary composite endpoint. The event rates in the comparator

group, 16.4 and 21.7 per 1000 patient-years for the 2 composite endpoints, support that the observed population is representative of the intended T2DM target population with an increased risk for CV events.

There was no evidence of an increase in CV events associated with dapagliflozin. The HR for the primary composite endpoint of CV death, MI, stroke, and hospitalization for unstable angina was 0.674 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078). These results met the requirement of an upper bound < 1.8 for the 95% CI for the HR in the FDA CV guidance.⁶³ A Kaplan-Meier curve for the cumulative probability of the primary composite endpoint over time is shown in [Figure 23](#).

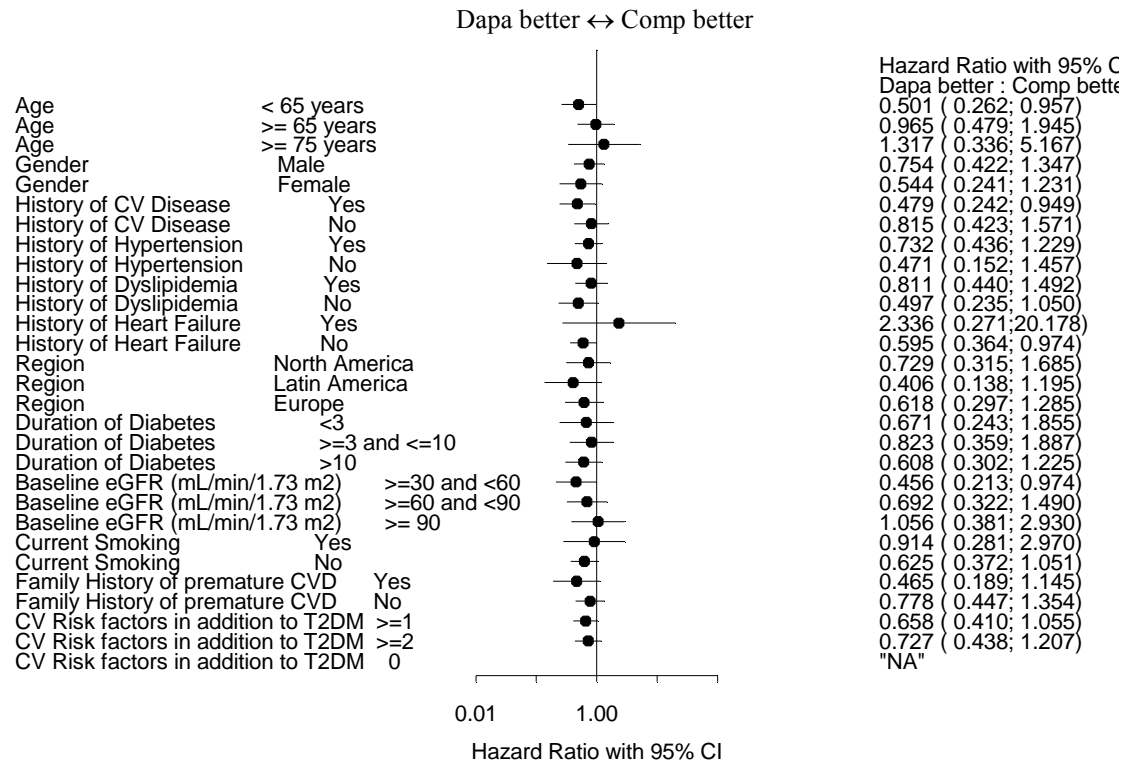
Supportive analyses of dose groups for the primary endpoint resulted in the following HR estimates: 0.877 for 2.5 mg (95% CI: 0.422, 1.822), 0.529 for 5 mg (95% CI: 0.253, 1.108), and 0.564 for 10 mg (95% CI: 0.290, 1.095). These results indicate that a higher dose (5 mg or 10 mg) of dapagliflozin is not associated with an increased CV risk compared to the lower dose (2.5 mg). By-study analyses for the primary endpoint were consistent with the results of the meta-analysis. Event rates per study were based on the individual study designs and populations.

Figure 23: Cumulative Probability of Primary CV Composite Endpoint over Time (Kaplan-Meier Estimate), During ST + LT Periods, Overall Stratified Analysis (NDA Dataset)



Supportive analyses by subgroups for the primary endpoint were generally consistent with the primary analysis (Figure 24).

Figure 24: Primary Cardiovascular Composite Endpoints by Subgroup



CI = Confidence Interval

"NA" = Not Applicable, value is infinite.

Studies MB102009 and MB102032 do not have at least one positively adjudicated event, hence excluded from analysis.

Dapa = dapagliflozin; Comp = comparator

5.5.3.4 Effects on Lipids

No deleterious or favorable effects on lipids were noted with dapagliflozin treatment. Small changes from baseline in mean lipid values in the short-term Placebo-controlled Pool were observed at Week 24 in patients treated with dapagliflozin 10 mg compared to placebo. Mean percent changes from baseline at Week 24 for dapagliflozin 10 mg vs placebo, respectively, were as follows: total cholesterol, 1.4% vs -0.4%; high-density lipoprotein (HDL) cholesterol, 5.5% vs 3.8%; low-density lipoprotein (LDL) cholesterol,

2.7% vs -1.9%; triglycerides, -5.4% vs 0.7%. %. The ratio between LDL cholesterol and HDL cholesterol was decreased for all treatment groups at Week 24.

5.5.4 Safety in Special Patient Categories

Subgroup analyses for safety, including data after rescue, for age, race, gender, female/age (female \leq 50 years, female $>$ 50 years) and ethnicity were conducted to assess the consistency of results across different subpopulations. There were no safety signals or trends based on subgroup analyses for race, female age, or ethnicity and no apparent difference in the safety profile based on baseline HbA1c.

A total of 1335 (21%) of the 6228 randomized patients were \geq 65 years and 169 (3%) patients were \geq 75 years in 14 double-blind, controlled, clinical safety and efficacy studies of dapagliflozin. Overall, the proportion of patients reporting AEs was consistent between those \geq 65 and $<$ 65 years of age. Given that older patients are more likely to have impaired renal function at baseline, it was not surprising that a higher proportion of patients \geq 65 years of age treated with dapagliflozin had events related to renal impairment or failure compared to placebo. The most commonly reported of these AEs were increased blood creatinine laboratory reports and events described as renal failure, but these AEs were reported in $<$ 1% of patients \geq 65 years of age in any dapagliflozin or placebo treatment group. Most did not require hospitalization and did not have progression of renal function.

5.5.5 Pregnancy and Lactation

Dapagliflozin has not been studied in pregnant or lactating women. In nonclinical studies, dapagliflozin was not teratogenic nor did it impact fertility in conventional reproductive toxicity assessments. However, in pre- and postnatal reproductive and juvenile rat toxicity studies, dapagliflozin administration was associated with dilatation of the renal pelvis at a stage of development corresponding to the second and third trimester in humans. Large urinary volumes produced by dapagliflozin-induced diuresis may produce a functional impact on fluid movement in the urinary tract and rat pups may lack the capacity to deal with these effects. Variable degrees of dilatation of the kidney pelvis have been observed in mice after administration of furosemide.⁵³ Dilatation of the urinary tract has also been observed in children with polyuria due to congenital diabetes

insipidus.⁶⁴ Because of these findings, dapagliflozin is not recommended for use in women during the second and third trimesters of pregnancy.

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available PD/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. As a risk to newborns/infants cannot be excluded, dapagliflozin should not be used by breastfeeding women.

6 LIMITATIONS OF USE OF DAPAGLIFLOZIN IN PATIENTS WITH RENAL IMPAIRMENT

Given dapagliflozin's MOA to improve hyperglycemia via direct elimination of glucose by the kidney, possible limitations of the use of dapagliflozin in patients with T2DM and varying degrees of renal impairment have been investigated. These analyses were aimed at providing a recommendation for use that may be limited based on a patient's underlying GFR, which at some level of impairment may not be sufficient to drive a clinically meaningful effect from dapagliflozin.

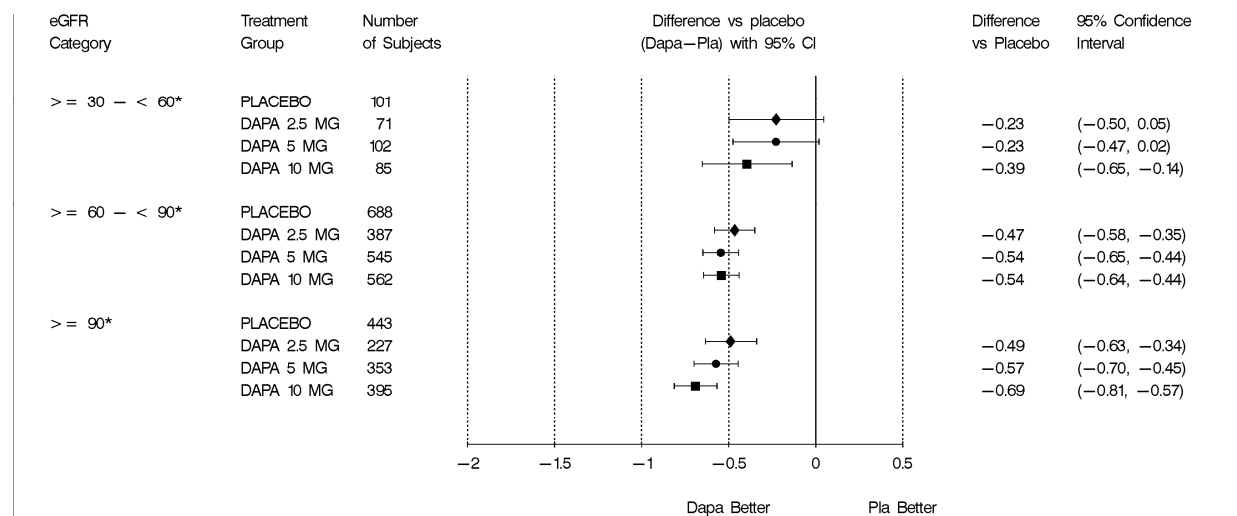
Across the dapagliflozin clinical program, patients with normal renal function accounted for less than half of treated patients in the Phase 2b and 3 clinical program, while 51% of patients had estimated glomerular filtration rate (eGFR) values consistent with mild renal impairment ($\text{eGFR} \geq 60$ to < 90 mL/min/1.73m²). The clinical database thus allows for the assessment of the efficacy of dapagliflozin across a range of patients with varying glomerular filtration rates. This experience was augmented with a special study of dapagliflozin in 252 patients with mean eGFR of 44.6 mL/min/1.73 m² (MB102029).

6.1 Efficacy of Dapagliflozin as a Function of GFR

To assess glycemic efficacy by eGFR category, a pooled analysis of patients with eGFR values consistent with either normal renal function, and mild or moderate renal impairment was conducted across 9 placebo-controlled studies (2 monotherapy studies; 4 combination add-on to metformin, pioglitazone, glimepiride, and insulin studies; a body weight and composition study; and 2 initial combination with metformin studies). This is the Monotherapy/Combination Therapy Pool from the initial NDA described in Section 3.2.1.1 (Figure 25). This pool did not include patients from the special study in moderate

renal impairment (MB102029). Mean HbA1c reductions were observed with dapagliflozin treatment vs comparator in all eGFR subgroups. As expected, greater reductions in HbA1c were seen in patients with higher baseline eGFR, and smaller HbA1c decrements in patients with lower baseline eGFR ($p = 0.0148$ for the interaction test with treatment, based on continuous eGFR; Figure 25). Overall, the efficacy profile of dapagliflozin in patients with mild renal impairment was comparable to effects seen in the overall population, with evidence of a clinically meaningful magnitude of glycemic improvements in patients with T2DM and either normal or mildly impaired renal function. Thus, adequate glucosuria, the primary PD indicator of SGLT2 inhibition by dapagliflozin, occurs in both categories of patients to provide clinically meaningful improvements in glycemic control.

Figure 25: Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 (LOCF) by eGFR* Category, Monotherapy/Combination Therapy Pool**



Randomized Patients/Full Analysis Set; excludes data after rescue

* Units of eGFR are mL/min/1.73m²

** Studies in Pooled Monotherapy/Combination Therapy Subgroup: monotherapy, low-dose monotherapy, excluding 1 mg, add-on to metformin, add-on to pioglitazone, add-on to glimepiride, add-on to insulin, body weight and composition, and initial combination with metformin (dapagliflozin 5 mg and 10 mg, excluding dapagliflozin only patients).

More modest glycemic efficacy was observed in patients Monotherapy/Combination Therapy Pool from with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73m²;

Figure 25). Dapagliflozin 10 mg demonstrated a placebo-corrected mean HbA1c reduction of -0.39% for these patients, with a 95% CI excluding zero. This moderate renal impairment sub-population with a mean eGFR of 52.8 mL/min/1.73m² was smaller than the normal and mild renal impairment groups, and most patients in this group (87%) had baseline eGFR values consistent with stage 3A renal impairment (≥ 45 and < 60 mL/min/1.73m²).

To provide a more accurate assessment of efficacy and safety for dapagliflozin in patients with T2DM and moderate renal impairment, a special study in 252 patients with mean eGFR of 44.6 mL/min/1.73 m² was conducted (MB102029). The primary endpoint of HbA1c change was not met for dapagliflozin 10 mg (n = 82), with mean change from baseline and placebo-corrected mean change at Week 24 equal to -0.44% and -0.11%, respectively, identifying a renal population where dapagliflozin is not delivering glycemic efficacy.

The results from this study of 252 patients varied from the assessment of glycemic efficacy in the moderate renal impairment population from a pooled analysis of the overall clinical program (n=359 patients). After further investigation, it appeared that this difference was driven by the subset of patients in the special study that were at the lower end of the eGFR range in this study (< 45 mL/min/1.73 m²).

Specifically, when the stage 3A sub-group population (eGFR ≥ 45 and < 60 mL/min/1.73m²) from the special study was analyzed for HbA1c effects of dapagliflozin 10 mg, the mean change from baseline and placebo-corrected mean change from baseline at Week 24 were -0.44% and -0.33%, respectively (n = 32). These mean changes are consistent with changes evident in the larger pooled analysis. However, the patients with eGFR values indicative of more advanced moderate renal impairment (stage 3B, eGFR ≥ 30 and < 45 mL/min/1.73m², n = 45) had markedly attenuated HbA1c changes with dapagliflozin 10 mg, with mean change from baseline and placebo-corrected mean change from baseline equaling -0.45% and +0.07%, respectively. Thus, the HbA1c-lowering effect of dapagliflozin in stage 3B patients is rendered ineffective as eGFR declines, consistent with the MOA of dapagliflozin.

In conclusion, dapagliflozin was effective in reducing HbA1c, FPG, and body weight in patients with eGFR values consistent with either normal renal function or mild renal

impairment. At the other extreme, dapagliflozin will not be indicated for use in patients with severe renal impairment or with end-stage renal disease (ESRD) on dialysis, as dapagliflozin's SGLT2 inhibition MOA was not studied and will not be operative in such patients. Dapagliflozin was modestly effective in patients with stage 3A moderate renal impairment ($\text{eGFR} \geq 45$ and < 60 mL/min/1.73m²). However, because efficacy was not observed in stage 3B patients with more advanced renal impairment (e.g., $\text{eGFR} \geq 30$ and < 45 mL/min/1.73m²), dapagliflozin should not be used in any patient with $\text{eGFR} < 45$ mL/min/1.73m² due to this lack of clinical efficacy.

6.2 Safety of Dapagliflozin as a Function of GFR

As for efficacy assessments, the safety profile of dapagliflozin in patients with mild renal impairment ($\text{eGFR} \geq 60$ to < 90 mL/min/1.73m²) was similar to the overall population. Specific safety analyses of stage 3A and 3B moderate renal impairment patients ($\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²) were conducted to better understand the safety profile of dapagliflozin in these patients, including patients with moderate renal impairment from the Placebo controlled Pool, and from the special study of dapagliflozin in patients with T2DM and moderate renal impairment. The populations for these analyses are described in more detail in Sections 3.2.2.3 and 3.2.2.5.

AEs related to renal impairment were reported in a higher proportion of patients treated with dapagliflozin 10 mg in the special moderate renal impairment study during short-term treatment (MB102029; [Table 51](#)) than in the 10-mg group in the short-term Placebo-controlled Pool ([Table 28](#)). Increased blood creatinine was the only event reported for any treatment group in the special study; it was also the most commonly reported event in the short-term Placebo-controlled Pool.

AEs related to volume status (including hypotension, dehydration, and/or hypovolemia) were reported in a higher proportion of patients treated with dapagliflozin 5mg or 10 mg, or placebo in the special moderate renal impairment study during short-term treatment ([Table 51](#)) than in the short-term Placebo-controlled Pool ([Table 22](#)). The most commonly reported event was hypotension, consistent with findings from short-term Placebo-controlled Pool.

Table 51: Renal or Volume Status Adverse Events of in the Special Moderate Renal Impairment Study (MB102029)*, Week 24 Short-term Double-blind Treatment, Including Data After Rescue, Treated Patients (NDA Dataset)

Special Moderate Renal Impairment Study (Short-term Treatment up to Week 24)*	Number (%) of Patients		
	Dapa 5 mg N = 83	Dapa 10 mg N = 85	Placebo N = 84
Renal Adverse Event	0	4 (4.7)	1 (1.2)
Hypotension/Dehydration/Hypovolemia Events	6 (7.2)	9 (10.6)	3 (3.6)

N is the number of treated patients or the number of patients with non-missing laboratory results.

Dapa = dapagliflozin

* Special study in patients with T2DM and moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73m²)

AEs include non-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 treatment plus 4 days, or before the start of long-term extension treatment if earlier.

AEs include 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 treatment plus 30 days, or before the start of long-term extension treatment if earlier.

AEs based on a predefined list of events of renal impairment/failure and hypotension/dehydration/hypovolemia.

There were no consistent differences in renal AEs or events related to volume depletion (hypotension/dehydration /hypovolemia) between the stage 3A and 3B subgroups with moderate renal impairment from the Placebo-controlled Pool combined with those from the special moderate renal impairment study (Table 52). The most commonly reported renal event in both subgroups was increased blood creatinine, and the most common event related to volume depletion was hypotension, both consistent with that reported in other populations.

Renal events were reported for slightly greater proportions of patients in both subgroups (Table 52) compared to patients in the special moderate renal impairment study (Table 51) across all treatment groups. There was a similar but larger difference between the patients in these subgroups (Table 52) and those in the short-term Placebo-controlled Pool (Table 28).

Events related to volume depletion occurred less often in most stage 3A and 3B patients (Table 52) compared to patients in the special moderate renal impairment study (Table 51); the exception was in the stage 3B placebo group. However, these events were reported more frequently in both subgroups (Table 52) compared to the short-term Placebo-controlled Pool (Table 22).

Table 52: Renal or Volume Status Adverse Events 3A[†] and 3B^{††} Subgroups, Week 24 Short-Term Treatment, Including Data After Rescue, Treated Patients (NDA Dataset)

	Number (%) of Patients		
	Dapa 5 mg N = 128	Dapa 10 mg N = 107	Placebo N = 138
Combined 3A Subgroup[†]			
Renal Adverse Event	4 (3.1)	7 (6.5)	6 (4.3)
Hypotension/Dehydration/Hypovolemia Events	3 (2.3)	5 (4.7)	2 (1.4)
Combined 3B Subgroup^{††}			
Renal Adverse Event	3 (5.5)	3 (4.8)	1 (2.3)
Hypotension/Dehydration/Hypovolemia Events	3 (5.5)	4 (6.5)	3 (6.8)

N is the number of treated patients or the number of patients with non-missing laboratory results.

Dapa = dapagliflozin

[†] 3A Subgroup of moderate renal impairment: patients with baseline eGFR ≥ 45 to < 60 mL/min/1.73m² from the Placebo-controlled Pool and from study in patients with T2DM and moderate renal impairment (MB102029), See Section 3.2.2.3.

^{††} 3B Subgroup of moderate renal impairment: patients with baseline eGFR ≥ 30 to < 45 mL/min/1.73m² from the Placebo-controlled Pool and from study in patients with T2DM and moderate renal impairment (MB102029). See Section 3.2.2.3.

AEs include non-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 treatment plus 4 days, or before the start of the long-term period or to the follow-up visit if earlier.

AEs include 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 treatment plus 30 days, or before the start of the long-term period or to the follow-up visit if earlier.

AEs based on a predefined list of events of renal impairment/failure and hypotension/dehydration/hypovolemia.

Although overall AE rates of fracture for the entire dapagliflozin clinical program were similar between dapagliflozin and comparator (see Section 5.4.5.4), there was a numeric

imbalance in fractures experienced among patients with moderate renal impairment and treated with any dose of dapagliflozin, particularly in patients with stage 3B moderate renal impairment when data up to the 4MSU is considered ($\text{eGFR} \geq 30$ and $< 45 \text{ mL/min/1.73m}^2$, Table 53). These results are based on patients with stage 3A and 3B moderate renal impairment from the Placebo-controlled Pool and the special study (MB102029).

Table 53: Fractures in Patients with Renal Impairment, Short-term plus Long-term Treatment, Placebo-controlled Pool including Special Study in Moderate Renal Impairment, Treated Patients (MB102029) (4MSU Dataset)

Treatment Group	<u>3A Subgroup*</u>		<u>3B Subgroup**</u>	
	N	n (%)	N	n (%)
Total Dapagliflozin	268	7 (2.6)	123	8 (6.5)
Placebo	109	2 (1.8)	43	0

* 3A Subgroup of moderate renal impairment: patients with baseline $\text{eGFR} \geq 45$ to $< 60 \text{ mL/min/1.73m}^2$ from the Placebo-controlled Pool and from study in diabetic patients with moderate renal impairment (MB102029). See Section 3.2.2.5.

**3B Subgroup of moderate renal impairment: patients with baseline $\text{eGFR} \geq 30$ to $< 45 \text{ mL/min/1.73m}^2$ from the Placebo-controlled Pool and from study in diabetic patients with moderate renal impairment (MB102029). See Section 3.2.2.5.

Total Dapagliflozin includes 2.5, 5, 10, 20, and 50 mg.

Although fractures involving miscellaneous and mostly non-osteoporotic sites were identified in the special study (MB102029), no connection was established between events of fracture and analyses of bone health for the overall T2DM population in the dapagliflozin program, including non-clinical assessments, bone biomarkers, and a bone mineral density study (see Section 5.4.5).

6.3 Recommendation for Use of Dapagliflozin in T2DM Patients with Moderate Renal Impairment

Modest, but clinically significant, efficacy remains evident in patients with stage 3A renal impairment. Based on the analysis of pooled data, including data from the special study in moderate renal impairment, low glycemic efficacy is expected after dapagliflozin treatment in patients with eGFR values ≥ 30 and $< 45 \text{ mL/min/1.73m}^2$ (stage 3B).

Therefore, a limitation to the use of dapagliflozin is most practically placed in patients with stage 3B moderate renal impairment.

The special moderate renal impairment study also suggested that there was an imbalance in fractures in patients at the lower range of moderate renal impairment ($\text{eGFR} \geq 30$ and $< 45 \text{ mL/min/1.73m}^2$), while fractures were balanced in patients with higher eGFR values and in the overall pooled analysis. In the absence of clinically meaningful efficacy in patients with stage 3B renal impairment this safety assessment supports a recommendation not to use dapagliflozin in patients with $\text{eGFR} < 45 \text{ mL/min/1.73m}^2$.

Therefore, based on multiple lines of evidence, BMS and AZ currently recommend use of dapagliflozin for patients with T2DM and stage 3A moderate renal impairment ($\text{eGFR} \geq 45$ and $< 60 \text{ mL/min/1.73 m}^2$ or calculated $\text{CrCl} \geq 60 \text{ mL/min}$). This recommendation outlines the use of dapagliflozin within a range of underlying renal function similar to the clinical practice recommendations for the use of metformin. Coupled with routine clinical practice to monitor renal status over time through standard laboratory chemistry testing, this recommendation will allow patients and health care providers to assess glycemic reduction effects in individual patients based on their individual benefit-risk profile.

7 RISK MANAGEMENT AND POST-MARKETING SAFETY ASSESSMENTS

Dapagliflozin has been studied in a broad and comprehensive Phase 2b and 3 clinical program. However, BMS and AZ recognize that these studies have limitations in their ability to adequately detect rarely occurring AEs, or AEs that may be associated with longer-term use. Consequently, proactive safety surveillance and evaluation in the post-marketing period is planned to enable the continued assessment of the benefit-risk profile of dapagliflozin.

A Risk Management Plan (RMP) has been submitted that describes an integrated, complementary set of pharmacovigilance activities designed to further identify, characterize, and evaluate risks relating to dapagliflozin use. Safety outcomes that will be monitored during the post-marketing period include genital infections, urinary tract infections, hypoglycemia, volume depletion, clinical consequences of increased hematocrit, renal impairment or failure, bone fracture, liver injury, and cancer.

Post-marketing safety assessments include: 1) routine and enhanced pharmacovigilance; 2) pharmacoepidemiology studies; 3) ongoing clinical studies; and 4) a large, clinical outcomes study. Information from the pharmacovigilance program will be used to add to or enhance risk communication and minimization measures as appropriate.

7.1 Routine and Enhanced Pharmacovigilance

Routine surveillance includes collection and evaluation of safety data from spontaneous post-marketing reports, controlled clinical studies, and reports from the literature. Standard signal detection methods along with medical review will be used to identify and refine potential safety signals. These ongoing, periodic evaluations will form the basis of periodic safety reports for submission to health authorities as well as revisions to product safety information, as appropriate, in a timely manner.

In addition to routine surveillance activities, the BMS and AZ will deploy targeted questionnaires to gather additional information and enhance the quality of data collected for events of interest reported in post-marketing settings. The use of specialized case-report forms will enable the collection of added information on selected events reported in ongoing and future clinical studies. For example, additional information gathered on events of pyelonephritis may provide insight on whether factors such as time to diagnosis or potential delays in treatment affected the clinical course.

BMS and AZ are further committed to continuously evaluating the benefit-risk profile of dapagliflozin through a series of observational database studies, and through ongoing and future controlled clinical trials.

7.2 Post-Marketing Pharmacoepidemiology Studies

BMS and AZ propose a program of prospectively designed, observational database studies of adult patients with T2DM as part of the post-marketing, enhanced surveillance activities to assess the safety profile of dapagliflozin in the T2DM population under conditions of usual care. This program will complement monitoring of AE data collected from clinical studies and spontaneous reporting.

These pharmacoepidemiology studies will be conducted using large administrative databases in the United States and the European Union. They are planned to start within

close proximity of the first approval of the initial marketing application. The study populations will be followed for approximately 3 to 5 years, and the number of dapagliflozin users required per study will depend on the outcome of interest. The primary comparison of interest will be new users of dapagliflozin compared to new users of other anti-diabetic treatments in classes other than SGLT2 inhibitors or insulin. These data will be initially analyzed 12 months after launch, and periodically thereafter (12 – 18 months), with interim reports provided to the FDA.

The risk of bladder and breast cancer among patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be monitored in a large cohort study using administrative databases. Secondary objectives of this study encompass the assessment of overall cancer risk. At minimum, a subset of breast and bladder cancer cases will be adjudicated based on review of the medical records.

The incidence and relative risk of hospitalization or emergency department visits for bone fracture in patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated in a cohort study. At minimum, a subset of cases will be adjudicated based on review of the medical records.

The incidence and relative risk of hospitalization or emergency department visits for severe complications of UTI, including acute pyelonephritis and urosepsis, in patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated as the primary outcome in this cohort study. At minimum, a subset of potential cases will be adjudicated based on review of the medical records.

The incidence and relative risk of hospitalization for acute kidney injury in patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated as the primary outcome in a large cohort study. As part of the secondary outcomes, death due to acute kidney injury, and composite hospitalizations for acute kidney injury and/or death due to acute kidney injury will also be estimated. At minimum, a subset of potential cases will be adjudicated based on review of the medical records.

The incidence and relative risk of hospitalization for acute liver failure in patients with T2DM who are new users of dapagliflozin vs new users of other anti-diabetic medications, excluding SGLT2 inhibitors and insulin, will be estimated as the primary outcome in this study. As part of the secondary outcomes, death due to acute liver failure, and composite hospitalizations for acute liver failure and/or death due to acute liver failure will also be estimated. At minimum, a subset of potential cases will be adjudicated based on review of the medical records.

These pharmacoepidemiology studies will enable the overall quantitative assessment of risks associated with dapagliflozin in the context of other anti-diabetic agents, and complement the risk information derived from ongoing clinical trials, spontaneous AE reports, and targeted questionnaires. The background rate of events of interest, and the patient-years of exposure to dapagliflozin and number of years after approval required to rule out a relative risk equal to 2 for each of the outcomes assessed in the pharmacoepidemiology program are presented in Table 54.

Table 54: Signal Detection Timing in Pharmacoepidemiology Studies*

Event	Event Background Rate per 10,000 Patient-years	Exposure to Dapagliflozin (patient-years)	Years to Rule out a Relative Risk = 2
All Malignancy	100	3,750	1
Bladder Cancer	4	93,750	3
Breast Cancer	30	12,500	2
Acute Liver Failure	2	187,500	5
Acute Renal Failure	10	37,500	2
Acute Pyelonephritis: Females	11	34,091	3
Acute Pyelonephritis: Males	3	125,000	5

* Assumes an equal sample size between dapagliflozin and comparator, $\alpha = 0.05$, power = 85%

Final study protocols and reporting timelines will be discussed with the FDA and external epidemiology experts prior to the implementation of the studies.

7.3 Ongoing Clinical Studies

Controlled clinical development studies and other scientific evaluations will continue during the post-approval period, enabling the further evaluation of the efficacy and safety profile of dapagliflozin. As of the date of this document, there are ongoing long-term extension treatment periods for 3 clinical studies (body weight and composition study, which includes DXA scanning [D1690C00012], the special study in patients with T2DM and moderate renal impairment [MB102029], and the add-on to sitagliptin study [D1690C00010], and short-term treatment periods of 6 other studies described in [Table 3](#); when complete, the results from these studies will provide additional information about the safety of dapagliflozin.

Specialized case report forms will continue to be used in the ongoing studies to gather additional details on events of hypoglycemia, genital infections, UTIs, and liver injury. One ongoing clinical study, D1690C000019, includes screening for asymptomatic bacteriuria.

7.4 Clinical Outcomes Study

BMS and AZ are committed to conducting a large, randomized, controlled clinical outcomes study to characterize the long-term benefit and risk of dapagliflozin for the treatment of T2DM. 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, non-fatal myocardial infarction, or non-fatal ischemic stroke, compared to placebo. This study will also provide continued assessment of various safety outcomes of interest including bladder cancers, breast cancers, bone fractures, urinary tract infections, and liver safety with long-term treatment and follow-up. The study will enable prospective adjudication of endpoints and other outcomes of interest and will complement the real-world evaluations from the epidemiologic, observational database studies. BMS and AZ are currently working with the FDA in planning the design and execution of this study.

7.5 United States Package Insert (USPI)

The USPI will be the primary means of communication about risks associated with dapagliflozin. The sponsor will work with FDA to ensure that prescribers and patients are

informed on the clinical profile of dapagliflozin, and to provide guidance to support its safe and appropriate use through package labeling and other available means, as appropriate.

8 SUMMARY AND BENEFIT–RISK ASSESSMENT

In order to conduct a comprehensive benefit–risk assessment of dapagliflozin, fundamental properties of this new oral agent to treat T2DM are summarized and discussed in this section, applying the perspective of how dapagliflozin might fit into the armamentarium of available medicines used to treat and manage T2DM in today’s US health care setting. This comparative assessment of dapagliflozin properties will be considered stepwise in this section.

First, intrinsic properties of dapagliflozin as a novel chemical agent will be reviewed briefly to set the context of its potential clinical use. Thereafter, beneficial pharmacodynamic efficacy properties will be characterized qualitatively and quantitatively, and weighed against demonstrated and preliminary risk properties, including both tolerability and safety findings. Findings related to the safety profile that are evident following the dapagliflozin clinical program, including information related to exploratory (and therefore non-definitive) safety assessments, will be summarized and discussed briefly. These properties are also tabulated in order to facilitate a comprehensive, semi-quantitative benefit–risk assessment of this first-in-class medicine for T2DM.

8.1 Pharmacologic Properties of Dapagliflozin and Implications of Clinical Use

Dapagliflozin is a new, first-in-class compound with a novel MOA. It works in the kidney specifically by inhibiting SGLT2. It lowers plasma glucose by inhibiting renal re-absorption and promoting urinary excretion of glucose. This targeted MOA is independent of insulin and makes dapagliflozin unique and complementary to other currently available anti-diabetic agents.

The pharmacokinetic and pharmacodynamic properties of dapagliflozin yield a simple treatment regimen: a single 10-mg dose, once daily, at any time of day regardless of meals. The effect of dapagliflozin to produce glucosuria is immediate, with an impact on

glycemic efficacy parameters measurable within the first week of treatment. Both FPG and PPG changes become evident promptly following onset of glucosuria. FPG as well as pre- and postprandial glycemic improvements are consistently achieved throughout the day in response to consistent SGLT2 inhibition, as adequate dapagliflozin drug levels maintain controlled and steady glucosuria.

As a result of its chemistry and metabolic profile, dapagliflozin has a low potential for drug-drug interactions and no clinically relevant interactions have been shown for the most commonly used concomitant medications in patients with T2DM. This compatibility with a wide variety of medications is an important attribute for a new medication to control T2DM.

The insulin-independent MOA and the absence of interactions with concomitant medications allows dapagliflozin to be used in a wide range of patients with T2DM: starting with newly diagnosed patients who are not controlled by diet and exercise alone, also including patients on all current classes of oral T2DM therapies, and ultimately in patients with longer disease durations requiring insulin therapy.

8.2 Benefits of Dapagliflozin

The beneficial efficacy properties of dapagliflozin are characterized quantitatively in [Table 55](#) and [Table 56](#). Key glycemic control and weight properties for the recommended dapagliflozin 10 mg dose are listed in relative comparisons established from primary and key secondary endpoints from the dapagliflozin clinical program: pooled data of dapagliflozin 10 mg compared to placebo after 24 weeks of treatment, single-study data of dapagliflozin 10 mg compared to metformin as initial monotherapy after 24 weeks of treatment, and single-study data of dapagliflozin 10 mg compared to glipizide on a background of metformin treatment after 52 weeks of treatment.

Table 55 shows the impact that dapagliflozin 10 mg has on HbA1c and FPG, the core measures used to assess glycemic efficacy of drugs in patients with diabetes.

Table 55: Glycemic Control Surrogate Benefits vs Specific Therapies

Endpoint	Placebo-controlled Pool (5-studies; Week 24) ^a		Initial Combination with Metformin (Week 24)		Direct Comparison to Glipizide (Week 52)	
	Dapagliflozin 10 mg (N = 690)	Placebo (N = 689)	Dapagliflozin 10 mg (N = 219)	Metformin (N = 208)	Dapagliflozin 10 mg (N = 400)	Glipizide (N = 401)
Hemoglobin A1c (HbA1c) (%)	N = 679	N = 675	N = 216	N = 203	N = 400	N = 401
Adjusted mean change from baseline (95% CI)	-0.91 (-0.98, -0.85)	-0.31 (-0.38, -0.24)	-1.45 (-1.59, -1.31)	-1.44 (-1.59, -1.29)	-0.52 (-0.60, -0.44)	-0.52 (-0.60, -0.44)
Mean difference from control (95% CI)	-0.60 (-0.70, -0.51)		-0.01 (-0.22, 0.20)		0.00 (-0.11, 0.11)	
p-value/testing result	—		NI ^b		NI ^b	
Fasting plasma glucose (FPG) (mg/dL)	N = 675	N = 672	N = 216	N = 207	N = 399	N = 394
Adjusted mean change from baseline (95% CI)	-26.9 (-29.8, -23.9)	-3.3 (-6.2, -0.4)	-46.4 (-51.3, -41.5)	-34.8 (-39.8, -29.8)	-22.4 (-25.5, -19.2)	-18.8 (-21.9, -15.7)
Mean difference from control (95% CI)	-23.6 (-27.7, -19.5)		-11.6 (-18.6, -4.6)		-3.6 (-8.0, 0.9)	
p-value	—		0.0012		0.1159	

Table 55: Glycemic Control Surrogate Benefits vs Specific Therapies

Endpoint	Placebo-controlled Pool (5-studies; Week 24) ^a		Initial Combination with Metformin (Week 24)		Direct Comparison to Glipizide (Week 52)	
	Dapagliflozin 10 mg (N = 690)	Placebo (N = 689)	Dapagliflozin 10 mg (N = 219)	Metformin (N = 208)	Dapagliflozin 10 mg (N = 400)	Glipizide (N = 401)
Proportion (%) patients achieving HbA1c of < 7%^c	N = 679	N = 675	N = 216	N = 203	N = 400	N = 401
Proportion adjusted (or unadjusted), n (%) ^d (95% CI)	232 (34.2) (30.6, 37.9)	124 (18.4) (15.5, 21.5)	69 (31.7) (25.7, 37.7)	72 (35.2) (28.8, 41.7)	110 (27.4) (23.0, 31.8)	128 (32.0) (27.4, 36.6)
Mean difference from control (95% CI)	15.8 (11.2, 20.4)		-3.5 (-12.5, 5.4)		-4.6 (-10.9, 1.7)	
p-value	—		—		0.1542	

^a A subset of 5 studies from the Monotherapy/Combination Therapy Pool described in Section 3.2.1.2, comprised of patients treated in the morning from the monotherapy study MB102013 (Group 1 QAM dose groups), and those from the add-on to metformin (MB102014), add-on to glimepiride (D1690C00005), add-on to pioglitazone (MB102030), and add-on to insulin (D1690C00006) studies.

^b The non-inferiority (NI) for the comparison of the dapagliflozin group with the control group in adjusted mean change in HbA1c from baseline at Week 24 (LOCF) for the initial combination with metformin study or Week 52 (LOCF) for direct comparison to glipizide study was established based on the statistical testing with the upper limit of 95% CI for the adjusted mean difference between dapagliflozin monotherapy and control, which is less than the non-inferiority margin on 0.35%.

^c For the comparison between the dapagliflozin and glipizide groups (study D1690C00004), analysis was conducted for patients with HbA1c \geq 7% at baseline since the inclusion criteria for this study is different from other studies, which allow patients with HbA1C as low as 6.5% to enter the study; however, for all other studies, analyses were conducted for all patients regardless of baseline levels.

^d Percent (%) unadjusted was evaluated for the pooled analyses (dapagliflozin vs. placebo). However, for all other studies (dapagliflozin vs. metformin and dapagliflozin vs. glipizide) percent adjusted from baseline and 95% CIs were evaluated. Statistical testing was not performed.

In the placebo-controlled studies, the effect of dapagliflozin on HbA1c is both clinically meaningful and statistically significant. In direct comparisons with other approved drugs, changes in HbA1c achieved with dapagliflozin 10 mg are comparable in magnitude to foundational T2DM therapies, including metformin and glipizide.

The impact of the mean glycemic parameter changes is also depicted in terms of a key categorical responder assessment. Across the placebo-controlled studies in the dapagliflozin program, 16% more patients treated with dapagliflozin compared to control achieved HbA1c values < 7% at Week 24. This corresponds to 1 additional patient out of every 6 treated patients achieving this HbA1c target. This quantification of added population benefit comes from a synthesis of studies in both the monotherapy setting and also in the setting of add-on therapy with metformin, SUs, pioglitazone, and insulin. These categorical target assessments also demonstrate that dapagliflozin 10 mg is comparable to usual doses of either metformin or glipizide in achieving such targets for a T2DM population ([Table 55](#)).

Beyond glycemic control, treatment with dapagliflozin 10 mg is associated with a modest reduction in total body weight, resulting from the caloric loss associated with urinary glucose excretion ([Table 56](#)). This weight loss is maintained over time and is primarily attributed to a reduction in body fat, rather than muscle or fluid loss, as metabolic responses to glucosuria ultimately enhances fatty acid oxidation leading to adipose tissue decrements. As most patients with T2DM are either overweight and/or obese, and efforts by patients to lose weight are often undermined by therapies that lead to weight gain, treatment with dapagliflozin can help patients achieve and maintain weight loss over time.

Table 56: Weight Control Surrogate Benefits vs. Specific Therapies

Endpoint	Placebo-controlled Pool (5-studies; Week 24) ^a		Initial Combination with Metformin (Week 24)		Direct Comparison to Glipizide (Week 52)	
	Dapagliflozin 10 mg (N = 690)	Placebo (N = 689)	Dapagliflozin 10 mg (N = 219)	Metformin (N = 208)	Dapagliflozin 10 mg (N = 400)	Glipizide (N = 401)
Total body weight (kg)	N = 685	N = 683	N = 219	N = 208	N = 400	N = 401
Adjusted mean change from baseline (95% CI)	-2.03 (-2.26, -1.80)	-0.43 (-0.65, -0.20)	-2.73 (-3.19, -2.27)	-1.36 (-1.83, -0.89)	-3.22 (-3.56, -2.87)	1.44 (1.09, 1.78)
Mean difference from control (95% CI)	-1.61 (-1.93, -1.29)		-1.37 (-2.03, -0.71)		-4.65 (-5.14, -4.17)	
p-value	—		< 0.0001		< 0.0001	
Total body fat mass (%)^b	N = 82/89	N = 79/91	N/A	N/A	N/A	N/A
Adjusted mean change from baseline (95% CI)	-1.2 (-1.6, -0.8)	-0.2 (-0.6, 0.2)				
Mean difference from control (95% CI)	-1.0 (-1.5, -0.5)					
p-value	0.0003					

Table 56: Weight Control Surrogate Benefits vs. Specific Therapies

Endpoint	Placebo-controlled Pool (5-studies; Week 24) ^a		Initial Combination with Metformin (Week 24)		Direct Comparison to Glipizide (Week 52)	
	Dapagliflozin 10 mg (N = 690)	Placebo (N = 689)	Dapagliflozin 10 mg (N = 219)	Metformin (N = 208)	Dapagliflozin 10 mg (N = 400)	Glipizide (N = 401)
Total visceral adipose tissue volume (cm³)^b	N = 25/37	N = 30/42	N/A	N/A	N/A	N/A
Adjusted mean change from baseline (95% CI)	-322.6 (-485.1, -160.2)	-8.7 (-154.8, 137.4)				
Mean difference from control (95% CI)	-314.0 (-535.2, -92.7)					
p-value	0.0063					
Proportion (%) patients achieving weight loss ≥ 3%	N = 685	N = 683	N = 219	N = 208	N = 400	N = 401
Proportion adjusted, n (%) (95% CI for proportion)	259 (37.8) (34.2, 41.6)	105 (15.4) (12.7, 18.3)	105 (47.9) (41.3, 54.5)	55 (26.6) (20.6, 32.6)	222 (55.6) (50.7, 60.4)	24 (6.0) (3.6, 8.3)
Difference from control (95% CI)	22.4 (17.9, 26.9)		21.3 (4.55) (12.4, 30.3)		49.6 (2.75) (44.2, 55.0)	
p-value	—		—		<0.0001	

Table 56: Weight Control Surrogate Benefits vs. Specific Therapies

Endpoint	Placebo-controlled Pool (5-studies; Week 24) ^a		Initial Combination with Metformin (Week 24)		Direct Comparison to Glipizide (Week 52)	
	Dapagliflozin 10 mg (N = 690)	Placebo (N = 689)	Dapagliflozin 10 mg (N = 219)	Metformin (N = 208)	Dapagliflozin 10 mg (N = 400)	Glipizide (N = 401)
Proportion (%) patients achieving weight loss ≥ 5%	N = 685	N = 683	N = 219	N = 208	N = 400	N = 401
Proportion adjusted, n (%) (95% CI for proportion)	116 (16.9) (14.2, 20.0)	35 (5.1) (3.6, 7.1)	62 (28.3) (22.4, 34.3)	31 (14.9) (10.1, 19.8)	133 (33.3) (28.7, 37.9)	10 (2.5) (1.0, 4.0)
Mean difference from control (95% CI)	11.8 (8.6, 15.2)		13.4 (39.2) (5.7, 21.1)		30.8 (2.48) (26.0, 35.7)	
p-value	—		—		< 0.0001	

^a A subset of 5 studies from the Monotherapy/Combination Therapy Pool described in Section 3.2.1.2, comprised of patients treated in the morning from the monotherapy study MB102013 (Group 1 QAM groups), and those from the add-on to metformin (MB102014), add-on to glimepiride (D1690C00005), add-on to pioglitazone (MB102030), and add-on to insulin (D1690C00006) studies.

^b Parameter was measured only in study D1690C0012 (dapagliflozin 10 mg group vs. placebo group). Statistical testing was not performed.

Just as for glycemic control parameters, the impact of these mean weight changes is also depicted in terms of categorical responder assessments (% of patients achieving weight loss $\geq 3\%$ and $\geq 5\%$). Across the placebo controlled studies in the dapagliflozin program, 22% and 12% more patients treated with dapagliflozin compared to control achieved a weight loss of $\geq 3\%$ and $\geq 5\%$, respectively, at Week 24. This corresponds to 1 additional patient out of every 4 or 8 treated patients to achieve weight loss of $\geq 3\%$ and $\geq 5\%$, respectively, compared to placebo.

There is a tendency of many anti-diabetic therapies to promote weight gain as a consequence of insulin release (SUs), insulin sensitization (TZDs), or exogenous administration of insulin. These data show that dapagliflozin has a different and beneficial effect on patient weight that derives directly from its unique MOA.

To summarize, the pharmacology of dapagliflozin is relatively simple, directly acting at its SGLT2 co-transporter target in the kidney to enable controlled release of glucose in the urine. Dapagliflozin leads to its fundamental PD activity to release glucose based on 2 factors: 1) the degree of hyperglycemia that determines the amount of glucose filtered by the kidney; and 2) the adequacy of underlying renal function to effectively filter and release glucose as a result of SGLT2 inhibition. Thus, if longstanding diabetes decreases renal function, dapagliflozin will not be able to work effectively.

Dapagliflozin also acts independently of insulin release or action, and therefore quite differently than other T2DM therapies. Clinical data in combination with these traditional therapies demonstrate that dapagliflozin is complementary to their insulin-based actions, allowing flexibility of dapagliflozin use in all stages of T2DM.

8.3 Risks of Dapagliflozin

This section summarizes the safety and tolerability profile of dapagliflozin relative to pooled comparator data, and in some cases relative to risks of specific T2DM medicines. At this stage of development, the dapagliflozin profile is understood through assessments of adverse events, and also with evaluation of selected laboratory and PD measures (such as renal and hepatic laboratory tests and quantitative bone densitometry measures) collected from the clinical program. The scope of the dapagliflozin clinical program, which includes a total of 6228 patients at all stages of T2DM and on many conventional therapies including insulin, facilitates a robust analysis of common safety events and

frequently monitored laboratory tests and also enables exploratory safety assessments of uncommon and rare clinical events.

Safety and tolerability risk assessments are grouped into 2 categories based on the robustness of the number of events available for assessments: 1) identifiable safety risk assessments, which are primarily derived from knowledge of the MOA and based on a sufficient number of reported events to allow a fairly accurate assessment of risk, either confirming or excluding risk; and 2) exploratory safety risk assessments, which attempt to understand more uncommon or rare events as completely as possible. Although the clinical program is large, these exploratory assessments are imprecise at this stage of drug development given the small number of events available for analysis. Nevertheless, these rare events are characterized as completely as possible and estimated using the best available statistical methods.

8.3.1 Hypoglycemia

For any T2DM treatment, a thorough assessment of properties related to the risks of hypoglycemia provides important safety and tolerability risk information, particularly as a separate treatment in the setting of monotherapy and also in combination with other medicines known to lead to hypoglycemia (insulin and SUs). Although major hypoglycemic events are the most immediately life-threatening, all hypoglycemic events, including minor events as defined in Section 5.4.1, represent disconcerting adverse events for patients with T2DM and can pose barriers to achieving glycemic control targets.

Results across the clinical program indicate a minimal risk of hypoglycemia due to treatment with dapagliflozin (Table 57). Based on monotherapy clinical studies and studies in combination with metformin and TZDs, treatment with dapagliflozin 10 mg was associated with a low intrinsic propensity to cause hypoglycemia (Table 57). When dapagliflozin is used in combination with other agents that are recognized to lead to hypoglycemia, dapagliflozin treatment was associated with a measurable but low increased risk of contributing to hypoglycemia (Table 57). The hypoglycemic profile for dapagliflozin was also considerably reduced compared to the commonly used SU, glipizide, with approximately 1 out of every 2.5 patients experiencing a hypoglycemic event on glipizide compared to approximately 1 out of 29 with dapagliflozin.

Table 57: Hypoglycemia in Placebo-controlled and Direct Comparison with Glipizide Studies. Short-term Treatment Period (NDA Database)

Population		Dapagliflozin 10 mg	Control
		n = 1193	n = 1393
Placebo-controlled Pool ^a	Total*	10.2%	7.0%
	Major**	0.1%	0.1%
		n = 245	n = 251
Monotherapy Pool	Total*	2.9%	2.0%
	Major**	0	0
Add-on Combination Treatment			
		n = 226	n = 228
+ Metformin (Pool)	Total*	3.1%	3.1%
	Major**	0	0
		n = 140	n = 139
+ Pioglitazone	Total*	0	0.7%
	Major**	0	0
		n = 151	n = 146
+ Glimepiride	Total*	7.3%	4.8%
	Major**	0	0
		n = 196	n = 197
+ Insulin	Total*	42.3%	35%
	Major**	0.5%	0.5%
		n=400	n=401
Direct Comparison with Glipizide	Proportion, n (%) (95% CI)	14 (3.5) (1.7, 5.3)	162 (40.4) (36.1, 45.5)
	Mean difference from control (95% CI)	-37.2 (-42.3, -32.2)	—
	p-value	< 0.001	

* Total hypoglycemia included minor hypoglycemia, which was defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode.

**Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.

^a In the Placebo-controlled Pool, the All Dapa includes 20 mg and 50 mg in addition to dapagliflozin 2.5 mg, 5 mg, and 10 mg. Includes studies shown as well as initial combination with metformin studies and the pilot add-on to insulin study (MB102009).

8.3.2 Risks Potentially Related to Glucosuria

Risks related to the glucosuria that is caused by dapagliflozin include volume depletion; vulvovaginitis, balanitis and related genital infections; and UTIs. Glucosuria and associated physiological effects such as increased hematocrit are rapidly reversible. Therefore, any side effects and/or laboratory changes related to glucosuria can be expected to normalize after stopping dapagliflozin treatment.

These safety and tolerability findings with dapagliflozin are consistent with the glucosuria and increasing urine volume resulting from the inhibition of SGLT2. Modest mean reductions in blood pressure, especially for SBP, in dapagliflozin-treated patients were observed without any increase in orthostatic hypotension. There were no major signals for events related to volume depletion (Table 58) and no clinically meaningful mean changes in serum electrolytes, such as sodium and potassium.

Increased risks of UTIs and vulvovaginitis, balanitis, and related genital infections are likely to be a consequence, in part, of increased levels of urinary glucose. These infections were characterized by signs and symptoms similar to infections commonly seen in routine care of patients with T2DM in clinical practice, were manageable with conventional therapies when encountered, and rarely led to serious sequelae or discontinuation of therapy. As quantified in Table 58, vulvovaginitis, balanitis, and related genital infections are established to be more frequent in dapagliflozin-treated patients relative to comparator data. Over the short-term period, there was a 4.2% greater proportion of patients with genital infections among dapagliflozin-treated patients relative to placebo. This corresponds to 1 additional patient experiencing a genital infection for 24 treated patients.

Table 58: Identifiable Clinical Event Benefits and Risks Based on Pooled^a Data

	Dapagliflozin^b	All Control^c
Urinary tract infections (ST PBO-controlled Pool, NDA)	N = 1193	N = 1124
Proportion of patients with at least 1 event, n (%)	51 (4.34)	40 (3.54)
Difference from control, (%) (95% CI)	0.80 (-0.83, 2.42)	—
Vulvovaginitis, balanitis, and related genital infections (ST PBO-controlled Pool, NDA)	N = 1193	N = 1124
Proportion of patients with at least 1 event, n (%)	57 (4.78)	9 (0.80)
Difference from control, (%) (95% CI)	4.23 (2.70, 5.82)	—
Hypotension/dehydration/hypovolemia events (ST PBO-controlled Pool, NDA)	N = 1193	N = 1124
Proportion of patients with at least 1 event, n (%)	9 (0.75)	5 (0.44)
Difference from control, (%) (95% CI)	0.23 (-0.59, 1.08)	—
Fractures (ST + LT All Phase 2b & 3 Pool, 4MSU)	N = 4310	N = 1962
Proportion of patients with at least 1 event, n (%)	56 (1.30)	25 (1.27)
Difference from control, (%) (95% CI)	-0.13 (-0.87, 0.54)	—
All ALT/AST 3× ULN (ST + LT All Phase 2b & 3 Pool, 4MSU)	N = 4281	N = 1943
Proportion of patients with at least 1 event, n (%)	74 (1.62)	37 (1.92)
Difference from control, (%) (95% CI)	-0.29 (-1.03, 0.44)	—

^a Dapagliflozin 10 mg for urinary tract infections; vulvovaginitis, balanitis, and related genital infections; and hypotension/dehydration/hypovolemia events. All dapagliflozin for fractures and hepatic events. See Section 3.2.2 for details on all safety data pools.

^b All pooled data excludes the 1 mg treatment group from the low-dose monotherapy (MB102032) and dose-ranging (D1692C00005) studies

^c Control = placebo or active comparator drug

ST = short-term; PBO = placebo; NDA = New Drug Application; LT = long-term; 4MSU = 4-month safety update; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal;

UTIs were also numerous enough to identify a smaller but likely increase with dapagliflozin treatment relative to comparator data. Over the short-term period, there was a 0.8% greater proportion of patients with UTI among dapagliflozin-treated patients relative to placebo. This corresponds to 1 additional patient experiencing a UTI for 125 treated patients. Pyelonephritis was rare and balanced between treatment groups in the exploratory safety analysis of this more serious form of urinary tract/renal infections (Table 59).

One of the goals of the post-marketing safety pharmacovigilance program planned by BMS and AZ is to track that lower UTIs in closely monitored clinical trials are not associated with or do not progress to more significant problems with pyelonephritis in real-world experience.

Table 59: Exploratory Clinical Event Assessments Based on Pooled^a and/or Specific Study Data

	Dapagliflozin ^b	Control ^c
CV MACE plus UA (ST + LT All Phase 2b & 3 Pool, NDA)	N = 4287	N = 1941
Incidence rates estimate (per 100 patient-year)	1.11	1.64
Difference from control	-0.54	
(95% CI)	(-1.22, 0.14)	—
(98% CI)	(-1.34, 0.28)	
Malignant and unspecified tumors (12-MAY ICS)	N = 4559	N = 2239
Incidence rates, estimate (per 100 patient-year)	1.29	1.28
Difference from control (%)	0.01	
(95% CI)	(-0.58, 0.59)	—
p-value	0.9851	
Breast cancer (12-MAY ICS), females	N = 2223	N = 1053
Unstratified incidence rates (per 100 female patient-year)	0.37	0.09
Difference from control (%)	0.34	
(95% CI)	(-0.38, 0.90)	—
p-value	0.4933	
Bladder cancer (12-MAY ICS + D1690C00018 + D1690C00019)	N = 5478	N = 3156
Unstratified incidence rates (per 100 patient-year)	0.16	0.03
Difference from control (%)	0.12	
(95% CI)	(-0.18, 0.38)	—
p-value	0.6772	

Table 59: Exploratory Clinical Event Assessments Based on Pooled^a and/or Specific Study Data

	Dapagliflozin ^b	Control ^c
Pyelonephritis (ST + LT All Phase 2b & 3 Pool, 4MSU)	N = 4310	N = 1962
Proportion of patients with at least 1 event, n (%)	3 (0.07)	4 (0.20)
Difference from control, (estimate) (95% CI)	-0.13 (-0.65, 0.23)	—
Fractures (eGFR ≥ 30 and < 60 mL/min/1.73 m ² , MB102029, Week 52)	N = 168	N = 84
Proportion of patients with at least 1 event (%)	12 (7.14)	0 (0)
Difference from control, (estimate) (95% CI)	7.14 (2.62, 12.20)	—
Fractures (eGFR ≥ 45 and < 60 mL/min/1.73 m ² , 3A Subgroup, ^d 4MSU)	N = 268	N = 109
Proportion of patients with at least 1 event, n (%)	7 (2.61)	2 (1.83)
Difference from control, estimate (%) (95% CI)	-0.09 (-6.07, 5.45)	—
Hepatic events (ALT/AST + TBL $> 2 \times$ ULN) (ST + LT All Phase 2b & 3 Pool, 4MSU)	N = 4281	N = 1942
Proportion of patients with at least 1 event, n (%)	5 (0.12)	3 (0.15)
Difference from control, (estimate) (95% CI)	-0.05 (-0.52, 0.33)	—

^a See Section 3.2.2 for details on all safety data pools.^b All pooled data excludes the 1 mg treatment group from the low-dose monotherapy (MB102032) and dose-ranging (D1692C00005) studies^c Control = placebo or active comparator drug^d 3A Subgroup of moderate renal impairment: patients with baseline eGFR ≥ 45 to < 60 mL/min/1.73m² from the Placebo-controlled Pool and from study in diabetic patients with moderate renal impairment (MB102029)

MACE = major adverse cardiac events; UA = unstable angina; ST = short-term; LT = long-term; NDA = New Drug Application; 4MSU = 4-month safety update; ICS = integrated cancer summary; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin

8.3.3 Potential Effects on Bone

Dapagliflozin treatment had no overall effect on bone health in the general study population. However, in the study in patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73m²), an imbalance in the proportion of patients with fractures was observed (Table 59). Across the entire dapagliflozin clinical program, which includes patients with moderate renal impairment, the proportions of patients with fractures was balanced between groups (Table 58). Moreover, a refined exploratory safety assessment of a smaller number of fracture events in a larger pool of T2DM patients with stage 3A of moderate renal impairment (eGFR ≥ 45 to < 60 mL/min/1.73 m²) from both the special study and in patients from the rest of the clinical program demonstrates a closer degree of equipoise than is evident in the special moderate renal impairment study (Table 59).

Proportions of patients with events of fracture were calculated for the total clinical program and for each of the subgroups of moderate renal impairment. Results from the total T2DM clinical program population, including patients with moderate renal impairment, demonstrated that the difference in the proportions of patients with a fracture was ~0.13% for between dapagliflozin and control patients over the total treatment time of these various studies (All Phase 2b and 3Pool, Table 58). Although numbers are small, incidence rates of fractures in the special study of T2DM patients with moderate renal impairment do indicate a potential increased risk of fracture for patients treated with dapagliflozin, with a difference in the proportions of patients with an event of fracture in this special study of ~7% between dapagliflozin and control, over a 1-year period of treatment (Table 59).

Further subgroup analyses of patients in stage 3A of moderate renal impairment did not show a clear difference between dapagliflozin and control patients in the proportion of patients with fractures during short-term or long-term treatment. The overall proportions of 3A patients with fracture were 2.6% for dapagliflozin and 1.8% for placebo. However, the difference in proportions was estimated to be -0.09% (slightly favoring dapagliflozin) when the analysis was stratified by study (Table 59). After selecting the stage 3A patients, some clinical studies represented larger proportions of the dapagliflozin stage 3A patient pool than of the control stage 3A pool. Stratification by study was performed to remove this imbalance and to provide comparability of the two treatment groups. Thus,

the preponderance of this potential risk of fracture may rest in the more severely affected stage 3B subgroup, based on these targeted exploratory safety risk assessments. This evaluation, coupled with the increased glycemic benefit demonstrated in stage 3A of moderate renal impairment in T2DM patients, underpins the current BMS and AZ recommendation to consider use of dapagliflozin only in patients with underlying stage 3A of moderate renal impairment or better renal function.

8.3.4 Potential Cancer Risks

As described extensively in Section 5.5.1, exploratory safety risk assessments demonstrated comparable incidence rates between dapagliflozin-treated and control patients for all unspecified and malignant tumors. Calculated incidence rates are 1290 and 1280 cases per 100,00 patient-years for dapagliflozin and control, respectively ([Table 59](#)). Despite this equipoise in total neoplasms, imbalances in small numbers of 2 types of malignancies, namely breast and bladder cancers, have been noted and were tracked closely during the dapagliflozin clinical program, including close monitoring of new cases since submission of the NDA datasets. The most up-to-date assessments for these 2 cancers are described in detail in Sections 5.5.1.2 and 5.5.1.3. Exploratory safety risk assessments for these 2 cancer types, including unstratified absolute incidence rates, are provided in Table 59.

Breast malignancies were reported in 9 female patients treated with dapagliflozin and 1 female patient in the control group. One patient remains blinded in an ongoing study. The estimated incidence rate difference vs control was 339 events per 100,000 patient-years (95% CI: -381, 899), corresponding to detection of 1 excess case per 295 patient-years. Given the wideness of the CI, this range could suggest 1 excess case per 111 patient-years caused by treatment with dapagliflozin as a worst case scenario, and at best, 1 case per 262 patient-years prevented by treatment with dapagliflozin. The estimated lower limit is below 0 and the p value did not indicate statistical significance ($p > 0.10$), suggesting that this imbalance may have occurred by chance. However, the small number of events of breast cancer for dapagliflozin-treated relative to control patients currently limits the ability to assess causality based on statistical analyses.

There were no nonclinical signals of breast cancer. The clinical characteristics of the breast malignancies were typical. The events occurred relatively early in treatment, after randomization, and may represent pre-existing tumors. Overall, the available data suggest

that the likelihood of a causal association between dapagliflozin and breast cancer is small.

Bladder malignancies were reported for 9 patients treated with dapagliflozin and 1 patient in the control group. The estimated incidence rate difference vs control was 125 events per 100,000 patient-years (95% CI: -180, 376), corresponding to detection of 1 excess case per 800 patient-years. Given the width of the CI, this range could suggest 1 excess case per 266 patient-years caused by treatment with dapagliflozin as a worst case scenario, and at best, 1 case per 556 patient-years prevented by treatment with dapagliflozin. The estimated lower limit is below 0 and the p value did not indicate statistical significance ($p > 0.10$), suggesting that this imbalance may have occurred by chance. However, the small number of events of bladder cancer in dapagliflozin-treated compared to control patients currently limits the ability to assess causality based on statistical analyses.

Similar to events of breast cancer, there were no nonclinical signals for bladder cancer. Dapagliflozin does alter urine composition in humans, exposing the urinary bladder to higher glucose concentrations. However, dapagliflozin also has this effect in rodents, and no increase in bladder cancer was seen in 2-year rodent carcinogenicity studies. The clinical characteristics of the bladder malignancies were typical. As for breast cancer, bladder cancer events occurred relatively early in treatment, after randomization, and may represent pre-existing tumors. Overall, the available data suggest that the likelihood of a causal association between dapagliflozin and bladder cancer is small.

BMS and AZ are committed to further characterizing the incidence of breast and bladder malignancies in patients receiving dapagliflozin therapy beyond the Phase 3 program. Such information will be obtained from a dedicated CV and other clinical event outcome trial and in post-marketing observational studies

8.3.5 Potential Liver Health Risks

Details on hepatic safety evaluations for dapagliflozin are presented in Section 5.5.2. Overall, there was no clear association of dapagliflozin treatment at any dose with liver toxicity, and no evidence of severe drug-induced liver injury. One of the hepatic AEs reported in a dapagliflozin-treated patient was a case with an initial diagnosis of drug-induced hepatitis, and a subsequent alternative diagnosis of autoimmune hepatitis. This

patient responded to anti-inflammatory treatments consisting of prednisolone and, subsequently, azathioprine. Nonetheless, this case remains a concern due to of the difficulty differentiating between a drug-induced event and autoimmune hepatitis.

More significant liver test abnormalities, specifically hepatic event cases involving combined elevations of ALT or AST $> 3 \times$ ULN plus TBL $> 2 \times$ ULN were also evaluated in an exploratory safety assessment across the entire dapagliflozin clinical program. For this evaluation, a total of 8 events were detected, with the proportion over the total clinical trial treatment periods equal to $\sim 0.12\%$ to $\sim 0.15\%$ for dapagliflozin and control, respectively. Overall, the difference in proportions of dapagliflozin-treated patients vs control for ALT or AST $> 3 \times$ and TBL $> 2 \times$ ULN within 14 days was 0.05% (95% CI: -0.52% , 0.33%), favoring the dapagliflozin group; this corresponds to 1 case per 2000 patients (Table 59). Given the imprecision of the estimate, this range could suggest 1 excess case per 303 patients caused by treatment with dapagliflozin as a worst case scenario, and at best, 1 case per 192 patients prevented by treatment with dapagliflozin. The small number of laboratory assessment of ALT or AST $> 3 \times$ ULN and concomitant or subsequent TBL $> 2 \times$ ULN in dapagliflozin-treated vs control patients currently limits the ability to assess causality based on statistical analyses.

Over the short-term plus long-term treatment period, there was a 0.29% smaller proportion of patients with ALT or AST $> 3 \times$ ULN among dapagliflozin treated patients relative to placebo (Table 58). This corresponds to prevention of 1 patient experiencing a ALT/AST elevation $> 3 \times$ ULN for 344 treated patients

8.3.6 Potential Cardiovascular Risks

Evaluation of effects on CV risk is particularly important in T2DM patients, who are at increased risk of experiencing morbid and mortal CV events. As established in a pre-specified exploratory CV safety meta-analysis described in detail in Section 5.5.3, dapagliflozin treatment was not associated with increased CV risk (see also Table 59). The estimated HR for the primary composite endpoint of MACE plus unstable angina using a Cox proportional hazards method was 0.674 (98% CI: 0.385 , 1.178). These results met the requirement of an upper bound < 1.8 for the 95% CI for the HR in the FDA CV guidance.⁶³

As noted earlier, safety analyses demonstrated a modest lowering of blood pressure, consistent with dapagliflozin's mild diuretic effect due to inhibition of renal tubular glucose and sodium re-absorption. This modest reduction in blood pressure was observed with no increase in measured orthostatic hypotension.

Small increases in mean hematocrit were observed, but were not associated with any imbalance in thromboembolic events between dapagliflozin and comparator based on the CV safety meta-analysis.

8.3.7 Benefit-Risk Summary

In summary, potential risks associated with dapagliflozin are mainly related to its MOA and can be managed within standard clinical practice, generally without interruption of dapagliflozin treatment. The dapagliflozin clinical program was large and comprehensive, enabling definitive identification of some safety and tolerability risks (vulvovaginitis, balanitis, and related genital infections) and excluding any meaningful risk of many potential safety and tolerability issues suggested by dapagliflozin's MOA. Other uncommon or rare events, which have emerged as potential safety issues based on exploratory safety assessments during the dapagliflozin clinical program (bladder and breast cancer imbalances, possible fracture risks in moderate renal impairment, and rare hepatic events), represent preliminary safety risks and will be better understood with more clinical and/or observational population data. These potential risks should be contrasted against the reassuring CV safety meta-analysis data demonstrating no evidence for an increased CV risk with dapagliflozin. Preliminary findings suggest a hypothesis for CV benefit with dapagliflozin treatment, due possibly to glycemic, weight, and potential BP improvements. The proposed post-marketing CV outcome clinical study and complementary observational and pharmacovigilance population studies will further define the chronic safety profile of dapagliflozin for these exploratory safety risk assessments.

9 CONCLUSIONS

Dapagliflozin, with its novel yet straightforward mechanism of action, represents an unexpected yet effective choice for treating T2DM patients. By acting directly and specifically at the SGLT2 target in the kidney to eliminate glucose via an insulin-independent mechanism, dapagliflozin provides a unique treatment option. In essence, the capacity of the kidneys to eliminate glucose in the urine is harnessed in a controlled way, offering a useful and novel approach to reduce the hyperglycemia of T2DM with minimal impact on volume and salt balance.

Dapagliflozin provides clinically meaningful glycemic benefits on par with commonly used agents (metformin, SUs), with weight loss that is mostly from fat. These benefits are seen across the spectrum of T2DM — in drug-naïve patients early in their course of diabetes; in patients who have failed to achieve treatment goals with metformin, SUs, or pioglitazone; and finally in patients at later stages who are treated with insulin-based regimens.

With its unique MOA, dapagliflozin can play an important treatment role in these various clinical settings, dapagliflozin can help to relieve the cycle of increased insulin resistance, which contributes to the propensity for T2DM to developing and/or deteriorating, while weight gain and other metabolic and/or cardiovascular co-morbidities, such as hyperlipidemia and hypertension, worsen. Clinical studies demonstrate that glucosuria persists over time and remains stable during long-term treatment, resulting in maintenance of the reductions in HbA1c and FPG. This maintenance of effect is an important benefit due to the progressive nature of T2DM, particularly with respect to beta-cell dysfunction and insulin resistance due to glucotoxicity, which limits the efficacy of several of the existing anti-diabetic medications over time.

Dapagliflozin has a positive benefit-risk profile in a broad range of patients. Specific risks highlighted for assessment due to dapagliflozin's MOA have been thoroughly evaluated and are better understood. Most findings were either found not to be relevant, such as minimally increased urine volumes or negligible symptoms of polyuria or nocturia, or represent manageable issues. For example, increased UTIs and vulvovaginitis, balanitis and related genital infections in the presence of glucosuria were identified in the dapagliflozin clinical program, but individual cases were similar to those

commonly encountered in patients with T2DM and were managed with treatment approaches used in routine clinical practice. Theoretical possibilities in patients with declining renal function, such as hyperphosphatemia, secondary hyperparathyroidism, and a possible increased risk of fractures, have been noted. The lack of an imbalance in fractures in the rest of the dapagliflozin clinical program and the bone mineral density results from the body weight and composition study suggest that these risks can be avoided by limiting the use of dapagliflozin to patients with T2DM with eGFR values ≥ 45 mL/min/1.73m².

Based on exploratory safety assessments, selected uncommon or rare clinical events have emerged as potential safety issues, including bladder and breast cancer, fractures in moderate renal impairment, and rare hepatic events. These potential safety risks will be better understood with additional clinical and/or observational population data. Results from a CV safety meta-analysis across the dapagliflozin program suggest that there is no evidence for increased CV risk with dapagliflozin treatment, and raises the hypothesis of possible CV benefit. The commitment by BMS and AZ to conduct a large, randomized clinical study to understand hypothesized CV benefits and concurrently evaluate cancer, fractures and liver safety, will further elucidate these preliminary findings.

Overall, dapagliflozin can provide value to the patient and the health care provider alike, contributing in a useful and complementary fashion toward more effective management of T2DM, one of the most progressive, challenging, and widely prevalent disorders we face.

10 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACEI	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AZ	AstraZeneca
BMD	Bone mineral density
BMI	Body mass index
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
CEC	Clinical evaluation committee
CI	Confidence interval
CKD	Chronic kidney disease
CrCL	Creatinine clearance
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome
DBP	Diastolic blood pressure
DPP-4	Dipeptidyl peptidase-4 inhibitor
DXA	Dual-energy X-ray absorptiometry
e	Estimated
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
Glip	Glipizide
HAC	Hepatic Adjudication Committee
HbA1c	Hemoglobin A1c
HCTZ	Hydrochlorothiazide

Abbreviation or special term	Explanation
HDL	High-density lipoprotein
HR	Hazard ratio
IU	International Unit
LD	Low-density lipoprotein
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
MOA	Mechanism of action
Mono	Monotherapy
MRHD	Maximum recommended human dose
NYHA	New York Heart Association
OAD	Oral anti-diabetic drug
OCT	Organic anion transporters
PD	Pharmacodynamic
PK	Pharmacokinetic
PPG	Post-prandial glucose
PT	Preferred term
PTH	Parathyroid hormone
QTc	A time measurement of a portion of a heartbeat
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGLT2	Sodium glucose cotransporter 2
SMQ	Standard MedDRA Query
SOC	System organ class
ST	Short-term
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin

Abbreviation or special term	Explanation
TZD	Thiazoldinedione
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
Vs	Versus
XR	Extended release
ZDF	Zucker Diabetic Fatty

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