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APPLICATION NUMBER:
202293Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 24, 2013
From	Karen Murry Mahoney, MD, FACE
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 202293
Supplement#	NDA resubmission for consideration for initial approval
Applicant	Bristol-Myers Squibb and AstraZeneca
Date of Submission	July 11, 2013
PDUFA Goal Date	January 11, 2014
Proprietary Name / Established (USAN) names	Farxiga® dapagliflozin
Dosage forms / Strength	Tablets, 5 and 10 mg
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	Approval

1. Introduction

Farxiga® (dapagliflozin), hereafter referred to as dapa, is a sodium glucose co-transporter 2 inhibitor (SGLT2i), proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. After a previous Complete Response action by the Agency, and after formal dispute resolution resulted in affirmation of the FDA decision, Bristol-Myers Squibb has resubmitted their application with new data to support reconsideration for approval.

For more complete information regarding dapagliflozin, please see the various discipline reviews from 2011 and 2013; and the original review cycle memoranda from the 2011 Cross-Discipline Team Leader (Dr. Ilan Irony, DARRTS 6 Dec 2011), Division Director (Dr. Mary Parks, DARRTS 22 Dec 2011), and Office Director (Dr. Curtis Rosebraugh, DARRTS 17 Jan 2012).

This Cross-Discipline Team Leader memorandum will discuss the major findings of updated reviews, by multiple FDA disciplines, of the 2013 NDA resubmission. Areas of focus in the memorandum include the following:

- Overall efficacy findings
- Malignancy, and in particular bladder cancer
- Hepatic safety
- Macrovascular adverse events
- Adverse events of special interest for the SGLT2i class, including genital mycotic infections, urinary tract infections, volume-depletion-related adverse effects, and renal adverse effects
- Current balance of risk and benefit

2. Background

Type 2 diabetes mellitus (DM2) is one of the most prevalent diseases in the United States, having been diagnosed in over 7% of the U.S. adult population, and DM2 is rising in incidence. The actual incidence far exceeds 7%, because screening studies have revealed that undiagnosed diabetes is even more common than diagnosed diabetes (Cowie et al 2009). The disease exerts an enormous negative impact on the lives of patients. In the United States, diabetes is the leading cause of blindness among adults ages 20-74 years, of end-stage kidney disease, and of nontraumatic limb amputation. The cost of diabetes is enormous; in 2007, estimated direct medical costs were \$174 billion, with an additional \$58 billion in indirect costs such as disability, work loss and premature mortality (National Institute of Diabetes and Digestive and Kidney Diseases, National Diabetes Information Clearinghouse, accessed 20 Dec 2013). These costs continue to increase.

At present, most published guidelines recommend metformin as the first drug to be used in the treatment of type 2 diabetes. However, some patients cannot tolerate metformin, and many (perhaps most) patients with type 2 diabetes will require an additional agent in order to achieve adequate glycemic control, particularly if the patient begins with a higher hemoglobin A1c (HbA1c) (Inzucchi et al 2012). Therefore, there is a need for additional agents for the treatment of DM2. Each of the currently available classes of drugs for the treatment of DM2 has its own set of limitations. Two particularly desirable attributes of a drug for the treatment of DM2 are a low incidence of hypoglycemia, and body weight neutrality (or a favorable body weight effect). The SGLT2i class, for which dapagliflozin would be the second-in-class if approved, appears to have both attributes.

Dapagliflozin's inhibition of SGLT2 blocks the primary method by which the kidney reabsorbs glucose, and results in excretion of glucose in the urine.

Dapagliflozin was previously considered for approval, after submission of its original NDA in December 2010. It underwent review, and then Advisory Committee (AC) discussion in July 2011.

At the time of the July 2011 AC, data for 14 Phase 2b and 3 trials were considered, with a total of approximately 4300 patient-years of dapagliflozin exposure. At that AC, the advisors were concerned about a relative lack of efficacy in patients with moderate to severe renal impairment, and about several safety concerns (imbalances in female breast cancer and male bladder cancer cases, and a case of possible drug-induced liver injury). The AC voted against approval (6 for, 9 against).

At the time of the initial NDA submission, several trials were still ongoing, and the Agency asked for updated information from these trials to better assess the impact of additional exposure on the malignancy and liver safety signals, and to further explore cardiovascular safety. The original NDA submission had had a favorable point estimate for a meta-analysis of major adverse cardiovascular events. In November, 2011, the applicant submitted additional

data; at that point, the Agency then had data from 19 trials, with dapagliflozin exposure of approximately 5700 patient-years. In those data, the male-specific incidence rate ratio (IRR) for bladder cancer increased slightly from 5.1 to 5.4 (95% CI 0.84, 122.2), and the female-specific breast cancer IRR declined from 4.0 to 1.9 (0.5, 8.9). The FDA's hepatic safety consultant felt that drug-induced liver injury could still not be ruled out for the previous case of concern. Regarding cardiovascular safety, rather than providing definitive evidence of CV benefit, or stable reassurance of CV safety, the new data actually showed an increase in the point estimate for the hazard ratio (HR) for major adverse cardiovascular events, with the HR increasing from 0.67 (95% CI 0.38, 1.18) to 0.82 (0.58, 1.15), for the "MACE+" composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina. This increase was due to discordant results between two trials (Trials 18 and 19) which had been enriched with patients with higher cardiovascular risk, and the other 17 trials in the database at that point. Trials 18 and 19 had been ongoing at the time of NDA submission; at the time of the Major Amendment, however, they contributed 40% of all events to the composite. When one considered only these two trials, the HR for MACE+ was >1 (1.07, 95% CI 0.64, 1.77). When one looked only at the standard MACE endpoint (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke), the HR was 1.27 (0.69, 2.31). Thus, the CV safety findings did not offset the other safety concerns, and the benefit:risk picture did not improve as a result of the November 2011 Major Amendment.

The drug was not approved, and on January 17, 2012, a Complete Response letter was issued. Safety concerns identified as reasons for non-approval of the application included:

- Numerical imbalances in cases of bladder and breast cancer
- A suspected case of drug-induced liver injury, for which another likely etiology could not be identified, and
- Discordant results for macrovascular risk evaluation between the original cardiovascular meta-analysis population (which had a favorable hazard ratio point estimate for composites of major adverse cardiovascular events), and a group of patients from two ongoing trials (Studies 18 and 19) enriched for higher baseline cardiovascular risk (this population had an unfavorable point estimate).

The "path forward" specified in the 2012 Complete Response letter stated:

"To address the above deficiencies, you will need to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, the resubmission must include data from patients in Studies 18 and 19 who have completed at least 52 weeks of these trials. Analyses of the data should include the following:

- Updated information on bladder cancer events and new risk estimates
- Updated review of hepatic safety, including cases that meet the definition of biochemical Hy's law with narratives of each case and incidence of transaminase elevations at 3x, 5x, 10x, and 20x ULN (upper limit of normal) in both dapagliflozin and comparator groups, and
- Updated CV (cardiovascular) meta-analysis including an analysis of MACE (major adverse cardiovascular events).

We acknowledge your plans to initiate a CV outcomes trial in the fourth quarter of 2012. We strongly advise you to continue with those plans should data from that trial be necessary for consideration in a resubmission to this complete response.”

After the Complete Response, the applicant requested formal dispute resolution. In their request, they proposed:

- That CV data from Studies 18 and 19 be viewed in the context of the overall CV risk assessment of dapagliflozin and not as stand-alone studies, and
- That the overall benefit/risk assessment of dapagliflozin recognize the demonstrated benefits of dapagliflozin on glycemic control, weight loss and reduction in blood pressure, as well as the “questionable and scientifically improbable” risks pertaining to bladder cancer and liver safety.

On September 14, 2012, the FDA denied the applicant’s request. In the denial letter, the “path forward” included the same requirements as had been specified in the Complete Response letter. Additionally, Dr. Kweder, the signatory authority for the Dispute Resolution Denial, stated that the resubmitted NDA should be brought before an Advisory Committee, for discussion of updated information on malignancy, hepatic safety, and CV risk. Dr. Kweder also stated that a nonclinical study should be conducted to assess the issue of potential tumor promotion by dapagliflozin, but she stated that it would be reasonable to conduct this study in the postmarketing period.

Although not approved in the United States, dapagliflozin is approved in several other countries, including those in the European Union, and in Argentina, Australia, Brazil, Mexico and New Zealand.

3. Chemistry, Manufacturing and Controls

Overall, the Chemistry, Manufacturing and Controls team recommends approval of this NDA.

No new CMC data were required to be submitted with this resubmission. In the previous review cycle, Dr. Xavier Ysern, the CMC reviewer, did not identify any issues that would preclude approval. In this review cycle, Dr. Ysern has reviewed the carton and container labeling, and the sections of the proposed Full Prescribing Information which are relevant to CMC, and he continues to find no issues which would preclude approval. He also reviewed newly submitted stability data, and concurs with a 24 month expiry (DARRTS 31 Oct 2013).

Dapagliflozin is to be supplied as film-coated tablets (5 mg and 10 mg) for oral administration.

4. Nonclinical Pharmacology/Toxicology

Overall, the nonclinical team recommends approval of dapagliflozin.

Please see Dr. Mukesh Summan's 2011 review of the original NDA, and his resubmission review from 2013 (DARRTS 9 Dec 2013).

Nonclinical studies were not required as part of the "path forward" for this resubmission, but the applicant chose to submit several studies intended to address the bladder cancer concern.

In 2011, dapagliflozin had not been found to be a direct carcinogen, after review of the applicant's standard 2-year rodent carcinogenicity study. However, this study did not address the potential of dapagliflozin to promote pre-existing bladder lesions in the *in situ* microenvironment of changes in urinary volume, flow and composition in the bladder that one might expect to see with clinical use of dapagliflozin. Although the applicant submitted the results of several other nonclinical studies related to bladder cancer, none of the newly submitted studies addresses this issue fully.

In a nonclinical rodent model of diabetes (ZDF male rats), transcriptional profiling was conducted for genes involved in cell cycle regulation and tumor promotion, for liver, kidney, fat and skeletal muscle. Of all genes examined, only one cell cycle and tumor-promoting gene (Stathmin 1) was upregulated, in adipose tissue, at end of treatment. Although this study did not suggest tumor promoter transcriptional changes, Dr. Summan felt the study was of limited value, as bladder tissue was not evaluated.

The applicant also examined six human bladder transitional cell carcinoma (TCC) cell lines, exposed to varying concentrations of dapagliflozin, the metabolite dapagliflozin-3-O-glucuronide, or glucose, *in vitro*. Transitional cell carcinoma cell line growth was not enhanced. Although this adds to the weight of evidence that dapagliflozin is not a tumor promoter, evaluation of TCC cell lines with dapagliflozin and glucose in isolation does not account for the bladder microenvironment changes in urine volume, flow and composition that would occur with dapagliflozin use in the clinical setting.

The applicant also used a tumor promotion xenograft model, in which human bladder TCC cell lines were implanted subcutaneously in the flank of immunodeficient (nude) mice. The human bladder tumors were allowed to establish themselves prior to low- and high- dose treatment with dapagliflozin and the glucuronide metabolite. These treatments did not enhance tumor growth relative to no treatment in control mice. Again, however, because the tumors were not implanted in the bladder itself, this study does not address potential promotion under the bladder microenvironment changes one might expect to see with dapagliflozin in clinical use.

Dr. Summan notes that there are more appropriate models which could be used to address this question, including orthotopic models where tumor cells are implanted into the bladder itself. Another rodent model for bladder tumors uses 4-hydroxybutyl(butyl)nitrosamine as a tumor initiator followed by the test promoter. Both of these models would more closely resemble the clinical use of dapagliflozin.

To summarize the updated nonclinical information regarding dapagliflozin, the drug and its metabolites do not show evidence of direct carcinogenicity. The applicant has submitted several studies intended to address tumor promoter potential, and none of these studies

demonstrate a risk. However, they do not fully address the question, because the animals did not have human bladder cancer in their bladders, exposed to the typical bladder microenvironment changes produced by dapagliflozin. There are possible models to address this question, and at the December 12, 2013, Advisory Committee meeting, the applicant stated in public that the applicant intends to conduct such studies in the postmarketing period. The FDA nonclinical team feels that the overall nonclinical evaluation supports approval of dapagliflozin at this time, and is in discussions of the most appropriate approach to further (postmarketing) evaluation of bladder tumor promotion potential.

5. Clinical Pharmacology/Biopharmaceutics

Overall, the Clinical Pharmacology team recommends approval.

No new clinical pharmacology data were submitted with this review. Please see Dr. Ritesh Jain's reviews from 2011.

Key elements of the Clinical Pharmacology review are briefly presented here.

Pharmacokinetics:

Absorption:

- Tmax 2 hours

Distribution:

- Protein binding 91%

Metabolism:

- Primarily by UGT1A9
- Half-life 12.9 hours

Excretion:

- 75% excreted renally, primarily as glucuronide metabolite
- 1.2% of dose excreted as parent drug

Pharmacodynamics:

- Characterized over wide dose range (1 mcg to 500 mg)
- Upper end of dose-response curve for glycosuria appears to be at 10 mg
- For doses >10 mg, no additional hemoglobin A1c lowering, but increased incidence of genitourinary infections, hyperphosphatemia and increases in hematocrit

Intrinsic/Extrinsic Factors:

- Intrinsic Factors: no dose adjustment appears necessary based on age, gender or hepatic function

- Extrinsic Factors: no dose adjustment appears necessary based on food intake, or for a wide variety of tested co-administered drugs

During this review cycle, Clinical Pharmacology commented on the proposed dosing regimen, and on the use of dapagliflozin in patients with moderate renal impairment (defined as an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73m²). Please see Dr. Jain's memorandum (DARRTS 17 Dec 2013).

The applicant's proposed dosing regimen is "5 or 10 mg taken once daily." In Dr. Jain's 2013 review, he recommended that the 10 mg dose be approved as the starting dose for most patients with normal renal function, and in patients with mild renal impairment (eGFR 60-<90 mL/min/m²), "if clinical review finds the safety profile of the 10 mg dose acceptable." He states that in phase 3 studies in which both the 5 and 10 mg doses were tested, the 10 mg dose consistently showed greater mean reductions in hemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG) than the 5 mg dose, and more patients achieved an HbA1c of <7% with the 10 mg dose than with the 5 mg dose. The safety profiles of the 5 and 10 mg doses appeared to be similar. For this reason, he recommended 10 mg as a starting dose for most patients. However, he recommended a 5 mg starting dose for patients at risk of volume depletion, and in elderly patients.

During internal labeling discussions, the pros and cons of various dosing regimens were discussed extensively. Dr. Jain's recommendations are well-considered. After discussion with full group of all review disciplines, the decision was made to recommend a dosing regimen which parallels that of the currently approved SGLT2i, canagliflozin, for which the lower available dose is the recommended starting dose for all patients, with the possibility of uptitration in patients who tolerate the starting dose well, but need additional glycemic control. For dapagliflozin, this would be a starting dose of 5 mg, with the possibility of uptitration to 10 mg. This approach has the advantage of identifying those patients who do not tolerate the volume-depletion-related effects of the drug at the lower dose of 5 mg, before exposing them to the higher dose of 10 mg (although one cannot definitively predict that volume depletion symptoms or other adverse effects would worsen with an increase in dose, as this was not noted in the trials). Dr. Jain and his team leader, Dr. Lokesh Jain, are in agreement with this approach. As of 21 Dec 2013, labeling negotiations with the applicant are ongoing.

Dr. Jain concurs with the applicant that dapagliflozin did not demonstrate efficacy in patients with eGFR < 60 mL/min/m². In Study 2029, a dedicated study in patients with eGFR in this range, the mean placebo-subtracted changes from baseline to 24 weeks in HbA1c were -0.08 (95% CI -0.37, 0.20) for the 5 mg dose, and -0.11(-0.40, 0.17) for the 10 mg dose. This reduction in HbA1c is not statistically significant, and even had it been statistically significant, would not be clinically meaningful in terms of absolute reduction.

6. Clinical Microbiology

No new microbiology data were submitted with this application. In 2011, Dr. Steven Fong recommended approval.

7. Clinical/Statistical- Efficacy

Dr. Wei Liu, the efficacy statistics reviewer, and Dr. Frank Pucino, the clinical reviewer, both recommend approval of this NDA.

Please see the 2011 reviews by Dr. Jonathan Norton (efficacy statistics) and Dr. Somya Dunn (clinical) and the reviews of the resubmission by Dr. Wei Liu (13 Dec DARRTS 2013) and Dr. Frank Pucino (DARRTS 22 Dec 2013).

In 2010/11, efficacy data from 11 trials were considered. For this resubmission, including those 11 original trials, efficacy data from a total of 16 trials were now considered. These included two monotherapy diabetes treatment trials, nine combination therapy diabetes treatment trials, one special population trial in patients with moderate renal impairment, two special population trials in patients with hypertension, and two special population trials in patients with cardiovascular disease. The following tables briefly list these trials:

Table 7.1: Phase 3 Trials for Dapagliflozin							
Type of Trial	Study ID	Pop	Dose (mg)	Bkgrd Therapy	Compar	I° Endpt	Dur (Wks)
Monotherapy	MB102013	Drug-naïve	Dapa 2.5, 5, 10	None	Pbo	HbA1c	24 (+ext)
	MB102032	Drug-naïve	Dapa 1, 2.5, 5	None	Pbo	HbA1c	24
Combination Therapy	MB102014	Inad contr on bkgrd	Dapa 2.5, 5, 10	Met	Pbo	HbA1c	24 (+ext)
	D1690C00005	Inad contr on bkgrd	Dapa 2.5, 5, 10	Glim	Pbo	HbA1c	24 (+ext)
	MB102030	Inad contr on bkgrd	Dapa 5, 10	Pio	Pbo	HbA1c	24 (+ext)
	D1690C00004	Inad contr on bkgrd	Dapa 2.5, 5, 10 (titr)	Met	Glip	HbA1c	52 (+ext)
	D1690C00012	Inad contr on bkgrd	Dapa 10	Met	Pbo	Body wt (HbA1c II°)	24 (+ext)
	D1690C00010	Drug-naïve or inad contr on bkgrd	Dapa 10 + sita	Sita and/or met	Pbo	HbA1c	24+24
	MB102021	Drug-naïve with higher HbA1c	Dapa 5 + met	None	Dapa 5, met	HbA1c	24

Table 7.1: Phase 3 Trials for Dapagliflozin							
Type of Trial	Study ID	Pop	Dose (mg)	Bkgrd Therapy	Compar	I° Endpt	Dur (Wks)
	MB102034	Drug-naïve with higher HbA1c	Dapa 10 + met	None	Dapa 10, met	HbA1c	24
Special pop (renal)	MB102029	eGFR 30-60	Dapa 5, 10	Any except met	Pbo	HbA1c	24 (+ext)
Special pop (htn)	MB102073	Htn	Dapa 10	OAD and/or insulin	Pbo	SBP + HbA1c (co- I°)	12
Special pop (htn)	MB102077	Htn	Dapa 10	OAD and/or insulin	Pbo	SBP + HbA1c (co- I°)	12
Special pop (CVD + htn)	D1690C00018	CVD + htn	Dapa 10	OAD and/or insulin	Pbo	3-part compos	24 (+ext)
Special pop (CVD)	D1690C00019	CVD	Dapa 10	OAD and/or insulin	Pbo	3-part compos	24 (+ext)

Source: Table 2.1, beg pg 6, statistical review by Dr. Wei Liu, DARRTS 13 Dec 2013
Abbreviations: 3-part comp = three-part composite endpoint of hemoglobin A1c reduction of $\geq 0.5\%$, body weight reduction of $\geq 3\%$, and systolic blood pressure reduction of ≥ 3 mm Hg; bkgrd = background; compar = comparator; compos = composite; CVD = cardiovascular disease; contr = control; Dapa = dapagliflozin; dur = duration; eGFR 30-60 = estimated glomerular filtration rate 30-60 mL/min/1.73 m²; endpt = endpoint; ext = extension; glim = glimepiride; glip = glipizide; HbA1c = hemoglobin A1c; htn = hypertension; ID = identification; inad = inadequate; met = metformin; OAD = oral antidiabetic agent; pbo = placebo; pop = population; SBP = systolic blood pressure; sita = sitagliptin; wt = weight

Baseline characteristics were generally similar between dapa-exposed and comparator-exposed patients.

Across these trials, the mean reductions in hemoglobin A1c were consistent, with the exception of the trial in patients with moderate renal impairment (Study MB102029), in which dapagliflozin was ineffective, as discussed above in the Clinical Pharmacology section. The applicant does not recommend use of dapagliflozin in patients with an eGFR < 60 mL/min/1.73m². Effects on secondary endpoints, such as the percentage of patients achieving an HbA1c $< 7\%$, and reductions in fasting plasma glucose, systolic blood pressure, and body weight, were also consistent across most trials. A consistent small increase in low-density lipoprotein cholesterol was also seen consistently. The following table provides an integrated analysis of the pooled placebo-controlled trials, with endpoints measured at 24 weeks:

Table 7.2: Efficacy Parameters After 24 Weeks of Treatment in Pooled Placebo-Controlled Studies for Dapagliflozin 5 mg and 10 mg in Patients with Type 2 Diabetes Mellitus

Endpoint	Dapa 5 mg	Dapa 10 mg
HbA1c, %, pbo-adj mean change from BL (95% CI, p-value)	-0.51 (-0.58, -0.43, <0.0001)	-0.52 (-0.58, -0.47, <0.0001)
Percentage of patients achieving HbA1c <7%	20%	20%
FPG, mg/dL, pbo-adj mean change from BL (95% CI, p-value)	-22 (-26, -19, <0.0001)	-25 (-27, -22, <0.0001)
Body wt, kg, pbo-adj mean change from BL (95% CI, p-value)	-1.4 (-1.6, -1.2, <0.0001)	-1.8 (-2.0, -1.7, <0.0001)
SBP, mm Hg, pbo-adj mean change from BL (95% CI, p-value)	-2.3 (-3.3, -1.3, <0.0001)	-3.2 (-4.1, -2.3, <0.0001)
LDL, mg/dL, pbo-adj mean change from BL (95% CI, p-value)	+2.5 (0.2, 4.7, 0.0337)	+3.3 (1.7, 5.0, 0.0001)

Source: Table 3.3.1, beg pg 6, statistical review by Dr. Wei Liu, DARRTS 13 Dec 2013

Abbreviations: adj = adjusted; BL = baseline; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein cholesterol; pbo = placebo; SBP = systolic blood pressure; wt = weight

The above integrated analyses were generated mostly for descriptive purposes, and Dr. Liu recommends some caution in interpreting the pooled results, but they are useful in illustrating the expected changes in these parameters. Please see Dr. Liu's 2013 review, Dr. Pucino's 2013 review, and Dr. Norton's 2011 review, for individual trial results.

Of note in the above table is the appearance that the 5 and 10 mg doses do not appear to differ much in their placebo-subtracted effects on HbA1c. However, when one looks at individual trials, where one can actually compare dose arms, there was a fairly consistent numerical difference between the 5 mg and 10 mg doses, as shown in the following table.

Table 7.3: Placebo-Subtracted Percent Change from Baseline in Hemoglobin A1c from Baseline to 24 Weeks, Placebo-Controlled Studies of Dapagliflozin with Both 5 mg and 10 mg Dose Arms

Study Number	Placebo-Subtracted Change in HbA1c (%)	
	5 mg Dose Group	10 mg Dose Group
MB102013	-0.54	-0.66
MB102014	-0.41	-0.54
D1690C00005	-0.49	-0.68
MB102030	-0.40	-0.55
D1690C00006	-0.52	-0.60

Source: Tables 4 (pg 11), 10 (pg 17), and 16 (pg 21), Dr. Jonathan Norton's statistical review from 2011

The observed changes in HbA1c are comparable to those seen with multiple other classes of drugs for the treatment of type 2 diabetes mellitus.

In Study -004, the active control trial versus glipizide, dapagliflozin was noninferior to glipizide at the primary endpoint of 52 weeks, but at multiple time points before 52 weeks, glipizide exhibited greater HbA1c reduction than did dapagliflozin.

The observed changes in systolic blood pressure and body weight are small, but are nevertheless desirable attributes in a drug for the treatment of DM2. Obesity is a primary causative factor in DM2, and weight loss is very difficult for most patients. Some other classes of drugs, such as sulfonylureas, thiazolidinediones and insulins, are associated with weight gain. Control of blood pressure is very important in DM2, particularly for prevention of progression of renal disease. While the magnitude of these changes might not warrant a primary indication for weight loss or blood pressure control for dapagliflozin, these small changes in a desirable direction contribute positively to the benefit:risk assessment of the drug.

On the other hand, the observed elevation in LDL is undesirable, although again, small in magnitude. Under current standards of care, patients with DM2 are to have LDL monitoring, and providers should add LDL-lowering medications when indicated.

One statistical issue which Dr. Liu discusses in his review is the use of the last-observation-carried-forward (LOCF) method as the primary method for accounting for missing data. This method disregarded observations recorded after rescue treatment. This method is sometimes problematic, but Dr. Liu repeated the analyses for several studies using a Mixed Model Repeated Measure method, and achieved comparable results to those seen with LOCF.

8. Safety

Dr. Eugenio Andraca-Carrera, the safety statistics reviewer, recommends approval of this application. As mentioned above, Dr. Frank Pucino, the clinical reviewer, also recommends approval. In 2011, Dr. Somya Dunn, the clinical reviewer at that time, also recommended approval. Please see Dr. Dunn's 2011 review, and Dr. Irony's 2011 CDTL memo, for a more comprehensive overview of the safety of dapagliflozin. This CDTL memo will concentrate on those issues which were identified in the "path forward" for the Complete Response from the original review cycle.

Please see Section 2 above for a regulatory history, and a description of the key safety findings which led to the original Complete Response action.

Across the pool of all Phase 2b and Phase 3 studies, 5936 patients were exposed to dapagliflozin, and 3403 patients were exposed to placebo. Total patient-years of exposure were 6738 for dapagliflozin and 3955 for placebo. This amount of exposure is higher than that which was available at the time of approval of canagliflozin, and reflects the Agency's requirement for additional dapagliflozin exposure in the resubmission, to further clarify dapagliflozin's risks.

The percentage of patients who died was similar between dapa- and comparator-treated patients (0.6% vs 0.7%). Causes of death were similar between treatments; as expected,

cardiovascular causes predominated. The percentage of patients with serious adverse event(s) was also similar (dapa 10.1%, comparator 12.0%), and the types of serious adverse events did not differ substantially between dapagliflozin and comparator.

The remainder of this safety section will focus on the following issues:

- Cardiovascular outcomes
- Malignancy, and in particular bladder cancer
- Hepatic safety
- Adverse events of special interest for the SGLT2i class, including genital mycotic infections, urinary tract infections, volume-depletion-related adverse effects, and renal adverse effects

8.1. Macrovascular Outcomes

Please see Dr. Andraca-Carrera’s safety statistics review (DARRTS 16 Dec 2013) for further details.

As discussed in Section 2, at the time of the July 2011 AC, dapagliflozin had been associated with a favorable hazard ratio for major adverse cardiovascular events. However, at the time of a Major Amendment in November 2011, additional data, largely from two trials enriched in patients at higher CV risk, resulted in an increase in that hazard ratio. Now, in 2013, additional patient-years of exposure are available. The following table details exposure and events available for the July 2011 AC, the November 2011 Major Amendment, and the 2013 resubmission.

Table 8.1.1: Data Available for Meta-Analysis, 2011 and 2013, for Prespecified Primary Composite Endpoint of MACE+ (Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke, and Hospitalization for Unstable Angina)				
		July 2011 AC (14 Trials)	November 2011 Major Amendment (19 Trials)	2013 Resubmission (21 Trials)
Subjects	Dapa	4287	5498	5936
	Comp	1941	3184	3403
Patient-years	Dapa	4344	5738	6594
	Comp	1849	3095	3831
Events	Dapa	48	82	97
	Comp	30	63	81
Source: Advisory Committee presentation by Dr. Andraca-Carrera, Slide 10, 12 Dec 2013 AC = Advisory Committee; Comp = comparator; Dapa = dapagliflozin				

In the 2013 meta-analysis, 43/97 events among dapa-treated patients came from Trials 18 and 19, two trials enriched with patients with cardiovascular disease.

The following table displays some baseline cardiovascular risk characteristics for patients enrolled in Studies 18 and 19, and those enrolled in the other 19 trials.

Study 8.1.2: Baseline Cardiovascular Risk Factors for Studies 18 and 19, and for the Pool of 19 Other Trials in the 2013 Meta-Analysis		
Risk Factor	Trials 18 and 19 N=1887 % with Risk Factor	Other Trials N=7452 % with Risk Factor
History of cardiovascular disease	99.5	17.9
History of hypertension	96.2	60.8
History of dyslipidemia	84.2	49.9
History of congestive heart failure	14.3	1.8
Current or former smoker	59.6	40.5
Systolic blood pressure at baseline >140 mm Hg	37.6	24.6
Diabetes duration ≥10 years	58.0	20.4
Estimated glomerular filtration rate <60 mL/min/1.73 m ²	17.4	10.2

Source: Slide 27, Dr. Andraca-Carrera's presentation, Advisory Committee 12 Dec 2013

The following table presents the 2013 meta-analysis results, for the overall meta-analysis, and for data from Studies 18 and 19 alone.

Table 8.1.3: Cardiovascular Outcomes Meta-Analysis Results for 2013 Resubmission, for All 21 Trials Combined, and for Trials 18 and 19 Alone							
Endpoint		All 21 Trials			Studies 18 and 19 Alone		
		Dapa N=5936 PY=6594	Comp N=3403 PY=3831	HR (95% CI)	Dapa N=942 PY=1118	Comp N=945 PY=1119	HR (95% CI)
Primary (MACE+)	n	97	81		43	44	
				0.81 (0.59, 1.09)			0.98 (0.64, 1.49)
MACE	n	73	62		32	29	
				0.78 (0.55, 1.11)			1.11 (0.67, 1.83)

Source: Slides 24 and 30, Advisory Committee presentation by Dr. Andraca-Carrera, 12 Dec 2013
Abbreviations: CI = confidence interval; HR = hazard ratio; MACE = cardiovascular death, myocardial infarction or stroke; MACE+ = cardiovascular death, myocardial infarction, stroke or hospitalization for unstable angina; PY= patient-years

For the overall results from all 21 trials, the point estimate for the hazard ratio for both endpoints is <1, and the upper bound of the 95% confidence interval is <1.8. The current Guidance for Industry regarding assessment of cardiovascular risk for diabetes drugs specifies that, premarketing, the upper bound of the 95% confidence interval for the composite of major adverse cardiovascular events should not exceed 1.8. Dapagliflozin meets this standard, for both MACE+ and MACE. Applicants are not required to meet this standard for individual trial results, but only for the overall assessment across the development program at the time of NDA submission. However, an evaluation of risk in a higher risk population, such as that in Studies 18 and 19, is of interest, as many patients with DM2 might be at higher CV risk. For

MACE+, Studies 18 and 19 still exclude an upper bound of 1.8. For MACE alone, the upper bound is 1.83.

Another observation regarding cardiovascular risk is that, similar to the findings in the canagliflozin development program, there is an imbalance in events during the first 30 days of exposure, not favoring the SGLT2i. For canagliflozin in the first 30 days, there had been 13 MACE+ events among 2886 canagliflozin-treated patients, and one MACE+ event among 1441 comparator-treated patients (0.45 vs 0.07%). For dapagliflozin, there were 8 MACE+ events among 5936 dapa-treated patients vs 2 among 3403 comparator patients (0.13% vs 0.06%). There did not appear to be an association between hypotension or hypoglycemia and these events. The overall number of events is small, which limits interpretability. There is a large ongoing cardiovascular outcomes trial with dapagliflozin, in which this observation can be assessed further.

Overall, it appears that dapagliflozin is not associated with unacceptably increased cardiovascular risk, and its overall meta-analysis result meets the standard set forth in the CV risk assessment Guidance. Additional evaluation of patients at high CV risk, and patients in the first 30 days of treatment, will be possible when the results of the required CV outcomes trial are received. The applicant is conducting a large cardiovascular outcomes trial, in which over 17,000 patients will be enrolled. It is an event-driven trial; over 77,000 patient-years of exposure are expected.

8.2 Malignancy

Across all Phase 2b/3 trials, the overall incidence of malignancies is similar between dapagliflozin and comparator (incidence rate ratio 1.03; 95% CI 0.71, 1.51).

The IRR for female breast cancer remains similar to what was seen at the time of the Major Amendment (IRR now 2.47; 95% CI 0.64, 14.10). This breast cancer risk imbalance is not robust at this time. Dr. Genevieve Schechter provided an Oncology consultation (21 Oct 2013). She notes a declining IRR, and multiple confounding factors. In her consultation, she states: "While an increased incidence of breast cancer is observed on the dapagliflozin relative to the placebo arm, the decline in the incidence risk ratio over time, the lack of screening mammography prior to study entry coupled with the occurrence of the breast cancers within the first year of dapagliflozin therapy, the median time from diagnosis of diabetes of seven years, the history of prior exposure to other oral hypoglycemic agents, and the hormone receptor positivity of the breast cancers suggest that the increased incidence of breast cancer is a spurious finding." She further states: "The data with regard to breast cancer risk in association with this drug is inconclusive and insufficient to recommend inclusion in the label."

The one imbalance that remains and requires further consideration is that for bladder cancer. At the time of the Major Amendment in 2011, there were 9 cases of bladder cancer among dapagliflozin-treated patients, and one among comparator-treated patients (male IRR 5.4; 95% CI 0.84, 122.2). Now, after submission of approximately 40% more patient-years of data, there

is one additional case of bladder cancer, in a 53 year-old dapagliflozin-treated woman (all-gender IRR 5.17; 95% CI 0.68, 233.55).

The following table and figure display the cases of bladder cancer which have been reported to date, and some of the characteristics of the cases.

Table 8.2: Bladder Cancer Cases in the Dapagliflozin Development Program

Age/Sex	Study Tx	Dx Day	Grade/Stage	Treatment**
75/M	2.5mg	43	Grade 2 / T2 N0 Mx; muscle invasive	TURBT, cystectomy Chemotherapy
48/M	10mg	74	Low grade / Non-muscle invasive	TURBT, BCG
53/F	10mg	114	Grade 1 / Non-muscle Invasive	TURBT
67/M	5mg	144	High grade / pT2M0; muscle invasive	Cystectomy
55/M	10mg	169	Grade 1 / pT1N0M0; non-muscle invasive	TURBT
63/M	5mg	358	Low grade / pTa : non-muscle invasive	TURBT
67/M	10mg	399	Grade 2 / Non-muscle invasive	TURBT local chemotherapy
60/M	5mg	512	Low grade / pTaNCM0; non-muscle invasive	TURBT
66/M	10mg	581	Low grade / pTa NC M0; non-muscle Invasive	TURBT
76/M	10mg	727	High grade / T1 M0; non-muscle Invasive	TURBT, BCG
66/M	Pbo	136	High grade / pT2N0M0; muscle invasive	TURBT, BCG

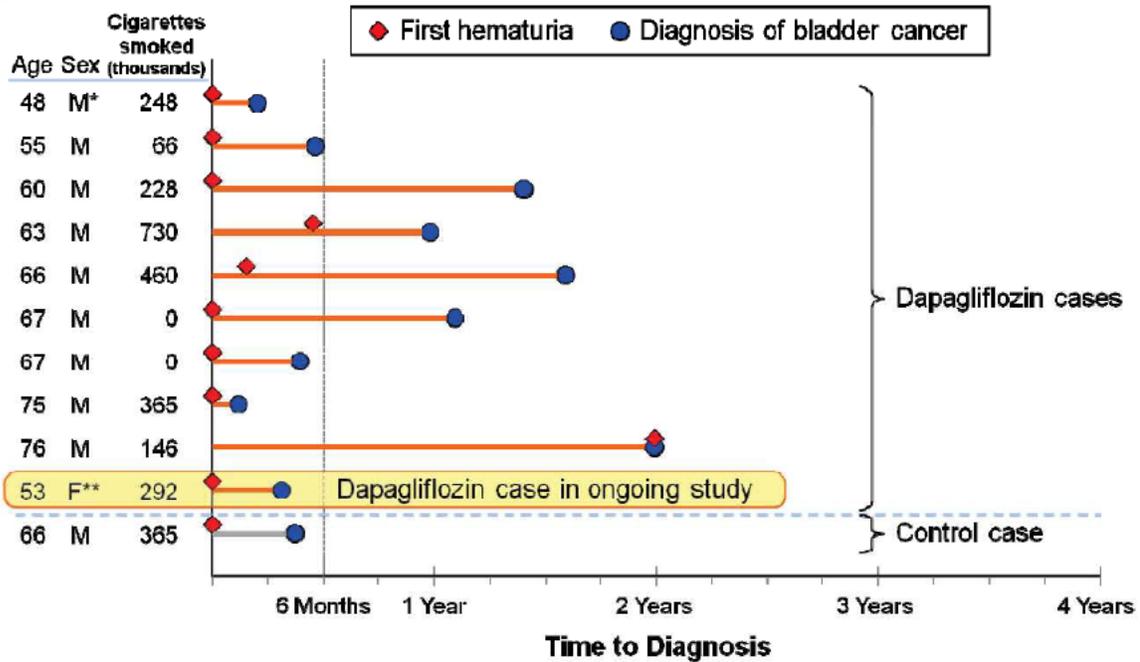
* Including one case in study -C05 identified after database cut.

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

Dx = date of diagnosis; Tx = treatment

Source: Applicant’s Table 30, pg 93, Advisory Committee Briefing Document

Figure 8.2: Time of Onset of Hematuria, and Time of Onset of Bladder Cancer



*Hematuria in this case was prior to study entry.

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

Source: 30-MU, Table 26

Source: Applicant’s Figure 31, pg 91, Advisory Committee Briefing Document

Of the ten cases diagnosed in dapagliflozin-treated patients, nine were in men. Eight out of ten were current or former smokers. Five out of ten cases were diagnosed after less than six months of dapagliflozin exposure; four were diagnosed after a year or more of exposure. Seven out of ten had hematuria at baseline or prior to study entry, and two additional patients had hematuria prior to six months of dapagliflozin exposure. One patient had a history of pioglitazone exposure.

Across the entire pooled study population, baseline hematuria was balanced.

Dr. Yangmin Ning provided an Oncology consultation (DARRTS 13 Oct 2013). In his consult, and in subsequent statements, he has taken care to note that dapagliflozin appears to be associated with a numerically increased risk of having a bladder cancer *diagnosis* (but not necessarily of acquiring bladder cancer caused by dapagliflozin). He states that attribution of causality is difficult because of multiple confounding factors. He states that “this risk should not be disregarded because of the small number of patients diagnosed with bladder cancer in the trials, but rather should be further studied, carefully monitored, and possibly labeled as a Precaution or Warning for its safe use if approved”.

There was discussion regarding whether this observation of an increased frequency of bladder cancer diagnosis could be related to “detection bias”. That is, since dapagliflozin is associated with a higher incidence of urinary tract infections, it seemed possible that dapagliflozin-treated patients were having urinalyses and other bladder-related tests done more frequently, and thus

may have been more likely to have bladder cancer detected. However, in the previous review cycle, analyses by both the Agency and the applicant did not note an increased frequency of monitoring of dapagliflozin-treated patients.

Please also see the discussion of nonclinical findings in Section 4.

Overall, although a diagnosis of bladder cancer was numerically more common among dapagliflozin-treated patients than among comparator-treated patients, and a contribution of dapagliflozin as a promoter cannot be excluded entirely, several observations seem to point away from a causative role of dapagliflozin for bladder cancer:

- Dapagliflozin was not a carcinogen in the two-year rodent carcinogenicity study.
- Several *in vitro* and *in vivo* nonclinical studies have not shown evidence of a tumor-promoting effect. (However, the nonclinical review team points out that the models used thusfar have not addressed the effect of dapagliflozin on bladder cancer within the expected bladder microenvironment that one would see clinically with dapagliflozin.)
- Half the cases (5/10) of bladder cancer in dapagliflozin-exposed patients were diagnosed after less than 6 months of exposure to dapagliflozin. This suggests their bladder cancer might have been pre-existing.
- Seven out of ten patients who were diagnosed with bladder cancer had hematuria at baseline or prior to study entry, and two additional patients had hematuria prior to six months of dapagliflozin exposure. This again suggests that bladder cancer might have been pre-existing.
- The majority of patients were current or former smokers; smoking is a known risk factor for bladder cancer. (However, it should be noted that both smoking history and hematuria were balanced at baseline between dapagliflozin and comparator groups.)
- For dapagliflozin to result in bladder cancer in such a short time frame, one would have to postulate that it is a very potent tumor promoter. This seems unlikely in the absence of any carcinogenicity signal in the two-year carcinogenicity study.

In the applicant's ongoing cardiovascular outcomes trial, which will include over 17,000 patients and over 77,000 expected patient-years, bladder cancer will be prospectively adjudicated. This will provide further evaluation of this risk. Enhanced postmarketing pharmacovigilance is also planned.

8.3. Hepatic Safety

In the previous review cycle, the primary issue of concern was related to a single serious adverse liver event, for which a causative role of dapagliflozin could not be excluded. Additional information for that case is now available, and is discussed below.

In general, there was no imbalance between dapagliflozin and comparator for the incidence of marked laboratory abnormalities of liver tests, as displayed in the following table:

Table 8.3: Liver Laboratory Test Abnormalities, All Phase 2b/3 Pool, Resubmission

Test	Dapa Total N = 5936 n/N (%)	Control Total N = 3403 n/N (%)
Any elevated liver laboratory test	255/5895 (4.3)	152/3380 (4.5)
AST >10x ULRR	8/5895 (0.1)	3/3379 (0.1)
AST >20x ULRR	4/5895 (0.1)	0
ALT >10x ULRR	7/5895 (0.1)	5/3380 (0.1)
ALT >20x ULRR	3/5895 (0.1)	2/3380 (0.1)
Total bilirubin >2x ULRR	22/5894 (0.4)	11/3379 (0.3)
ALT or AST >3x ULRR and total bili >2x ULRR	7/5894 (0.1)	4/3379 (0.1)
Source: 30-month safety update, pages 16952-3		
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; bili = bilirubin; dapa = dapagliflozin; ULRR – upper limit of reference range		

Dr. Leonard Seeff (first review cycle) and Dr. John Senior (current review cycle, DARRTS 11 Nov 2013) provided liver safety consultations. They reviewed all the cases of ALT/AST >3x ULRR and total bilirubin >2x ULRR. In the first review cycle, all cases but one were felt to have another, more likely, etiology, than study drug. In the second review cycle, all cases were felt to have a more likely etiology.

The following paragraphs describe what was known about the case of suspected drug-induced liver injury at the time of the first review cycle, and the updated information now available.

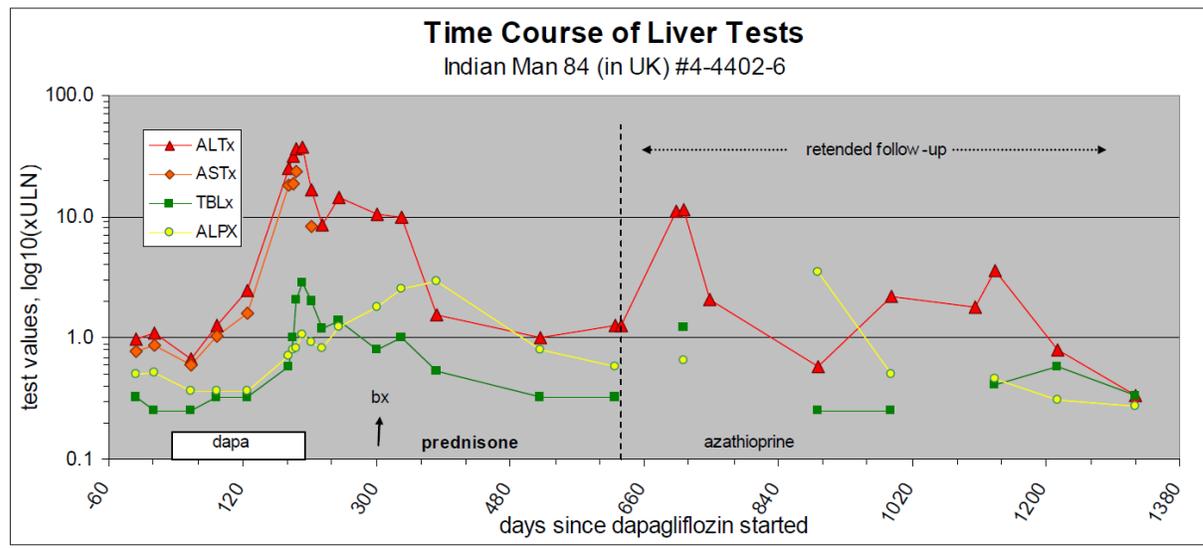
The patient was a 78 year old man from India, who was living in the United Kingdom. He was treated with low-dose (2.5 mg) dapagliflozin. He had a history of compound heterozygous hemochromatosis, and his baseline transaminases were mildly elevated. After approximately three months of dapagliflozin exposure, he developed further elevation in transaminases, which progressively increased. On Study Day 192, dapagliflozin was stopped. On Day 200, his ALT peaked at 1858 U/L (37x ULRR), and his total bilirubin peaked at 4.2 mg/dL (2.8x ULRR). On Day 264, he underwent liver biopsy, which was reported to show some portal inflammatory infiltrate without frank necrosis. Little fibrosis was reported, but there were some bands of collapsed liver tissue; mild siderosis was noted. The pathologist favored a diagnosis of autoimmune hepatitis. However, serologic markers for autoimmune etiologies were negative. Serology did not reveal evidence of viral hepatitis. The patient was started on prednisolone on Study Day 349; transaminases had already begun to decline somewhat before the steroid was started. On the steroid, the patient's transaminases rapidly returned to near-normal (1.3x ULRR) levels, and his bilirubin normalized.

At the time of the last review cycle, the applicant had obtained opinions from three hepatologists, who were mixed in the assessment of potential causality related to dapagliflozin. After careful consideration, Dr. Seeff, the FDA's hepatology consultant, concluded that, with the data available to him at that time, this appeared to be a case of dapagliflozin-induced liver injury. In his consultation, he wrote:

“Based on these data, despite the histology with features suggestive of autoimmune hepatitis, and even though treatment with corticosteroids was initiated after which liver chemistries improved, a definitive diagnosis of autoimmune hepatitis seems unlikely, since the acute injury developed for the first time in an older male and the serologic markers of autoimmune hepatitis were negative. Such histology is by no means absolutely indicative of AIH and can be found in other causes of acute liver injury, including drug-induced liver injury. It should be noted that, with discontinuation of dapagliflozin, the serum aminotransferase and bilirubin values began a slow decline but the alkaline phosphatase level continued to increase slightly before falling to a normal level; nevertheless, the pattern of liver dysfunction appeared consistent with that of an acute hepatocellular injury. It is my view, therefore, that the probable diagnosis is mild to moderately severe dapagliflozin-induced liver injury.”

The figure below illustrates the time course of liver tests for this patient, with the vertical hatched line demarcating the point at which additional follow-up began after the last review cycle.

Figure 8.3. Time Course of Liver Tests for Case Being Evaluated for Possible Drug-Induced Liver Injury



Source: Pg 6, hepatic consultation by Dr. John Senior

The patient is now 84 years old, and has been followed for 5.5 years since he started dapagliflozin (and now for 5 years since he stopped dapa). Since the last review cycle, he has had two more flares while off dapa, and has been treated with azathioprine and glucocorticoids. Dr. Senior feels that it is now clear that the patient has autoimmune hepatitis. The possibility that dapagliflozin was a triggering factor in the autoimmune process could not be excluded entirely.

Dr. Senior does not recommend routine monitoring of liver laboratory for dapagliflozin. He does recommend a statement in the Full Prescribing Information that patients should report any signs of liver dysfunction (e.g. anorexia, fatigue, nausea, dark urine, vomiting, yellowish sclera, abdominal discomfort) to their doctors immediately.

Overall, it seems that this case is unlikely to have been caused by dapagliflozin, although the possibility cannot be excluded entirely. In the CDTL's opinion, this case should not preclude approval at this time.

Adverse liver events are being systematically evaluated and prospectively adjudicated in the ongoing cardiovascular outcomes trial, and enhanced postmarketing pharmacovigilance is to be a postmarketing requirement.

8.4. Genital Mycotic Infections

During this review cycle, the findings related to genital mycotic infections were very similar to those seen in the original review cycle, and very similar to those seen with canagliflozin, the approved SGLT2i.

A total of 5.5% of dapagliflozin-treated patients experienced some type of genital infection, compared to 0.6% of comparator-treated patients. Although no events were classified as serious or severe, five dapagliflozin-treated patients discontinued study due to genital infection. Women had more infections than men, but the proportions between dapa and comparator were similar by gender. The most common infections were vulvovaginal mycotic infections in women, and balanitis in men. Most infections responded to a single course of an antimicrobial agent. Among the 130 dapagliflozin patients who had one genital infection, 22 (17%) had a second infection. Among the 15 comparator-treated patients who had one genital infection, 1 (7%) had a second infection.

8.5. Urinary Tract Infections

During this review cycle, the findings related to urinary infections (UTIs) were very similar to those seen in the original review cycle, and very similar to those seen with canagliflozin, the approved SGLT2i.

A total of 4.7% of dapagliflozin-treated patients had a UTI, compared to 3.5% of comparator-treated patients. One dapa case and two comparator cases were classified as serious adverse events. Withdrawals due to UTI events occurred in 5/2360 (0.2%) of dapa-treated and 2/2295 (0.1%) of comparator-treated patients. Women had more infections than men, but the proportions between dapa and comparator were similar by gender. Infections generally responded to a single course of antimicrobial therapy. Among the 110 dapagliflozin patients who had one UTI, 18 (16%) had a second infection. Among the 81 comparator-treated patients who had one UTI, 7 (9%) had a second infection.

8.6. Renal Impairment Events

The applicant used a Customized MedDRA Query to search for adverse events related to renal impairment. Please see Section 7.3.5.4 of Dr. Pucino's review for a listing of the included Preferred Terms.

The percentage of patients who experienced any event from the group of terms was similar between treatments (dapa 4.0%, comparator 3.8%). Adverse events of “Renal Failure” and “Renal Failure Acute” occurred with equal frequency between dapa and comparator.

8.7. Adverse Events Related to Volume Depletion

The applicant used a Customized MedDRA Query to search for adverse events related to volume depletion. Please see Section 7.3.5.4 of Dr. Pucino’s review for a listing of the included Preferred Terms.

Across the entire group of placebo-controlled trials, events related to volume depletion occurred among 1.9% of dapa-treated and 1.4% of comparator-treated patients. Serious adverse events occurred in 0.1% of patients treated with 10 mg dapa, and in 0.2% of patients treated with comparator. Certain groups had a somewhat higher risk, including patients treated with loop diuretics, patients over age 65 years, and patients with an eGFR < 60 mL/min/1.73m². However, the number of events occurring in these subgroups was small, which limits conclusions.

8.8. Hypoglycemia

Findings for hypoglycemia were similar to those seen in the first review cycle.

Serious events of hypoglycemia (i.e. events that required the assistance of another person) were uncommon in the development program. One case occurred in a patient concomitantly treated with dapa and glimepiride. In Study -006, in which dapa or pbo was added to insulin, by Week 104, 1% of dapa+insulin patients and 0.5% of pbo+insulin patients had had a major hypoglycemic episode. Across all placebo-controlled trials, 21.5% of dapa-treated and 22.3% of comparator-treated patients experienced an event of hypoglycemia of any degree of seriousness. Minor adverse events of hypoglycemia were more common among dapa-treated patients who took sulfonylureas or insulin concomitantly than among dapa-treated patients who took other antidiabetic agents, or who were on dapa monotherapy.

8.9. Bone Safety

Because dapagliflozin may alter renal tubular transport of several minerals, cause weight changes, and affect metabolism of vitamin D, bone safety was of interest.

In the first review cycle, the Division of Reproductive and Urologic Products was consulted regarding bone risk of dapagliflozin. The consultant concluded that there was no evidence that dapagliflozin exerts a clinically significant effect on either bone loss or fracture risk. Study 0012 had shown no statistically significant differences between dapa and comparator for bone biomarkers and bone mineral density. At the femoral neck, the placebo-subtracted change from baseline to 102 weeks in bone mineral density was -0.94 (95% CI -2.21, 0.35), but this result was not statistically significant.

Updated fracture data showed that, across all placebo-controlled trials, 1.1% of dapa-treated and 1.6% of comparator-treated patients experienced a fracture.

In the dedicated study (MB102029) in patients with moderate renal impairment, thirteen dapa-treated and no placebo-treated patients had fractures. The applicant reported at the time of the Advisory Committee meeting that all patients who had a fracture had a fall. As mentioned earlier, the applicant is not recommending use of dapagliflozin in patients with an eGFR under 60 mL/min/1.73 m².

9. Advisory Committee Meeting

On December 12, 2013, an Advisory Committee meeting was held to discuss the resubmitted dapagliflozin application.

As of December 23, 2013, the transcript of the AC is not yet available, and therefore the summary of discussion below is paraphrased from the CDTL's notes and memory. Please refer to the final transcript when it becomes available for the most accurate rendering of the discussion.

At that AC, there were three discussion questions, and two voting questions.

“Question 1:

(Discussion Topic): Cardiovascular Risk Evaluation

DISCUSS: Based on the information provided in the briefing package and the presentations at today's meeting, please address the following with regard to the cardiovascular risk assessment for dapagliflozin.

- a. Comment on which data (i.e., overall population, enriched population) best inform the cardiovascular risk associated with dapagliflozin use and discuss the weight you place on the evidence provided by the subgroup of patients specifically recruited on the basis of established cardiovascular disease in Trials 18 and 19.
- b. Discuss whether you believe the updated cardiovascular risk data derived from Trials 18 and 19 are consistent with the overall findings reported for the pool of 21 clinical trials.
- c. Discuss the clinical importance you place on the observed changes in blood pressure, weight, glycemic control and lipid parameters in informing overall cardiovascular risk of dapagliflozin.
- d. Discuss additional concerns, if any, you may have with regard to dapagliflozin and cardiovascular risk.”

In general, the AC members felt that the decision regarding cardiovascular safety should be based on the meta-analysis across all 21 trials, rather than on just Trials 18 and 19. The discussion did indicate that the latter two trials provided useful information regarding a

vulnerable population that is represented in patients with DM2. A minority of members had concerns about the overall adequacy of the database, in terms of total numbers of major adverse cardiovascular events. The small favorable effects on blood pressure and weight were considered positive attributes in the overall benefit:risk assessment, while the small unfavorable effect on LDL was of some concern, but not of great enough concern to limit approvability.

“Question 2:

(Discussion Topic): Malignancy

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

In general, the AC members felt that overall malignancy and breast cancer risk were not major concerns. The imbalance in diagnoses of bladder cancer was felt to be difficult to interpret, given that many patients had baseline hematuria, and multiple confounding factors. Overall, the likelihood that dapagliflozin was causative seemed to be low. Further evaluation in the postmarketing setting was generally felt to be appropriate.

“Question 3:

(Discussion Topic): Liver Toxicity

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

Most members of the committee felt that the additional data provided for the case of possible DILI were reassuring. Routine monitoring of liver function tests was not felt to be appropriate.

Question 4:

(Voting Question): Cardiovascular Risk

VOTE: In accordance with FDA’s Guidance for Industry titled “Diabetes Mellitus – Evaluating Cardiovascular Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes”, has the Applicant provided sufficient evidence that dapagliflozin, relative to comparators, has an acceptable cardiovascular risk profile?

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

Vote: Yes= 10 No = 4 Abstain = 0

The majority of the committee members expressed the opinion that the Applicant had provided sufficient evidence that dapagliflozin, relative to comparators, has an acceptable cardiovascular risk profile. The committee members who voted “No” indicated that some of the results from the subgroups raised concerns, or that a larger number of events would have aided in evaluation.

Question 5:

(Voting Question): Overall Risk:Benefit

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

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

Vote: Yes= 13 No = 1 Abstain = 0

The majority of the committee members felt that the benefits of dapagliflozin use outweigh identified risks and support marketing of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Some of the committee members who voted “Yes” commented that the cancer risk does not rise to the level of non-approval. On the other hand, the committee member who voted “No” commented that dapagliflozin does appear to increase the risk of cancer, infections and cardiovascular events.

There were several suggestions regarding postmarketing risk evaluation, such as support for prospective adjudication of malignancy and adverse hepatic events in the ongoing cardiovascular outcomes trial.

10. Pediatrics

As is the case for other products intended for the treatment of type 2 diabetes mellitus, study of children under ten years of age will not be required for dapagliflozin, because the incidence of DM2 in prepubertal children is very low.

As is the case for most other products for DM2, a pharmacokinetic/pharmacodynamic study, and a clinical efficacy and safety trial, will be required for children and adolescents ages 10 to 17 years.

11. Other Relevant Regulatory Issues

In the first review cycle, the Office of Scientific Investigations conducted inspections, and did not note major deficiencies. Because two years had elapsed since the last review, The Office of compliance re-inspected the facilities, and found no major deficiencies (29 Oct 2013).

12. Labeling

The applicant's proposed proprietary name, "Farxiga", has been reviewed and found acceptable.

As of 23 Dec 2013, labeling negotiations with the applicant are ongoing, and further input may occur from the FDA signatory authority and other leadership. Current significant labeling issues under discussion include:

- **Section 2 Dosage and Administration:** Please see the discussion in the Clinical Pharmacology section above. The Applicant recommends the use of either a 5 or 10 mg dapagliflozin daily dose at any time of day, but advises initiating therapy with the 5 mg dose in patients at risk for volume depletion. Since glycemic efficacy has been demonstrated with the 5 mg dose, and because the canagliflozin label recommends starting with the lower of two approved doses, the Agency prefers that the dose for initiation of therapy be 5 mg once daily. This may help to minimize the risk for potential adverse events (e.g., volume depletion and renal impairment) in vulnerable patient populations. Those patients who tolerate the 5 mg dose and need additional glycemic control can have their dose increased to 10 mg.
- **Section 4 Contraindications:** (b) (4)
The Agency has recommended that dapagliflozin be contraindicated for patients with a history of a serious hypersensitivity reaction to dapagliflozin and those with severe renal impairment, end stage renal disease or patients on dialysis. There were a few serious hypersensitivity-type reactions have been observed in the dapagliflozin clinical program, including one case of a "Stevens-Johnson-like reaction"; and patients with severe renal dysfunction have limited efficacy and a predisposition to adverse events.
- **Section 5 Warnings and Precautions:** (b) (4)
information regarding the observed imbalance in bladder cancers. (b) (4) should be added to Warnings.
- **Section 14 Clinical Studies:** In this section, the Applicant includes study results (b) (4)

(b) (4) These results should be removed.

- **Promotional language:** Some language in the Full Prescribing Information could be considered promotional (b) (4) and the language will need to be modified to simply state the findings without an implied claim of benefit.

A Medication Guide is included, and has undergone extensive review and editing by the Patient Labeling team. Negotiations with the applicant are ongoing, and signatory authority and other leadership review are pending.

Carton and container labeling have been reviewed, and discussions are ongoing between the CMC review team and the applicant.

13. Recommendations/Risk Benefit Assessment

The Cross-Discipline Team Leader recommends approval of dapagliflozin as an adjunct to diet and exercise, for improvement of glycemic control in patients with type 2 diabetes mellitus.

Regarding benefit, dapagliflozin is effective in lowering hemoglobin A1c, to a degree comparable with other approved agents for the same indication. Additionally, dapagliflozin has several favorable attributes:

- It does not increase weight, but rather is actually consistently associated with a small amount of weight loss. This is a very desirable attribute for a drug for the treatment of type 2 diabetes, which is strongly tied to obesity.
- Dapagliflozin is associated with a small decrease in systolic blood pressure. Control of cardiovascular risk factors, such as blood pressure, is very important in patients with DM2. Poor control of SBP increases cardiovascular and renal risk.
- Dapagliflozin alone, or with agents other than insulin or sulfonylurea, is not associated with hypoglycemia. Hypoglycemia is a major limiting factor in diabetes management.

Overall, these benefits outweigh the identified risks, the most significant of which are:

- A numerical, but not statistically significant, increased risk of diagnosis of bladder cancer. There are many confounders for the identified cases, and most had onset of hematuria prior to six months of dapagliflozin exposure. While a promoter role of dapagliflozin cannot entirely be excluded, it seems unlikely when considering currently available data.
- Genital mycotic infections
- Urinary tract infections (nonserious)
- Volume-depletion-related events
- Nonserious renal impairment events, without an imbalance in renal failure events

The previously considered risks of breast cancer and serious adverse liver events no longer appear to be significant risks, but should be monitored in the postmarketing setting.

Dapagliflozin is not associated with an unacceptably increased risk of major adverse cardiovascular events.

No Risk Evaluation and Mitigation Strategy (REMS) is recommended.

Recommended Postmarketing Requirements include:

- A pharmacokinetic/pharmacodynamic study in children and adolescents ages 10-17 years.
- A clinical efficacy and safety study in children and adolescents ages 10-17 years.
- Completion of the ongoing cardiovascular outcomes trial. The applicant has agreed to include blinded prospective adjudication of bladder cancer and hepatic adverse events in this trial. Other safety outcomes of interest to which the applicant has agreed include serious urinary tract infections, serious genital infections, renal events, fractures, events related to volume depletion, and overall malignancies.
- Enhanced pharmacovigilance for bladder cancer, serious hepatic events, and hypersensitivity reactions.

The nonclinical team is in discussions regarding whether additional study of tumor promotion potential in a nonclinical model should be required.

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/s/

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12/24/2013