

FDA BRIEFING DOCUMENT

NDA 202293

DAPAGLIFLOZIN TABLETS, 5 AND 10 MG

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**ADVISORY COMMITTEE MEETING
JULY 19, 2011**

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

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To: Endocrine and Metabolics Drugs Advisory Committee Panel and
Invited Participants

Subject: Dapagliflozin

Date: July 19, 2011

Introduction

The FDA has convened this advisory committee to discuss a new drug application for dapagliflozin, a first-in-class anti-diabetic therapy that treats hyperglycemia through inhibition of the sodium glucose cotransporter-2 (SGLT-2), located predominantly in the S1 segment of the proximal renal tubules where it is responsible for the reabsorption of approximately 90% of glucose filtered through the nephron. Hence, the glucose-lowering ability of the drug is due to the renal excretion of glucose and is dependent upon the amount of glucose filtered through the glomeruli. This effect is independent of insulin secretion which minimizes the risk of hypoglycemia. However, by virtue of this same pharmacologic action, efficacy wanes as glomerular filtration rates decline with progressive renal impairment.

The clinical development program for dapagliflozin is similar to several recently approved anti-diabetic therapies. Three Phase 2b and 11 Phase 3 clinical trials investigated the efficacy and safety of dapagliflozin in drug-naïve patients or patients who were inadequately controlled with other oral agents and/or insulin. These studies evaluated the efficacy of dapagliflozin used as monotherapy, add-on therapy to metformin, sulfonylureas, pioglitazone or insulin, and as initial combination therapy with metformin. In addition, a 52-week placebo-controlled study was conducted in patients with moderate renal impairment and a body composition study was conducted to investigate the effect of dapagliflozin on weight loss.

Similar to other recently approved anti-diabetic therapies, the applicant conducted a meta-analysis of several controlled Phase 2 and 3 clinical trials to evaluate cardiovascular (CV) safety as outlined in a recent FDA guidance published in December 2008.¹ As summarized in the FDA statistical review by Dr. Anita Abraham, dapagliflozin does not appear to be associated with excess cardiovascular risk with an overall HR of 0.67 (95% CI 0.42-1.08) relative to comparators for the primary composite of CV deaths, myocardial infarctions (MI), stroke, and hospitalization for unstable angina. The applicant has proposed to

¹ Guidance for Industry – Diabetes Mellitus – Evaluating CV risk in New Anti-diabetic therapies to treat type 2 diabetes
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>)

conduct a CV outcomes trial whose primary objective is to demonstrate a cardioprotective effect of dapagliflozin. FDA concurs with the applicant that a CV outcomes trial is necessary to better characterize the CV safety of this drug and to evaluate safety issues that have arisen in the course of this NDA review. If approved, this CV outcomes trial will be a required postmarketing trial.

The FDA background package includes reviews from selected disciplines covering topics intended for discussion at this meeting. Dr. Jonathan Norton will present the primary efficacy findings from several Phase 3 trials, including the impact of patient discontinuation and differential rates of glycemic rescue on the treatment effect and secondary efficacy endpoints of interest. Dr. Norton will also discuss efficacy in patients with moderate renal impairment from Study MB102029 with a focus on the subgroup analysis performed by the applicant. Following the FDA presentation on efficacy, Dr. Somya Dunn will provide an overview of the safety data with a focus on bladder and breast cancer imbalance, hepatic safety, genital-urinary infections, bone safety, and adverse events in the renal impaired population.

At the conclusion of today's presentations given by representatives from Bristol-Myers Squibb/Astra-Zeneca and FDA, the advisory committee members will be asked to consider the following as topics for discussion.

Topics for Discussion by Panel

1. Efficacy

Dapagliflozin's efficacy is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment, the efficacy of the SGLT-2 inhibitor is also diminished. This was demonstrated in a PK/PD study of patients with normal, mild, moderate and severe renal impairment, and in a clinical trial enrolling patients with moderate renal impairment. In this latter trial, patients with moderate renal impairment (eGFR 30 mL/min/1.73m² to 59 mL/min/1.73m²) showed no significant difference in HbA1c reduction between dapagliflozin 5 and 10 mg compared to placebo. The applicant analyzed efficacy results by further categorizing renal impairment into subcategories 3A (eGFR 45-59 mL/min/1.73m²) and 3B (30-44 mL/min/1.73m²) and noted numerically greater placebo-corrected HbA1c reductions from baseline in 3A versus 3B patients; however, neither subcategories had a significant difference in HbA1c reduction compared to placebo. The applicant is recommending that the drug not be used in patients with moderate to severe renal impairment defined as eGFR < 45 mL/min/1.73 m² or CrCl < 60 mL/min and is therefore not excluding use in patients in subcategory 3A renal impairment based on eGFR.

- a. Please discuss the labeling recommendations proposed by the applicant which includes use of dapagliflozin in patients with eGFR 45-59 mL/min/1.73m².
- b. Please discuss the implications of this reduced efficacy in T2DM where renal impairment can impact a sizeable proportion of individuals with this disease.

2. Safety

Several unexpected safety issues identified in this clinical development program were of sufficient concern to FDA to merit discussion of their impact on the overall benefit-risk consideration of dapagliflozin.

Hepatic Safety

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

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

Breast and Bladder Cancer

Numeric imbalances in breast and bladder cancer were observed in the clinical development program. The clinical development programs were not of adequate design, size, or scope to detect a significant risk difference between dapagliflozin and comparators for these two types of cancers. Based on evaluation of the Surveillance Epidemiology and End Results (SEER) database and review of the literature on the incidence of these cancers in T2DM, it was determined that the number of observed breast and bladder cancers in the dapagliflozin-treated group exceeded the expected number of cases in the general T2DM population. For both of these types of cancer, please discuss the following:

- b. Any imbalance of baseline risk factors which might have contributed to the imbalance in number of cases observed
- c. Whether detection bias could have contributed to the imbalance in number of cases observed

Draft Questions to the Panel

1. Has the applicant provided sufficient evidence that dapagliflozin is an effective glucose-lowering agent for the treatment of hyperglycemia in T2DM?
 - a. If no, please explain.
 - b. Are there any additional studies recommended to characterize effectiveness of this drug?
2. Has the applicant provided sufficient evidence that the efficacy of dapagliflozin outweighs the safety concerns identified in this drug application?
 - a. If yes, are there any additional studies recommended to further evaluate the benefit-risk of this drug in the post-marketing setting?
 - b. If no, what additional studies should be performed prior to consideration for approval?



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

CLINICAL BRIEFING MATERIAL

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON DAPAGLIFLOZIN

Clinical Briefing Material: Division of Metabolism and Endocrinology Products Advisory
Committee Meeting, July 19, 2011

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Section I. Introduction

I(a). Product Description

Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT2) inhibitor proposed for the treatment of type 2 diabetes mellitus. It is a competitive, reversible, highly selective active inhibitor of SGLT2, the major transporter responsible for the renal glucose reabsorption. Dapagliflozin causes insulin-independent, renal elimination of glucose. SGLT2 is almost exclusively expressed in the kidney.

Dapagliflozin reaches maximum concentration (C_{max}) in about two hours. The half-life is 12.5 hours. It is inactivated by UGT1A9, an enzyme present in the liver and kidney, to an inactive glucuronidated metabolite (dapagliflozin 3-O-glucuronide).

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). There are currently no

approved SGLT2 inhibitors available for treatment of T2DM. If approved, dapagliflozin will be a first-in-class therapy.

The proposed dose is 10 mg, taken once daily at any time of day. There is no proposed dose adjustment based on renal function. However, the applicant proposes that dapagliflozin should not be taken by patients with moderate to severe renal impairment (defined estimated glomerular filtration rate <45 mL/min/1.73 m² or creatinine clearance < 60 mL/min). The efficacy of dapagliflozin is dependent on the filtered load of glucose, which in turn is dependent on glomerular filtration rate (GFR). Because dapagliflozin causes an increase in urinary volume excretion, the proposed dose for patients at risk for volume depletion (i.e., those who are on loop diuretics) is 5 mg once daily.

1(b). Description of Clinical Trial Development

The dapagliflozin clinical development program consisted of 26 pharmacology trials, three Phase 2b trials, and 11 Phase 3 trials. Cumulative exposures to dapagliflozin and control in the Phase 2b and 3 clinical trials were 4009 patient-years and 1682 patient-years, respectively, at the time of the NDA submission. There were 2.2 times more subjects exposed to dapagliflozin (N=4287) than to control (N=1941). Table 1 lists the Phase 2b and Phase 3 trials. These trials comprise the main efficacy and safety review of dapagliflozin. The applicant conducted a 24-week trial in diabetics (MB102029) with moderate renal impairment with the main purpose of assessing the safety of dapagliflozin in this specific population.

Table 1. Phase 2b and Phase 3 Trials in T2DM in the Dapagliflozin Development Program

Study Number	Study Description	Patient Population	Duration	Doses (mg)	Number of Subjects per Arm (dose—N)
MB102008	Monotherapy vs. placebo	Drug naïve and inadequate control with diet and exercise alone	12 weeks	2.5, 5, 10, 20, 50	2.5mg-59, 5mg-58, 10mg-47, 20mg-59 / Placebo-54 / Metformin-56
D1692C00005	Monotherapy vs. placebo	Drug naïve and inadequate control with diet and exercise alone	12 weeks	1, 2.5, 5, 10	1mg-59, 2.5mg-56, 5mg-58, 10mg-53 / Placebo-54
MB102009	Add-on to insulin vs. placebo (50% insulin + metformin or TZD)	Pilot study; patients on high doses of exogenous insulin	12 weeks	10, 20	10mg-24, 20mg-24 / Placebo-23
MB102013	Monotherapy vs. placebo	Inadequate control with diet and exercise alone	24 weeks 78 week extension	2.5, 5, 10, 20, 50	AM dosing 2.5mg-65, 5mg-64, 10mg-70 / Placebo-75
MB102032	Low dose monotherapy vs. placebo	Inadequate control with diet and exercise alone	24 weeks	1, 2.5, 5	1mg-72, 2.5mg-74, 5mg-68 / Placebo-68
MB102014	Add-on to metformin IR vs. placebo (metformin \geq 1500 mg)	Inadequate glycemic control on background therapy alone	24 weeks 78 week extension	2.5, 5, 10	2.5mg-137, 5mg-137, 10mg-135 / Placebo-137
D1690C00005	Add-on to SU vs. placebo (glimepiride 4 mg)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension	2.5, 5, 10	2.5mg-154, 5mg-142, 10mg-151 / Placebo-145
MB102030	Add-on to TZD vs. placebo (pioglitazone \geq 30 mg)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension	5, 10	5mg-141, 10mg-140 / Placebo-139
D1690C00006	Add-on to insulin vs. placebo (Insulin \geq 30 IU \pm 2 OAD)	Inadequate glycemic control on background therapy alone	24 weeks 24 week extension 56 weeks—ongoing	2.5, 5, 10	2.5mg-202, 5mg-211, 10mg-194 / Placebo-193
D1690C00004	Add-on to metformin IR vs. glipizide (metformin \geq 1500 mg)	Inadequate control on metformin	52 weeks 52 week extension—ongoing 104 week extension—ongoing	Dapa 2.5, 5, 10 / Glipizide 10 or 20 mg	Dapa-400 Glipizide-401
MB102034	Initial combo with metformin XR vs. metformin XR or Dapagliflozin monotherapy	Baseline HbA1c \geq 7.5 to \leq 12	24 weeks	Dapa 10 mg / Metformin up to 2000 mg	Metformin 208 Dapa 10 mg-219 Metformin plus Dapa-211
MB102021	Initial combo with metformin XR vs. metformin XR or Dapagliflozin monotherapy	Baseline HbA1c \geq 7.5 to \leq 12	24 weeks	Dapa 5 mg / Metformin up to 2000 mg	Metformin 201 Dapa 10 mg-203 Metformin plus Dapa-194
MB102029	Monotherapy vs. placebo (any AD combination except metformin)	Moderate renal impairment with inadequate glycemic control on a stable regimen	24 weeks 28 week extension 52 weeks—ongoing	5, 10	5mg-83, 10mg-85 / Placebo-84
D1690C00012	Add-on to metformin vs. placebo	Baseline HbA1c \geq 6.5 to \leq 8.5 and BMI \geq 25 kg/m ²	24 weeks 78 week extension	10	10mg-91 / Placebo-91

TZD=Thiazolidinedione; OAD=oral anti-diabetic medication; AD=anti-diabetic medication; Dapa = dapagliflozin

I(c). Study Design

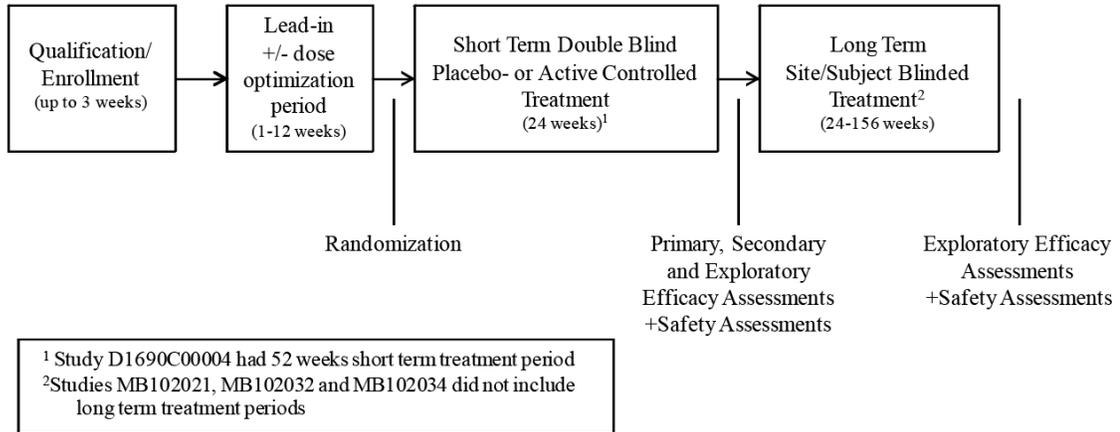
The primary endpoint for nine of the Phase 3 trials was change in HbA1c from baseline at 24 weeks of treatment with dapagliflozin. For Study D1690C00004, the active comparator trial, the primary efficacy endpoint was change from baseline in HbA1c at week 52. The last study in Table 1, D1690C00012, had a primary endpoint of total body weight and is not discussed in this Study Design subsection.

The Phase 3 trials included a diverse group of patients drawn from the T2DM population. There were drug-naïve subjects at an early stage of disease and subjects taking oral antidiabetic agents or insulin at a later stage of the disease.

The Phase 3 trials included a qualification / enrollment phase of up to three weeks (Figure 1) used for screening. This phase was followed by a placebo lead-in period. A lead-in period was included in all of the trials with the exception of the combination with insulin trial (D1690C00006). In this trial, patients had to be on a stable insulin regimen with a mean insulin dose of ≥ 30 IU for at least eight weeks prior to enrollment. Long-acting, short-acting, and sliding scale insulin regimens were all allowed. For the other trials, during the placebo lead-in period, patients were given diet and lifestyle instruction. In addition, compliance with placebo was assessed. For trials with background medication (except the insulin add-on trial), doses of background medications were added or stabilized.

The trials included a short-term double-blind treatment period of 24 weeks, with the exception of study D1690C00004 (active comparator), which had a short-term period of 52 weeks. In seven of the other 10 trials, the short-term treatment period was followed by a protocol pre-specified, double-blind, long-term extension treatment period of at least 24 weeks duration. Placebo-treated patients entering the long-term extension treatment period continued treatment with placebo, except for those in the monotherapy trial with a 78-week extension, Study MB102013. In this trial, placebo-treated patients who completed week 24 and who had not received glycemic rescue were treated with blinded metformin 500 mg daily during the long-term extension. One of the monotherapy trials (MB102032) and the initial combination therapy trials (MB102021 and MB102034) did not include an extension.

Figure 1. General Study Design of Phase 3 Trials



Source Applicant SCE Figure 1

I(d). Rescue Criteria

Patients who did not meet protocol-specified glycemic targets at specified timepoints during the trial received rescue medication, which varied from trial to trial. The pre-specified targets (Table 2) became more stringent over time. In Study D1690C00006, the add-on to insulin study, the insulin dose was uptitrated for rescue and there was no oral rescue therapy. In Study D1690C00004, the active comparator trial, there was no rescue medication and patients were discontinued if they could not maintain glycemic control.

Table 2 Rescue Criteria Phase 3 Trials—Short-term Treatment Period

Background	Monotherapy		Add-on combination, placebo-controlled				Add-on combination vs SU Metformin D1690C00004	Initial combination with Metformin XR		Weight and body composition Metformin D1690C00012	Moderate renal impairment Any ^a MB102029
	MB102013	MB102032	Metformin MB102014	SU D1690C00005	TZD MB102030	Insulin D1690C00006		MB102021	MB102034		
None							none				
FPG >270 mg/dL	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7	Weeks 4 to 7			Weeks 6,7	Weeks 6,7		Weeks 4,5
FPG >240 mg/dL	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 8 to 11	Weeks 1 to 12 ^b		Weeks 8 to 11	Weeks 8 to 11	Weeks 4 to 7	Weeks 6 to 11
FPG >220 mg/dL						Weeks 13 to 24 ^b					
FPG >200 mg/dL	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24	Weeks 12 to 24			Weeks 12 to 20	Weeks 12 to 20	Weeks 8 to 24	Weeks 12 to 24

Source: Protocols for MB102013, MB102032, MB102014, D1690C00005, MB102030, D1690C00006, D1690C00004, MB102021, MB102034, D1690C00012, MB102029

^a Except metformin

^b At least 3 fasting SMBG diary measurements from the past 7 days or visit measurement

Source Applicant’s SCE Appendix A2.5.1.1 Table 1

I(e). Demographics

Baseline disease characteristics and demographics for the Phase 3 placebo-controlled monotherapy and add-on combination therapy trials are summarized in Table 3 and the same parameters in the Phase 3 active comparator, initial combination with metformin, body composition and renal impairment trials are shown in Table 4. Generally the treatment groups were balanced for relevant disease parameters at baseline and

demographic characteristics, so the data shown in the table for each trial are for the treatment groups combined.

The total number of treated subjects in the Phase 3 trials was 5693, of which 1581 (27.8%) were North American (1104 [19.4%] in the US) and 2361 (41.5%) were European. The mean age was 56 years; 1212 (21.3%) patients were ≥ 65 years old and 157 (2.8%) patients were ≥ 75 years old. The proportion of males (50.5%) was similar to the proportion of females (49.5%). Across the trials, 83.7% of the patients were white, 3.4% were black or African American and 10.2% were Asian.

There were few black or African American patients (3.4%) in the entire clinical program. Hispanic/Latino ethnicity was reported for 11.8% of the subjects, though this information was requested only from sites in the U.S.

Table 3. Demographic and Baseline Disease Characteristics in the Phase 3 Placebo-controlled Monotherapy and Add-on combination Trials

Category	Monotherapy			Add-on Combination			
	MB102013		MB102032 N=282	MB102014 (metformin) N=546	D1690C00005 (SU) N=592	MB102030 (TZD) N=420	D1690C00006 (Insulin) N=800
Group 1 N=485	Group 2 N=73						
Mean Age (yr) (SD)	52.6 (10.74)	48.1 (10.79)	53.0 (10.57)	53.9 (9.73)	59.8 (9.60)	53.5 (10.86)	59.3 (8.22)
Age <65 (%)	417 (86.0)	70 (95.9)	240 (85.1)	467 (85.5)	399 (67.4)	353 (84.0)	603 (75.4)
≥ 65 Age < 75 (%)	64 (13.2)	2 (2.7)	38 (13.5)	75 (13.7)	163 (27.5)	57 (13.6)	175 (21.9)
Age ≥ 75 (%)	4 (0.8)	1 (1.4)	4 (1.4)	4 (0.7)	30 (5.1)	10 (2.4)	22 (2.8)
Male n (%):	229 (47.2):	47 (64.4):	141 (50.0):	292 (53.5):	285 (48.1):	208 (49.5):	382 (47.8):
Female n (%):	256 (52.8)	26 (35.6)	141 (50.0)	254 (46.5)	307 (51.9)	212 (50.5)	418 (52.3)
Race (%):							
White	460 (94.8)	69 (94.5)	229 (81.2)	480 (87.9)	411 (69.4)	305 (72.6)	760 (95.0)
Black/Afr. Amer.	9 (1.9)	1 (1.4)	12 (4.3)	17 (3.1)	0	22 (5.2)	19 (2.4)
Asian	10 (2.1)	2 (2.7)	38 (13.5)	11 (2.0)	181 (30.6)	71 (16.9)	13 (1.6)
Other	6 (1.2)	1 (1.4)	3 (1.1)	38 (7.0)	0	22 (5.2)	8 (1.0)
Ethnicity (%):							
Hispanic	59 (12.2)	18 (24.7)	9 (3.2)	51 (9.3)	0	59 (14.0)	11 (1.4)
Non-hispanic	130 (26.8)	20 (27.4)	43 (15.2)	88 (16.1)	592 (100.0)	97 (23.1)	789 (98.6)
Not reported	296 (61.0)	35 (47.9)	230 (81.6)	407 (74.5)	0	264 (62.9)	0
Geographic region (%):							
North America	244 (50.3)	36 (49.3)	94 (33.3)	198 (36.3)	0	188 (44.8)	169 (21.1)
Latin America	171 (35.3)	37 (50.7)	79 (28.0)	348 (63.7)	0	172 (41.0)	0
Europe	70 (14.4)	0	78 (27.7)	0	411 (69.4)	0	631 (78.9)
Asia/Pacific	0	0	31 (11.0)	0	181 (30.6)	60 (14.3)	0
Mean Baseline HbA1C (%) (SD)	7.92 (0.943)	10.77 (0.884)	7.92 (1.054)	8.06 (0.916)	8.11 (0.763)	8.38 (0.997)	8.53 (0.819)
Mean Duration of Diabetes (yr) (SD)	1.73 (2.849)	1.97 (2.617)	1.38 (2.518)	6.09 (5.620)	7.40 (5.722)	5.49 (5.644)	13.60 (7.267)
Mean Baseline weight (kg) (SD)	90.19 (20.145)	88.04 (20.994)	86.90 (18.557)	85.89 (17.730)	81.10 (17.839)	86.33 (21.390)	93.80 (17.701)
Baseline eGFR <30 mL/min/1.73 m ² (%)	0	0	0	0	0	0	0
Baseline eGFR ≥ 30 and <60 mL/min/1.73 m ² (%)	31 (6.4)	1 (1.4)	13 (4.6)	58 (10.6)	63 (10.6)	24 (5.7)	130 (16.3)
Baseline eGFR ≥ 60 and <90 mL/min/1.73 m ² (%)	270 (55.7)	28 (38.4)	153 (54.3)	294 (53.8)	342 (57.8)	218 (51.9)	451 (56.4)
Baseline eGFR ≥ 90 mL/min/1.73 m ² (%)	184 (37.9)	44 (60.3)	116 (41.1)	194 (35.5)	187 (31.6)	178 (42.4)	219 (27.4)

Source Applicant's SCE Table 6

Table 4. Demographic and baseline disease characteristics in the Phase 3 active comparator, initial metformin combination, body weight / composition and renal impairment trials

Category	Active Comparator	Initial Combination (with metformin XR)		D1690C00012 Body composition N=180	MB102029 Mod. Renal Impairment N=252
	D1690C00004 N=801	MB102021 Dapa 5 mg N=598	MB102034 Dapa 10 mg N=638		
Mean Age (yr) (SD)	58.4 (9.58)	52.0 (9.77)	51.6 (10.72)	60.7 (7.49)	67 (8.4)
Age <65 (%)	581 (72.5)	544 (91.0)	563 (88.2)	123 (68.3)	104 (41.3)
≥65 Age < 75 (%)	192 (24.0)	50 (8.4)	70 (11.0)	57 (31.7)	148 (58.7)
Age ≥75 (%)	28 (3.5)	4 (0.7)	5 (0.8)	0	44 (17.5)
Male n (%):	441 (55.1):	265 (44.3):	308 (48.3):	100 (55.6):	164 (65.1):
Female n (%)	360 (44.9)	333 (55.7)	330 (51.7)	80 (44.4)	88 (34.9)
Race (%):					
White	650 (81.1)	477 (79.8)	516 (80.9)	180 (100.0)	211 (83.7)
Black/Afr. Amer.	50 (6.2)	18 (3.0)	32 (5.0)	0	12 (4.8)
Asian	61 (7.6)	100 (16.7)	82 (12.9)	0	13 (5.2)
Other	40 (5.0)	3 (0.5)	8 (1.3)	0	16 (6.3)
Ethnicity ^a :					
Hispanic	203 (25.3)	75 (12.5)	103 (16.1)	0	7 (2.8)
Non-hispanic	598 (74.7)	117 (19.6)	171 (26.8)	180 (100.0)	81 (32.1)
Not reported	0	406 (67.9)	364 (57.1)	0	164 (65.1)
Geographic region (%):					
North America	0	213 (35.6)	294 (46.1)	0	140 (55.6)
Latin America	205 (25.6)	136 (22.7)	80 (12.5)	0	55 (21.8)
Europe	596 (74.4)	154 (25.8)	194 (30.4)	180 (100.0)	29 (11.5)
Asia/Pacific	0	95 (15.9)	70 (11.0)	0	28 (11.1)
Mean Baseline HbA1C (%) (SD)	7.72 (0.870)	9.19 (1.343)	9.06 (1.280)	7.17 (0.489)	8.35 (1.110)
Mean Duration of Diabetes (yr) (SD)	6.32 (5.299)	1.61 (2.711)	2.03 (3.718)	5.77 (4.911)	16.94 (9.562)
Mean Baseline weight (kg) (SD)	88.02 (16.645)	85.33 (20.210)	88.08 (19.452)	91.48 (13.894)	92.69 (19.529)
Baseline eGFR <30 mL/min/1.73 m ² (%)	2 (0.2)	1 (0.17)	0	0	10 (4.0)
Baseline eGFR ≥ 30 and <60 mL/min/1.73 m ² (%)	41 (5.1)	33 (5.52)	37 (5.8)	6 (3.3)	231 (91.7)
Baseline eGFR ≥ 60 and <90 mL/min/1.73 m ² (%)	379 (47.3)	309 (51.67)	343 (53.8)	110 (61.1)	11 (4.4) (eGFR ≥60)
Baseline eGFR ≥ 90 mL/min/1.73 m ² (%)	379 (47.3)	255 (42.64)	258 (40.4)	64 (35.6)	NA

Source: Applicant's SCE Table 7

I(f). Disposition

In the Phase 3 trials, 86.5% of patients in all treatment groups completed the short-term period treatment periods (Table 5). There were more patients in the control groups that were rescued or discontinued from the trials due to lack of efficacy compared to patients treated with dapagliflozin. Study D1690C00004, the active comparator trial, with a longer (52 week) short-term period, did not include rescue criteria during this period. This trial had a lower completion rate than other trials (79.3% in the dapagliflozin treated group and 77% in the glipizide treated group).

Table 5. Disposition/Rescue in the Phase 3 Trials

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy ^a n (%)	Rescued n (%)
Phase 3 placebo-controlled studies					
MB102013					
Group 1 QAM dosing					
	Placebo	75	63 (84.0)	1 (1.3)	9 (12.0)
	Dapa 2.5 mg	65	60 (92.3)	0 (0.0)	7 (10.8)
	Dapa 5 mg	64	52 (81.3)	0 (0.0)	1 (1.6)
	Dapa 10 mg	70	57 (81.4)	0 (0.0)	0 (0.0)
Group 1: QPM dosing					
	Dapa 2.5 mg	67	58 (86.6)	0 (0.0)	2 (3.0)
	Dapa 5 mg	68	57 (83.8)	0 (0.0)	2 (2.9)
	Dapa 10 mg	76	65 (85.5)	0 (0.0)	0 (0.0)
Group 2 QAM dosing					
	Dapa 5 mg	34	28 (82.4)	0 (0.0)	3 (8.8)
	Dapa 10 mg	39	34 (87.2)	0 (0.0)	3 (7.7)
MB102032					
	Placebo	68	65 (95.6)	1 (1.5)	13 (19.1)
	Dapa 1 mg	72	68 (94.4)	1 (1.4)	4 (5.6)
	Dapa 2.5 mg	74	67 (90.5)	0 (0.0)	3 (4.1)
	Dapa 5 mg	68	63 (92.6)	1 (1.5)	3 (4.4)
MB102014					
	Placebo	137	119 (86.9)	3 (2.2)	22 (16.1)
	Dapa 2.5 mg	137	121 (88.3)	0 (0.0)	5 (3.6)
	Dapa 5 mg	137	122 (89.1)	1 (0.7)	5 (3.6)
	Dapa 10 mg	135	121 (89.6)	0 (0.0)	5 (3.7)
D1692C00005					
	Placebo	146	133 (91.1)	2 (1.4)	23 (15.8)
	Dapa 2.5 mg	154	140 (90.9)	0 (0.0)	9 (5.8)
	Dapa 5 mg	145	132 (91.0)	1 (0.7)	8 (5.5)
	Dapa 10 mg	151	141 (93.4)	0 (0.0)	3 (2.0)
MB102030					
	Placebo	139	116 (83.5)	3 (2.2)	16 (11.5)
	Dapa 5 mg	141	125 (88.7)	0 (0.0)	2 (1.4)
	Dapa 10 mg	140	126 (90.0)	1 (0.7)	5 (3.6)
D1690C00006					
	Placebo	197	168 (85.3)	1 (0.5)	54 (27.4)
	Dapa 2.5 mg	202	179 (88.6)	1 (0.5)	20 (9.9)
	Dapa 5 mg	212	186 (87.7)	0 (0.0)	24 (11.3)
	Dapa 10 mg	196	178 (90.8)	0 (0.0)	19 (9.7)
D1690C00012					
	Placebo	91	86 (94.5)	0 (0.0)	2 (2.2)
	Dapa 10 mg	91	83 (91.2)	0 (0.0)	0 (0.0)
MB102029					
	Placebo	84	63 (75.0)	2 (2.4)	13 (15.5)
	Dapa 5 mg	83	72 (86.7)	0 (0.0)	9 (10.8)
	Dapa 10 mg	85	69 (81.2)	0 (0.0)	2 (2.4)
Phase 3 active comparator Add-on combination Study					
D1690C00004^b					
	SU (titrated dosing)	408	314 (77.0)	15 (3.7)	NA
	Dapa (titrated dosing)	406	322 (79.3)	1 (0.2)	NA
Phase 3 active comparator Initial Combination Studies					
MB102021					
	Metformin XR	201	171 (85.1)	0 (0.0)	26 (12.9)
	Dapa 5 mg	203	170 (83.7)	1 (0.5)	15 (7.4)
	Dapa 5 mg + Metformin XR	194	177 (91.2)	0 (0.0)	1 (0.5)
MB102034					
	Metformin XR	208	181 (87.0)	1 (0.5)	27 (13.0)
	Dapa 10 mg	219	188 (85.8)	1 (0.5)	17 (7.8)
	Dapa 10 mg + Metformin XR	211	183 (86.7)	0 (0.0)	3 (1.4)

^a Discontinuation due to lack of efficacy is determined from the glycemic control page of the CRF, or study termination page for study D1690C00005

Source Applicant's SCE Table 9

Section II. Efficacy

II(a). Analysis Datasets

The dataset for the primary analysis of efficacy in the Phase 3 trials included all randomized subjects who took at least one dose of double-blind treatment with a non-missing baseline efficacy value and at least one post-baseline efficacy value. The applicant used the Last Observation Carried Forward (LOCF) as the primary method for imputation of missing data for analysis.

II(b). Primary Endpoint

Please refer to Dr. Jon Norton's review for a full discussion of efficacy. I will only highlight a few aspects not covered by Dr. Norton.

For the proposed doses of 5 mg and 10 mg, the placebo-adjusted mean reductions in HbA1c in the monotherapy and add-on trials were consistently statistically significant and ranged from -0.4% to -0.8%. It is notable that in these trials, the mean change in HbA1c in the placebo group over 24 weeks in the majority of these trials (excluding subjects who required glycemic rescue) ranged from 0 up to -0.4%.

Comparison between dapagliflozin and metformin

For the trials assessing the glycemic effects of the combination of dapagliflozin and metformin as initial therapy in treatment naïve patients (MB102021 and MB102034), statistical inferential comparisons were made for the combination of dapagliflozin plus metformin XR up to 2000 mg versus dapagliflozin alone and versus metformin alone. All were statistically significant and favorable to the dapagliflozin and metformin combinations as compared to the individual components. For Study MB102021, the mean difference between dapagliflozin plus metformin treatment and metformin alone was 0.7% (95% CI -0.94, -0.45). For Study MB102034, the mean difference between dapagliflozin plus metformin and metformin alone was -0.54 (95% CI -0.75, -0.33). As part of the hierarchical testing strategy for study MB102034, there was a secondary assessment of non-inferiority for change from baseline in HbA1c at week 24 between dapagliflozin 10 mg monotherapy and metformin XR monotherapy with doses up to 2000 mg daily (non-inferiority margin of 0.35%). Dapagliflozin 10 mg was found to be non-inferior to metformin XR in lowering HbA1c (95% CI for difference -0.22 to 0.20).

Comparison between dapagliflozin and glipizide

In the active comparator study, D1690C00004, treatment with either dapagliflozin or glipizide resulted in a mean reduction of 0.5% in HbA1c compared to baseline at week 52. Dapagliflozin was non-inferior to glipizide with doses up to 20 mg daily for change in

HbA1c at Week 52 according to predetermined statistical criteria of a non-inferiority margin = 0.35%, with 95% confidence interval completely below that margin. The mean difference between the treatment arms was 0.0 (dapagliflozin and glipizide) (95%CI - 0.11, -0.11).

Lack of efficacy in patients with moderate renal impairment

Prior to Phase 3, the applicant conducted a single and multiple dose pharmacokinetic and pharmacodynamic study in patients with T2DM with normal (estimated GFR ≥ 90 mL/min/1.73 m²), mild (estimated GFR ≥ 60 and ≤ 89 mL/min/1.73 m²), moderate (estimated GFR ≥ 30 and ≤ 59 mL/min/1.73 m²), and severe renal impairment (estimated GFR ≥ 29 mL/min/1.73 m² and ≤ 15 mL/min/1.73 m²). Following administration of dapagliflozin 20 mg once daily for 10 days, patients with mild, moderate, or severe renal impairment had higher steady-state mean dapagliflozin AUC (tau) as compared to T2DM patients with normal renal function. Despite higher systemic exposures of dapagliflozin in subjects with moderate and severe renal impairment, the 24-hour glucosuric effect decreased progressively (Table 6)

Table 6. Effect of degree of renal impairment on PK/PD of dapagliflozin 20 mg daily. Values shown as % increase or % decrease in geometric mean (GM) compared to patients with normal renal function

	% Increase in GM exposure AUC(tau) at Day 10 of dosing compared to patients with normal renal function	% Decrease in cumulative amount of 24-h glucose excretion at Day 10 compared to patients with normal renal function
Normal		
Mild	↑ 39%	↓ 42 %
Moderate	↑ 100%	↓ 80 %
Severe	↑ 200%	↓ 90 %

Source: Dr. Jain’s Clinical Pharmacology review of NDA 202293

As noted by the applicant, glycemic efficacy was not expected in patients with severe renal impairment and these patients were excluded from the large controlled clinical trials. A separate study was conducted to specifically evaluate the efficacy and safety of dapagliflozin compared to placebo in patients with moderate renal impairment, defined as an eGFR between 30 and 60 mL/min/1.73m². In this study, the HbA1c mean changes from baseline by week 24 were small in both the dapagliflozin 5 mg and 10 mg treatment groups, and were not statistically significant.

In what was defined as an ad-hoc analysis, the applicant subdivided moderate renal impairment into two sub-stages: 3A which defines a group with GFR 45 to 59 mL/min/1.73 m², and 3B which defines a group with GFR 30 to 44 mL/min/1.73 m².

Table 7. HbA1c (%) Placebo Adjusted Mean Change from Baseline for Groups 3A and 3B

Dose	Change from Baseline HbA1c (%) in 3A (SE)	Change from Baseline in HbA1c (%) in 3B (SE)
5 mg	N=35 -0.37 (0.23)	N=41 0.05 (0.21)
10 mg	N=33 -0.33 (0.24)	N=45 0.07 (0.21)

Source CSR ST and LT Appendices 38 and 39

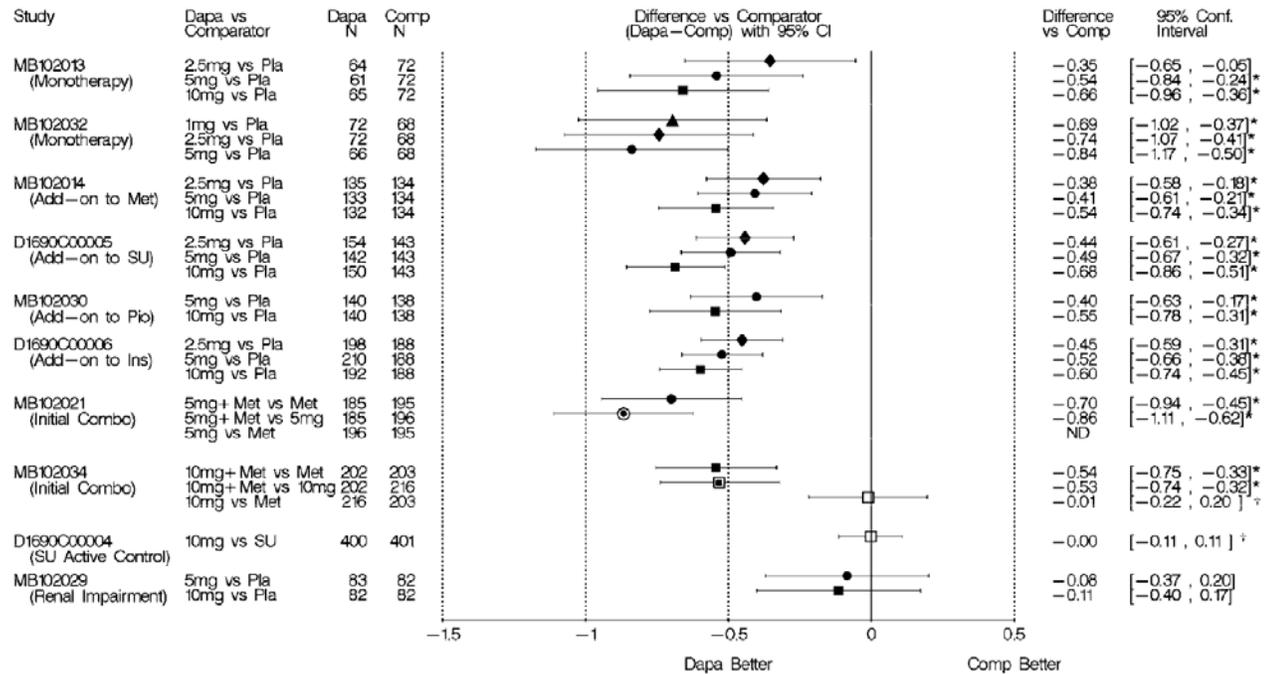
This breakdown of data into subcategories of moderate renal impairment shows that efficacy decreases with progressive decline in renal function. Although patients in the subcategory of 3A had a greater placebo-subtracted HbA1c reduction than 3B subcategory, the mean difference from placebo was not statistically significant. The mean difference in HbA1c reduction between the dapagliflozin 5 and 10 mg groups versus placebo in the 3A subcategory was -0.37 (95% CI -0.83, 0.10) and -0.33 (95% CI -0.80, 0.14), respectively.

In the overall phase 3 program, patients randomized to dapagliflozin who had moderate or severe renal impairment required glycemic rescue therapy more often and much sooner than patients with normal renal function. It is important to note that patients with T2DM are at risk for worsening renal function over the course of their disease. Unlike treatment with other classes of antidiabetic medications that rely on either insulin secretion or sensitivity, dapagliflozin's effect is dependent on GFR and independent of beta cell function. Therefore, secondary failure of glycemic control with dapagliflozin may represent deterioration of renal function, rather than beta cell function, and discontinuation of dapagliflozin (in contrast to the practice of adding drugs of complementary effects) may be recommended.

Overall efficacy estimates and 95 % CI in Phase 3 trials

Figure 2 presents a forest plot of the primary endpoint in 10 Phase 3 trials. The difference versus comparator (point estimate and 95% confidence intervals) is displayed. For all but the active comparator trial and the renal impairment trial, discussed above, the point estimates do not cross zero.

Figure 2. HbA1c (%) Adjusted Mean Change from Baseline at end of Short-term Period Versus Comparator



Source Response to FDA Inquiry May 18, 2011

Trial D1690C00012—Body Weight and Body Composition Study

This trial assess the effect of dapagliflozin on body weight and on body fat mass as measured by dual energy X-ray absorptiometry (DEXA) and visceral adipose tissue volume as measured by magnetic resonance imaging (MRI). The change from baseline in total body weight at 24 weeks was the primary efficacy variable. There were 89 patients on dapagliflozin 10 mg daily and 91 patients on placebo. The placebo adjusted mean weight loss at 24 weeks was -2.08 kg (95% CI -2.84, -1.31). At this time, these data are not being considered for inclusion in the label, if dapagliflozin is approved. These are insufficient to meet the requirements listed in the *Guidance for Industry: Developing Products for Weight Management*.

II(c). Analyses in Subgroups

Treatment-by-subgroup interaction was an exploratory analysis designed to detect differential patterns by comparing the effect of dapagliflozin to placebo across T2DM subpopulations based on demographic and baseline disease characteristics. This testing was performed in individual trials and the results were also pooled. The renal impairment study, MB102029 was not included in this testing, while the weight composition study D1690C000012 was. In addition, D1690C00004, the active comparator study, was also not included.

The p-values calculated represent all treatment groups in the primary analysis of each trial, except for the initial combination trials, where only the combination and metformin arms are included in the test (Table 8). In the pooled analyses, only the dapagliflozin 2.5 mg, 5 mg, 10 mg and placebo groups are included. The numbers in bold indicate those treatment-by-subgroup interactions with a p-value<0.1, a threshold traditionally used for this purpose. In the pooled analyses, the most notable interactions are between treatment and baseline HbA1c (a finding common to many antidiabetic drugs) and between treatment and baseline eGFR (conceivably due to the mechanism of action of dapagliflozin).

Table 8. Treatment by Subgroup Interaction P-values for HbA1c (%) Change From Baseline at Week 24

Background: Study	Monotherapy, placebo-controlled		Add-on Combination, placebo-controlled				Initial combination with metformin XR		Weight and Body Composition Metformin D1690C00012	Number of studies where p<0.10 for inter-action test	Pooled inter- action
	MB102013	MB102032	Metformin MB102014	SU D1690C00005	TZD MB102030	Insulin D1690C00006	MB102021	MB102034			
Baseline HbA1c ^a	0.1919	<0.0001	0.0681	0.2546	0.0001	0.0023	<0.0001	0.5332	0.3710	5	<0.0001
Baseline eGFR ^a	0.9355	0.7067	0.8912	0.0115	0.0571	0.0819	0.3080	0.5644	0.5139	3	0.0148
Age	ND	ND	0.0140	0.9166	0.0484	0.8512	0.6929	0.5185	0.5322	2	0.0538
Gender	0.6178	0.2881	0.5373	0.9164	0.6790	0.4030	0.7246	0.7115	0.0005	1	0.4563
Ethnicity	ND	ND	0.8359	ND	0.0374	ND	0.2637	0.1950	ND	1	0.9616
Female age	ND	0.5279	0.6413	ND	0.2451	0.2920	0.5167	0.6984	NA	0	0.0911
Region	0.2323	0.8739	0.5624	0.4089	0.9465	0.1612	0.1218	0.7105	ND	0	0.1320
Race	ND	ND	ND	0.4089	0.7998	ND	0.5028	0.8521	ND	0	0.5502
Baseline BMI	ND	ND	0.9481	0.9041	0.1975	0.1234	0.3757	0.1673	0.8587	0	0.7100
Duration of T2DM	ND	ND	0.7275	0.7160	0.7189	0.7530	0.9001	0.3603	0.2285	0	0.9780

Source Applicant’s SCE Table 6

Section III. Major Safety Issues

III(a). Analysis Datasets

There are two major safety pools discussed for the safety events in this briefing. One is the All Phase 2b and 3 trials (Group 1 in Table 9) including both the short and long term extension phase of the trials. The other pool is the Placebo-controlled pool with both a short-term and a short plus long-term treatment period (Group 2 in Table 9).

Table 9. Major Safety Pools

Population	Treatment Period	Studies	Treatment Groups
1. All Phase 2b and 3 Studies Pool Data from all Phase 2b and 3 placebo- or active controlled studies, with or without other background antidiabetic medications, were pooled and analyzed.	ST + LT	MB102008	Dapagliflozin 2.5 mg
		MB102009	Dapagliflozin 5 mg
		MB102013	Dapagliflozin 10 mg
		MB102014	Control (placebo with or without background medications or active control including benchmark treatments)
		MB102021	
		MB102029	
		MB102030	
		MB102032	A total dapagliflozin treatment group includes all subjects who received either dapagliflozin 2.5, 5, or 10 mg as defined above plus dapagliflozin 20 mg and 50 mg. Safety tables for this pool are presented with total dapagliflozin only.
		MB102034	
		D1690C00004	
		D1690C00005	
		D1692C00005	
		D1690C00006	
D1690C00012			
2. Placebo-controlled Pool Data from placebo-controlled studies, with or without other background antidiabetic medications, are pooled and analyzed.	ST	MB102008	Dapagliflozin 2.5 mg
		MB102009	Dapagliflozin 5 mg (including Dapagliflozin plus metformin from MB102021)
		MB102013	Dapagliflozin 10 mg (including Dapagliflozin plus metformin from MB102034)
		MB102014	Control (placebo with or without background medications, and for MB102021 or MB102034, placebo plus metformin)
		MB102021	
		MB102030	
		MB102032	
		MB102034	A total dapagliflozin treatment group includes all subjects who received dapagliflozin 2.5, 5, or 10 mg (as defined above) plus dapagliflozin 20 mg (MB102008 and Cohort 2 of MB102009) and dapagliflozin 50 mg (MB102008).
		D1690C00005	
		D1692C00005	
		D1690C00006	
		D1690C00012	
		ST + LT	
MB102014	Dapagliflozin 5 mg		
MB102030	Dapagliflozin 10 mg		
D1690C00005	Control (placebo with or without background medications)		
D1690C00006			
			A total dapagliflozin treatment group includes all subjects who received dapagliflozin 2.5, 5, or 10 mg.

Source Applicant’s SCE Table 3

III(b). Bladder Cancer

An imbalance in bladder cancer cases was noted in the All Phase 2b and 3 Pool and reported with the Four Month Safety Update (4MSU), when the safety pool consisted of 4310 subjects with 4354 patient-years of exposure treated with at least 1 dose of dapagliflozin 2.5 mg or higher. A total of 1962 subjects with 1899 patient-years of exposure were treated with placebo/comparator. At the cutoff date designated for the 4MSU, there were a total of 7 (0.2%) cases of bladder cancer in dapagliflozin-treated patients versus 0 subjects treated with control (Table 10). Three additional cases were reported about one month later via dapagliflozin Investigational New Drug Safety

Reports. Two of these cases were in dapagliflozin-treated patients, and one was in a placebo-treated patient. This can be extrapolated to 207 cases per 100,000 person year exposure in dapagliflozin treated patients versus 53 cases per 100,000 person year exposure in control.

For a full discussion of bladder cancer in patients with T2DM compared to that seen and expected in the dapagliflozin clinical program, please refer to the review prepared by Dr. Christian Hampp, from the Office of Surveillance and Epidemiology.

This subsection will describe the patients with reported bladder cancer in the dapagliflozin development program.

All 7 subjects reported with the 4MSU with bladder cancer were male; all were ≥ 60 years of age and all received dapagliflozin: 1, 3, and 3 in the 2.5, 5, and 10 mg groups, respectively (1 subject in the 10 mg group had his dapagliflozin dose titrated from 2.5 to 5 to 10 mg). The 7 events of bladder cancer in subjects receiving dapagliflozin were reported within 2 years of beginning dapagliflozin treatment, with a median time for appearance of 399 days, ranging from 43 to 727 days.

The 7 subjects were from 7 different countries across 4 continents. Six of the 7 subjects with bladder cancer received concomitant antidiabetic medication: insulin (3 subjects), metformin (2 subjects), and pioglitazone (1 subject taking pioglitazone 45 mg for 3 years). Five of the subjects with bladder cancer were either current or former smokers. Microscopic hematuria was noted in 3 of the 7 subjects (prior to taking the first dose of dapagliflozin) and 1 additional subject had trace hematuria before or at randomization. One patient in Table 10, MB102-030 90-880, had a family history of bladder cancer.

Table 10. Patients with Bladder Cancer in the Dapagliflozin All Phase 2b and 3 Pool

Subject No. Age/Sex/Race	Country	Study Drugs	Preferred Term	Diagnosis Study Day	Action (Study Drugs)	Smoking History	Microscopic Hematuria (Y/N) ^a	Relevant Medical History/AEs	Histology
D1692C00005 -1-11 75/male/Asian	Japan	Dapa 2.5 mg	Bladder cancer	43	Disc	Former smoker, 20 cigarettes/ day for 50 years	Yes (2+)	AE: Occult blood positive onset Day 36	Papillary and broad base elevated lesion from neck to trigone of the bladder, Urinary cytology results revealed Class IV malignant cells
D1690C00006 -1004-6 63/male/white	Austria	Dapa 5 mg + insulin	Bladder cancer	393	None	Current smoker, 40 cigarettes/ d	No (Negative)	AEs: Benign prostatic hyperplasia Day 136, AE: Bladder neoplasm Day 358	Urothelial carcinoma pTa G2, noninvasive
MB102014- 34-524 60/male/white	Canada	Dapa 5 mg + metformin	Bladder transitional cell carcinoma	512	None	Former smoker, 25 cigarettes/ d for 25 y, stopped 1989	Yes (2+)	AE: Calculus ureteric Day 509	Location: Right ureteric orifice, Growth pattern: Papillary, Histological type: transitional, TNM classification: pTa, pNo, Mo., Grade/Stage: Stage 0
MB102030- 90-880 67/male/white	Argentina	Dapa 5 mg + pio- glitazone	Squamous cell carcinoma	144	Disc	Never smoked	No (trace)	AEs: Genital candidiasis Day 19, UTI Day 84, Urinary symptoms: urgency, pollakiuria, AEs: Haematuria Day 130, Urinary bladder polyp Day 144	Location: fundus, Growth pattern: nests and cords, Histological type: squamous, TNM classification: unknown Grade/Stage: unknown
D1690C00004 -4916-2 76/male/white	Germany	Dapa 10 mg ^b + metformin	Bladder transitional cell carcinoma	727	None	Former smoker, 20 pack years until 1980	No (Negative)	AE: Benign prostatic hyperplasia Day 727	Papillary, submucosal, stroma-invasive urothelial carcinoma, high-grade (formerly G3) with partial squamous cell differentiation
D1690C00006 -1501-6 67/male/white	Hungary	Dapa 10 mg + insulin	Bladder transitional cell carcinoma stage II	399	None	Never smoked	Yes (3+)	AE: Haematuria Day 372	Carcinoma transitional grade II of the urinary bladder
D1690C00006 -2206-14 66/male/white	United States	Dapa 10 mg + insulin	Bladder transitional cell carcinoma	581	None	Former smoker 30 cigarettes/ d for 42 y, stopped 2001	No (Negative)	AE: Haematuria Day 577	Non-invasive low grade papillary urothelial carcinoma.

^a Highest value before or at randomization.

^b The dapagliflozin dose for this subject was up-titrated from 2.5 to 5 to 10 mg. At the time of event, the dose was 10 mg.

Source Applicant's 4MSU Table 10

One of the additional cases reported after the 4MSU (was blinded in the 4MSU) was in a 49 year old white male in an ongoing study, D1690C00018. He had a history of renal stones and hematuria several years prior to trial initiation. After approximately 10 weeks of treatment with dapagliflozin 10 mg, he was diagnosed with non-invasive low-grade papillary urothelial carcinoma of the urinary bladder (grade 2). There was no history noted of smoking.

The other case recently reported was in the same trial referenced above. This case was in a 56 year old man who was treated with dapagliflozin 10 mg for six months. There was no smoking or hematuria at baseline noted. The patient had three months of intermittent

hematuria prior to diagnosis. Post surgical diagnosis was papillary urothelial carcinoma, low grade (papillary transitional cell carcinoma, grade 1).

The applicant has explored possible explanations for the bladder cancer imbalance, including the summary of baseline risk factors in the cases summarized above. However, the baseline characteristics of risk factors for bladder cancer in the dapagliflozin-treated patients and the control group were similar (Table 11), reducing the likelihood that any such imbalance of risk might have contributed to the numerically higher number of cases observed with dapagliflozin.

Table 11. Bladder Cancer Risk Factor Summary Phase 2b and 3 Pool, Treated Subjects

	DAPA TOTAL N=4310	All CONTROL N=1962
HEMATURIA AT BASELINE		
SUBJECTS WITH AT LEAST ONE URINE DIPSTICK PRIOR TO RECEIVING STUDY DRUG SHOWING 1+, 2+, 3+ OR GREATER BLOOD	387 (9.0)	176 (9.0)
SMOKING STATUS (%)		
NEVER	2589 (60.1)	1172 (59.7)
CURRENT	711 (16.5)	318 (16.2)
FORMER	1007 (23.4)	472 (24.1)
UNKNOWN	3 (0.1)	0 (0.0)
GENDER		
MALE	2192 (50.9)	1033 (52.7)
FEMALE	2118 (49.1)	929 (47.3)
RACE		
WHITE	3486 (80.9)	1591 (81.1)
BLACK/AFRICAN AMERICAN	158 (3.7)	73 (3.7)
ASIAN	558 (12.9)	242 (12.3)
OTHER	108 (2.5)	56 (2.9)
HISTORY OF CHRONIC CYSTITIS	4 (0.1)	5 (0.3)
USE OF CYCLOPHOSPHAMIDE	0	0

Source Response to FDA Information Request May 20, 2011

A nonclinical finding of carcinogenicity could not be identified as discussed by both the applicant and summarized by FDA's pharmacology/toxicology review staff.

Several studies have reported a higher risk of bladder cancer in patients with T2DM compared to the general population. In the clinical development programs of several recently approved anti-diabetics, no cases of bladder cancer was identified in saxagliptin and liraglutide NDAs and three cases were identified in linagliptin-treated patients versus none in control.

It is possible that the mechanism of action of dapagliflozin and related genito-urinary adverse effects in dapagliflozin-treated patients due to glucosuria may contribute to a detection bias. For example, more frequent assessments of urinalysis in the dapagliflozin group might result in post-baseline detection of hematuria requiring further work-up and higher rate of cancer diagnosis than control group which might not have received as extensive monitoring. In this regard, it is interesting to note that concerns of bladder cancer associated with pioglitazone use arose during pre-marketing development due to nonclinical findings of bladder cancer in male rodents. This led to a prospective assessment of urine cytology in approximately 1800 patients in clinical trials up to one

year duration. Despite similar active surveillance for bladder cancer in pioglitazone and control groups, no clinical cases were detected premarketing. Imbalance of clinical bladder cancer risk with pioglitazone was not observed until after approval, as recently described in the media and by several regulatory agencies, including FDA.

III(c). Breast Cancer

The initial NDA submission reported nine (0.2% of the total population, 0.4% of the female population) patients in the dapagliflozin group and none in the control with breast cancer. These cases were found in the All Phase 2b and 3 Pool; however one of these cases was in the long-term period of Study D1690C0012 (the body weight/ composition trial) which was not part of the All Phase 2b and 3 Pool, due to report cutoff date. At that time, the exposure for the All Phase 2b and 3 Pool was a total of 4287 patients treated with dapagliflozin and a total of 1941 patients treated with placebo or control. This exposure was calculated to be 4009 patient-years and 1682 patient-years in control. The breast cancer incidence can be extrapolated to 224.5 cases per 100,000 person years.

For a full discussion of breast cancer incidence in the T2DM population and that reported in the dapagliflozin clinical program, please refer to the breast cancer review prepared by Dr. Julia Ju, from the Office of Surveillance and Epidemiology.

This subsection will describe the patients with reported breast cancer in the dapagliflozin development program.

Two of the nine subjects were diagnosed within six weeks of initiation of dapagliflozin treatment. The treatment duration (< 1 year) in these trials is shorter than the average of more than 5 years of exposure suggested as sufficient for detection of breast cancer. Seven of the nine subjects were ≥ 60 years of age.

The breast cancer cases are summarized in Table 12.

Table 12. Breast Cancer Cases in the Dapagliflozin Clinical Program

Subject Number	Age/Sex/Race	Diagnosis (Study Day)	Weight Change at Diagnosis (kg)	<u>Histological Grade/Stage/ Histologic Type</u> ^a
Dapagliflozin 2.5 mg				
MB102013-33-261	74/Female/White	321	-2.5	Stage 1, grade 2 ductal carcinoma
D1690C00006-1403-2	63/Female/White	6	-1.1	<u>Grade 2, invasive ductal</u> Not provided
D1690C00006-1803-7	58/Female/White	292	+1.0	<u>Not provided Grade 2 breast cancer</u>
Dapagliflozin 5 mg				
MB102021-59-482	53/Female/White	39	-1.2	<u>Not provided Grade 3 intraductal carcinoma</u>
Dapagliflozin 10 mg				
D1690C00004-4405-20 ^b	60/Female/White	193	0	Grade 1 ductal carcinoma
MB102014-50-151	64/Female/White	285	-10.0	<u>Grade is reported as high, Grade 3 adenocarcinoma</u>
D1690C00005-4012-46	69/Female/Asian	334	-3.4	<u>Not provided Grade 1</u>
D1690C00006-1005-18	61/Female/White	204	-9.0	<u>Grade 2, multifocal, invasive, lobular carcinoma</u> Not provided
D1690C00012-202-4	64/Female/White	211	-0.3	<u>Grade 2-3, invasive ductal carcinoma with TNM classification of PT1c, pN1M0</u>

^a Provided when biopsy information was available.

^b The dapagliflozin dose for this subject was up-titrated from 2.5 to 5 to 10 mg.

Source Applicant's SCS Erratum Submission Table 36

Breast cancer risk factors at baseline were similar between the dapagliflozin treated patients and the control patients (Table 13).

Table 13. Baseline Breast Cancer Risk Factor Summary Phase 2b and 3 Pool, Treated Subjects

	DAPA TOTAL N=2110		ALL CONTROL N=922	
BODY MASS INDEX (KG/M²)				
N	2110		922	
MEAN	32.24		32.17	
MEDIAN	32.00		31.90	
MIN , MAX	16.90 , 48.40		17.50 , 45.20	
Q1 , Q3	28.10 , 36.20		28.00 , 36.20	
STANDARD DEVIATION	5.643		5.794	
BODY MASS INDEX CATEGORIZATION (%)				
< 30 KG/M ²	768 (36.4)		351 (38.1)	
>= 30 KG/M ²	1342 (63.6)		571 (61.9)	
NOT REPORTED	0		0	
AGE CATEGORIZATION (%)				
<=50 YEARS	576 (27.3)		256 (27.8)	
>50 YEARS	1534 (72.7)		666 (72.2)	
< 45	271 (12.8)		128 (13.9)	
>= 45 - < 55	589 (27.9)		248 (26.9)	
>= 55 - < 65	823 (39.0)		320 (34.7)	
>= 65 - < 75	376 (17.8)		194 (21.0)	
>= 75	51 (2.4)		32 (3.5)	
NOT REPORTED	0		0	
BODY MASS INDEX AND AGE CATEGORIZATION (%)				
>=30 KG/M ² AND >50 YEARS	940 (44.5)		409 (44.4)	
ALCOHOL CONSUMPTION AT BASELINE (%)				
YES	654 (31.0)		273 (29.6)	
NO	1456 (69.0)		649 (70.4)	
NOT REPORTED	0		0	
TOBACO USE AT BASELINE (%)				
NEVER	1608 (76.2)		713 (77.3)	
CURRENT	235 (11.1)		88 (9.5)	
FORMER	267 (12.7)		121 (13.1)	
UNKNOWN	0		0	
PRE-RANDOMIZATION USE OF OESTROGEN MEDICATION				
YES	79 (3.7)		45 (4.9)	
NO	2031 (96.3)		877 (95.1)	
NOT REPORTED	0		0	

Source Response to FDA Information Request May 18, 2011

III(d). Hepatic Events

Marked Elevations in Liver Enzymes

Please refer to the Office of Surveillance and Epidemiology review of the hepatic data related to dapagliflozin.

Liver-related tests were monitored during the dapagliflozin development program. Investigators completed supplemental CRFs for events of increased liver tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3× upper limit of normal

[ULN]). Patients with clinical liver disease and elevated hepatic parameters were excluded from the clinical studies.

Elevations of 3x, 5x, 10x and 20x in liver aminotransferases across the largest safety pool, the Phase 2b and 3 pool, display similar rates between dapagliflozin and control groups (Table 14). Review of these individual patient cases revealed likely etiology in dapagliflozin-treated patients with marked elevations. The patients in whom causality assessment was questionable will be discussed below.

Table 14. Marked Liver Enzyme Elevations in the Phase 2b and 3 Pool

	X/N# (Percent)	
	DAFA TOTAL N = 4287	ALL CONTROL N = 1941
TOTAL SUBJECTS WITH ELEVATED LIVER TESTS	206/4258 (4.8)	85/1922 (4.4)
AST ELEVATION		
> 3X ULN	38/4258 (0.9)	16/1922 (0.8)
> 5X ULN	11/4258 (0.3)	8/1922 (0.4)
> 10X ULN	5/4258 (0.1)	3/1922 (0.2)
> 20X ULN	4/4258 (0.1)	0/1922
ALT ELEVATION		
> 3X ULN	61/4258 (1.4)	28/1922 (1.5)
> 5X ULN	17/4258 (0.4)	9/1922 (0.5)
> 10X ULN	4/4258 (0.1)	3/1922 (0.2)
> 20X ULN	2/4258 (<0.1)	1/1922 (0.1)
AST OR ALT ELEVATION		
> 3X ULN	73/4258 (1.7)	33/1922 (1.7)
> 5X ULN	19/4258 (0.4)	12/1922 (0.6)
> 10X ULN	5/4258 (0.1)	5/1922 (0.3)
> 20X ULN	4/4258 (0.1)	1/1922 (0.1)
TOTAL BILIRUBIN ELEVATION		
> 1.5X ULN	55/4258 (1.3)	18/1921 (0.9)
> 2X ULN	18/4258 (0.4)	5/1921 (0.3)
AST OR ALT (AT) AND TOTAL BILIRUBIN (TBL) ELEVATION (AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 1.5X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	8/4258 (0.2)	4/1921 (0.2)
(AST > 3X ULN OR ALT > 3X ULN) AND (TBL > 2X ULN WITHIN 14 DAYS ON OR AFTER AT ELEVATION)	5/4258 (0.1)	3/1921 (0.2)
(AST > 3X ULN OR ALT > 3X ULN) AND { (TBL > 2X ULN AND NO ALP ≥ 2X ULN) WITHIN 14 DAYS ON OR AFTER AT ELEVATION }	3/4258 (0.1)	2/1921 (0.1)
ALP ELEVATION		
> 1.5X ULN	105/4258 (2.5)	49/1922 (2.5)
> 3X ULN	6/4258 (0.1)	4/1922 (0.2)

Source Applicant's SCS Table 84

Possible Drug Induced Liver Injury (DILI)

The applicant had a blinded adjudication process for liver abnormalities. Criteria for referral to the adjudication panel were:

- AST and/or ALT > 3X upper limit of normal (ULN) and total bilirubin (TB) > 1.5X ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT > 5X ULN
- Liver-related serious or non-serious standardized MedDRA queries (SMQ) adverse event (SAE or AE, respectively) in subjects who prematurely discontinued study treatment due to any SAE/AE
- Liver-related SMQ SAE or AE in any subjects who died

Cases for adjudication were identified through a search of all reported AEs using liver-related SMQs. Laboratory abnormalities were also reviewed for possible adjudication referral. There were three hepatologists on the adjudication committee, blinded to treatment assignment, and each submitted an opinion regarding probability of drug induced liver injury. This was followed by a consensus agreement on each case. The cases adjudicated were from the All Phase 2b and 3 pool. For the majority of the trials, the events were adjudicated retrospectively.

Based on the above criteria, 54 cases from these trials were referred for adjudication. Of these 54 cases, 35 were treated with dapagliflozin, 17 with either placebo or a comparator drug, and 2 were from blinded ongoing studies. The proportion of patients reported was similar between the groups, considering the differences in exposure. No case was assessed as definitely or highly likely associated with the blinded drug treatment. The two cases of liver-related events that were deemed “probable” by this panel were patients randomized to the control group. There were nine cases that were determined as “possibly” related to study medication in patients that were on dapagliflozin and five in the control group. There is one case that remains blinded.

There were a total of five cases in the Phase 2b and 3 Pool that met laboratory criteria for Hy’s Law (AST or ALT greater than 3x the Upper Limit of Normal [ULN] in addition to elevation of total bilirubin greater than 2x ULN).

- Two of these cases had clear etiology other than drug induced liver damage, and thus do not meet the definition of Hy’s Law;
- A third patient had dapagliflozin discontinued due to liver enzyme elevations. Subsequently, it was restarted and the patient had no elevation of liver enzymes or other liver related complications (negative re-challenge).
- Thus the remaining two of these cases remain suspicious for drug-induced liver injury. The blinded hepatic adjudication panel established by the applicant had deemed these two cases “possible.”

The Office of Surveillance and Epidemiology was consulted on these and other cases. They determined Case One as “probable” and Case Two below as “difficult to establish etiology”. All three of these cases are described below. The five cases of marked AST and/ or ALT elevations (defined as >10x the ULN) are also summarized below.

Summaries for these cases are as follows:

Patient Identification D1690C00004-4402-6 - Case One, Possible DILI

The patient was a 78 year old man from India with T2DM, coronary artery disease, hypertension, dyslipidemia and benign prostatic hypertrophy. He received the study drug plus metformin. Concomitant drugs included atorvastatin, cromolyn, *lecarnlidipine*, atenolol, parendopril, naproxen, acetylsalicylic acid and some herbal products. The patient is a C282Y/H63D compound heterozygote for hemochromatosis. Although the patient had a slight increase in ALT on study day 1 (not shown in the table below), ALT increased from baseline at study day 85. By study day 196, the patient had complaints of

dark urine and stool along with upper abdominal discomfort. He was noted to have a “tinge of jaundice”.

Of note, dapagliflozin was discontinued on day 192. The elevated aminotransferases and bilirubin started to decrease by day 213. Review of a liver biopsy led the treating physicians to a suspicion of autoimmune hepatitis and prednisone was started on day 349; at that point, the serum aminotransferases and bilirubin concentrations had already decreased considerably. The timing of the therapeutic intervention with regard to the oscillation of liver tests suggests a drug induced liver injury diagnosis as opposed to autoimmune hepatitis.

Liver Enzymes were as follows:

Date	Day	ALT(U/L)	AST (U/L)	ALP(U/L)	Bilirubin (mg/dL)
23-Aug-2008 ^a	85	62			
4-Oct-2008 ^a	127	117	72		
29-Nov-2008 ^a	183	1204	825	103	0.7
5-Dec-2008 ^a	189	1498	853	117	1.2
Study drug stopped 8-Dec-2008					
9-Dec-2008 ^a	193	1748	1060	120	2.5
16-Dec-2008 ^b	200	1858		128	4.2
29-Dec-2008 ^a	213	805	374	133	2.4
12-Jan-2009 ^b	227	431		98	1.8
3-Feb-2009 ^b	249	729		149	2.1
4-Mar-2009 ^b	278	439		162	1.1
27-Mar-2009 ^b	301	524		216	1.1
28-Apr-2009 ^b	333	498		302	1.5
28-May-2009 ^b	363	166			
16-Jun-2009 ^b	382	77		354	0.8
7-Jul-2009 ^b	403	60		267	0.8
13-Aug-2009 ^b	440	54		156	0.6
2-Nov-2009 ^b	521	50		95	0.5
10-Feb-2010 ^b	621	64		71	0.5
<p>a Central lab ref. ranges: ALT:6-48 U/L, AST: 10-45 U/L, ALP: 45-145 U/L, Bilirubin: 0.2-1.2 mg/dL</p> <p>b Local lab ref-ranges: ALT: 10-50 U/L, ALP 30-120 U/L, Bilirubin 0.2-1.5 mg/dL</p>					

Source Applicant’s Case Narrative Hepatic Adjudication Report

Serologic markers for autoimmune hepatitis were negative, although the liver biopsy had some suggestive features of autoimmune hepatitis with acute necroinflammation and interface hepatitis. In addition, the patient had an elevated IgG 22.4 g/L (reference range 5.3-16.5), IgA 8.93 g/L (0.80-4.00) IgM 2.90 g/L (reference range 0.50-2.00) on day 357. CMV IgG and EBV IgG were both positive implying past infection and the patient had increased transferrin levels. Anti-Hepatitis C was non-reactive at enrollment (07-May-2008). There were no subsequent tests for Hepatitis C. The summary of the tests that were done: HBsAg: Negative; HBcAb: Negative; Hepatitis A IgM: Negative; Hepatitis E IgM and IgG: Negative; CMV IgM: Negative; CMV IgG and EBV Nuclear Antigen IgG: both Positive.

Patient Identification D1690C00005-6013-3 Case Two– Difficult to Establish etiology

This was an 83 year old white man who was randomized to dapagliflozin and also took glipizide. Concomitant drugs include albendazole, pantoprazole, and nutritional supplements that included St John’s Wort and fern. The patient had a history of cholelithiasis together with obstructive jaundice requiring hospitalization for papillotomy; cholecystectomy was recommended but patient refused.

Treatment with dapagliflozin was started nine months later and subsequently the patient then developed two episodes of liver dysfunction. The first began on day 85 lasting presumably to day 93. Albendazole started on or after day 90. Values returned to normal despite continued use of study drug. The second episode began on day 141, at which time the drug was discontinued. This lasted to day 148 when the values peaked: ALT 271 U/L, bilirubin 2.7 mg/dL. The values gradually returned to normal. The patient did not have symptoms during the abnormalities and the presence or absence of fever is not reported. An ultrasound showed cholelithiasis but no evidence of dilated biliary ducts. The patient did report taking St Johns Wort and fern before each episode of abnormality. Liver enzymes were as follows:

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

There was no report of abdominal pain in this patient. However, an ultrasound performed 10 days after discontinuation of dapagliflozin showed cholelithiasis with hyperechogenic and thickened wall of the gallbladder and no distension of common bile duct. Both episodes of aminotransferase and bilirubin elevations during the study were accompanied by increases in alkaline phosphatase, consistent with biliary obstruction.

The following tests were performed: HEPATITIS B CORE AB, IgM: NONREACTIVE, ANTI-HCV: NONREACTIVE, HBsAg SCREEN w/CONFIRMATION: NONREACTIVE

Patient Identification D1690C00005-2003-3 (>10x ULN for AST and ALT)

This was a 70 year old white female. On study day 225, ALT 511 U/L (ref. range 6-37), AST 940 U/L (ref. range 10-36), ALP 139 U/L (ref. range 40 - 100 IU/L) and bilirubin 1.5 mg/dL (ref. range 0.2-1.2) were recorded. The patient had no symptoms or physical findings and no risk factors for elevated liver enzymes. Hepatitis serology on study day 232 and on study day 240 was negative. Study medication was temporarily stopped for two weeks (Study day 228 to 245). After study medication was resumed the liver tests remained normal and the subject completed 48 weeks treatment according to the study protocol. There was no imaging performed.

Patient Identification D1690C00004-3104-4 (>10x ULN for AST and ALT)

This was a 63 year old white male who passed away from hepatic failure. He had received two weeks of dapagliflozin before developing hyponatremia and subsequently requiring hospitalization. Study treatment was discontinued and the patient continued to worsen; he died of fulminant hepatic failure. On autopsy, he was found to have **primary small cell lung cancer with massive metastasis in the liver.**

Patient Identification D1690C00005-7002-4 (>10x ULN for AST and ALT)

This was a 60 year old Asian female with stone in the common bile duct diagnosed on day 333 of the trial.

Patient Identification MB102030-90-706 (>10x ULN for AST and ALT)

This was a 60 year old white female with enzyme elevations concurrent with a diagnosis of cholelithiasis on day 345 of trial.

Patient Identification D1690C00006-1511-6 (>10x ULN AST only)

This was a 61 year old white female with enzyme elevations and abdominal pain. The ultrasound on study day 209 showed cholelithiasis and hepatic steatosis. She underwent laparoscopic cholecystectomy on study day 217.

Other Information on Liver Tests

Of note, the mean changes from baseline in the short-term placebo-controlled pool for AST and ALT showed a small mean decrease in dapagliflozin-treated patients. There was a slight elevation in mean change of total bilirubin from baseline in this group.

Table 15 Mean (SD) Change from Baseline for Liver Tests, Short-term Placebo Controlled Pool

Treatment	Aspartate Aminotransferase (U/L)	Alanine Aminotransferase (U/L)	Bilirubin (mg/dL)
Dapagliflozin	-1.985 (10.32)	-3.994 (15.09)	0.015 (0.195)
Placebo	-1.096 (9.602)	-1.703 (17.96)	-0.011 (0.20)

These changes seen in AST, ALT and bilirubin are not clinically significant.

III(e). Genital Infections

Prespecified Preferred Terms (PTs) were used to identify genital infections. This list was referred to as events suggestive of genital infection. Some of these clearly indicate a candidal infection. Some terms (e.g., pruritus) are nonspecific and could have been due to other causes, such as chemical irritation.

In the short-term treated pool, the number of infections was higher in both the 5 and 10 mg groups compared with the 2.5 mg group and placebo (Table 16). In all treatment groups, events suggestive of genital infection were more common in females than males. In general, most events responded to treatment, resolved and were not recurrent. Few of these patients had events leading to discontinuation of study drug.

Table 16 Genital Infections in the Short-term Placebo Controlled Pool

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	29 (2.1)	47 (5.8)	80 (7.0)	83 (7.0)	223 (6.8)
VULVOVAGINAL MYCOTIC INFECTION	5 (0.4)	8 (1.0)	13 (1.1)	20 (1.7)	45 (1.4)
PRURITUS GENITAL	7 (0.5)	7 (0.9)	7 (0.6)	15 (1.3)	29 (0.9)
VAGINAL INFECTION	1 (0.1)	6 (0.7)	14 (1.2)	10 (0.8)	33 (1.0)
VULVOVAGINAL PRURITUS	6 (0.4)	5 (0.6)	11 (1.0)	9 (0.8)	26 (0.8)
BALANITIS	1 (0.1)	4 (0.5)	7 (0.6)	7 (0.6)	18 (0.5)
GENITAL INFECTION FUNGAL	1 (0.1)	6 (0.7)	7 (0.6)	6 (0.5)	20 (0.6)
VULVOVAGINAL CANDIDIASIS	1 (0.1)	3 (0.4)	10 (0.9)	4 (0.3)	18 (0.5)
VULVOVAGINITIS	0	2 (0.2)	4 (0.3)	3 (0.3)	9 (0.3)
BALANITIS CANDIDA	0	2 (0.2)	2 (0.2)	2 (0.2)	7 (0.2)
GENITAL CANDIDIASIS	0	0	3 (0.3)	2 (0.2)	5 (0.2)
GENITAL INFECTION	0	0	2 (0.2)	2 (0.2)	4 (0.1)
GENITAL BURNING SENSATION	2 (0.1)	1 (0.1)	0	1 (0.1)	2 (0.1)
GENITAL DISCHARGE	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
GENITAL INFECTION MALE	0	0	0	1 (0.1)	1 (<0.1)
GENITAL RASH	0	1 (0.1)	0	1 (0.1)	2 (0.1)
PENILE INFECTION	0	0	0	1 (0.1)	2 (0.1)
VAGINAL DISCHARGE	3 (0.2)	0	0	1 (0.1)	1 (<0.1)
VAGINAL INFLAMMATION	0	0	0	1 (0.1)	1 (<0.1)
VULVITIS	0	2 (0.2)	1 (0.1)	1 (0.1)	4 (0.1)
BALANOPOSTHITIS	0	1 (0.1)	1 (0.1)	0	2 (0.1)
BALANOPOSTHITIS INFECTIVE	0	0	1 (0.1)	0	1 (<0.1)
GENITOURINARY TRACT INFECTION	0	0	1 (0.1)	0	1 (<0.1)
POSTHITIS	0	0	1 (0.1)	0	1 (<0.1)
VAGINITIS BACTERIAL	2 (0.1)	1 (0.1)	1 (0.1)	0	3 (0.1)
VULVAL ABSCESS	1 (0.1)	0	0	0	0
VULVOVAGINAL BURNING SENSATION	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)
VULVOVAGINAL ERYTHEMA	0	0	1 (0.1)	0	1 (<0.1)

Source Applicant's SCS Table 49

These events were more common in females (Table 17). In females, the most common PT was vulvovaginal mycotic infection. Pruritus was the most common event in the male patients accounting for almost a quarter of events.

Table 17. Females and Males with Events of Genital Infection in Short-term Placebo Controlled Pool

Subjects with an Event	Placebo N (%)	Dapagliflozin Total N (%)
Females	23 (3.4)	165 (10.0)
Males	6 (0.8)	58 (3.5)

The rate of recurrence for these events did not differ between the placebo and the dapagliflozin treatment arms for two events. However, for three or more events, recurrence was only noted in 11 patients treated with dapagliflozin (Table 18).

Table 18. Recurrence of Genital Infection in the Short-term Placebo Controlled Pool

	PLA N = 694	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 2160
SUBJECTS (N#)	20	53	77	83	213
NUMBER OF SUBJECTS EXPERIENCING: (A)					
1 EVENT	16 (80.0)	41 (77.4)	53 (68.8)	63 (75.9)	157 (73.7)
2 EVENTS	4 (20.0)	7 (13.2)	12 (15.6)	9 (10.8)	28 (13.1)
3 EVENTS	0	5 (9.4)	6 (7.8)	6 (7.2)	17 (8.0)
>3 EVENTS	0	0	6 (7.8)	5 (6.0)	11 (5.2)
TOTAL EVENTS	24	70	163	121	354
NUMBER OF SEVERE OR VERY SEVERE EVENTS	1	1	2	3	6
GIVEN ANTIMICROBIAL TREATMENT? (B)					
YES	14 (58.3)	49 (70.0)	138 (84.7)	89 (73.6)	276 (78.0)
NO	9 (37.5)	19 (27.1)	22 (13.5)	29 (24.0)	70 (19.8)
UNKNOWN	1 (4.2)	2 (2.9)	3 (1.8)	3 (2.5)	8 (2.3)
ADDITIONAL TREATMENT GIVEN DUE TO INADEQUATE RESPONSE TO INITIAL COURSE (B)					
YES	0	1 (1.4)	11 (6.7)	4 (3.3)	16 (4.5)
NO	14 (58.3)	48 (68.6)	127 (77.9)	85 (70.2)	260 (73.4)
UNKNOWN	0	0	0	0	0
NOT APPLICABLE	10 (41.7)	21 (30.0)	25 (15.3)	32 (26.4)	78 (22.0)

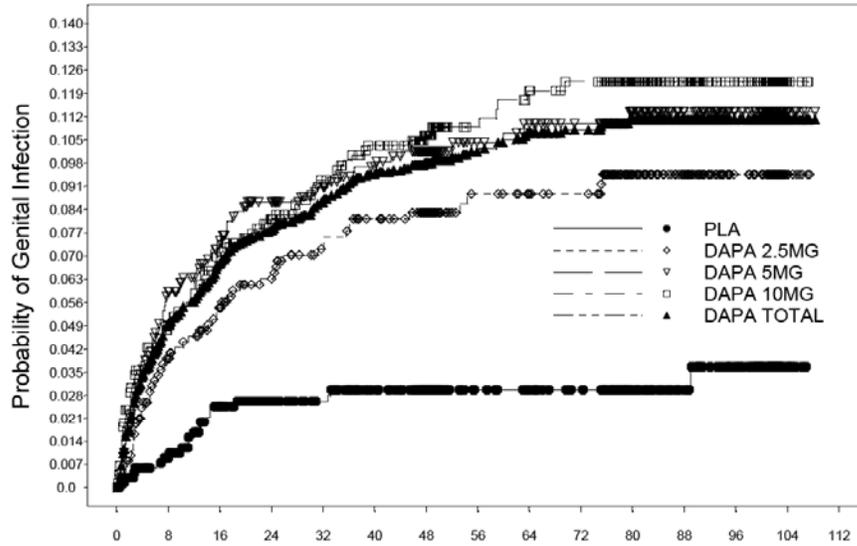
Source Applicant's SCS Table 56

Rates in the placebo controlled short and long-term treatment pool were consistent with those in the short-term treatment period only. The total in the dapagliflozin treated group was 160 patients (14.5%) and the total in the placebo treated group was 18 patients (5.2%).

None of these events were classified as serious. There were three patients in the dapagliflozin treated group who discontinued treatment due to an event of genital infection; there were no patients discontinuing for this reason in the placebo treated group.

The Kaplan-Meier curves of the time to onset of first event suggestive of genital infection dapagliflozin showed that patients were at greater risk for a first event than those treated with placebo as early as 1 month after treatment initiation (Figure 3). By eight months, those treated with dapagliflozin 5 and 10 mg were at more risk than the 2.5 mg treated patients. Overall, a first event occurred more often in the first 24 weeks than after 24 weeks in all groups.

Figure 3. Time to First Event of Genital Infection in the Short and Long-term Placebo Controlled Pool



	Number of Subjects at Risk														
	Weeks														
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112
PLA	694	650	608	583	564	545	470	262	257	248	190	145	123	12	0
DAPA 2.5MG	625	574	550	530	510	498	464	326	319	314	237	194	154	11	0
DAPA 5MG	767	681	650	623	602	588	511	321	313	302	240	191	163	8	0
DAPA 10MG	768	702	667	637	614	596	519	326	320	314	250	198	172	9	0
DAPA TOTAL	2160	1957	1867	1790	1726	1682	1494	973	952	930	727	583	489	28	0

Symbols represent censored observations.

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

Number of subjects at risk is the number of subjects at risk at the beginning of the period.

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

Source Applicant's SCS Figure 2

III(f). Urinary Tract Infection (UTI)

A prespecified list of PTs was used to identify cases of UTI (with confirmed positive culture in some cases). This list contained the terms for diagnoses, symptoms, signs, and abnormal laboratory findings suggestive of UTI, as well as events indicating "specific involvement of the kidney". Events identified with this list are termed events suggestive of UTI.

More patients in the dapagliflozin group reported events suggestive of UTI compared to those treated with placebo (Table 19). These events were more commonly overall in females than males. Most events were mild or moderate in intensity and resolved while the patients were on study medication. The PT "UTI" was most common for this category and "dysuria" was the second most common PT identified.

Table 19. UTI Related Events in the Short-term Placebo Controlled Pool

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	63 (4.5)	34 (4.2)	84 (7.3)	77 (6.5)	209 (6.4)
URINARY TRACT INFECTION	38 (2.7)	25 (3.1)	54 (4.7)	43 (3.6)	131 (4.0)
DYSURIA	10 (0.7)	5 (0.6)	18 (1.6)	25 (2.1)	49 (1.5)
CYSTITIS	11 (0.8)	2 (0.2)	7 (0.6)	8 (0.7)	21 (0.6)
LEUKOCYTURIA	0	0	0	2 (0.2)	2 (0.1)
CANDIDURIA	0	0	0	1 (0.1)	1 (<0.1)
ESCHERICHIA URINARY TRACT INFECTION	0	0	1 (0.1)	1 (0.1)	2 (0.1)
TRIGONITIS	0	0	0	1 (0.1)	1 (<0.1)
BACTERIURIA	2 (0.1)	0	1 (0.1)	0	1 (<0.1)
GENITOURINARY TRACT INFECTION	0	0	1 (0.1)	0	1 (<0.1)
PROSTATITIS	2 (0.1)	1 (0.1)	2 (0.2)	0	3 (0.1)
PYELONEPHRITIS	1 (0.1)	2 (0.2)	1 (0.1)	0	3 (0.1)
PYURIA	2 (0.1)	0	1 (0.1)	0	1 (<0.1)
URETHRITIS	1 (0.1)	0	0	0	0
URINARY TRACT INFECTION FUNGAL	0	0	1 (0.1)	0	2 (0.1)
URINARY TRACT INFLAMMATION	0	0	1 (0.1)	0	1 (<0.1)
WHITE BLOOD CELLS URINE POSITIVE	1 (0.1)	0	0	0	0

Source: Applicant’s SCS Table 57.

UTI was a common adverse event in the placebo controlled short-term pool.

Pyelonephritis was an uncommon event, and occurred at equal rates in the placebo and dapagliflozin treated groups (0.1% in both groups).

Events were more common in females treated with dapagliflozin than males (Table 20).

Table 20. Females and Males with Events of UTI in the Short-term Placebo Controlled Pool

Subjects with an Event	Placebo N (%)	Dapagliflozin Total N (%)
Females	52 (7.7)	165 (10.0)
Males	11 (1.5)	44 (2.7)

In the short-term period, urine culture was obtained for 42% and 50% of the events suggestive of UTI in the dapagliflozin total group (all doses combined) and the placebo group, respectively. Most of the organisms obtained from urine culture are well established causes of UTI in the general population and include Escherichia coli, with skin flora or sample contamination, such as Staphylococcus epidermidis, or fungi such as Candida. Recurrence occurred in 14.7-18.2% of patients taking dapagliflozin of any dose compared to 9.5% of placebo patients (Table 21). This table also depicts the proportion of patients that had a positive urine culture.

Table 21 Recurrence, Treatment and Culture in UTI in the Short-term Placebo Controlled Pool

	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
SUBJECTS (N#)	63	34	84	77	209
NUMBER OF SUBJECTS EXPERIENCING: (A)					
1 EVENT	56 (88.9)	28 (82.4)	70 (83.3)	61 (79.2)	172 (82.3)
2 EVENTS	6 (9.5)	5 (14.7)	13 (15.5)	14 (18.2)	33 (15.8)
3 EVENTS	0	1 (2.9)	1 (1.2)	2 (2.6)	4 (1.9)
>3 EVENTS	1 (1.6)	0	0	0	0
TOTAL EVENTS	72	41	99	95	250
NUMBER OF SEVERE OR VERY SEVERE EVENTS	1	0	4	0	4
GIVEN ANTIMICROBIAL TREATMENT? (B)					
YES	54 (75.0)	31 (75.6)	57 (57.6)	59 (62.1)	147 (58.8)
NO	14 (19.4)	6 (14.6)	29 (29.3)	27 (28.4)	62 (24.8)
UNKNOWN	4 (5.6)	4 (9.8)	13 (13.1)	9 (9.5)	41 (16.4)
ADDITIONAL TREATMENT GIVEN DUE TO INADEQUATE RESPONSE TO INITIAL COURSE (B)					
YES	8 (11.1)	2 (4.9)	1 (1.0)	11 (11.6)	14 (5.6)
NO	45 (62.5)	29 (70.7)	56 (56.6)	48 (50.5)	133 (53.2)
UNKNOWN	1 (1.4)	0	0	0	0
NOT APPLICABLE	18 (25.0)	10 (24.4)	42 (42.4)	36 (37.9)	103 (41.2)
URINE CULTURE OBTAINED? (B)					
YES	36 (50.0)	19 (46.3)	49 (49.5)	37 (38.9)	105 (42.0)
NO	27 (37.5)	14 (34.1)	34 (34.3)	39 (41.1)	88 (35.2)
UNKNOWN	9 (12.5)	8 (19.5)	16 (16.2)	19 (20.0)	57 (22.8)
POSITIVE URINE CULTURE? (B)					
YES	21 (29.2)	13 (31.7)	30 (30.3)	24 (25.3)	67 (26.8)
NO	15 (20.8)	6 (14.6)	19 (19.2)	13 (13.7)	38 (15.2)
UNKNOWN	0	0	0	0	0

Source Applicant's SCS Table 60

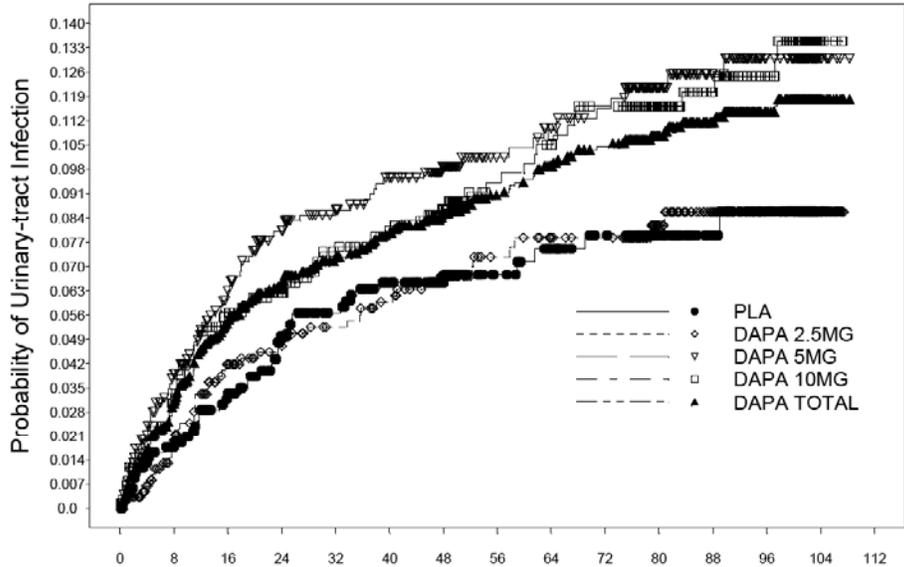
Rates in the short plus long-term placebo treated pool were consistent with that in the short-term pool, but higher, as expected, given the more prolonged monitoring and exposure. In the dapagliflozin treated patients, the rate was 9.4% (202 patients) and the rate in placebo treated patients was 6.6% (46 patients).

Only one patient in this pool had an UTI-related SAE (pyelonephritis) and this patient was in the control group.

Events suggestive of UTI leading to discontinuation occurred in 0.4%, 0.2%, 0.3% of subjects in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 0.1% of subjects in the placebo group. In the placebo group, an AE of pyelonephritis led to discontinuation. The dapagliflozin-treated subjects included one male (with pyelonephritis) and 8 females (one with pyelonephritis, five with UTI, one with cystitis, and one with dysuria).

The Kaplan-Meier curves of the time to onset of first event suggestive of UTI show separation of the curves for the dapagliflozin (5 mg, 10 mg, and dapagliflozin total) groups from the dapagliflozin 2.5 mg and placebo groups starting at approximately eight weeks and continuing through Week 104 (Figure 4). A first event suggestive of UTI was reported more often in the first 24 weeks than after 24 weeks in all treatment groups.

Figure 4. Time to First Event of UTI in the Short and Long-term Placebo Controlled Pool



	Number of Subjects at Risk														
	Weeks														
	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112
PLA	694	644	604	569	546	524	452	253	245	235	181	139	116	11	0
DAPA 2.5MG	625	585	555	538	521	510	469	333	323	318	242	201	161	11	0
DAPA 5MG	767	696	658	626	601	586	514	323	314	302	242	194	163	7	0
DAPA 10MG	768	713	676	648	625	610	534	331	326	316	254	202	175	9	0
DAPA TOTAL	2160	1994	1889	1812	1747	1706	1517	987	963	936	738	597	499	27	0

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

Source Applicant's SCS Figure 3

III(g). Both Genital Infection and Urinary Tract Infection Events

The proportion of patients that had both types of infection was small compared to that seen with each type of event alone (Table 22). This suggests that urinary tract infection, or treatment of infection, was not a predisposition to developing a genital infection or vice versa.

Table 22. Subjects with Both Events of UTI and Genital Infection in the Short-term Placebo Controlled Pool

	Number of Subjects (Percent)				
	PLACEBO N=1393	DAPA 2.5MG N=814	DAPA 5MG N=1145	DAPA 10MG N=1193	DAPA TOTAL N=3291
BOTH URINARY TRACT INFECTION AND GENITAL INFECTION					
TOTAL	7/1393 (0.5)	3/ 814 (0.4)	16/1145 (1.4)	19/1193 (1.6)	40/3291 (1.2)
MALES	1/ 716 (0.1)	1/ 414 (0.2)	1/ 564 (0.2)	5/ 595 (0.8)	7/1643 (0.4)
FEMALES	6/ 677 (0.9)	2/ 400 (0.5)	15/ 581 (2.6)	14/ 598 (2.3)	33/1648 (2.0)

Source Response to FDA Information Request May 18, 2011

III(h). Bone Health

Fractures and markers of bone metabolism were monitored in the dapagliflozin clinical program with special interest, due to dapagliflozin’s mechanism of action and potential effects on tubular transportation of bone minerals.

We consulted with the Metabolic Bone Disease Team within the Division of Reproductive and Urology Products for a review of all bone-related data submitted with the NDA, including fracture data, effects on serum bone biomarkers, bone mineral density (from the body composition study), and serum minerals. The text below consists of the executive summary of this consultation review.

The effects of dapagliflozin on bone metabolism are not well-defined. The overall fracture rate was low (1.4%) and balanced between dapagliflozin and control groups. The apparent increased fracture rate in the moderate renal dysfunction population study (MB102029) was not demonstrated when all subjects (Phase 2b and Phase 3) with moderate renal dysfunction were pooled. These fracture events were also associated with various risks for falls (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state) or suffered significant trauma. It is well recognized that propensity to fall is a risk factor for fracture independent of bone mineral density. In addition, while not directly connected to the fracture events, rates of hypoglycemia, hypotension, dizziness, syncope, and falls were higher in this population. The 2-fold increase in fractures in patients with normal renal function was associated with negligible laboratory changes suggesting that this imbalance may also not be significant. In addition, there were minimal effects on mean bone mineral density (BMD) overall despite outliers with larger positive and negative changes of approximately 8-12%. Bone biomarkers showed small increases in bone resorption with no pattern seen with bone formation. No clinically significant changes were seen in laboratory values, including calcium, 25-OH vitamin D, magnesium, phosphorus and PTH (beyond what would be expected for the degree of renal dysfunction).

Due to the cross-reactivity of dapagliflozin at SGLT sites, potential effects at SGLT-1 were investigated to determine if the noted alterations could be attributable to off-target effects and not related to bone metabolism. When evaluated, no imbalances were seen in off-target SGLT-1 sites, i.e. gastrointestinal and cardiac organ systems, at the clinical level. This may be due to the high specificity of dapagliflozin for SGLT-2 (1600-fold).

From the data reviewed, there is no indication that dapagliflozin exerts a clinically significant effect on bone loss or fracture. Full review of the 2-year data would be reassuring. While bone loss due to weight loss is a primary concern, further surveillance of bone formation/hyperostosis based on nonclinical evidence of vascular tissue mineralization, and increased bone resorption should also be monitored. We note that Study D1690C00012 is ongoing and data from 102 weeks of exposure will be provided when available.

III(i). Renal Laboratory and Adverse Events

Changes in Renal Lab Values in the Placebo-controlled Pool Short-term Treatment

The Abbreviated Modification of Diet in Renal Disease Study (MDRD) equation was used throughout the dapagliflozin clinical program to calculate estimated glomerular filtration rate (eGFR).

Mean changes from baseline in renal function tests were reported (Table 23). In the dapagliflozin groups, eGFR decreased slightly initially then increased slightly toward or above baseline values by week 24.

Table 23. Mean Changes in eGFR (mL/min/1.73 m²) from Baseline at 4 and 24 Weeks

Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
4 Weeks (SE)	N=1347 0.6 (0.3)	N=796 -2.2 (0.4)	N=1109 -1.9 (0.4)	N=1149 -2.1 (0.3)	N=3187 -2.0 (0.2)
24 Weeks (SE)	N=1087 0.8 (0.3)	N=619 -0.9 (0.4)	N=899 0.8 (0.4)	N=935 0.3 (0.4)	N=2453 0.2 (0.2)

Source Applicant's SCS App 40B

Mean estimated creatinine clearance (eCrCl) decreased from baseline to Week 24 in all treatment groups; this decrease was greater in the dapagliflozin treated groups, but unlikely to be clinically significant (Table 24).

Table 24. Estimated CrCl (mL/min) Mean Changes from Baseline at 4 and 24 Weeks

Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
4 Weeks (SE)	N=1324 0.1 (0.4)	N=794 -4.0 (0.4)	N=1108 -3.7 (0.4)	N=1125 -4.4 (0.4)	N=3136 -4.0 (0.3)
24 Weeks (SE)	N=1086 -0.4 (0.4)	N=618 -4.0 (0.4)	N=898 -2.2 (0.5)	N=934 -3.5 (0.5)	N=2450 -3.1 (0.3)

Source Applicant's SCS App 38B

Mean serum creatinine levels changed minimally (< 0.1 mg/dL) from baseline to week 24 in all treatment groups.

Mean blood urea nitrogen (BUN) levels increased 0.3 mg/dL in the placebo group and 1.5 to 1.8 mg/dL in each dapagliflozin group from baseline to week 24 (Table 25).

Table 25. BUN (mg/dL) Mean Changes from Baseline at 4 and 24 Weeks

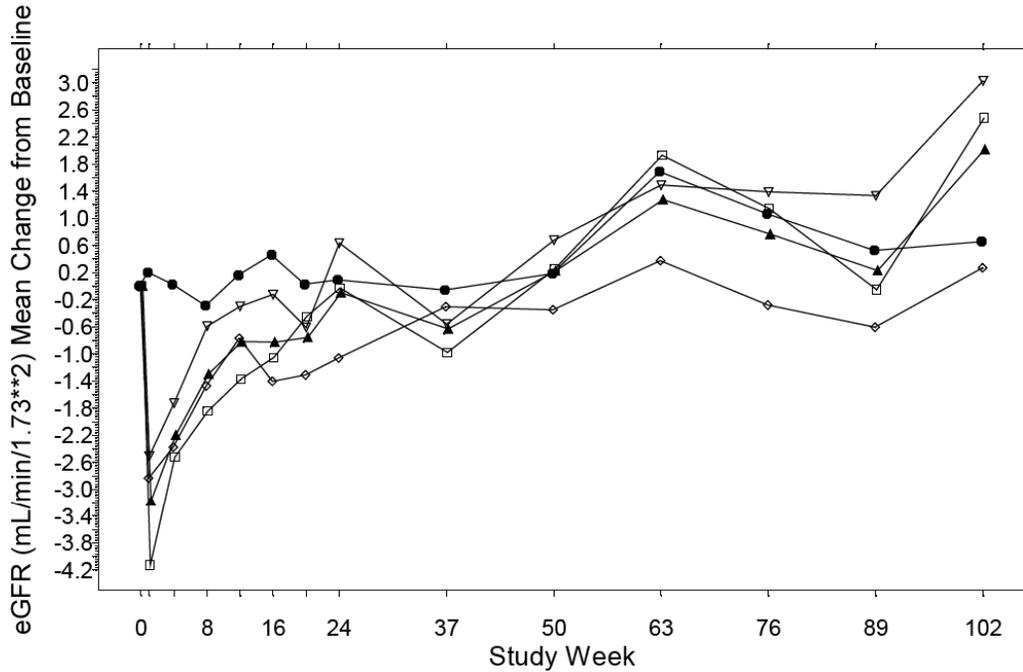
Mean Change	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa Total
4 Weeks (SE)	N=1347 0.0 (1.0)	N=797 1.1 (0.1)	N=1109 1.2 (0.1)	N=1149 1.3 (0.1)	N=3188 1.2 (0.1)
24 Weeks (SE)	N=1087 0.3 (0.1)	N=619 1.5 (0.2)	N=899 1.4 (0.1)	N=935 1.6 (0.1)	N=2453 1.5 (0.1)

Source Applicant's SCS App 36B

Changes in Renal Lab Values in the Placebo-controlled Pool Long-term Treatment

Small mean decreases in eGFR from baseline were reported in dapagliflozin-treated patients at Week 1 in the short-term plus long-term Placebo-controlled Pool. Following this initial drop in eGFR, there was a gradual return to baseline over 16-24 weeks without evidence of progressive renal dysfunction (Figure 5). These small and transient changes were dose-dependent.

Figure 5. Mean changes in estimated GFR from baseline to week 102 (short term and long term periods) in the Placebo-controlled Pool



	0	8	16	24	37	50	63	76	89	102
PLA	694	649	616	598	578	546	266	219	148	107
DAPA 2.5 MG	625	593	574	555	548	525	349	284	199	136
DAPA 5MG	767	714	696	669	659	628	354	288	208	159
DAPA 10 MG	768	728	706	676	670	646	367	310	220	166
DAPA TOTAL	2160	2035	1976	1900	1877	1799	1070	882	627	461

Treatment Group

- (N= 694) PLA
- ◇ (N= 625) DAPA 2.5 MG
- ▽ (N= 767) DAPA 5MG
- (N= 768) DAPA 10 MG
- ▲ (N= 2160) DAPA TOTAL

Source: Applicant’s SCS Figure 4

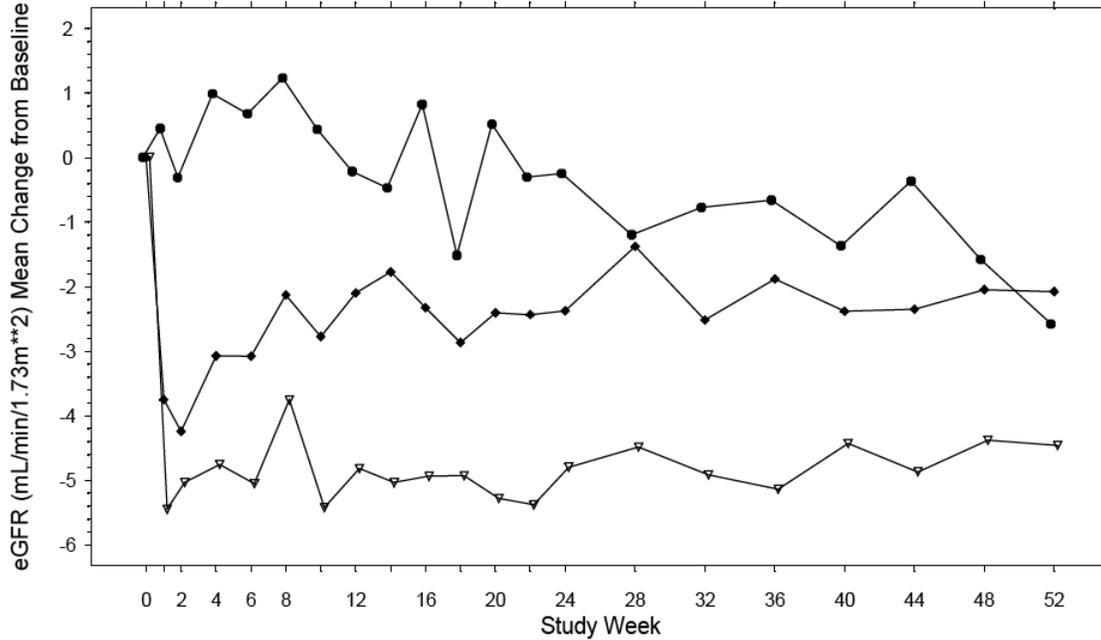
Small mean decreases (-1 to -5 mL/min) in eCrCl were reported in all dapagliflozin groups compared to placebo (-1 mL/min) that persisted to week 102. These are not clinically relevant.

Changes in renal lab values in the renal impairment trial

Estimated GFR and eCrCl decreased from baseline to Week 1 in the dapagliflozin 5 and 10 mg groups then stabilized, with mean reductions from baseline at Week 52 that were slightly less than those seen at Week 1. By comparison, the mean eGFR and eCrCl in the placebo group were essentially unchanged from baseline to Week 24 and then decreased slowly (Figure 6). While mean reductions from baseline to Week 52 in eGFR and eCrCl were observed in all treatment groups for subgroups of subjects with baseline GFR 45 to 59 mL/min/1.73 m² and 30 to 44 mL/min/1.73 m², the magnitude of the mean decreases

were consistently larger in the 30 to 44 mL/min/1.73 m² subgroup compared with the 45 to 59 mL/min/1.73 m² subgroup.

Figure 6. Change in eGFR (mL/min/1.73m²) from Baseline to week 52 in the Short-term Plus Long-term in Study MB102029



Sample Size per Time Point

847878	74	71	70	68	70	67	62	61	62	63	62	62	60	55	58	56	55	49
837878	80	79	76	76	77	76	72	75	73	72	70	68	71	68	70	64	63	64
858181	79	75	73	71	72	70	71	69	69	68	69	68	66	66	65	65	64	63

Treatment Group

- (N= 84) PLACEBO
- ◆ (N= 83) DAPA 5MG
- ▼ (N= 85) DAPA 10MG

Markedly Abnormal Renal Laboratory Values

Marked abnormalities for BUN (> 60 mg/dL) or creatinine (> 2.5 mg/dL) were reported in similar proportions of subjects in all treatment groups: 0% to 0.2% in the dapagliflozin groups and 0% in the placebo group. Similar proportions of subjects in each dapagliflozin group and the placebo group had elevated renal tests based on laboratory values (creatinine: $\geq 1.5X$ pre-treatment creatinine [1.4% - 1.9% in the dapagliflozin groups; 1.6% in the placebo group] or creatinine ≥ 2.5 mg/dL [0% - 0.2% in the dapagliflozin groups; 0% in the placebo group]). Similar proportions of subjects in each dapagliflozin group and the placebo group had elevated renal tests based on laboratory values and/or reported AEs of renal impairment or failure (< 3% in each treatment group). In addition, marked abnormalities of BUN and serum creatinine were noted in similar proportions of subjects across treatment groups, including subjects using diuretics or ACE-I or ARB anti-hypertensive agents.

Additional Renal Data—Lab Related AEs

Across the placebo-controlled pool short and long term treatment groups, renal related AEs were generally balanced (these were selected by the applicant and are displayed in Table 26 below). However, in the short plus long term treated pool, there were 23 (1.1%) patients reported with blood creatinine increased in the dapagliflozin group versus 4 (0.6%) placebo treated patients.

The subgroup with eGFR ≥ 30 to < 60 mL/min/1.73 m² (moderate renal impairment) had the highest proportion of subjects with AEs of renal impairment or failure. AEs of renal impairment or failure were more common in dapagliflozin-treated subjects with no dose dependence. AEs across other renal categories displayed similar rates between dapagliflozin and placebo treated patients.

Table 26. Renal Related AEs in the Moderate Renal Impairment in the Short-term Placebo Controlled Pool

Preferred Term (%)	PLA N = 107	DAPA 2.5MG N = 74	DAPA 5MG N = 107	DAPA 10MG N = 89	DAPA TOTAL N = 277
TOTAL SUBJECTS WITH AN EVENT	6 (5.6)	8 (10.8)	7 (6.5)	7 (7.9)	23 (8.3)
BLOOD CREATININE INCREASED	3 (2.8)	6 (8.1)	3 (2.8)	6 (6.7)	16 (5.8)
CYSTATIN C INCREASED	0	0	0	1 (1.1)	1 (0.4)
GLOMERULAR FILTRATION RATE DECREASED	0	1 (1.4)	0	1 (1.1)	2 (0.7)
OBSTRUCTIVE UROPATHY	0	0	1 (0.9)	0	1 (0.4)
RENAL FAILURE	2 (1.9)	0	1 (0.9)	0	1 (0.4)
RENAL IMPAIRMENT	1 (0.9)	1 (1.4)	2 (1.9)	0	3 (1.1)

Source Applicant's SCS Table 67

III(j). Hematology, Volume Depletion and Thromboembolic Events

Dapagliflozin induces diuresis. This leads to hemoconcentration and can also put patients at risk for events of volume depletion or thromboembolic events.

Hematology

Placebo-controlled Pool—Short-term Treatment

In the dapagliflozin groups, there were small increases in mean hematocrit and hemoglobin levels starting at week 1 and continuing up to week 16, when the maximum difference from baseline was observed. The mean change from baseline in hematocrit by week 16 ranged from 1.7% to 2.2% in the dapagliflozin groups and -0.3% in the placebo group. At week 24, the mean changes from baseline in hematocrit were 1.6%, 1.8%, and 2.1% in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and -0.4% in the placebo group (Table 27).

Table 27. Hematocrit (%) Mean Changes from Baseline at 24 Weeks

Period Visit	Treatment Group	N#	Mean	SD	Min	Percentiles				Change From Baseline				
						25	Median	75	Max	N#	Mean	SE	Median	IQR
ST TREAT SCS WK 24	PLA	1063	42.08	3.859	24.3	39.40	42.00	44.70	55.8	1063	-0.40	0.0713	-0.30	2.80
	DAPA 2.5MG	610	43.60	4.182	29.9	40.90	43.70	46.40	58.1	610	1.57	0.0971	1.60	2.80
	DAPA 5MG	875	44.09	3.921	29.1	41.40	44.20	46.70	58.6	875	1.81	0.0789	1.90	2.80
	DAPA 10MG	911	44.46	4.098	28.9	41.70	44.40	47.40	57.8	911	2.15	0.0834	2.20	2.80
	DAPA TOTAL	2396	44.11	4.068	28.9	41.40	44.10	46.80	58.6	2396	1.88	0.0497	1.90	2.80

Source Applicant's SCS App 20B

The mean change from baseline in hemoglobin reflected those reported for hematocrit.

There was also a small decrease in mean platelet levels in all treatment groups that was slightly larger. At week 24, the mean change from baseline was -7.4, -7.3, and -8.4 x 10⁹ c/L for dapagliflozin 2.5, 5, and 10 mg, respectively, and -5.1 x 10⁹ c/L for placebo.

Placebo-controlled Pool—Short-term Plus Long-term Treatment

At week 76, the mean change from baseline in hematocrit ranged from 1.8% to 2.5% in the dapagliflozin groups and -0.2% in the placebo group. At week 76, the mean change from baseline in hemoglobin ranged from 0.4 to 0.6 g/dL in the dapagliflozin groups and -0.3 g/dL in the placebo group. No further increases were observed at week 89 and up to week 102.

Volume Depletion

Placebo-controlled Pool—Short-term Treatment

Events defined by the applicant as those of volume depletion (hypotension / hypovolemia / dehydration) were reported slightly more common frequently in the dapagliflozin groups versus comparator (0.7% vs 0.4% in the short-term period), with no clear dose dependence (Table 28). Hypotension was the most common event. A 67 year old male subject receiving dapagliflozin 10 mg added to insulin background in a Phase 2b trial was discontinued due to volume depletion and consequent pre-renal azotemia. Clinically important medical history included hypertension, myocardial infarction, and congestive heart failure. Relevant medications included carvedilol, enalapril, furosemide, digoxin, and gemfibrozil. On Day 8, he was found to have increased blood urea, increased blood creatinine, and dehydration. On Day 9, he complained of lightheadedness (preferred term: dizziness). Study medication was discontinued on Day 11 due to his symptoms and laboratory results. On Day 12, a diagnosis of “pre-renal failure” (preferred term: renal failure) of severe intensity was made by the investigator. Treatment with enalapril and furosemide was stopped. Dehydration was considered resolved on Day 15. Treatment with furosemide and enalapril resumed on Day 15 and Day 26, respectively, at reduced dosages. The event of pre-renal failure was determined to be fully resolved on Day 46 with normalization of renal function. The investigator categorized the event as probably related to study medication.

Table 28. Events related to Volume Depletion

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	5 (0.4)	8 (1.0)	7 (0.6)	8 (0.7)	24 (0.7)
HYPOTENSION	2 (0.1)	6 (0.7)	5 (0.4)	5 (0.4)	16 (0.5)
SYNCOPE	1 (0.1)	0	0	2 (0.2)	2 (0.1)
URINE FLOW DECREASED	0	0	0	1 (0.1)	1 (<0.1)
BLOOD PRESSURE DECREASED	1 (0.1)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	1 (0.1)	2 (0.2)	0	4 (0.1)
URINE OUTPUT DECREASED	1 (0.1)	1 (0.1)	0	0	1 (<0.1)

Source Applicant's SCS Table 72

Most events occurred after more than three weeks of therapy. Only two events in dapagliflozin treated patients occurred within 10 days of starting therapy: orthostatic hypotension (Day 3) and hypotension (Day 1) in the dapagliflozin 2.5 mg group.

In the 24 week treatment, the subgroup of patients that received loop diuretics and subgroup of patients ≥ 65 years of age treated with dapagliflozin had a higher rate of hypovolemic events.

Table 29. Events of Volume Depletion in Patients Receiving Loop Diuretics

Preferred Term (%)	PLA N = 55	DAPA 2.5MG N = 37	DAPA 5MG N = 40	DAPA 10MG N = 31	DAPA TOTAL N = 114
TOTAL SUBJECTS WITH AN EVENT	1 (1.8)	3 (8.1)	0	2 (6.5)	6 (5.3)
HYPOTENSION	0	3 (8.1)	0	1 (3.2)	4 (3.5)
SYNCOPE	0	0	0	1 (3.2)	1 (0.9)
BLOOD PRESSURE DECREASED	1 (1.8)	0	0	0	0
ORTHOSTATIC HYPOTENSION	0	0	0	0	1 (0.9)

Source Applicant's SCS App 222B

Table 30. Events of Volume Depletion in Patients ≥ 65 Years of Age

Preferred Term (%)	PLA N = 276	DAPA 2.5MG N = 193	DAPA 5MG N = 216	DAPA 10MG N = 204	DAPA TOTAL N = 631
TOTAL SUBJECTS WITH AN EVENT	1 (0.4)	5 (2.6)	1 (0.5)	2 (1.0)	8 (1.3)
SYNCOPE	0	0	0	1 (0.5)	1 (0.2)
URINE FLOW DECREASED	0	0	0	1 (0.5)	1 (0.2)
HYPOTENSION	1 (0.4)	5 (2.6)	0	0	5 (0.8)
ORTHOSTATIC HYPOTENSION	0	0	1 (0.5)	0	1 (0.2)

Source SCS App 228B

Of note, the rate of these events was higher in patients on dapagliflozin that had been treated with thiazides as well (24 week data--1.3%--8 patients in the dapagliflozin total group versus 0.8%--2 patients in the placebo group). This was also the case with both ACE-I or ARBs (1.0%--17 patients in the dapagliflozin total group versus 0.5%--4

patients in the placebo group). These trends were consistent with those seen across short plus long-term treatment as well.

The applicant has proposed a lower dose of 5 mg in these patients at higher risk for volume depletion. If dapagliflozin is approved, this is an acceptable proposal for these patients.

Placebo-controlled Pool—Short-term Plus Long-Term Treatment

In the short-term plus long-term period, SAEs of hypotension/dehydration/hypovolemia (volume depletion) occurred in two subjects treated with dapagliflozin and in two subjects treated with placebo; all four of these events were defined as syncope.

Pulmonary Embolism and Deep Venous Thrombosis (DVT)

The risk of deep vein thrombosis and/or pulmonary embolism may also be related to volume depletion. Dapagliflozin has diuretic effect and this can result in hemoconcentration.

All Phase 2b/ Phase 3 Safety Pool

This pool was selected in order to capture the most number of events to evaluate for any notable difference. Overall, there were few events related to venous thrombosis in this pool. Although there were more events in patients treated with dapagliflozin, the rates are very similar (Table 31).

Table 31. Number (%) of patients with DVT, thrombosis and pulmonary embolism in the All Phase 2b/ Phase 3 Pool

Event	Control	All Dapagliflozin
	N=1941	N=4287
DVT	0	4 (0.1)
Thrombosis	2 (0.1)	2(<0.1)
Pulmonary Embolism	1 (0.1)	4 (0.1)

Source Applicant's SCS Appendices 89A

Section IV. Conclusion

Dapagliflozin is the first in a new class of antidiabetic drugs, namely, SGLT2 inhibitors. Its effects on glycemia are unrelated to changes in insulin secretion or insulin sensitivity. The magnitude of glycemic reduction in the clinical trials has been consistent, and in line with recently approved antidiabetic drugs, such as dipeptidyl peptidase inhibitors. In active-controlled trials, dapagliflozin demonstrated equivalent effects on HbA1c as near maximally effective doses of metformin and glipizide at one year. In addition, dapagliflozin has been demonstrated to have mild reductions in blood pressure and body weight, and is neutral to blood lipids. The cardiovascular risk profile, evaluated through a

metanalysis of major cardiovascular events in a pool of Phase 2b and Phase 3 trials, meets the December 2008 Guidance, ruling out the unacceptable risk greater than 80% above comparator groups. While this can be an important addition to the antidiabetes drug armamentarium, its efficacy is limited to patients with normal renal function or mild impairment. With further decreases in glomerular filtration rate, dapagliflozin glyceic effects are significantly lessened, and the drug is thus not recommended for patients with moderate, severe and end-stage renal impairment.

The efficacy of dapagliflozin needs to be balanced against safety signals identified in the clinical trials: the imbalance in cases of bladder cancer and breast cancer not favoring dapagliflozin, a potentially serious case of drug-induced liver injury (meeting the biochemical threshold for “Hy’s Law”), the unknown long term effect of increased urinary infections and genital infections on renal function and reproduction, as well as the short term risks to renal function related to hypovolemia and dehydration in the elderly and in those patients on diuretic and antihypertensive therapy.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 2, 2011

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Subject: Review of the published literature and the sponsor's epidemiological study entitled "A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population."

Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-1476

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EXECUTIVE SUMMARY

As background information for an upcoming Advisory Committee meeting for the New Drug Application (NDA) of dapagliflozin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE) to provide information on the background incidence rate of breast cancer among type 2 diabetes patients.

Nine cases of breast cancer have been observed in the dapagliflozin treatment groups versus none in the comparator groups in dapagliflozin clinical trials. The epidemiologic literature was reviewed to evaluate the background incidence rate of breast cancer among type 2 diabetes patients. A study report conducted by the sponsor titled “A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population” was also reviewed.

A total of 6 studies (3 prospective and 3 retrospective cohort studies) that contained quantifiable incidence estimates were included in this review. The reported incidence rates of breast cancer among diabetes patients (mostly type 2 diabetes) ranged from 0.62 to 4.04 per 1,000 person-years of follow-up. The U.S. female type 2 diabetes patients were found to have the highest incidence rates of breast cancer, which were 4.04 and 3.41 per 1,000 person-years in two studies. Second to the U.S. females, the Canada postmenopausal women with newly diagnosed type 2 diabetes had incidence rates of 3.02 and 2.90 per 1,000 person-years for those who were 65 years and older, and those between 55 and 65 years, respectively. Two studies conducted in Sweden reported that the incidence rates of breast cancer in type 2 diabetes patients were 2.44 and 1.67 per 1,000 person-years for females, and 0.03 and 0.02 per 1,000 person-years for males. The Japanese women were reported with the lowest incidence rate of breast cancer at 0.62 per 1,000 person-years. Compared to the reported incidence rates of breast cancer among type 2 diabetes patients in the literature, the age-specific incidence rates of breast cancer were consistently higher in the dapagliflozin clinical trial program.

The sponsor used age- and sex-specific incidence rates of breast cancer data from the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) program to calculate the expected number of breast cancer cases in the dapagliflozin clinical trials. A standardized incidence ratio (SIR) was calculated to evaluate the observed incidence of breast cancer for the female cohort of the dapagliflozin clinical program compared to the expected incidence from SEER estimates. An adjustment factor of 20% increased risk of breast cancer in type 2 diabetes was applied and 95% confidence intervals were calculated for the SIR. The adjusted total number of expected incident breast

cancer cases among female patients exposed to dapagliflozin was 7.1. The calculated SIR was 1.27 (95% CI, 0.58-2.41) for dapagliflozin-treated patients. The adjusted total number of expected incident breast cancer cases among female patients in the comparator arms was 2.9.

There is insufficient evidence to support the sponsor's statement that the results provide some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age. The expected number of cases in the comparator arms was 2.9. However, no case was observed in the comparator arms of the dapagliflozin clinical program. This finding suggests that the study participants in the dapagliflozin clinical program may have a lower risk of breast cancer compared to the general type 2 diabetes population of the same age. However, the number of observed breast cancer cases (n=9) in the dapagliflozin trials were more than the expected number of cases (n=7.1) in the dapagliflozin-treated arms. One possible explanation to this finding is that dapagliflozin treatment may be associated with an increased risk of breast cancer. The application of a 20% diabetic risk adjustment factor to SEER data may have overestimated the expected number of cases to be seen in the dapagliflozin clinical trials because some patients in SEER were actually diabetes patients. The overestimated expected number of cases would have resulted in an underestimated SIR. Another limitation of using SEER data is that the dapagliflozin clinical trials were conducted internationally and the U.S. represented with approximately 20% of the total trial population. As rates of breast cancer vary across countries, the estimates from SEER (U.S. data) could be biased. With those limitations and concerns, we can not be reassured that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age.

In summary, the finding that the age-specific incidence rates of breast cancer were higher than those reported in the literature could be a safety signal that dapagliflozin may be associated with an increased risk of breast cancer. The SIR calculated by the sponsor using SEER data as an external reference group is not reassuring due to the study limitations. It is not feasible to establish the relative risk with any degree of certainty at this time given the small number of events (9 cases in the dapagliflozin treatment groups and zero in the comparator groups) and a wide confidence interval for the incidence rate ratio that includes 1.0 and infinity. Therefore, it is uncertain whether dapagliflozin treatment is associated with an increased risk of breast cancer. Continued follow-up of all participants in the dapagliflozin trials for breast cancer and further analysis with a direct comparison between the dapagliflozin treatment arms

and the comparator arms should be conducted to evaluate the relative risk of breast cancer associated with dapagliflozin treatment.

1 INTRODUCTION

As background information for an upcoming Advisory Committee meeting for the New Drug Application (NDA) of dapagliflozin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE) to provide information on the background incidence rate of breast cancer among type 2 diabetes patients.

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose co-transporter, the major transporter responsible for renal glucose reabsorption. This new molecular entity (NME) is currently undergoing NDA review as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin lowers both fasting and postprandial plasma glucose by inhibiting the renal reabsorption of glucose and by promoting its urinary excretion. The dapagliflozin sponsors are Bristol-Myers Squibb and AstraZeneca.

Nine cases of breast cancer were observed in the female dapagliflozin-treated patients versus none in the comparator arms of the dapagliflozin clinical trials. The epidemiologic literature was reviewed to evaluate the background incidence rate of breast cancer among type 2 diabetes patients. A study report conducted by the sponsor titled “A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population” was also reviewed.

2 METHODS AND MATERIALS REVIEWED

2.1 LITERATURE

A systematic literature search was conducted in PubMed for publications in English language published through May 23, 2011. The keywords used in this search were (“incidence of breast cancer” OR “risk of breast cancer”) AND “diabetes”.

All abstracts were reviewed for study design and relevance to this review. Case reports and review studies were excluded from this review because they did not contain population-based or original breast cancer risk estimates. Studies that estimated incidence rates of breast cancer among patients with type 1 diabetes were also excluded. The full text of observational cohort studies and studies that were

referenced in a meta-analysis of breast cancer risk associated with diabetes were reviewed. Studies that contained breast cancer incidence estimates were included in this literature review.

2.2 SPONSOR'S STUDY REPORT

A study report conducted by the sponsor titled "A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population" was also reviewed.

3 RESULTS & DISCUSSION

3.1 LITERATURE

After screening the medical literature for relevant information to quantify incidence rate of breast cancer among type 2 diabetes, a total of six studies that contained quantifiable incidence estimates were selected, which included three prospective cohort and three retrospective cohort studies (Table 1). Two studies each were conducted in the U.S. and Sweden, and one each was conducted in Canada and Japan.

The reported incidence rates of breast cancer among diabetes patients (mostly type 2 diabetes) ranged from 0.62 to 4.04 per 1,000 person-years of follow-up. The U.S. female patients were found to have the highest incidence rates of breast cancer, which were 4.04 and 3.41 per 1,000 person-years in two studies. Second to the U.S. females, the Canada postmenopausal women with newly diagnosed type 2 diabetes had incidence rates of 3.02 and 2.90 per 1,000 person-years for those who were 65 years and older, and those between 55 and 65 years, respectively. Two studies from Sweden reported that the incidence rates of breast cancer were 2.44 and 1.67 per 1,000 person-years for females, and 0.03 and 0.02 per 1,000 person-years for males. The Japanese women were reported with the lowest incidence rate of breast cancer at 0.62 per 1,000 person-years.

3.1.1 Study Summaries & DEPI Comments

3.1.1.1 Study Summary

Mink et al¹. examined the incidence of breast cancer in a cohort of women aged 45-64 years at baseline during 1987-1989 from four U.S. communities in Minnesota, North Carolina, Maryland, and Mississippi. Incidence breast cancers diagnosed between January 1, 1987 and December 31, 1995 were ascertained by linkage to a cancer registry and/or medical record review of potential cases identified through annual telephone follow-up surveys. Patients with a history of cancer at baseline were excluded.

Person-years at risk were calculated for each participant as time between the baseline examination date and December 31, 1995, or the date of breast cancer diagnosis, death, or loss to follow-up, whichever occurred first. The incidence of breast cancer was 4.04 per 1,000 person-years among those women with newly diagnosed type 2 diabetes over an average follow-up period of 7.1 years.

3.1.1.2 Comments

Since the study subjects were from four U.S. communities, they were not nationally representative. The study results cannot be generalized to the U.S. population.

3.1.1.3 Study Summary

Another U.S. study conducted by Michels et al². reported an incidence rate of invasive breast cancer of 3.41 per 1,000 person-years among female nurses who were 30-55 years old and free of cancer in 1976 over 22 years of follow-up period. Participants were followed from 1976 through 1996 for the occurrence of type 2 diabetes and through 1998 for subsequent invasive breast cancer. Cases of breast carcinoma in situ (n=612) and ductal carcinoma in situ were censored from the analysis. Twenty nine cases of breast cancer that developed during follow-up period were excluded because the dates of diagnosis were not available.

3.1.1.4 Comments

The incidence rate in this study was under-estimated since cases of breast carcinoma in situ, ductal carcinoma in situ, and cases of breast cancer without dates of diagnosis were excluded. A fraction of the breast carcinoma in situ may progress to become invasive and some of the cases without dates of diagnosis may be subsequent incidence cases of breast cancer after the development of type 2 diabetes.

3.1.1.5 Study Summary

Lipscombe et al³. conducted a retrospective population-based cohort study to examine the incidence of invasive breast cancer among postmenopausal women aged 55-79 years with newly diagnosed diabetes between April 1, 1994 and March 31, 2002 in Canada. Women with a history of breast cancer, those who developed breast cancer within the first year of study entry, who died, moved out from the province, or became 80 years of age within the first year were excluded. Follow-up began at the date of the first diabetes diagnosis. During the median follow-up period of 4.5 years, 451 and 560 breast cancer cases were identified in women age 55-65 years (2.90 per 1,000 person-years) and ≥ 65 years (3.02 per 1,000 person-years), respectively, in the Ontario Cancer Registry. The registry relies on

four sources for data: hospital discharge summaries, pathology reports, clinical records from cancer centers, and death certificates.

3.1.1.6 Comments

The estimated incidence of invasive breast cancer may be underestimated because women who developed breast cancer (n=308) within the first year after the diagnosis of diabetes were excluded, which was an approach to minimize detection bias. However, some of those cases may be true incidence cases and should be included in the incidence analysis.

3.1.1.7 Study Summary

Weiderpass et al⁴. conducted a retrospective cohort study to assess the incidence of breast cancer among patients who had at least one hospital discharge diagnosis of diabetes in 1965-1983 in Sweden. The person-time of observation was from the date of discharge from the first recorded hospitalization with a diabetes diagnosis until diagnosis of breast cancer, emigration, death, or end of follow-up period (December 31, 1989). The breast cancer cases (194 women and 2 men) detected within the first year of follow-up and corresponding person-years were excluded from the incidence analysis. Cases diagnosed incidentally at autopsy were also excluded (n=21). The incidence rate of breast cancer reported in this study was 2.44 and 0.03 per 1,000 person-years for women and men, respectively.

3.1.1.8 Comments

This study probably underestimated the incidence rate of breast cancer among type 1 and 2 diabetes patients who had at least one hospitalization for diabetes. As the follow-up started from the date of hospital discharge, patients may have had diabetes for a while before their hospitalizations. Therefore, the exclusion of breast cancer cases detected within the first year of follow-up was not appropriate as many of those cases could have been incident cases.

Most diabetic patients do not require hospitalizations unless they have severe complications. Therefore, this study population had more severe diabetes because those patients had at least one hospitalization for diabetes. Since this is a non-representative sample of the diabetic population, the results for breast cancer incidence would only be applicable to patients requiring hospitalizations for diabetes.

3.1.1.9 Study Summary

Another study conducted in the same patient population in Sweden by Adami et al⁵. ended the follow-up period on December 31, 1984 instead of December 31, 1989 as in the Weiderpass study. The study design is the same as the Weiderpass study, which is a retrospective cohort study to assess the incidence of breast cancer among patients who had at least one hospital discharge diagnosis of diabetes in 1965-1983 in Sweden. The person-time of observation was from the date of discharge from the first recorded hospitalization with a diabetes diagnosis until diagnosis of breast cancer, emigration, death, or end of follow-up period (December 31, 1984). The breast cancer cases detected within the first year of follow-up and corresponding person-years were excluded from the incidence analysis. This study reported that the incidence rates of breast cancer were 1.67 and 0.02 per 1,000 person-years in women and men, respectively.

3.1.1.10 Comments

Similar to the Weiderpass study, this study probably underestimated the incidence rate of breast cancer among type 1 and 2 diabetes patients who had at least one hospitalization for diabetes. As the follow-up started from the date of hospital discharge, patients may have had diabetes for a while before their hospitalizations. Therefore, the exclusion of breast cancer cases detected within the first year of follow-up was not appropriate as many of those cases could have been incidence cases. Since the study population had more severe diabetes because those patients had at least one hospitalization for diabetes, the incidence rate is unlikely to be the same for the general diabetes population who do not always require hospitalizations.

3.1.1.11 Study Summary

A prospective cohort study conducted by Inoue et al⁶. examined the incidence rate of breast cancer among Japanese persons aged 40 to 69 years who responded to a baseline questionnaire from January 1990 to December 1994. The person-years in the follow-up started from the date of the baseline survey until the date of cancer diagnosis, emigration from the study area, death, or the end of the study period of December 31, 2003, whichever came first. The incidence rate of breast cancer among women with self-reported diabetes (type 1 and 2) was 0.6 per 1,000 person-years.

3.1.1.12 Comments

The incidence of breast cancer in this study was probably underestimated. This study obtained information on history of diabetes and history of cancer through the baseline questionnaire and the follow-up started from the date of the baseline survey. All subjects with a history of cancer at baseline (n=2219) were excluded. However, some of these cancer patients may have been incident cases of breast cancer with a history of diabetes.

Table 1. Reported incidence rates of breast cancer among type 2 diabetes patients in the literature

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
Lipscombe 2006 Retrospective Cohort	4/1/1994 – 3/31/2002	4/1/1995 – 12/31/ 2002. Median duration of follow-up: 4.5 years	Postmenopausal women (55-79 years) with newly diagnosed diabetes (vast majority were type 2 diabetes)	Canada	Female 55-65	31,142	155,311	451	2.90	Invasive breast cancer cases only. Women with a history of breast cancer, those who developed breast cancer within the first year of study entry, who died, moved out from the province, or became 80 years of age within the first year were excluded.
					Female ≥65	42,654	185,152	560	3.02	
Inoue 2006 Prospective cohort	Not available	Through 2003	Aged 40 to 69 years who responded to the baseline questionnaire between 1990 and 1994	Japan	Female		16,246.7	10	0.62	Diabetes status was self-reported and included both type 1 and 2. Diabetes Patients with a history of cancer were excluded.
Michels 2003 Prospective cohort	1976- 1996	1976-1998. Over 22 years of follow-up	Female nurses aged 30-55 and free of cancer in 1976	U.S.	Female		59,171	202	3.41	Invasive breast cancer cases only. Cases of breast carcinoma in situ (n=162) were excluded to minimize detection bias. 29 cases of newly developed breast cancer cases were excluded as the dates of diagnosis were not available.

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
Mink 2002 Prospective cohort	1987- 1995	1/1/1987 – 12/31/1995. Follow-up ended on 12/31/1995.	Women aged 45- 64 years with newly diagnosis of type 2 diabetes from Minnesota, North Carolina, Maryland, Mississippi	U.S.	Female		6,436	26	4.04	Patients with a history of cancer were excluded.
Weiderpass 1997 Retrospective cohort	1965- 1983	Up to 12/31, 1989. Mean duration of follow-up 6.7 years	Patients with at least 1 hospital admission with a discharge diagnosis of diabetes	Sweden	Female	70,110	468,497	1145	2.44	Both type 1 and 2 diabetes patients were included. 194 female and 2 male cases diagnosed during the first year of follow-up and corresponding person-years were excluded assuming those cases were prevalence at cohort entry and possibly diagnosed as ascertainment bias. 21 cases diagnosed at autopsy were excluded.
					Male	63,988	432,650	13	0.03	
Adami 1991 Retrospective cohort	1965- 1983	Through 1984	Patients with at least one hospital discharge diagnosis of	Sweden	Female	27,862	143,618	240	1.67	Both type 1 and 2 diabetes patients were included. The person- years that elapsed in

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
			diabetes		Male	23,146	119,643	2	0.02	the first year of follow-up and cases detected during the same period were excluded to minimize the ascertainment bias.

3.1.2 Discussion of Literature Findings

As shown in Table 2, compared to the reported incidence rates of breast cancer among female type 2 diabetes patients in the literature, the age-specific incidence rate of breast cancer were consistently higher in the dapagliflozin clinical trial program. However, this finding should not be interpreted as dapagliflozin treatment is associated with increased risk of breast cancer. Definitions and diagnoses of breast cancer varied and there were differences in study populations by country, calendar time, patient age, and other risk factors. The breast cancer identified in the dapagliflozin clinical trials included all cases of breast cancer irrespective of grade or stage, while only invasive breast cancer was included in Lipscombe and Michels' studies.

Table 2. Female age-specific incidence rate of breast cancer in the dapagliflozin clinical trials compared with those reported in the literature

Age	Study	Incidence rate of breast cancer per 1,000 person-years	
		Literature	Dapagliflozin clinical trials *
55-64	Lipscombe (Canada)	2.90	5.73
65-79		3.02	7.15
40-69	Inoue (Japan)	0.62	3.87
50-75	Michels (U.S)	3.41	4.98
45-64	Mink (U.S)	4.04	4.11

* Calculated by DEPI based on the data from the dapagliflozin clinical trials

3.2 SPONSOR'S STUDY REPORT

3.2.1 Study Summary

The sponsor used age- and sex-specific incidence rates of breast cancer data from the Surveillance Epidemiology and End Results (SEER) program to calculate the expected number of breast cancer cases in the dapagliflozin clinical trials. Since SEER data provide incidence rates in the general population, an adjustment factor of 20% was applied to calculate the incidence rates of breast cancer in patients with type 2 diabetes based on findings from a meta-analysis⁷ that women with type 2 diabetes have a 20% increased risk of breast cancer compared to women without type 2 diabetes.

A standardized incidence ratio (SIR) was calculated to evaluate the observed incidence of breast cancer in the female cohort of the dapagliflozin clinical program compared to the expected incidence in

a population without dapagliflozin treatment. The age- and sex-specific person-time of the dapagliflozin-treated patients was multiplied by the age- and sex-specific incidence rates of breast cancer in the SEER population. The number of expected cases was calculated for each age- and sex-stratum. Those stratum-specific expected number of cases were summed to provide the total expected number of cases in the dapagliflozin-treated population. An adjustment factor for the 20% increased risk of breast cancer in type 2 diabetes was applied and 95% confidence intervals were calculated for SIR. The same analyses were conducted for female patients in the comparator arms of the dapagliflozin clinical program.

The total number of expected incident breast cancer cases among female patients exposed to dapagliflozin was 7.1. The calculated SIR was 1.27 (95% CI, 0.58-2.41) for dapagliflozin-treated patients. The total number of expected incident breast cancer cases among female patients in the comparator arms was 2.9. An SIR was not calculated for the comparator group because no incident breast cancer cases were reported in the female comparator patients of the dapagliflozin clinical trials.

The sponsor stated that the results provided some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within what one would expect for a similar population of untreated females with type 2 diabetes of the same age.

3.2.2 Comments

The use of external data source (SEER) as the reference population to evaluate the risk of breast cancer associated with dapagliflozin treatment has important limitations. The dapagliflozin clinical trials were conducted internationally and the U.S. represented with approximately 20% of the total trial population. As rates of breast cancer vary across countries, the estimates from SEER (U.S. data) could not be applicable to the international study subjects. The breast cancer identified in the dapagliflozin clinical trials included all cases of breast cancer irrespective of grade or stage, while only invasive breast cancer was included in SEER. The background incidence rates of breast cancer estimated from the SEER data are for the general population in the U.S, but not the type 2 diabetes population. Even with the adjustment factor to obtain the incidence rate of breast cancer in type 2 diabetes patients from SEER data, the patient population is different from those included in the dapagliflozin clinical trials. With the strict inclusion and exclusion criteria used in the dapagliflozin clinical program, the trial participants would be expected to be healthier than the general type 2 diabetes population. For example, patients with BMIs greater than 45 kg/m² were excluded from the dapagliflozin clinical trials. However, obesity is positively associated with both type 2 diabetes and breast cancer. Therefore, the incidence rate of

breast cancer in the general type 2 diabetes patient population in SEER should be higher than that in the dapagliflozin clinical trials. Thus using expected number of cases based on the background incidence rate of breast cancer from SEER, the calculated SIR could be underestimated.

The application of 20% increased risk of breast cancer for type 2 diabetes patients compared to non-diabetic patients to the estimated expected number of cases from SEER overestimated the expected number of cases to be seen in the dapagliflozin clinical trials. Since some patients in SEER are actually diabetes patients and the 20% diabetic risk adjustment factor should not be applied to those patients. With the over-estimated expected number of cases, the SIR may be under-estimated. Another concern is that it is unknown whether the 20% increased risk is constant across all age groups.

The expected number of cases in the comparator arms was 2.9. However, no case was observed in the comparator arms of the dapagliflozin clinical program. This finding suggests that the study participants in the dapagliflozin clinical program have a lower risk of breast cancer compared to the general type 2 diabetes population of the same age. One possible explanation is that the participants in the dapagliflozin trials are healthier because of the inclusion and exclusion criteria. According to this logic, the number of observed breast cancer cases in the dapagliflozin-treated arms should be fewer than the expected number of cases. However, the number of observed breast cancer cases (n=9) in the dapagliflozin trials were more than the expected number of cases (n=7.1) based on SEER data. One possible explanation to this finding is that dapagliflozin treatment may be associated with increased risk of breast cancer.

Based on the SIR of 1.27 (95% CI, 0.58-2.41), the sponsor concluded that the results provide some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age. However, this reviewer disagrees with the sponsor's conclusion. First of all, the few number of cases (n=9) resulted in wide confidence intervals. Secondly, the SIR may be under-estimated due to the limitations discussed above. Thirdly, the excess number of cases observed over expected in the dapagliflozin-treated patients in a potentially healthier type 2 diabetes population suggests that dapagliflozin treatment may be associated with increased risk of breast cancer. Without evaluating the relative risk of breast cancer with an internal reference group (e.g. the placebo arm) and with the study limitations, we can not be reassured that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age.

4 CONCLUSIONS & RECOMMENDATIONS

Although the ideal reference population to evaluate the relative risk of breast cancer associated with dapagliflozin treatment are patients in the comparator arms of the dapagliflozin trials as those patients are expected to have similar characteristics to those in the dapagliflozin treatment arms because of randomization, it is not feasible to establish the relative risk with any degree of certainty at this time. With nine cases of breast cancer observed in the female dapagliflozin-treated patients versus none in the comparator arms of the dapagliflozin clinical trials, it is technically not feasible to estimate the incidence rate ratio with the denominator of zero as no cases was observed in the control groups of the dapagliflozin clinical trials.

The finding that the age-specific incidence rates of breast cancer were higher than those reported in the literature could be a safety signal that dapagliflozin may be associated with an increased risk of breast cancer. The SIR calculated by the sponsor using SEER data as an external reference group may be underestimated and is not reassuring due to study limitations.

It is uncertain whether dapagliflozin treatment is associated with an increased risk of breast cancer with the current available data. Continued follow-up of all participants in the dapagliflozin clinical trials for breast cancer and further analysis with a direct comparison between the dapagliflozin treatment arms and the comparator arms should be done to evaluate the relative risk of breast cancer associated with dapagliflozin treatment.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
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Date: 6/7/2011

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Subject: Incidence of Bladder Cancer in a Diabetic Population

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Application Type/Number: IND 068652
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Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1476

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EXECUTIVE SUMMARY

The sponsor of dapagliflozin (NDA 202293, Bristol-Myers Squibb and AstraZeneca) reported 10 cases of bladder cancer in male subjects in the phase 2b and phase 3 clinical trial program. Nine of these cases occurred in the active treatment arm and one with placebo. Concerns about an imbalance in risk for bladder cancer led the Division of Metabolism and Endocrinology Products to request from the Division of Epidemiology I information on the background rate of bladder cancer in the diabetic population.

For this review, incidence rates of bladder cancer in the US general population were extracted from the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute. These rates were adjusted with a literature-based factor to reflect a 40% increased risk for bladder cancer in a diabetic population. A standardized incidence ratio was calculated to compare observed case numbers in the dapagliflozin arms to expected numbers in an age-matched diabetic background population.

In the clinical trials of dapagliflozin, no cases of bladder cancer were observed in female patients. Nine cases occurred during a total follow-up of 2,237.1 subject-years in males in the dapagliflozin arms, amounting to a rate of 402 (95% CI, 184 – 764) per 100,000 subject-years. This compared to 1 case during 989.8 subject-years in male controls, or 101 (95% CI, 1.3 – 562) new cases per 100,000 subject years. The two-sided p-value comparing the incidence of bladder cancer between active treatment and controls was 0.28 for males. Based on SEER data, only two cases would be expected in the male dapagliflozin population, at a rate of 91.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 4.39 (95% CI, 2.01 – 8.33), $p < 0.001$. Consistent with actual occurrence, one case would be expected among the male controls.

To summarize, the clinical trials were not powered to statistically distinguish between 9 cases of bladder cancer in the active treatment arms compared to 1 case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Limitations suggest that comparisons between clinical trial data and a reference population should be interpreted with caution.

1 BACKGROUND

In the phase 2b and phase 3 clinical trial program of dapagliflozin (NDA 202293), the sponsor (Bristol-Myers Squibb and AstraZeneca) reported 10 subjects with a diagnosis of bladder cancer; all of these subjects were males. Nine of these cases occurred in the active treatment arms and one in a placebo arm. To provide context for these observations, the Division of Metabolism and Endocrinology Products (DMEP) requested a review of the background rate of bladder cancer in the diabetic population. DMEP further requested information on the background rate of breast cancer to address similar concerns. Information on breast cancer is the subject of a parallel review by Dr. Jing (Julia) Ju, Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology.

2 METHODS

For this review, age- and sex-specific incidence rates of bladder cancer in the US general population were extracted from the Surveillance Epidemiology and End Results (SEER) database

of the National Cancer Institute. This rate was adjusted with a literature-based factor to reflect the increased risk for bladder cancer in a diabetic population. For the male participants in the dapagliflozin clinical trial program, observed case counts were compared to expected case counts in an age-matched diabetic background population.

3 RESULTS

3.1 LITERATURE REVIEW

The National Cancer Institute estimates that 52,760 men and 17,770 women developed urinary bladder cancer in 2010, and 14,680 men and women died from it (1). The median age at diagnosis was 73 and the median age at death from bladder cancer was 78.

A meta-analysis, published in 2006, combined 16 observational studies to obtain a summary estimate of bladder cancer risk associated with diabetes mellitus (2). Separate estimates were provided for studies based on whether their estimates were adjusted for a history of smoking (Table 1). Smoking is a strong risk factor for bladder cancer, responsible for up to 25% of incident cases (3). Because smoking is also more prevalent in subjects with diabetes mellitus, it meets the definition of a confounder, and the extent of confounding introduced by smoking is not negligible. For this reason, this review focused on studies that adjusted for smoking and were included in the meta-analysis by Larsson et al., as well as studies published since the meta-analysis, if smoking was included in the analysis. Eight studies from the meta-analysis (1, 3-9) and five studies published since then (10-14) were included in this review.

Table 1. Results, meta-analysis by Larsson et al.

Subgroup	No. of studies	References	Relative risk (95% CI)	Tests for heterogeneity		
				<i>Q</i>	<i>p</i>	<i>I</i> ² (%)
Geographical region						
North America	8	[13–15, 19–21, 23, 24]	1.29 (1.06–1.56)	14.49	0.04	51.7
Europe	6	[16, 18, 25–28]	1.03 (0.89–1.18)	7.29	0.20	31.4
Other ^a	2	[17, 22]	1.71 (0.98–2.99)	6.81	0.01	85.3
Publication year						
1970–1999	8	[13–16, 23–26]	1.07 (0.93–1.23)	14.48	0.04	51.7
2000–2005	8	[17–22, 27, 28]	1.47 (1.21–1.78)	15.49	0.03	54.8
Adjustment for smoking						
Yes	8	[13, 15, 17–22]	1.48 (1.25–1.77)	16.86	0.02	58.5
No	8	[14, 16, 23–28]	1.01 (0.91–1.11)	7.72	0.36	9.4
Adjustment for BMI						
Yes	3	[19–21]	1.45 (0.99–2.13)	4.74	0.09	57.8
No	13	[13–18, 22–28]	1.20 (1.03–1.39)	38.92	<0.0001	69.2

^aOne study each in Israel and Korea

Source: Larsson et al.(2); reference numbers do not apply to this document

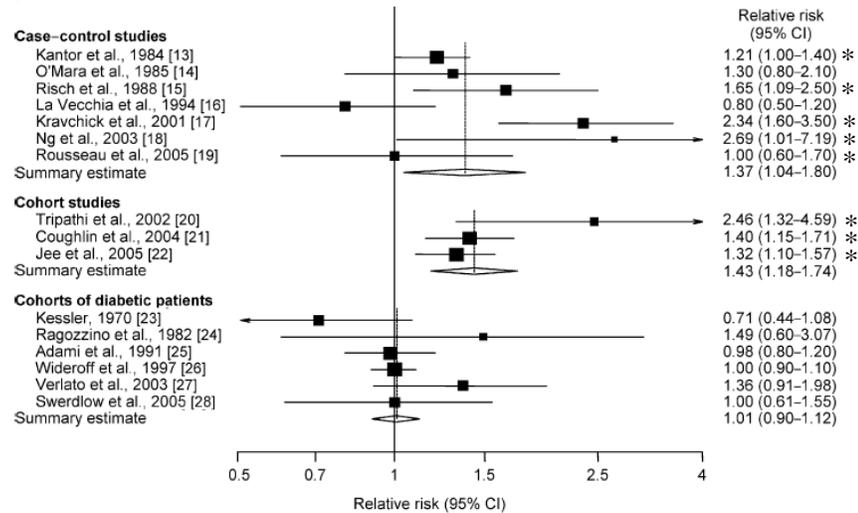
3.1.1 Studies included in meta-analysis

Figure 1 shows effect estimates from the studies that adjusted for smoking (marked with *). These estimates range from a relative risk of 1.0 (95% CI, 0.60 – 1.70) in a study by Rousseau et al.(8) to 2.69 (95% CI, 1.01 – 7.19) in a study conducted by Ng et al.(9). The summary estimate for studies that adjusted for smoking was a relative risk of 1.48 (95% CI, 1.25 – 1.77) for bladder cancer among diabetic patients, compared to non-diabetics. The eight

included studies differ in their outcome definition: one study (4) used *cancer mortality* as primary outcome and did not include *carcinoma in situ* cases. All other studies investigated *new diagnoses of cancer*; some of them explicitly included *carcinoma in situ* cases (3, 5, 7), while the case definition for the remaining studies is unclear in this regard.

Figure 1. Meta-analysis by Larsson et al.

Fig. 1 Relative risks for the association between diabetes mellitus and bladder cancer in case-control studies, cohort studies, and cohort studies of diabetic patients. Studies are ordered according to study design and year of publication. The *squares* represent study-specific relative risks, and the size of the squares is proportional to the weight of each study in the summary estimate. The *horizontal lines* represent 95% CIs. The *diamonds* represent the summary relative risk estimates with 95% CIs



Source: Larsson et al.(2); reference numbers do not apply to this document

* Studies that included adjustment for smoking and were selected for this review

3.1.2 Studies published after publication of the meta-analysis

Five studies on the risk of bladder cancer associated with diabetes mellitus were published since the meta-analysis (10-14). All of these studies included adjustment for the effects of smoking. In a cohort study in Swedish men, Larsson et al.(10) found no significant increase in the risk for bladder cancer (excluding *carcinoma in situ*) associated with diabetes (rate ratio, 1.16 [0.81 – 1.64]), but the risk increased when only high-grade (grades II or III) cancers were analyzed (rate ratio, 1.48 [0.99 – 2.21]). In a prospective cohort study in European men and women (12), investigators analyzed data based on blood glucose levels and found a higher risk increase for women (hazard ratio, 1.45 [1.05 – 2.01]) than for men (hazard ratio, 1.17 [1.00 – 1.37]) per 1mmol/l increment in blood glucose level. A large retrospective cohort study in Taiwanese men and women older than 40 years at baseline (13) found a hazard ratio associated with diabetes of 1.39 (95% CI, 1.12 – 1.72) in both sexes combined. This study did not include *carcinoma in situ* cases. A recent 10-year prospective cohort study conducted in Hawaii and Los Angeles (14) found a small, nonsignificant increase in risk for urothelial cancer in men of 1.18 (95% CI, 0.96 – 1.47) and a significant increase of 1.48 (95% CI, 1.02 – 2.14) in women; however, the interaction was not significant (p=0.19). Of note, this study found essentially the same effect of diabetes on *carcinoma in situ* or localized cancers (relative risk, 1.23 [0.99 – 1.51]) as on regional or distant cancers (relative risk, 1.25 [0.78 – 2.00]). Finally, MacKenzie et al. (11) conducted a case-control study in New Hampshire and found a risk increase for bladder cancer associated with diabetes (odds ratio, 2.2 [1.3 – 3.8]), not appreciably different based on age or sex. This study found a stronger association for noninvasive cancer (odds ratio, 2.8 [1.6 – 4.9]) than for invasive cancer (odds ratio, 1.5 [0.7 – 3.2]) but it is acknowledged that this difference could be due to chance.

3.1.3 Diabetes and bladder cancer by sex

Unfortunately, the meta-analysis did not provide sex-specific estimates on the risk of bladder cancer associated with diabetes mellitus.

Only one study was conducted solely in women (3) and found a significant increase in the risk for bladder cancer associated with diabetes (relative risk, 2.46 [1.32 – 4.59]).

Two studies were conducted solely in men and found either no increase in risk (odds ratio, 1.0 [0.6 – 1.7]) (8) or a small, non-significant overall increase associated with diabetes (rate ratio, 1.16 [0.81 – 1.64]), but the risk increased when only high-grade (grades II or III) cancers were analyzed (rate ratio, 1.48 [0.99 – 2.21]).

Several studies included both sexes and provided sex-specific risk estimates for bladder cancer associated with diabetes. Coughlin et al.(4) found an increased risk for fatal bladder cancer in men (relative risk, 1.43 [1.14 – 1.80]) and a non-significant increase in fatal bladder cancer in women (relative risk, 1.30 [0.85 – 2.00]). A study in Koreans (15) reported an increase for men (hazard ratio, 1.32 [1.10 – 2.67]), but provided no estimate for women. In contrast, a European study (12) found a higher risk of bladder cancer per 1mmol/l increment in blood glucose level in women (hazard ratio, 1.45 [1.05 – 2.01]) than in men (hazard ratio, 1.17 [1.00 – 1.37]). Similarly, Woolcott et al. (14) found a higher increase in risk for urothelial cancer in women (rate ratio, 1.48 [95% CI, 1.02 – 2.14]) than in men (relative risk, 1.18 [95% CI, 0.96 – 1.47]). The remaining studies did not provide separate risk estimates by sex.

Taken together, these studies did not provide conclusive evidence of a differential risk increase for bladder cancer associated with diabetes mellitus in women versus men.

3.1.4 Summary of Literature Review

Although not all studies published after the meta-analysis found statistically significant increases in the risk for bladder cancer associated with diabetes mellitus, almost all point estimates suggested a possible increase. The order of magnitude of these estimates is comparable with what the meta-analysis found in studies that adjusted for smoking. Therefore, this review used the summary estimate from the 8 studies that adjusted for smoking found in the meta-analysis (hazard ratio, 1.48 [1.25 – 1.77]) to adjust SEER data to provide a background incidence rate for bladder cancer in the diabetic population in the U.S.

3.2 SEER DATA EXTRACTION

The hazard ratio for bladder cancer associated with diabetes was derived from studies that compared diabetic populations to non-diabetics. However, SEER data provide estimates for the US general population, which includes diabetic subjects. Thus, multiplying the SEER estimates with the hazard ratio of 1.48 would result in an overestimated incidence for a diabetic population. According to the American Diabetes Association, 11.3% of all Americans older than 20 years have diabetes (16). For this review, a downward-adjusted hazard ratio of 1.40 was calculated and applied to a population with an 11.3% prevalence of diabetes to provide the same incidence rate for a pure diabetic population as the hazard ratio of 1.48 when applied to a pure non-diabetic population.

Tables 2 and 3 provide age- and sex-specific incidence rates for bladder cancer in the US general population and projected incidence rates for the diabetic population. Both age and sex are strongly associated with the risk for bladder cancer. Table 3 provides different age categories and, in addition, staging information. These data suggest little difference in cancer stages based

on age or sex. SEER data include *carcinoma in situ* cases and so did the sponsor's definition, as communicated to FDA on 5/27/2011 in a response to a related inquiry from 5/26/2011.

Table 2. Incidence rates for bladder cancer based on SEER data, 2000 - 2008

Age at diagnosis	Males		Females	
	Incidence, general population*	Projected incidence, diabetic population*	Incidence, general population*	Projected incidence, diabetic population*
15-19	0.1	0.2	--	--
20-24	0.3	0.4	0.2	0.2
25-29	0.5	0.7	0.3	0.4
30-34	1.1	1.5	0.4	0.6
35-39	2.3	3.2	0.9	1.3
40-44	5.0	7.0	1.8	2.6
45-49	11.2	15.6	3.7	5.1
50-54	22.7	31.8	7.2	10.0
55-59	45.6	63.8	12.7	17.8
60-64	79.8	111.8	21.8	30.5
65-69	130.8	183.1	34.4	48.1
70-74	196.6	275.3	46.0	64.4
75-79	266.0	372.5	60.4	84.6
80-84	325.4	455.5	73.6	103.0
85+	362.1	506.9	79.1	110.7

*per 100,000 person-years

Table 3. Incidence rates for bladder cancer based on SEER data, 2000 - 2008

	Age at diagnosis	Incidence, general population*	Projected incidence, diabetic population*	Stages [%]			
				Localized	Regional	Distant	Unstaged
Males	20-49	3.1	4.3	69.4	15.9	8.8	5.9
	50-64	39.6	55.5	70.6	16.2	7.7	5.5
	65-74	147.8	206.9	73.2	15.2	6.5	5.1
	75+	297.4	416.3	74.0	12.4	6.0	7.6
Females	20-49	1.1	1.5	59.1	20.2	14.2	6.5
	50-64	11.8	16.5	65.5	18.4	10.3	5.8
	65-74	36.5	51.1	67.3	17.4	10.0	5.4
	75+	66.4	92.9	69.1	12.5	8.7	9.7

*per 100,000 person-years

3.3 COMPARISON WITH CLINICAL TRIAL DATA

At the time of writing this review, 10 subjects were reported as having been diagnosed with bladder cancer in the phase 2b and phase 3 clinical trials on dapagliflozin. Nine of these cases occurred in the active treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76. Diagnoses were made between study day 43 and 727. Total follow-up of male patients randomized to dapagliflozin was 2,237.1 subject-years (Table 4). With nine cases of bladder cancer occurring during this time, this rate amounts to 402 (95% CI, 184 – 764) new cases per 100,000 subject-years. This compares to 1 case during 989.8 subject-years in controls, or 101 (95% CI, 1.3 – 562) new cases per 100,000 subject-years. The two-sided p-value comparing the incidence of bladder cancer between active treatment and controls was 0.28 (Fisher’s exact). The rate ratio between active treatment and control was 3.98 [95% CI, 0.51 – 31.4]. These estimates are pooled summary estimates and do not take heterogeneity between clinical trials into account, including potential imbalances in active treatment versus control ratios that may introduce confounding.

Based on SEER data, only two cases (2.05) would be expected in the male dapagliflozin population (Table 4) at a rate of 91.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 4.39 (95% CI, 2.01 – 8.33), $p < 0.001$. Consistent with actual occurrence, one case would be expected among the male controls.

In comparison, 0.5 cases would be expected in the female subjects exposed to dapagliflozin, at a rate of 23.5 per 100,000 subject-years. In female controls, 0.22 cases would be expected. No cases of bladder cancer were observed either in the dapagliflozin or control arms.

Table 4. Expected cases of bladder cancer in the male clinical trial sample

Age at diagnosis	Males			Expected bladder cancer cases in dapagliflozin patients
	Observed cases, dapagliflozin	Dapagliflozin, person-time, males	Projected incidence, diabetic population*	
<25	0	1.4	0.4	0.0000
25-29	0	15.6	0.7	0.0001
30-34	0	43.7	1.5	0.0007
35-39	0	81.6	3.2	0.0026
40-44	0	160.7	7.0	0.0113
45-49	1	274	15.6	0.0428
50-54	0	332.6	31.8	0.1058
55-59	1	445.7	63.8	0.2844
60-64	2	395.6	111.8	0.4421
65-69	3	277.2	183.1	0.5077
70-74	2	146.1	275.3	0.4022
75-79	0	49.8	372.5	0.1855
80-84	0	12.7	455.5	0.0578
85+	0	0.4	506.9	0.0020
sum	9	2237.1	--	2.05

4 DISCUSSION

This review provides background incidence rates for bladder cancer in the US general population and projected incidence rates for the diabetic population. Several mechanisms have been suggested to explain the increased risk in diabetics. Insulin has a mitogenic effect and increased insulin levels in the blood could stimulate tumor growth by increasing bioactive insulin-like growth factor-1 (17). Alternatively, diabetes is associated with changes in urine composition and bladder function as well as an increased risk for urinary tract infections, which, in turn, are linked with increased risk for bladder cancer (6).

Findings of this review should be viewed in the light of several limitations. Cancer rates in SEER reflect the US general population, while most of the clinical trial subjects were enrolled outside of the US. This could impact comparability, since, for instance, Asian populations are at lower risk for bladder cancer. A Korean study found only 22.3 cases per 100,000 subject-years in diabetic men (15) compared to 53.9/100,000 subject-years in diabetic women in Iowa (3) and 142.8/100,000 subject-years in diabetic men in Sweden, although the latter did not include *carcinoma in situ* cases (10). Also, clinical trial populations are often highly pre-screened for certain co-morbidities, which may result in an underestimated cancer incidence. Nevertheless, both limitations would result in a lower case count and therefore, the risk of bladder cancer associated with exposure to dapagliflozin would be underestimated. On the other hand, increased surveillance in a clinical trial setting, together with urinary symptoms associated with dapagliflozin could increase case detection of bladder cancer and lead to higher estimates compared to the background population. Lastly, it should be considered that the literature-based factor to adjust SEER estimates for a diabetic population is subject to uncertainty.

To summarize, the clinical trials were not powered to statistically distinguish between 9 cases of bladder cancer in the active treatment arms compared to 1 case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Limitations suggest that comparisons between clinical trial data and a reference population should be carefully interpreted.

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cc: EganA/ParksM/DunnS/IronyI/BishaiJ/DMEP
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1**

Date: 21 June 2011

To: Mary Parks, MD, Director
Division of Metabolic and Endocrine Products

Reviewer: Leonard Seeff, MD, Hepatologist
John Senior, MD, Hepatologist
Office of Surveillance and Epidemiology

Through: Allen Brinker, MD, MS, Medical Team Leader
Division of Pharmacovigilance 1

Mark Avigan, MD, CM, Associate Director,
Office of Surveillance and Epidemiology

Drug Name: Dapagliflozin

NDA Number: 202293

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1474

Issue: Review of cases of serious liver toxicity arising in
NDA 202293 (dapagliflozin)

INTRODUCTION

Based on the consult request, dapagliflozin is an inhibitor of SGLT2 (sodium glucose cotransporter 2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin results in the direct, and insulin-independent, elimination of glucose by the kidney. The Agency is currently evaluating dapagliflozin (as NDA 202293) which, if approved, will be a first-in-class treatment of Type 2 Diabetes.

The primary assessment of safety in subjects with T2DM has been based on three Phase 2b and eleven Phase 3, double-blind, placebo/active-controlled, randomized clinical studies. Dapagliflozin was administered as:

- Monotherapy in 4 studies.
- Add-on combination therapy with other antidiabetic medication in 6 studies.
- Initial combination therapy with metformin in 2 studies.
- A direct comparison with SU.
- Monotherapy in subjects with moderate renal impairment.

In total, over 4000 subjects with T2DM have been exposed to dapagliflozin (2.5 mg or higher) and 2000 subjects were exposed to the 10 mg dose in the Phase 2b and 3 clinical program. Overall, there were 2.2 times as many subjects exposed to dapagliflozin (N = 4,287), compared with control (N = 1,941).

For patients treated or randomized to dapagliflozin (N=4,287), patient counts by exposure window are as follows:

- 3,333 @ 6 months
- 2,232 @ 12 months
- 1,317 @ 18 months
- 441 @ 24 months

Cumulative exposure to dapagliflozin in Phase 2b and 3 studies was 4009.1 patient-years and 1681.9 patient-years to control. Based on these metrics, the average duration of observation in dapagliflozin arms was 341 days and 316 days in control arms.

During review, it has come to the attention of DMEP that there have been at least 8 cases treated with dapagliflozin who developed liver-related test dysfunction with elevations of both serum ALT and bilirubin in the clinical development program for dapagliflozin. Among the 8 cases, 5 reported values that reached the laboratory threshold¹ for potential Hy's Law cases. Of note, nonclinical findings with dapagliflozin were minimal. There was some hepatic toxicity in the one month rat and dog studies, but at very high multiples of the human exposure dose. Also, the 6 month rat study and 12 month dog studies had increased liver weights.

¹ ALT or AST > 3X ULN and concomitant or subsequent TBL > 2X ULN within 30 days after discontinuation of study medication

Given the regulatory importance of a validated case(s) of liver injury consistent with Hy's law based on the FDA Guidance Document² and based on currently available data³, DMEP requested review of case summaries for the 8 patients with elevated serum ALT and bilirubin levels including 5 that are consistent with Hy's Law for validation as Drug-Induced Liver Injury (DILI). In addition, DMEP requested review of 27 other cases in dapagliflozin-treated individuals and two patients on blinded treatment identified by the sponsor with a clinical or laboratory assessment of liver injury not included in the 8 cases with reported elevations of both serum ALT and bilirubin.

BACKGROUND

The Guidance document is quite clear on the regulatory impact of Hy's Law cases for drugs in their clinical development program. This is outlined in the following text extracted from the Guidance:

'Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. '...

Briefly, Hy's Law cases have the following three components:

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

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population. Clinical trials of the beta blocker dilevalol

² Guidance for Industry – Drug-Induced Liver Injury: Premarketing Evaluation. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

³ Including case narratives from the Four Month Safety Update (4MSU), SCS Appendices, and Report of the Independent Adjudication Committee for Adverse Hepatic Events

(enantiomer of labetalol, a diastereoisomeric mixture) showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned.

Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of the so-called Hy's Law cases.⁴ This observation was recently confirmed in large studies of DILI in Spain⁵ and in Sweden⁶ in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants. Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing.⁷

Thus, due diligence on the part of drug sponsors and the Agency is necessary in pursuit Hy's Law cases in drug development programs.

METHODS AND MATERIALS

Case narratives and other information were reviewed from materials provided to OSE from DMEP. These materials were limited to:

- Four Month Safety Update (4MSU)
- SCS Appendices
- Report of the Independent Adjudication Committee for Adverse Hepatic Events with cases and data elements reported through 15-Oct-2010.

A grading system of probabilistic causal association developed by the NIH Drug-Induced Liver Injury Network (DILIN) Study has been used in this analysis.⁷ This grading system has been applied by DILIN in the analysis of causality of cases of liver injury that have occurred in patients in a clinical practice setting treated with marketed drugs who were then referred to the DILIN network for evaluation. The grading of causal association with a particular drug is as follows: Definite - >95% likelihood; Highly Likely = 75% to 94% likelihood; Probable = 50% to 74%; Possible = 25% to 49%, Unlikely = <25%.

⁴ Temple, R, 2001, Hepatotoxicity Through the Years: Impact on the FDA, presented 2/12/2001, <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm122149.pdf>.

⁵ Andrade, RJ, MI Lucena, and MC Fernandez et al., 2005, Drug-Induced Liver Injury: An Analysis of 461 Incidences Submitted to the Spanish Registry Over a 10-Year Period, *Gastroenterology*, 129(2):512-21.

⁶ Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, *Hepatology*, 42(2):481-9.

⁷ Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009; 32 (1):55-68.

SUMMARY OF RESULTS AND DISCUSSION

Eight cases with elevated serum ALT and bilirubin were identified and among these 5 reported laboratory values consistent with potential Hy’s law (serum ALT > 3X ULN and bilirubin > 2X ULN), conditional upon finding that the liver problems were not principally cholestatic and that no alternative probable cause could be found after reasonable and thorough search, as identified by the sponsor are outlined in Table 1. These cases were identified through inspection of a table which begins on page 11 of the Hepatic Adjudication Report as prepared by the sponsor. All individuals received dapagliflozin. A summary of each of these cases follows on the following page as Table 1.

Table 1. Reformulation of Table 3.1 from sponsor’s Hepatic Adjudication Review listing 8 dapagliflozin-treated cases with elevated serum ALT and bilirubin levels, including 5 consistent with Hy’s Law and FDA assessment of drug causality.

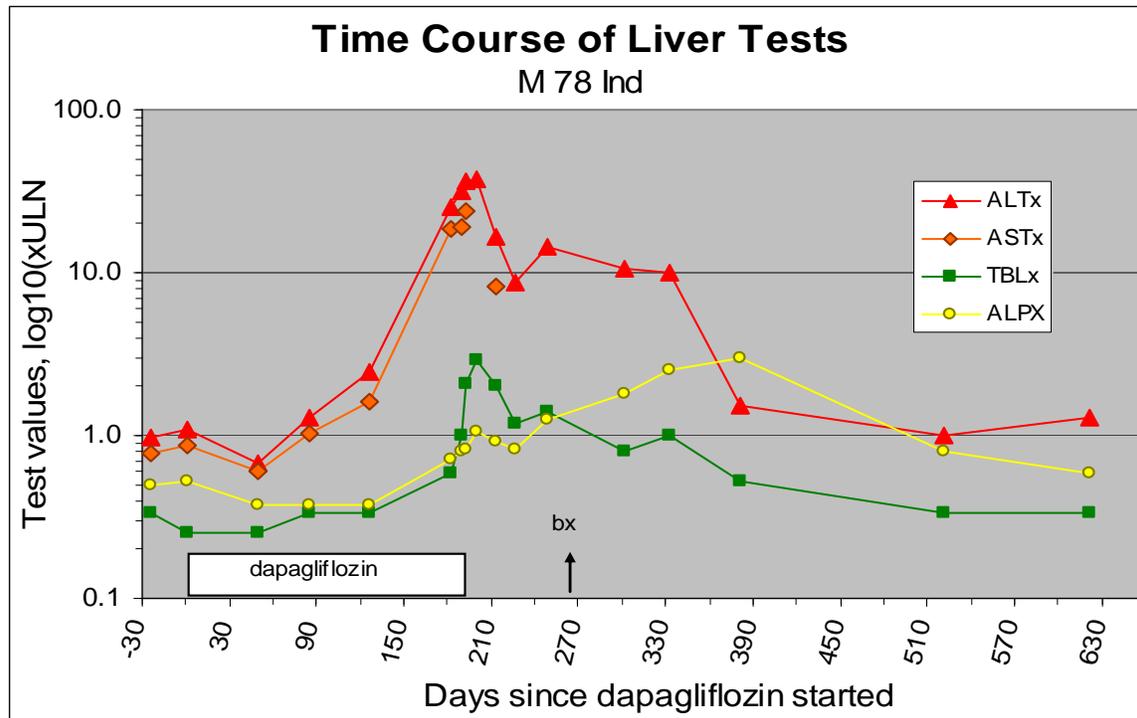
	ID	Causality per CDER
1	D1690C00004-4402-6	Probable
2	D1690C00005-6008-10	Unlikely
3	D1690C00005-6013-3	Unlikely
4	D1690C00005-7002-4	Unlikely
5	D1690C00006-1511-6	Unlikely
6	D1690C00006-2004-6	Not DILI
7	D1690C00012-403-1	Insufficient data
8	MB102030-9-92	Unlikely

Case narratives for the 8 cases with elevations of serum ALT and bilirubin identified by the sponsor.

D1690C00004-4402-6: 78 year old man from India with type 2 diabetes, coronary artery disease, hypertension, dyslipidemia and benign prostatic hypertrophy, Participated in the trial and received the study drug plus metformin. Concomitant drugs included atorvastatin, cromolyn, lecanlidipine, atenolol, parendopril, naproxen, acetylsalicylic acid and a couple of herbal products. The patient also carried a diagnosis of hemochromatosis, C282Y/H63D compound heterozygote.

At baseline, the ALT value was slightly increased and the AST was normal. On day 85 of treatment, he was found to have an ALT value of 62 (no AST performed) that reached a value of 1204 on day 183 with an AST of 825, an alkaline phosphatase (ALP) level of 103 and a serum total bilirubin of 0.7. His prothrombin time was 12.4 seconds and his INR was 1.2. The study medication was discontinued on day 191. The values peaked on day 200, as follows: ALT, 1858, AST (day193) 1060, ALP 128, bilirubin 4.2. The serum

biochemical time course associated with the liver injury event in this study subject is outlined in the figure on the following page.



A liver biopsy was performed on day 264, read by two different pathologists. The report indicated that, “there is evidence of hepatitis with severe inflammatory activity of relatively short duration. However, the presence of prominent interface hepatitis and associated pattern of fibrosis in periportal regions favors progression to chronic hepatitis. Underlying etiology is uncertain. Viral agents, drugs, and autoimmune hepatitis are three main possibilities to be considered in the differential diagnosis and a number of histologic features would favor a diagnosis of autoimmune hepatitis. However, results of other investigations do not appear to support this diagnosis. The clinical presentation appears to favor drug toxicity as a likely cause of liver injury. Siderosis is mild and has a mixed parenchymal / mesenchymal distribution. This finding suggests that that there is unlikely to be significant liver injury related to genetic iron overload.” On day 349, it was decided to treat with prednisolone for 4 weeks. Thereafter, all values began a slow decline reaching near normal values approximately 6 months later and remained normal thereafter.

Workup for other etiologies revealed that serologic markers for hepatitis A, B and E were negative. The test for hepatitis C at baseline was negative but it was not repeated later. Serologic markers for autoimmune hepatitis were all negative even though the liver biopsy had some suggestive features of AIH with acute necro-inflammation and interface hepatitis. CMV IgG and EBV IgG were both positive implying past infection and the

patient had increased transferrin levels. During treatment, the patient developed back pain associated with findings of osteoporosis.

Comment: 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 phosphate 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.

D1690C00005-6008-10: 55 year old white female treated with study medication. She used alcohol occasionally. She apparently had increased AST and bilirubin levels and a slight increase in ALT values at baseline and, during the course of treatment, she had intermittent increases in AST and bilirubin levels. The values peaked on day 294: AST 129, ALT 74, and bilirubin peaked on day 287. The study drug was temporarily discontinued (days 309-317) and then treatment was resumed without causing apparent further liver dysfunction. Hepatitis serology was negative. No data are supplied

Comment: The cause for the persistent but fluctuating liver-related tests that began at baseline cannot be determined from the data that are available. Regardless, given the fact that liver dysfunction already existed when use of the test drug was begun, the drug cannot be held responsible for the observed liver injury.

D1690C00005-6013-3: 83 year old white male with type 2 diabetes. Started on study drug together with glipizide. Concomitant drugs include albendazole, pantoprazole, and nutritional supplements. Patient had a history of cholelithiasis together with obstructive jaundice requiring hospitalization for papilotomy; cholecystectomy recommended but patient refused. Treatment with study drug begun 9 months later, and subsequently he develops two separate episodes of liver dysfunction. The first began on day 85 lasting presumably to day 93 (no actual levels reported). The aminotransferase values increased modestly, the ALP increasing from a baseline of about 85 to 236 associated with a slight increase in serum bilirubin. The values then returned to normal despite continued use of study drug. The second episode began on day 141- at which time the drug was discontinued- lasting presumably to day 148 when the values peaked: ALT 271, bilirubin 2.7. The values for ALP increased only slightly on this occasion. No other values given although it is stated that the values gradually returned to normal. The patient did not have symptoms during the abnormalities and the presence or absence of fever is not reported. Ultrasound showed cholelithiasis but no evidence of dilated biliary

ducts. Serology for the hepatitis viruses were reported to be negative. No markers of autoimmune hepatitis were reported but it is unlikely that the abnormalities were a result of AIH in this older man.. The patient did report taking St Johns Wort and fern before each episode of abnormality.

Comment: The patient developed 2 episodes of transient increases in liver chemistries, the first characterized by an elevation especially of the alkaline phosphatase value as well as of the serum bilirubin, and the second by mild increases in the ALT and ALP and an increase in serum bilirubin. Given the past history of gall stones for which surgery was recommended but was not done because of patient refusal, the likeliest diagnosis in this patient remains that of biliary tree disease. This is particularly so for the first episode during which ALP values increased and recovery occurred even though the drug treatment continued. The ALP during the second episode was only mildly increased which may give credence to another cause for the abnormality but, in my opinion, could still represent passage of a small stone. Thus, while DILI cannot be absolutely ruled out, the likelihood is extremely low that the study drug was responsible for the liver dysfunction.

D1690C00005-7002-4: 60 year old Asian female treated with the study drug. Develops abdominal pain, fatigue and anorexia, but without specifying the date. Ultrasound reveals small stone with sludge in distal common bile duct. The patient had multiple tests for liver chemistries during treatment and even before starting the test drug, all of which were normal. On day 278 of treatment, all liver chemistries were still normal. At the time of the next test, on day 334, the ALT was 732, the AST was 842, the ALP was 206, and the serum bilirubin 4.0. She undergoes ERCP with unsuccessful effort to remove stone, so stent is inserted with surgery planned for the future. By day 351, all liver-related biochemical values have returned to normal. There is no mention of whether the drug was stopped.

Comment: Based on what is reported, it appears that the patient develops jaundice because of extrahepatic biliary obstruction and not because of drug induced liver injury.

D1690C00006-1511-6: 61 year old white female with type 2 diabetes and diabetic complications started on study drug. Has a history of “biliary colic” with planned cholecystectomy. Preoperative liver tests all normal with the exception of an increase value for ALP (291). Ultrasound revealed cholelithiasis and fatty liver. Treatment temporarily discontinued and laparoscopic cholecystectomy performed revealing a gall bladder filled with stones. Post surgery, developed transient increases in amino-transferases and serum bilirubin. Study drug discontinued again for a few days and then re-started without further problems.

Comment: The cause of the liver dysfunction, which is only minimally described here, is almost certainly cholelithiasis and post-cholecystectomy liver dysfunction. Clearly, there is no evidence of drug-induced liver injury.

D1690C00006-2004-6: 61 year old white male begun on study drug. Concomitant medications included atorvastatin, amlodipine, irbesartan, acetylsalicylic acid, acetaminophen, chlorquinaldol, dexamethasone, hydrochlorothiazide and omeprazole. Began to lose weight on about day 97 and on day 112, developed jaundice and asthenia. Work up (not specified) revealed evidence of pancreatic cancer with hepatic metastases. Peak ALT 191, peak AST 153, peak bilirubin 31.6. ALP not reported. Study drug stopped. Patient died on day 159.

Comment: Diagnosis: Pancreatic cancer with hepatic metastases.

D1690C00012-403-1: 52 year old white male with type 2 diabetes and onychomycosis started on study drug. Concomitant drugs are itraconazole, intapamide, atenolol, ramapril, multivitamins. Also received metformin. Baseline ALT slightly elevated but bilirubin value normal. Day 29, ALT 79, AST 108, total bilirubin 1.7. On days 57, 64 and 78, ALT values 155, 187, and 150, respectively; AST values 89, 128, and 93, respectively; and total bilirubin 2.0, 1.4, and 2.2, respectively. Thereafter, values decreased slightly but remained abnormal. Investigator thought that itraconazole was responsible for the liver dysfunction. Study drug discontinued on day 91 and on day 122, the adverse event said to be resolved. No report on hepatitis serology or AIH markers. No imaging reported and no further data available.

Comment: Cannot determine cause for liver dysfunction because of paucity of data; need sequential liver tests; need evidence that the patient was evaluated for all other possible etiologies, i.e. hepatitis serologies, autoimmune markers; need to have display of all drugs received with start and stop dates for each relative to the onset of abnormal liver tests. In sum, there are insufficient data available to either rule in or rule out drug-induced liver disease and, if so, which drug.

MB102030-9-92: 60 year old white male started on study drug. Concomitant drugs include pioglitazone, allopurinol, valsartan, apap/hycod, hydromorphone, ibuprofen, acetylsalicylic acid, ondansetron, multivitamins. 164 days after starting study drug, the patient was admitted to hospital complaining of right upper quadrant pain, anorexia, nausea and vomiting. On admission, he was afebrile but had tachycardia. Physical examination revealed a soft, moderately tender right upper quadrant and epigastrium. At this time, his AST was 240, ALT 139, ALP 120 and bilirubin 2.0. Clearly, the working diagnosis was possible biliary tree disease, such as gallstones, but imaging was unrevealing although there was concern that the picture was obscured by bowel gas. Over the next 3-5 days, the aminotransferase values began to decline although the serum bilirubin increased, peaking at 7.6 on day 165. His ALP remained normal. By day 175, all values had returned to normal. Importantly, his WBC remained normal although he did develop a transient fever. Hepatitis serology tests were said to be normal. A HIDA scan was performed and was unrevealing. Also, an ERCP was planned but was not carried out. Finally, he had an MRCP scan which raised the suspicion of a gall stone at

the gallbladder neck without obvious calculi in the common bile duct. The symptoms and elevated biochemical values subsided and were apparently normal within 10 days.

Comment: The likely diagnosis in this patient with abrupt onset of RUQ pain, nausea and vomiting, the late development of fever, and RUQ tenderness on abdominal palpation, is acute partial gallstone obstruction. Furthermore, this diagnosis is supported by finding a “suspicion” of a gallstone on MRCP.

FDA adjudication of the remaining 27 patients randomized to dapagliflozin and identified by the sponsor as potential liver toxicity cases is provided in Table 2 on the following page. This table includes CDER adjudication for causality and includes 2 cases whose treatment arm remained blinded as of the date of the Hepatic Adjudication Report (14 April 2011). A brief description and assessment of each of these cases is included in this document (ADDENDUM).

Table 2. Reformulation of Table 3.1 from sponsor’s Hepatic Adjudication Review identified by the sponsor as cases of potential liver toxicity other than potential Hy’s Law severity with FDA causality.			
	Injury category	ID	Causality per CDER
Dapagliflozin treated			
9	Other Liver	D1690C00004-3104-4	Not DILI
10	Other Liver	D1690C00004-4919-3	Not DILI
11	Other Liver	D1690C00004-5419-9	Not DILI
12	Other Liver	D1690C00005-2003-3	Adaptation
13	Other Liver	D1690C00005-4010-3	Possible DILI – not dapagliflozin
14	Other Liver	D1690C00005-6032-25	Unlikely
15	Other Liver	D1690C00006-1101-10	Not DILI
16	Other Liver	D1690C00006-1219-13	Not DILI
17	Other Liver	D1690C00006-1812-18	Insufficient data
18	Other Liver	D1690C00006-2202-7	No evidence of liver injury
19	Other Liver	D1690C00006-2203-7	Not DILI
20	Other Liver	D1690C00012-304-6	Not DILI
21	Other Liver	MB102008-76-149	Not DILI
22	Other Liver	MB102013-28-542	Not DILI
23	Other Liver	MB102013-52-188	Unlikely
24	Other Liver	MB102013-87-179	Unlikely
25	Other Liver	MB102013-96-136	Unlikely
26	Other Liver	MB102014-16-11	Unlikely
27	Other Liver	MB102014-43-75	Unlikely
28	Other Liver	MB102029-4-276	Unlikely
29	Other Liver	MB102029-88-538	Not DILI
30	Other Liver	MB102029-89-338	Unlikely

31	Other Liver	MB102030-90-706	Unlikely
32	Other Liver	MB102032-67-399	Unlikely
33	Other Liver	MB102034-83-764	Unlikely
34	Other Liver	MB102-034-143-763	Not DILI
35	Other Liver	MB102-034-156-775	Not DILI
Treatment Arm Blinded			
36	Other Liver	D1690C00018-6710-4	Not DILI
37	Other Liver	D1690C00018-7835-7	Possible DILI – not dapagliflozin

DISCUSSION

After review of 37 cases of liver injury from the dapagliflozin clinical development program, it appears that based on currently available data there is one Hy’s law case in which a causal association with dapagliflozin is “Probable.” Although there are a number of cases in which information to help make a diagnosis and causality assessment is lacking, the abnormalities identified were by and large quite mild. Follow-up information with the sponsor may be useful to make a disposition concerning causality for some of these cases.

Assessing the likelihood of hepatotoxicity is a difficult problem and in general is based on identifying liver dysfunction that develops within a few days to up to six months after starting a drug that does not appear to be a result of other conditions that cause liver disease and that may mimic drug-induced liver disease (DILI). Thus it can be viewed as a “diagnosis of exclusion.” Accordingly, this requires that in clinical trials when liver injury is observed, as outlined in the CDER Guidance document, all other conditions that can mimic DILI are sought and excluded. Even after concluding that DILI is the probable cause after excluding potentially competing causes, identifying the specific drug, herbal, or dietary supplement can be challenging if, in fact, more than one or even numerous products are being received. Selecting a specific product takes into account an appropriate temporal relationship between the start of the drug and the first identification of possible liver disease (based generally on the development of increased serum enzymes or bilirubin levels or on appropriate symptoms) as well as considering the past history of the drug with regard to its potential for causing hepatotoxicity. The latter, of course, is not relevant if the drug in question is currently in development. Finally, given the fact that a diagnosis of DILI is rarely certain since there is no specific biomarker that permits a definitive diagnosis of DILI, and thus there are subjective differences in attempting to make the diagnosis, efforts have gone into developing grading systems of likelihood of the diagnosis.

For the present analysis, a major problem in regard to assessment for potential DILI for some of the cases was the paucity or complete absence of data that would permit reaching a reasonable diagnosis of the liver injury, whether DILI or another definable cause.

CONCLUSION

In total, approximately 3,000 individuals with T2DM have been exposed to dapagliflozin (2.5 mg or higher) for over 6 months and 2000 subjects were exposed to the 10 mg dose in the Phase 2b and 3 clinical program. The average duration of observation in dapagliflozin arms was 341 days and 316 days in control arms. Based on data available at this time and the size of the exposure population in the development program, one case consistent with Hy's law has been identified in association with dapagliflozin. In this review, an analysis of protocols for the monitoring of serum liver biochemistry values and study protocol adherence has not been performed. Moreover, any potential impact of study subject drop-outs and loss to follow-up has not been analyzed in this review. There are a number of other cases that lack sufficient data to link them to treatment with dapagliflozin. There are also cases of limited serum ALT elevation identified by the sponsor and assessed as probably caused by dapagliflozin by the sponsor's Independent Adjudication Committee for Adverse Hepatic Events. Although there is no imbalance in hepatic events between dapagliflozin and control arms per the sponsor's analysis (and reproduced herein in the Appendix as Tables 3 and 4), because of the importance of recognizing sentinel cases of DILI in registrational trials as outlined in the 2009 pre-marketing guidance⁸ it is prudent to gather more information on all relevant cases as part of an in-depth review of the dapagliflozin NDA in order to assess whether this agent may be hepatotoxic. As further clinical studies are performed, careful serum and clinical monitoring of dapagliflozin study subjects should be preformed to definitively determine whether this agent is associated with risk to cause clinically serious DILI.

⁸ Guidance for Industry – Drug-Induced Liver Injury: Premarketing Evaluation. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

APPENDIX

Table 3. Proportion of Subjects with Elevated Serum Aminotransferases – Short-term and Long-term Treatment Period – All Dapagliflozin Phase 2b and 3 Pool Treated Subjects. Adapted from Table 84 in Sponsor’s Summary of Clinical Safety (Report date 30-Nov-2010)		
	Dapa arms (N=4287)	Control arms (N=1941)
	n / N (%)	n / N (%)
Total subjects with “elevated liver tests” as defined by the sponsor	206 / 4258 (4.8)	85 / 1922 (4.4)
AST elevation		
> 3X ULN	38 / 4258 (0.9)	16 / 1922 (0.8)
> 5X ULN	11 / 4258 (0.3)	8 / 1922 (0.4)
> 10X ULN	5 / 4258 (0.1)	3 / 1922 (0.2)
>20X ULN	4 / 4258 (0.1)	0 / 1922 (0)
ALT elevation		
> 3X ULN	61 / 4258 (1.4)	28 / 1922 (1.5)
> 5X ULN	17 / 4258 (0.4)	9 / 1922 (0.5)
> 10X ULN	4 / 4258 (0.1)	3 / 1922 (0.2)
>20X ULN	2 / 4258 (<0.1)	1 / 1922 (0.1)
AST or ALT elevation		
> 3X ULN	73 / 4258 (1.7)	33 / 1922 (1.7)
> 5X ULN	19 / 4258 (0.4)	12 / 1922 (0.6)
> 10X ULN	5 / 4258 (0.1)	5 / 1922 (0.3)
>20X ULN	4 / 4258 (0.1)	1 / 1922 (0.1)

Table 4. Proportion of Subjects with Elevated Serum Bilirubin with and without Concurrent Elevations of Serum Aminotransferases – Short-term and Long-term Treatment Period – All Dapagliflozin Phase 2b and 3 Pool Treated Subjects. Adapted from Table 84 in Sponsor’s Summary of Clinical Safety (Report date 30-Nov-2010)		
	Dapa arms (N=4287)	Control arms (N=1941)
	n / N (%)	n / N (%)
Total Bilirubin Elevation		
> 1.5X ULN	55 / 4258 (1.3)	18 / 1921 (0.9)
>2X ULN	18 / 4258 (0.4)	5 / 1921 (0.3)
AST or ALT > 3X ULN and Total Bilirubin > 1.5X ULN: window = +/- 14 days	8 / 4258 (0.2)	4 / 1921 (0.2)
AST or ALT > 3X ULN and Total Bilirubin > 2X ULN: window = +/- 14 days	5 / 4258 (0.1)	3 / 1921 (0.2)
AST or ALT > 3X ULN and Total Bilirubin > 1.5X ULN and AlkPhos < 2X ULN: window = +/- 14 days	3 / 4258 (0.1)	2 / 1921 (0.1)

ADDENDUM

D1690C0004-3104-4: 63 year man, apparently a heavy alcoholic, develops “hepatic failure” on “study day 58, 45 days after study medication was discontinued days after stopping the test drug”. He was somnolent and rectal examination revealed melena. His ALT was 794, AST 1604, and bilirubin 51 μ mol. An abdominal scan showed a markedly enlarged liver with possible metastases. He dies the next day. Autopsy: Primary small cell lung cancer with widespread liver metastases.

Comment: Not drug-induced liver injury

D1690C00004-4919-13: 71 year old man develops coagulation defect on day 16. Day 35 found to have increased AST and ALT (both 123). No bilirubin reported. Withdrawn from study because of renal failure. Sonography reported to show cirrhosis. Hepatitis markers all negative, ANA 1:320. ALT back to normal days 46 and 57.

Comment: No evidence of drug-induced liver injury. There are insufficient data to explain transient increase in ALT and AST.

D1690C0004-5419-9: 52 year old man, discontinued from study medication on day 20 because of severe abdominal pain, nausea and vomiting. No liver-related biochemical tests shown. CT scan shows evidence of liver abscess and diverticulitis; the abscess was aspirated.

Comment: Diagnosis is diverticulitis with liver abscess soon after starting study with normal baseline liver chemistries.

D1690C00005-2003-3: 70 year old female with a BMI of 29. Day 225 found to have asymptomatic elevation in liver chemistries (ALT 511, AST 940, ALP 139, bilirubin 1.5). No follow-up values reported. Hepatitis serology was said to be negative. Study drug was discontinued on day 228 for two weeks and values returned to normal. Drug started again day 245 and liver tests reported to remain normal (values not shown). No other cause for abnormalities reported.

Comment: Cause of abnormalities uncertain because of sparse data. Drug induced liver injury may be considered unlikely in view of a negative re-challenge. However, since there is no other obvious cause for the raised enzymes, and there is a temporal relationship between receipt of the drug and evidence of liver dysfunction, drug-induced liver injury cannot be completely exonerated because of the possibility of drug adaptation. Nevertheless, drug-induced liver injury is only a low possibility.

D1690C00005-4010-3: 59 year old man had a “mild” automobile accident on day 105 of study treatment. Had cervical sprain and on day 272, started on loxoprofen, eperisone, rebamipide, azelastin. Six days later developed ALT 5 x ULN. No other values reported. Investigator implicated the new medication (without specifying which one) and stopped the medications on day 277. A week later, ALT fell to 1.4 x ULN and remained at 1.1 x ULN when subject completed the study. No hepatitis or autoimmune serology reported.

Comment: Reported data insufficient to reach a definitive diagnosis for what appears to have been a transient elevation in ALT values without indicating results of other liver-related chemistries. The investigator suggests the possibility of drug-induced liver injury because of resolution of abnormal values after discontinuing the “medications for cervical sprain” without indicating which one. However, the reported incomplete data suggest that the test medication was continued without causing liver dysfunction that suggests it could not have been responsible for the liver dysfunction.

D1690C00005-6032-25: 54 year old female. No information other than that an adverse event developed that resolved when the drug was discontinued. Further, no other data supplied except for mention of an ALT of 52 and an AST of 21. Upper limits of normal not stated. Patient was hospitalized from day 35 to 44.

Comment: Data completely insufficient to reach any diagnostic conclusion. No evidence of drug-induced liver injury, however.

D1690C00006-1101-10: 70 year old man with a history of cholecystitis, status post-cholecystectomy. No laboratory data shown. Stated that “event of moderate pancreatic neoplasm started on day 85.” Hospitalized day 97. Developed RUQ pain, anorexia and weight loss; CT demonstrated tumor at head of pancreas. Study drug discontinued. Discharged from hospital day 109 not fully recovered.

Comment: Apparent diagnosis is pancreatic cancer and not drug-induced liver injury.

D1690C00006-1219-13: 63 year old obese male treated with study drug until day 138 which was discontinued because of planned elective cardiac surgery for aortic valve replacement and coronary artery bypass surgery. Had “pulmonary laceration” and developed aortic dissection. Developed acute hypotension and renal and hepatic insufficiency and died a day later. No laboratory values reported.

Comment: Diagnosis of “hepatic insufficiency” a result of apparent complications during cardiac surgery, presumably acute hypotension in addition to “cardiogenic hepatopathy.” Clearly not drug-induced liver injury.

D1690C00006-1812-18: 59 year old female with normal ALT values through 365 days of treatment, develops a spike in the ALT value to 351 (no other labs shown) on day 456 (all values before that time were normal), which falls to 75 on day 462, returning to normal on day 537, the time of next testing. She remains asymptomatic. No further information and no comment on potential etiology. Also, no mention of whether the test drug was discontinued.

Comment: There are insufficient data to draw any conclusions. If the use of the test drug was continued, the abnormality would not be attributed to the test drug.

D1690C00006-2202-7: 64 year old obese male develops increased level of serum creatinine on day 233 of treatment. Creatinine remained elevated through day 446. No liver tests reported. Patient withdrew from study.

Comment: No report of liver dysfunction and therefore not drug induced liver injury.

D1690C00006-2203-7: 59 year old obese male diagnosed with liver cancer on day 42, etiology undefined because most potential etiologies were excluded. Left study day 85 and died the same day. No laboratory values shown.

Comment: Not drug-induced liver injury.

D1690C00012-304-6: 72 year old male with COPD and numerous other pathological conditions including tachyarrhythmia, develops pneumonia on study day 64. Treated with antibiotics and low MW heparin, Develops atrial fibrillation with tachycardia. Transferred to ICU where he develops sudden massive and unmanageable upper GI bleeding and dies. Autopsy reveals a large liver but histology not reported. Varices identified. No history of liver disease. Live-related biochemical tests (not shown) reported to be normal.

Comment: Death due to massive upper GI bleeding from varices and not due to drug-induced liver injury.

MB102008-76-149: 60 year old male developed a single set of abnormal chemistries on study day 32 (ALT 346; AST 364, bilirubin 1.7, ALP 117). Values before were quite normal, the ALT remained slightly elevated on day 27, and all returned to normal thereafter. Bilirubin values were always a little elevated but fractionated values were not reported so it is unknown whether the patient had Gilbert's disease. Treatment was not discontinued.

Comment: Data reported insufficient to establish cause for sudden transient increase in aminotransferase levels. Could conceivably be a mix-up in blood sample. No etiology advanced. Presumably not drug-induced liver injury.

MB102013-28-542: 43 year old male develops a dramatic increase in CPK and an AST of 229 on day 115, the values returning to normal at the next testing, day 124. Worked up for an MI that was ruled out. Was not on any other pertinent medication and had no muscle cramping or pain. Was this also a miss-labeled blood sample?

Comment: Diagnosis unknown but not drug-induced liver injury.

MB102013-52-188: 32 year old female with mild liver test abnormalities present before starting the study (ALT 99, AST 62, ALP 89, Bili 0.4). Similarly at baseline, abnormalities were present in the same range (ALT 92, AST 34, ALP 89, Bili 0.5). No explanation offered for the cause of these persisting abnormalities including no hepatitis serology. On day 110, the ALT increases into the 100s (ALT 124) with a slight increase in the AST from baseline (AST 52). Thereafter, the ALT value fluctuates but remains well above 100, increasing to 190 with an AST value of 82 on day 536, peaking on day 551 at an ALT of 273. At no time was there an increase in serum bilirubin. The drug was discontinued on day 563 and the last value recorded for the ALT on day 564 was 239. Incredibly, no information is provided with regard to the etiology of the persisting liver dysfunction – could this be, for example, chronic hepatitis C? One might wonder why this patient with abnormalities to begin with, was entered into this trial.

Comment: Clearly this patient had pre-existing chronic liver disease of undetermined etiology. The late doubling of the ALT value also remains undetermined; conceivably it might be a consequence of a flare of the underlying chronic liver disease or perhaps worsening as a result of the drug. Hepatitis serology is clearly needed. In my view, this is more likely to be a flare of underlying chronic liver disease, but superimposed acute drug injury cannot be entirely excluded in the absence of additional information. Still, I would consider drug induced liver injury superimposed upon underlying chronic liver disease a very low possibility

MB102013-87-179: 53 year old female develops a sudden elevation in the aminotransferases values (actual value not reported but graphic display indicates that the ALT increased to a little over 300 and the AST increased to approximately 150), falling considerably when tested 10 days later and then shortly thereafter, returning to normal. Study drug was discontinued on day 176 and then re-started on day 183 but no further abnormalities developed despite apparent continued treatment (description difficult to understand).

Comment: Cause for the sudden transient increase in serum aminotransferase values not apparent because either it was not sought or simply not commented upon. The likelihood

of drug-induced liver injury is remote to unlikely given the fact that r-challenge did not recreate the abnormality.

MB102013-96-136: 58 year old female who started with a slight increase in the ALP level (161), a slight increase in the ALT (60) and normal AST and bilirubin values. On day 265, there was a single increase in values (ALT 107, AST 45 with normal ALP and bilirubin) that was back to normal at the next reported testing, day 351. On day 628, a second increase occurred (ALT 200, AST 156, ALP 135, bilirubin 1.3), the ALT returning to near normal on day 631. There were no associated symptoms. The drug was withheld for 3 days and on observing the reduction in the ALT, was re-started and continued until day 720 without further elevations.

Comment: Like the previous case, the cause for a single increase in liver tests remains unclear, but in the absence of evidence of recurrence of abnormalities with re-challenge, drug induced liver injury is unlikely.

MB102014-16-11: 55 year old female with pre-treatment elevated ALT of 50 (AST 35), and baseline ALT of 99 (AST 62). The patient continued to have persistent mild and fluctuating elevations in ALT and occasionally in AST. The drug was stopped on day 43 because of very slight worsening of the ALT value. No cause for these abnormalities is offered. No comment of whether screening was performed for viral hepatitis or AIH serology.

Comment: Precise cause for persistent ALT elevation unknown – could this be fatty liver disease? Almost certainly not drug-induced liver injury.

MB102014-43-75: 56 year old female with slightly elevated ALT and AST at baseline. First test reported is at day 148 when her ALT is 230, AST 120 with no other data reported. No report of seeking hepatitis or AIH serologies. Raised serum enzymes, particularly ALT, persist until day 184. The next set of values is on day 260 when enzymes are normal. No data reported on serum bilirubin. Patient is on multiple drugs.

Comment: Cause of abnormalities completely unknown; no evidence of workup for etiology. Therefore, until a definitive etiology can be identified, drug induced liver injury cannot be completely excluded. Thus, drug-induced liver injury a low possibility.

MB102029-4-276: 83 year old man with a complicated medical history. Patient started with normal liver chemistries until day 173 of treatment when he was found to have an ALT of 419, an AST of 355, an ALP of 355 and a serum bilirubin of 1.0 (double the earlier values). By day 175, his ALT was 444, AST 320, ALP 410, and bilirubin 1.0. The next set of values, on day 197, showed a marked reduction in both aminotransferase values (both down to 63) but an increase in both the ALP, to 445, and the bilirubin, to

8.9. Thereafter, the aminotransferases stayed at a moderately increased level but the ALP and bilirubin remained quite elevated finally returning to normal by day 372, following which aminotransferases showed fluctuating increases, staying abnormal until the last value reported; this suggests possible evolution to chronic hepatitis. The patient was without symptoms when the event began. The test drug as well as pravastatin and nicotinic acid were discontinued when the first abnormalities were noted. Serologic tests for hepatitis A, B and C were all negative. The obstructive pattern of liver chemistries obviously prompted evaluation for causes of obstructive jaundice. Ultrasonography demonstrated slight hepatomegaly. An MRI showed intra-hepatic duct dilatation with normal sized common bile duct and no obvious mass. An ERCP was then performed showing stricture of the common hepatic duct at the bifurcation suggestive of cholangiosarcoma. Cytologic brushings, however, were negative for malignancy. He had an elevated CA-19.9 and an elevated CEA. On day 276, patient developed a urinary tract infection and on day 277, developed acute congestive failure as a consequence of an acute MI. The patient was said to be stable but the last value reported shows a second increase in the AP from a previous level of 132 to 404 and an increase in bilirubin from 0.7 to 2.9. The narrative does not mention this.

Comment: The overall data regarding liver disease points to an obstructive pattern, most likely some cause for extrahepatic obstruction. The earlier return to normal values had lowered the likelihood of a malignancy, but the apparent recurrence of obstruction at the last report is disturbing and once again raises the possibility of a malignant process. Drug induced liver injury seems unlikely.

MB102029-88-538: 62 year old female. Extremely short narrative does not mention abnormal liver chemistries or any evidence for liver disease whatsoever. Only issue reported is painful defecation and abdominal pain.

Comment: Not drug-induced liver injury.

MB102029-89-338: 77 year old female with initial normal liver chemistries develops an ALT value of 212 on day 156, falling to 106 on day 167, to 88 on day 170, returning to normal on day 199. Other than ALP value that remained normal throughout, no other values are shown although there is mention of a normal AST value on the first day of an abnormal ALT. No mention of a specific evaluation of the abnormality. Study medication was discontinued on day 165 and was re-started on day 170. Thereafter, serum enzymes remained normal suggesting a negative re-challenge.

Comment: Information too sparse to define etiology. However, drug-induced liver injury seems unlikely in view of a negative re-challenge.

MB102030-90-706: 60 year old white female treated with test drug. Two weeks before starting treatment and for 259 day while on treatment, the patients had completely normal

liver-related biochemical tests. On day 345 of treatment, she is reported to have developed upper abdominal pain and “cholelithiasis.” At the same time, she was found to have liver test abnormalities: ALT 805, AST 941, ALP 306, bilirubin 1.4. Follow-up on day 351, representing the only additional set of chemistries, displays an ALT of 102, a normal AST value (20) and a normal bilirubin value (0.3) with a falling ALP (170). Absolutely no other information is supplied (i.e. no viral hepatitis and AIH serology, the absence or presence of fever and/or leucocytosis, imaging studies for potential gall stones in the gallbladder or dilated bile ducts, a history of cholelithiasis, etc.). Also, no information is presented regarding whether or not the test medication was discontinued and what other drugs might have been given the patient. Therefore, a potential diagnosis has to be inferred on the background of extremely skimpy data.

Comment: Based on data made available, I infer that the patient’s abnormal liver chemistries were probably due to biliary tree disease, perhaps the passing of a gallstone, based on a history of upper abdominal pain, the development of relatively short-lived serum enzyme elevations, particularly of the ALP, the slight elevation of serum bilirubin, and the fact that the patient’s upper abdominal pain resolved 2 days after its initiation. I think that, despite the lack of serologic markers, it is unlikely that viral hepatitis or autoimmune hepatitis were responsible for this short lived abnormality. I believe that drug induced liver injury is unlikely.

MB102031-67-399: 50 year old female from India develops an ALT of 224, an AST of 165, and ALP of 223 with a normal serum bilirubin on day 14 of study treatment. The test drug was withheld on day 19. On day 20, the ALT is 82 and the AST is near normal. All values return to normal by day 26. Tests for hepatitis B and C were negative. The patient had developed fever, weakness and myalgias and a chest X-ray revealed findings suggestive of TB. The test drug was restarted on day 25 and treatment for TB was begun. Despite continued treatment with the test drug, serum enzymes remained normal.

Comment: Unclear what the cause was for the transient biochemical dysfunction but may somehow be related to the acute onset of TB. Given the fact of a negative re-challenge with the study drug, drug-induced liver injury is unlikely.

MB102034-83-764: 47 year old female with a past history of abnormal amino-transferases and which are slightly abnormal up to the time of starting study drug. However, they are normal as the study begins, the ALT rising to 52 and the AST rising to 48 on day 15. Serum bilirubin values are normal. On day 32, ALT is now 112 and the AST is 165 with a normal bilirubin, The next and last set of values reported, on day 43, still show abnormal values for ALT and AST although a little less so. The investigator therefore stops medication on day 57. No further information.

Comment: The basis for the pre-existing abnormal chemistries is not reported and could be a result of fatty liver disease or treatment with statins. The cause for the later abnormalities is also not defined and there are no follow-up data to determine whether

withdrawal of the drug was followed by dechallenge. Too little information supplied to define the cause for the abnormalities, but drug induced liver injury cannot be entirely excluded.

MB102034-143-763: 46 year old male with normal bilirubin value prior to starting treatment. On day 1, his bilirubin level was found to be 2.1 with all serum enzymes normal. Bilirubin not fractionated. Patient had no symptoms. Screening serologies for hepatitis B and C all negative. Treatment was discontinued on day, stated to be “due to the event.” Bilirubin said to normalize on day 6.

Comment: Not drug induced liver injury. Patient presumably has Gilbert’s syndrome.

MB102034-156-775: 52 year old female had mild elevation of serum enzymes at baseline (ALT 49, AST 40, ALP 137). During treatment, developed fever, vomiting, cramps and diarrhea on day 27; no changes in liver chemistries at the time. Admitted to the hospital diagnosed as gastroenteritis and dehydration. Given IV fluids and anti-emetics and was discharged from hospital within 24 hours. Diarrhea resolved day 38. Baseline hepatitis B and C both negative. Slight increase in serum enzymes occurred on day 59 (ALT 68, AST 110 with normal ALP and bilirubin). Levels back to normal 1 week later but study drug discontinued on day 63. Patient was receiving a statin drug.

Comment: No etiology for abnormal aminotransferases (mostly mild) offered. This is not drug induced liver injury. Could be due to statin use or fatty liver disease.

D1690C00018-6710-94 (Blinded to treatment arm): 66 year old man started with normal liver panel tests (ALT 15, AST 15, bili 9 μ mols, ALP 84). At visit 5 (1 week after starting drug), ALT 687, AST 341, ALP 173, LDH 285, bili 10 μ mols. Patient had no symptoms. Three days later, ALT 267, AST 71, AP 155, bili 15 μ mols. Tests for hepatitis A, B, C and EBV all negative as were the AIH markers. Baseline test for HEV negative but HEV IgM was positive on July 13 suggesting that the patient had developed acute hepatitis E infection. Study drug was not interrupted.

Comment: Patient did not have drug induced liver injury but appears to have developed acute hepatitis E. Strangely, this diagnosis was not acknowledged in the case summary.

D1690C00018-7835-07 (Blinded to treatment arm): 55 year old female. Baseline liver chemistries all normal. At visit 7, approximately 2 months after starting study drug, was found to have an ALT of 283, an AST of 288, an ALP of 102 and a normal serum bilirubin value. A week later, her ALT was 192, her AST 80, ALP 120. A week beyond that, her values were still elevated but all returned to normal a week after that and remained normal. Hepatitis serology, A, B, C and EBV were all negative. Results pending were for HEV and AIH markers. The study drug was discontinued when

abnormalities were noted and was re-started about 4 months later without apparent adverse effect on the liver.

The investigator was uncertain of the diagnosis but suggested that it might have been a reaction to azithromycin that was administered because of an URI.

Comment: Drug induced liver injury due to the study drug unlikely but may possibly be due to azithromycin. No recurrence when study drug was re-started.

Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2009
Drug Safety**

Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

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Guidance for Industry¹ Drug-Induced Liver Injury: Premarketing Clinical Evaluation

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug² to cause *severe* liver injury (i.e., irreversible liver failure that is fatal or requires liver transplantation). In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Databases may, however, show evidence or signals of a drug's *potential* for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries. This guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause severe liver injury from signals that do not suggest such a potential. This guidance does not address issues of preclinical evaluation for signals of DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Division of Gastroenterology Products in the Office of New Drugs, the Office of Medical Policy, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

² This guidance uses the term *drug* or *product* to refer to all products, except whole blood and blood components, regulated by CDER and CBER, including vaccines, and uses the term *approval* to refer to both drug approval and biologic licensure.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND: DILI

DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs, including isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate (Temple 2001). Several drugs have not been approved in the United States because European marketing experience revealed their hepatotoxicity (e.g., ibufenac, perhexiline, alpidem). Finally, some drugs were not approved in the United States because premarketing experience provided evidence of the potential for severe DILI (e.g., dilevalol, tasosartan, ximelagatran). Although most significant hepatotoxins have caused predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from injured liver cells without prominent evidence of hepatobiliary obstruction or intrahepatic cholestasis, the pattern of injury can vary. Many drugs cause cholestasis, but in general this condition is reversible after administration of the offending drug has stopped. Cholestatic injuries are less likely to lead to death or transplant, although there have been exceptions.

Drugs cause liver injuries by many different mechanisms. These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain. Therefore, when possible DILI is suspected, it is essential to gather additional clinical and laboratory information necessary for differential diagnosis of the cause. It is important to observe the time course of the injury, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, or C; concomitant use of a hepatotoxic drug or exposure to hepatotoxins; autoimmune or alcoholic hepatitis; biliary tract disorders; and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug. It should be recognized that DILI may occur also in persons with preexisting liver disease as a superimposed problem.

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). Overtly hepatotoxic agents (e.g., carbon tetrachloride, chloroform, methylene chloride) are toxic to anyone receiving a large enough dose, and drugs that cause such predictable and dose-related injury generally are discovered and rejected in preclinical testing. More difficult to detect is toxicity that is not predictable or clearly dose-related that occurs at doses well tolerated by most people, but seems to depend on individual susceptibilities that have not as yet been characterized. Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of ≤ 1 per 10,000, so that a single case of such an event rarely would be found even if several thousand subjects were studied. Severe DILI cases rarely have been seen in drug development programs of significantly hepatotoxic drugs.

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What are often seen during drug development are mild elevations of serum aminotransferases, usually without any symptoms. The problem is that these types of signals can be generated by drugs that are capable of causing severe DILI as well as by drugs that have a low potential for causing severe injury (e.g., aspirin, tacrine, heparin, hydroxyl-methylglutaryl coenzyme A-reductase inhibitors (*statins*)). Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in AT activities in serum reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that can cause hepatocellular injury extensive enough to reduce the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. It is important to identify those drugs as early as possible.

The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and, as noted, generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). One of the few exceptions to these findings is acetaminophen, whose toxicity can be shown in animal models and whose toxicity is clearly dose-related. These reactions thus appear to reflect host factors and individual susceptibility. Consequently, they have been termed *idiosyncratic*, meaning dependent upon the individual person's particular constitution. Whether they are the result of genetic and/or acquired differences has not yet been established, and to date no genetic, metabolic, or other characteristic has been found to reliably predict severe DILI in an individual.

Some severe DILI examples have presented differently from the more commonly seen hepatocellular idiosyncratic type. Perhexiline, an anti-anginal drug marketed in Europe, produced toxicity within months of starting the drug that had the histological appearance of alcoholic cirrhosis (Pessayre and Biachara et al. 1979). Fialuridine caused modest acute liver injury, but most strikingly led to severe metabolic acidosis and multiorgan failure as mitochondrial oxidative capacity was obliterated over a period of months (Kleiner and Gaffey et al. 1997; Semino-Mora and Leon-Monzon et al. 1997). Valproic acid causes hyperammonemic encephalopathy even without notable rises in serum AT activities. Benoxaprofen (Oralflex) induced intrahepatic cholestasis that over many months led to significant, sometimes fatal, liver injury, especially in elderly patients (Taggart and Alderdice 1982).

Past experience indicates that appropriate testing and analysis in premarketing trials can detect drugs that can cause severe hepatocellular injury.

III. SIGNALS OF DILI AND HY'S LAW

Hepatocellular injury (usually detected by serum AT elevations) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin) as well as by drugs

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that do cause such injury. Evidence of hepatocellular injury is thus a necessary, but not sufficient, signal of the potential to cause severe DILI (note, however, that the drugs causing hepatic injury through mitochondrial toxicity may not cause early hepatotoxicity). The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI, because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver *function* accompanying or promptly following evidence of hepatocellular injury (see below).

As noted, a typical NDA or biologics license application (BLA) database usually will not show any cases of severe DILI, even for a drug that can cause such injury, because the rate of severe injury is usually relatively low (1/10,000 or less). Many drugs, however, including both significant hepatotoxins and drugs that do not cause severe liver injury, cause laboratory evidence of mild, transient hepatic injury, with leakage of liver enzymes and the appearance in serum of elevations in AT activities to levels of 3, 5, and sometimes greater than 5 times the upper limits of normal (ULN). Generally, ALT is considered a somewhat more liver-specific aminotransferase enzyme than AST, although it also occurs in many tissues (Green and Flamm 2002). The finding of a higher rate of such elevations in drug-treated subjects than in a control group is a sensitive signal of a potential to cause severe DILI, but it is not a specific signal.

A more specific signal of such potential is a higher rate of more marked peak AT elevations (10x-, 15xULN), with cases of increases to >1,000 U/L causing increased concern. The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). The reason for this now seems clear. Because the liver has a large excess of bilirubin-excreting capacity, injury to hepatocytes sufficient to cause jaundice or even mild hyperbilirubinemia (i.e., a bilirubin >2xULN) represents an extent of liver injury so great that recovery may not be possible in some patients. Zimmerman's observation that hepatocellular injury sufficient to impair bilirubin excretion was ominous has been used at the Food and Drug Administration (FDA) over the years to identify drugs likely to be capable of causing severe liver injury. The observation of the critical importance of altered liver function has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004).

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Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. In all cases to date, the small number of Hy's Law cases has arisen on a background of an increased incidence of more modest signs of hepatocellular injury (e.g., greater incidence of 3xULN elevations in AT than seen in a control group).

Briefly, Hy's Law cases have the following three components:

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

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population. Clinical trials of the beta blocker dilevalol (enantiomer of labetalol, a diastereoisomeric mixture) showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned.

Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of the so-called Hy's Law cases (Temple 2001). This observation was recently confirmed in large studies of DILI in Spain (Andrade and Lucena et al. 2005) and in Sweden (Björnsson and Olsson 2005) in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants.

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing. These examples are described in detail in Appendix A.

Hy's Law cases represent one end of a spectrum of laboratory abnormalities that indicate liver injury. Each of these cases has different sensitivity and specificity as a predictor for the potential for severe liver injury. Although it is not possible to provide precise specificity and sensitivity

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estimates for the various signals, guidance can be provided on use of these major indicators of a potential for severe DILI, as follows:

- **An excess of AT elevations to >3xULN compared to a control group**

AT elevations to >3xULN are relatively common and may be seen in all groups, but an excess of these elevations compared to a control group is nearly always seen for drugs that ultimately prove severely hepatotoxic at relatively high rates (1/10,000). Therefore, the sensitivity of a significantly increased incidence compared to control (e.g., of >3xULN AT elevations) as an indicator of a potential for liver injury is high. But many drugs show this signal without conferring a risk of severe injury (e.g., tacrine, statins, aspirin, heparin), indicating low specificity for an excess of AT elevations alone. There are no good data to predict how great this excess incidence of AT elevations should be compared to controls to suggest an increased risk of DILI. Such an excess may not be apparent for drugs with a potential to cause idiosyncratic DILI that are used for short treatment courses, such as many antibiotics.

- **Marked elevations of AT to 5x-, 10x-, or 20xULN in modest numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group**

Many, but not all, severely hepatotoxic drugs show such elevations, indicating high sensitivity for predicting severe DILI; again, however, some drugs, such as tacrine and others that are not severely hepatotoxic, also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

- **One or more cases of newly elevated total serum bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic (treatment with atazanavir or other drugs) factors), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased incidence of AT elevations >3xULN in the test drug group compared to placebo³**

The sensitivity of this observation appears high for any given incidence rate of severe DILI if enough people are exposed to the drug. For example, if the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 exposed subjects (*Rule of 3*) would be needed to have a 95 percent probability of observing at least one Hy's Law case in the treated population (Rosner 1995).⁴ The specificity of this

³ This constellation of findings is the hallmark of a Hy's Law case. The predictive value of these three findings for a drug's potential to cause DILI may be different if these findings are identified in patients with preexisting liver disease, fatty liver disease such as NASH, chronic hepatitis C or B, or bilirubin metabolism abnormalities (Gilbert syndrome), or in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

⁴ The Rule of 3 is derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in n subjects, and the group is well observed.

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finding appears very high if two or more cases are seen (e.g., dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of the occurrence of false positive Hy's Law findings for a drug that was subsequently found not to cause severe DILI in a larger treatment population. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant risk of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe DILI. The degree of assurance depends on the population exposed for a long enough time, the discontinuation rules used in the protocols, and the true incidence rate of severe DILI.

IV. CLINICAL EVALUATION OF DILI

A. General Considerations

For most drugs in development that reach phase 3 testing, the chances of encountering severe DILI are low. An increased incidence of mild hepatotoxicity (AT elevations) in early trials usually results in heightened screening to detect and evaluate liver injury during phase 3 testing. It is critical, however, to determine whether mild hepatotoxicity reflects a potential for severe DILI or reflects a capacity for only limited injury. To make this distinction, it is important to detect any cases of more severe injury and to examine such cases closely, observing the course and outcome of the injury, and seeking additional information that might identify other causes. The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data. In addition, clinical trials of cellular and gene therapies and of vaccines pose specific challenges related to trial size and design, biodistribution and persistence of vectors, the function and anatomic location of cellular products, and other factors. Applicants are encouraged to discuss these issues with the relevant review division.

1. Patients with Liver Abnormalities or Disease

Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and an effect of the test drug. Patients with acute viral, autoimmune, alcoholic, or other types of hepatitis are unstable and generally not appropriate subjects for clinical trials other than trials of treatments for their acute illness. Patients with stable underlying liver disease can be included cautiously in late-stage clinical trials, but probably not if bilirubin excretory or protein synthetic functions are impaired, unless there is a strong need that they be treated. This implies that diagnostic screening for liver test abnormalities should be conducted before enrolling subjects into trials. Patients with stable liver disease generally should be included in at least some phase 3 trials if they are likely to be treated with the drug if it is marketed. Preexisting liver disease has not been thought to make patients more susceptible to DILI (Zimmerman 1978, 1999), but it may be that a diminished *liver reserve* or the ability to recover could make the consequences of injury worse. This appears to be the case with highly active antiretroviral therapy in patients with chronic viral hepatitis. If the drug

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is intended to be prescribed or marketed to such patients after approval, they should be enrolled in controlled trials.

2. Detection of DILI

Depending on the mechanism underlying DILI, different drugs can be associated with different treatment time/hazard profiles. In many cases, there is a delay of at least a few weeks between initiation of treatment and onset of liver injury. However, for some drugs, rapid onset of injury may occur, sometimes in the presence of a systemic hypersensitivity reaction that can be associated with multi-organ involvement, fever, eosinophilia, and/or rash. In general, early trials of a drug in trial subjects with presumably normal liver function should involve obtaining liver enzyme (ALT, AST, ALP) and bilirubin tests every 2 to 4 weeks, at least for a few months. For drugs being studied with short treatment courses, both baseline and post-treatment liver enzyme testing should be performed, since there may be a gap between the end of treatment and the onset of liver injury. In circumstances when there is a high likelihood that such a drug will be chronically used in an off-label fashion, long-term treatment trials to measure risk for DILI may be warranted.

It is uncertain whether early and nonspecific symptoms (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) precede or follow the first laboratory signs of hepatic injury (rising ALT, AST, or ALP), and the pattern of clinical and laboratory changes may vary with different drugs and recipients. In most cases, however, the first evidence of a problem is the discovery of elevated AT or ALP during routine serial measurements. In longer trials, if there is no sign of liver injury after a reasonable length of exposure (e.g., 3 months), the monitoring interval can be increased to once every 2 to 3 months. Later trials also can use less frequent liver chemistry monitoring if there is no indication of hepatotoxicity in earlier trials.

As previously noted, if symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. Reliance on early symptoms, rather than serum enzyme monitoring, has become the standard for monitoring isoniazid therapy for prophylaxis of tuberculosis and seems to prevent severe liver injury if acted upon promptly by discontinuation of isoniazid (Nolan and Goldberg et al. 1999). Attention to symptoms does not supplant routine periodic assessment of AT, TBL, and ALP in trials of investigational drugs.

3. Confirmation

In general, an increase of serum AT to $>3xULN$ should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to

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follow. The need for prompt repeat testing is especially great if AT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening (see below). If close monitoring is not possible, the drug should be discontinued.

4. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

5. Decision to Stop Drug Administration

It has been observed that *dechallenge* (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen

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overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity). Promptly stopping the offending drug usually is the only potentially effective therapy.

A difficult question is when should the investigational drug be stopped? Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of *functional* impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

6. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

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- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binge exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).
- **Hepatobiliary disorders.** Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.
- **NASH.** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.
- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.
- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

7. *Follow-Up to Resolution*

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

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8. *Rechallenge*

Whether or not to rechallenge a subject who showed mild DILI is a difficult decision. Reexposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with reexposure. Rechallenge may not be considered *negative* unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A *negative rechallenge* does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of rechallenge to verify drug causation would give a false negative result.

Generally, rechallenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.

B. Research Opportunities

It is not known why only a few people show severe DILI in response to a hepatotoxic drug while others show nothing or seem to adapt. The current thinking is that both genetic and acquired factors may be important in determining the susceptibility to injury. Close observation provides a major opportunity to gather and store serial samples of blood and urine, to investigate characteristics of subjects who show evidence of mild or severe DILI, and to see how they differ from each other and from people who do not show any effects despite being similar in age, sex, and drug exposure. These serial samples can be studied by genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons.

As part of the Critical Path Initiative,⁵ the FDA is working with industry, academia, and other experts to broaden its understanding of the biochemical and genetic bases of DILI. It is hoped that predictive bioassays and biomarkers can be identified through analysis of systematically collected biospecimens that will help determine which patients are most likely to suffer liver injury from specific compounds. If tests that identify people susceptible to severe DILI can be developed, a drug that is hepatotoxic to them could remain available to other people who are not susceptible to severe DILI.

In addition, identification of common genotypic characteristics among patients experiencing DILI in response to one or more class-related hepatotoxic drugs might permit the development of

⁵ See <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>.

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in vitro or ex vivo tests or genetically altered animal strains that can be used to better predict serious hepatotoxic potential, or the lack thereof, of new drugs belonging to the same or closely related classes.

C. Case Report Forms

Because DILI has resulted in the marketing withdrawal or cessation of development of many drugs, every clinical trial should include case report form pages specifically designed to capture information pertinent to the evaluation of treatment-emergent liver abnormalities. In addition to collecting information on laboratory abnormalities, clinical symptoms, and the potential cause of any hepatic illness, case report forms and narratives should include the following information for cases in which liver injury is found (including control subjects with such injury):

- Time and date from start of drug administration to start of illness.
- Time and date of cessation of drug, or interruption of drug administration.
- Complete description of the injury, including systemic symptoms, other organ involvement, rash, fever, and eosinophilia.
- Outcomes such as death, liver transplant, hospitalization, recovery, and treatment for DILI.
- Free text describing the course of illness, including pertinent physical examination findings, such as hepatomegaly, splenomegaly, right-upper quadrant tenderness, the time course of abnormalities of aminotransferases, ALP, TBL with dates of testing, normal ranges, and results for tests done in addition to those specified in the original protocol, and tests done during any unscheduled visits. These additional laboratory test results, including reference ranges, should also become part of the overall database. Supportive tabular and/or graphical display of serial laboratory data is often desirable in addition to narrative information. Pre-study AT values should be sought, which may suggest chronic liver disease and/or an acute process that may have preceded exposure to the investigational drug.
- Risk factors, especially history of alcohol use; risk factors for NASH such as diabetes, obesity, and hypertriglyceridemia, which may prompt ultrasound examination of the liver to detect steatosis.
- All concomitant drugs (dose, start and stop dates, whether they are known to be hepatotoxic, information on rechallenge or dechallenge with drugs with the same or similar structure).
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology; evidence for biliary obstruction; imaging study results; acute alcoholic hepatitis (recent drinking and AST >2xALT are supportive); recent history of severe hypotension or congestive heart failure; other underlying viral disease.
- All supplemental information, including consultation reports, narrative information, and special studies.

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly (i.e., even before all other possible causes of liver injury have been excluded). It should be promptly reported to the FDA before fully working up the patient to rule out other etiologies. Reporting should include all available

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information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

D. Interpretation of Signals of DILI or Acute Liver Failure

1. Frequency and Magnitude of Liver AT Abnormalities

The presence of even a single case of severe liver injury resulting from treatment in the premarketing clinical trials database is a signal of a high level of hepatotoxic risk. More commonly, however, there will be no identifiable cases of severe liver injury, but rather varying degrees of serum AT abnormalities that need to be interpreted. As previously noted, slight abnormalities of this kind (to $<3xULN$) are common in untreated and placebo-treated subjects and are not informative about the potential for the development of severe DILI. Subjects with such abnormalities should be watched.

Therefore, it has become standard practice to look at greater deviations, such as AT values $\geq 3x$ -, $5x$ -, or $10xULN$. Because these abnormalities are often associated with other causes, such as NASH or hepatitis C, they can occur in placebo-treated groups, and it is important to compare their incidence in drug-exposed subject groups to that observed in control groups (i.e., placebo or treatment with products that do not cause elevation of aminotransferases). A significantly increased incidence of AT abnormalities $>3xULN$ is a signal of a potential for severe DILI, but, even though it has high sensitivity, it is not specific. Abnormalities of greater magnitude (e.g., $\geq 10xULN$) are rarely seen spontaneously in placebo arms of clinical trials in most settings. Therefore, greater magnitude AT elevations can be examined in the entire clinical trials database, not just in the controlled trials. Serum AT activity is a relatively volatile measurement, often rising and falling within days. It cannot be concluded from one measurement that a peak value has been seen, so detection of an abnormal rise calls for serial measures to determine which way the abnormality is moving, whether increasing or decreasing.

A number of factors may confound interpretation of AT abnormalities seen in NDA or BLA databases. Although the more extreme AT elevations may be better predictors of toxicity than smaller elevations, close monitoring can affect the magnitude of abnormalities seen if it leads to earlier cessation of drug treatment. In addition, the contribution of drug treatment to an exacerbation of preexisting liver disease or the effects of concomitant hepatotoxic drugs may be difficult to determine. Finally, normalization of abnormalities on continued treatment is not proof that the abnormality was not drug-caused, as it can result from liver adaptation to the drug.

2. Combined Elevations of Aminotransferases and Bilirubin

When AT abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation $>2xULN$), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI. Experience has indicated that the occurrence of even

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one or two well-documented cases of this combination is ominous, indicating a likelihood that the drug will cause severe liver injury.

The absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3 derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in n subjects, and the group is well observed. Thus, if no cases of AT and bilirubin elevations are seen in 3,000 well-observed subjects, it can be concluded with 95 percent confidence that the true rate of such occurrences is not more than 1 per 1,000. This calculation would then suggest a rate of expected severe liver injury ≤ 1 per 10,000 exposed patients, assuming that the rate of severe injury among patients with concomitant AT and TBL elevations is about 10 percent (Andrade and Lucena et al. 2005; Björnsson and Olsson 2005).

E. Analysis of Signals of DILI

Based on the FDA's experience, the following analyses related to liver injury potential should be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can markedly affect the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

2. Assessment of Liver-Related Adverse Events in Controlled Trials

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels seen in subjects in controlled trials with at least one dose of drug exposure. Generally, the analysis should be for pooled data, although trial-to-trial differences may be of interest. Incidence can be given as the number of events per number of subjects exposed, or can incorporate treatment exposure, as the number of events per subject-years of exposure, preferably both. Changes in mean values for groups are not informative. For many drugs, it appears that a minimum duration of exposure is needed before DILI occurs. Therefore, it is useful to describe liver-related adverse events for subjects who have had the minimum duration of exposure (e.g., subjects with at least 1-month exposure). For some drugs, patterns of early injury after initiation of treatment may occur, and for these patients testing intervals should be modified appropriately. Incidences for pooled data should include, but are not limited to:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated TBL to $>2xULN$.
- Any elevations of ALP $>1.5xULN$.
- Elevation of AT ($>3xULN$) accompanied by elevated bilirubin ($>1.5xULN$, $>2xULN$).
- Elevation of AT in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.

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- Possibly liver-related deaths and liver-related treatment discontinuations. These cases should be described and time-to-event analyses should be performed. Follow-up status also should be provided. There should be a description of any histologic and rechallenge data.

All incidences should be calculated separately for drug-, placebo-, and active-controlled groups. Normal ranges for all tests should be provided. Time-to-event analyses for events occurring with increased incidence should be provided (e.g., elevated AT, bilirubin). The contribution of sex, age, risk factors, and drug dose or regimen to the abnormalities seen should be explored.

3. Assessment of Liver-Related Adverse Events in the Entire Clinical Trials Database

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels for the entire clinical trials database, including subjects with exposure of at least one dose of trial drug in phase 1 or phase 2 trials, or in uncontrolled, open label, extension trials. We recommend the same evaluation as for the controlled trials database discussed in section IV.D.2. Time-to-event analyses of events occurring at increased incidence, and rates of death and trial withdrawal in subjects with abnormalities, should be provided. The contribution of sex, age, drug dose or regimen, use of concomitant drugs, and underlying disease to the abnormalities seen should be explored.

4. Assessment of Hy's Law Cases in the Clinical Trials Database

NDA and BLA submissions should include a listing of possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of $>3xULN$, ALP $<2xULN$, and associated with an increase in bilirubin $\geq 2xULN$). A narrative summary for each Hy's Law case should be provided. Narrative summaries should not only provide, in text format, the data that are already presented in the case report tabulation, but also should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing for a better understanding of what the subject experienced. For a narrative summary to be useful, it should contain the following information:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing to exposure
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant drugs with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)
- Time course of serum enzyme and bilirubin elevations (consider tabular and/or graphical display of serial laboratory data)
- A summary of all available clinical information including, if known:
 - Prior or current history of ethanol use
 - Presence of risk factors for NASH (e.g., obesity, diabetes, marked hypertriglyceridemia)

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- Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease, pre-study AT values, if available
- Symptoms and clinical course including follow-up to resolution
- Special studies (i.e., ultrasound, radiologic examinations, liver biopsy results)
- Presence or absence of possible confounders, including concomitant illness, use of concomitant drugs that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of the treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

The availability of liver biopsy, explant, or autopsy slides for pathology review by review staff or external expert consultants has been helpful in the FDA's assessment of Hy's Law cases. Reports of external consultant opinions solicited by the applicant should be provided to the FDA.

Applicants also should provide complete narrative summaries that include the components previously listed for all subjects who died of hepatic illness, or who discontinued trial drugs for hepatotoxicity, including subjects with abnormalities consistent with protocol-specific stopping rules.

In some cases, a drug under consideration in the United States will have been marketed in other countries. In these cases it is important for the applicant to provide a synopsis of the global safety experience and level of usage and to describe in detail all cases of hepatotoxicity observed or suspected.

5. Overall Assessment of a Drug's Potential to Cause DILI

The overall assessment should characterize a drug's potential for DILI and should consider at least the following questions:

- Was liver monitoring sufficiently frequent and thorough to characterize DILI risk?
- Were there any cases of probable severe DILI?
- Were there signals of a potential for DILI (e.g., AT elevations, Hy's Law cases) and how were these signals assessed?
- What doses and durations of exposure were associated with hepatotoxicity signals?
- What approximate incidence of mild, moderate, and severe DILI can be expected postmarketing?
- Is the trial information sufficient to inform an overall risk-benefit assessment?
- Was there sufficient drug exposure (i.e., number of trial subjects and duration of treatment of each trial subject) and adequate liver test monitoring to reliably set an upper boundary for risk of severe DILI after marketing?

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- What rate of severe injury (assuming Hy's Law cases occur at about 10 times the rate of severe injury) has been suggested or has been ruled out (e.g., no Hy's Law cases in 3,000 subjects implies a rate of such cases of $<1/1,000$ and thus a rate of severe DILI of $<1/10,000$)? This consideration should reflect the presence or absence of other signals, such as marked elevations of AT.
- Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it. If so, effectiveness of monitoring, whether by symptoms or laboratory tests, and at what intervals should be discussed, and whether the results justify a monitoring recommendation in product labeling at the time of marketing approval.

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APPENDIX A: ILLUSTRATIVE EXAMPLES OF DILI

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional Letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other effective NSAIDs, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects in the Diabetes Prevention Trial with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The

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second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports of acute liver failure associated with troglitazone use (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999), and four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional Letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003; Graham and Drinkard et al. 2003). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the U.S. market in March 2000, when other drugs in the same class with similar efficacy but little or no evidence of hepatotoxicity became available (i.e., rosiglitazone, pioglitazone).

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed.

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer term trials (more than 35 days) in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months postrandomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the trial on treatment,

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while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients with ximelagatran and 5 of 6,230 patients with comparator. At least 13 of 37 patients in the ximelagatran group had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but in most cases the deaths were not clearly hepatotoxicity-related. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006). Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases, did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients from subsequent liver toxicity, further supporting such an estimate.

Advisory Committee Briefing Document NDA 202-293

Drug: [REDACTED] (dapagliflozin propanediol) tablets

Indication: Improve glycemic control in adults with type 2 diabetes mellitus

Statistical Reviewer: Jonathan D. Norton, Ph.D., Division of Biometrics II

1. EXECUTIVE SUMMARY

The Applicant, Bristol-Myers Squibb, has submitted eleven Phase 3 efficacy and safety studies in support of their New Drug Application for dapagliflozin propanediol as a treatment for type 2 diabetes mellitus. Based on consultation with the medical team leader, I determined that my statistical review would focus primarily on six key clinical trials. Four of these studies were placebo-controlled, and they tested dapagliflozin either as monotherapy (MB102013), or as an add-on therapy to metformin (MB102014), pioglitazone (MB 102030), or insulin (D1690C00006). The fifth study used glipizide as an active control (D1690C00004), with metformin as background therapy. Except for the monotherapy trial, all of the studies randomized patients who had been inadequately controlled by background therapy. Finally, the sixth study tested dapagliflozin as an initial combination with metformin. The primary endpoint in all of these studies was change in HbA1c from baseline. Except for the glipizide-controlled study, which used a 52-week endpoint, the primary endpoint was evaluated at 24 weeks.

I find these studies to provide convincing evidence that dapagliflozin is efficacious for both of the proposed daily doses, 5 mg and 10 mg. In the four placebo-controlled studies (out of the six that I focused on), both the 5 mg and 10 mg doses of dapagliflozin were shown to be superior to the comparator on the primary endpoint, using the planned primary analysis. The active-controlled study showed that titrated doses of dapagliflozin and glipizide yielded quite similar results at Week 52. Although dapagliflozin was statistically non-inferior at Week 52, it should be noted that glipizide was clearly superior at some earlier time points. (See Figure 3 at the end of this report.) Findings for fasting plasma glucose (FPG) also support a finding of efficacy for both doses.

The results in the previous paragraph are based on the planned primary analysis, which used last-observation-carried-forward (LOCF) imputation, disregarding observations recorded after any rescue treatment. While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. In particular, the argument has been made that LOCF can be anti-conservative (i.e., it sometimes favors the alternative hypothesis more than other approaches) and the findings from the placebo-controlled studies that I reviewed bear this out.

The concerns about LOCF make it all the more important to examine the results of the sensitivity analyses. In the monotherapy trial, for example, the Applicant's own analyses showed the effect of the 10 mg dose vs. placebo on HbA1c at Week 24 to be as large as 0.66% or as small as 0.25%. (Note that these are absolute differences in HbA1c.) This disparity is largely based on how one handles the data from the 9 (out of 75) patients in the placebo arm who received rescue treatment. (No patients in the 10 mg arm were rescued.) The largest estimate of the treatment effect was from the LOCF analysis, which assumes that patients who were rescued would have

not gotten any better or worse without rescue. The smallest effect was found by simply excluding patients who had been rescued. The latter approach is clearly disadvantageous to the dapagliflozin arms, because the placebo arm pays no penalty for under-treating patients to the degree that they need rescue.

My own preferred analysis simply uses the observed values of patients who were rescued. This approach may seem counterintuitive if one believes that rescue treatment makes the subsequent outcomes less relevant to evaluation of the test agent. It has the virtue, however, of respecting the intent-to-treat principle, in the sense that the analysis is based on the randomized treatment rather than the treatment actually received (i.e., planned treatment plus rescue). In the case of the monotherapy study, this approach yields an estimated treatment effect of 0.45% (95% confidence interval = [0.19%, 0.72%]) for the 10 mg dose, compared to 0.66% from the LOCF analysis. For the metformin add-on study, this analysis estimates the treatment effect to be 0.44% (95% confidence interval = [0.24%, 0.63%]), compared to 0.54% from LOCF.

Due to time constraints, I have not closely reviewed the other five Phase 3 studies. The Applicant, however, reported results from these studies that broadly support a finding of efficacy for the 5 and 10 mg doses of dapagliflozin. The only Phase 3 trial in which either of these doses was reported to fail on the primary endpoint was Study 2029 in patients with moderate renal impairment.

2. OVERVIEW OF STUDIES

The Applicant submitted eleven Phase 3 efficacy and safety studies which are outlined in Table 1. Based on input from Ilan Irony, M.D., the medical team leader, I determined that my review efforts would be primarily focused on the six studies which are italicized in the table.

Table 1: Phase 3 Studies

Study ID (Short Name)	Population	Test Tx	Background Tx (Rescue)	Comparator(s)
Monotherapy				
<i>MB102013 (2013)</i>	Drug-naïve	DAPA 2.5, 5, 10 mg	None (Metformin)	Placebo
MB102032 (2032)	Drug-naïve	DAPA 1, 2.5, 5 mg	None (Metformin)	Placebo
Add-On				
<i>MB102014 (2014)</i>	Inadequate control on background	DAPA 2.5, 5, 10 mg	Metformin (Pioglitazone or acarbose)	Placebo
D1690C00005 (C00005)	Inadequate control on background	DAPA 2.5, 5, 10 mg	Glimepiride (Metformin or TZD)	Placebo
<i>MB102030 (2030)</i>	Inadequate control on background	DAPA 5, 10 mg	Pioglitazone (Metformin or SU)	Placebo
<i>D1690C00006 (C00006)</i>	Inadequate control on background	DAPA 2.5, 5, 10 mg	Insulin and up to two oral anti-diabetics (Insulin up-titration)	Placebo
<i>D1690C00004 (C00004)</i>	Inadequate control on background	DAPA 2.5, 5, 10 mg (titrated)	Metformin (None)	Glipizide*
D1690C00012 (C00012)	Inadequate control on background	DAPA 10 mg	Metformin (Sitagliptin)	Placebo**
MB102029 (2029)	Moderate renal impairment and inadequate control on stable regime	DAPA 5, 10 mg	Any except metformin (Any except metformin)	Placebo
Initial Combination				
MB102021 (2021)	Drug-naïve with higher HbA1c	DAPA 5 mg + metformin	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 5 mg, Metformin
<i>MB102034 (2034)</i>	Drug-naïve with higher HbA1c	DAPA 10 mg + metformin	None (Pioglitazone, acarbose, or sitagliptin)	DAPA 10 mg, Metformin

Notes: Proposed doses are 5, 10 mg. SU = sulfonylurea, TZD = thiazolidinedione. *Italics = focus of review.*

*Noninferiority comparison; other studies used superiority comparison.

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

Although each study had a slightly different design, I will summarize only the key features. Four of the six studies (2013, 2014, 2030, C00006) were placebo-controlled; note, however, that three

of these studies incorporated background therapy. The fifth study (C00004) used glipizide as an active control, and the sixth (2034) compared the combination of dapagliflozin and metformin to its components. Study C00004 differed from the other studies in basing the primary efficacy analysis on a noninferiority comparison. It also differed in not including rescue therapy.

3. STATISTICAL ISSUES

For all six studies, the primary analysis set consisted of treated subjects who had a baseline and at least one post-baseline value for HbA1c. The primary analysis method was an analysis of covariance (ANCOVA) and used LOCF imputation, excluding observations taken after rescue. FDA has accepted LOCF as the primary imputation method for diabetes studies in the past. In February 2008, FDA issued a draft guidance for industry titled *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*. This draft guidance describes LOCF as “easy to apply and transparent” and states that it will “tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug’s effect.” It also states, however, that additional sensitivity analyses should be conducted and, in particular, different ways of handling rescue medication should be examined. More recently, the National Academy of Sciences released a report on missing data which was commissioned by FDA (National Research Council 2010). The report recommends that, “Single imputation methods like [LOCF] ... should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.” (The report also states that these assumptions will not hold in most circumstances.) In light of this recommendation, it is all the more important to consider alternatives to the prespecified LOCF analysis.

The impact of rescue medication on the analysis merits further discussion. Although rescue therapy is ethically appropriate in some cases, it can complicate statistical inference because it is an additional intervention that occurs after randomization and is not controlled by it. Subjects who received rescue differed from the other subjects in at least two ways. First of all, they experienced the effect of rescue treatment, and this is the effect that one would want adjust for if it were possible. Secondly, they also met glycemic criteria in order to be eligible for rescue. It is not possible to disentangle the effect of rescue from the underlying response to the randomized treatment. If one found, for example, that rescued patients did substantially worse than non-rescued patients, then that could either mean that the rescue treatment was ineffective or that the patients would have had *even worse* outcomes without it. One way around this problem would be to randomize some rescue-eligible patients to receive sham rescue, but this would undermine the ethical purpose of including rescue treatment in the first place.

For the primary analysis, the Applicant excluded observations after a patient was rescued, carrying forward the pre-rescue values. Since eligibility for rescue indicates a lack of efficacy, it is reasonable from a certain standpoint for the imputed value at the end of study to be the poor, pre-rescue value. Note, however, that this is not a reliably conservative (in the sense of favoring the null hypothesis) approach; it will be seen in the next section that it can actually give a relatively optimistic estimate of the treatment effect.

The Applicant also conducted a sensitivity analysis which incorporated rescue treatment as an independent variable in the linear model. I do not believe that this is appropriate due to the

confounding described previously. Instead I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue. This approach is also imperfect, but it comes closer to being a true intent-to-treat (ITT) analysis because it disregards the non-randomized rescue treatment. As it turns out, this more ITT-like analysis of studies 2013 and 2014 did not show a substantial difference from the Applicant’s rescue-adjusted analysis. The results of the sensitivity analyses can be found in Section 4.

4. EFFICACY RESULTS

Primary Efficacy Endpoint – HbA1c

Table 2 shows the results for the primary endpoint for the four placebo-controlled studies (of the six that this review focuses on). The results were statistically-significant ($p < .001$) for both proposed doses (5 mg and 10 mg) in all 4 studies. Despite the varied background therapies in the trials, the estimated effect of a given dose of dapagliflozin on change in HbA1c at Week 24 is fairly consistent. For example, in the 10 mg arm it ranged from -0.54% to -0.66%. These results are from the prespecified primary analysis, which used LOCF imputation and excluded post-rescue data. See Table 6 for the number of treated subjects in each study arm.

Table 2: Change in HbA1c from Baseline at Week 24 (LOCF) by Study and Dose, Placebo-Controlled Studies

Study		Dapagliflozin Dose			
		0 mg	2.5 mg	5 mg	10 mg
2013 (AM dosing)	Adj. Mean	-.23 (.10)	-.58 (.11)	-.77 (.11)	-.89 (.11)
	Diff. vs. Placebo	--	-.35 (.15)*	-.54 (.15)**	-.66 (.15)**
2014	Adj. Mean	-.30 (.07)	-.67 (.07)	-.70 (.07)	-.84 (.07)
	Diff. vs. Placebo	--	-.38 (.10)**	-.41 (.10)**	-.54 (.10)**
2030	Adj. Mean	-.42 (.08)	N.A.	-.82 (.08)	-.97 (.08)
	Diff. vs. Placebo	--	N.A.	-.40 (.12)**	-.55 (.12)**
C00006	Adj. Mean	-.30 (.05)	-.75 (.05)	-.82 (.05)	-.90 (.05)
	Diff. vs. Placebo	--	-.45 (.07)**	-.52 (.07)**	-.60 (.07)**

Standard error in parentheses

* $p < .05$ vs. placebo ** $p < .001$ vs. placebo (Adjustment for multiplicity not applied.)

The glipizide-controlled study, C00004, also showed a positive result on the primary endpoint. Both the dapagliflozin (N=400) and the glipizide (N=401) arms showed an estimated reduction from baseline to Week 52 of 0.52%. The 95% confidence interval for the difference between treatment arms was (-0.11%, 0.11%). The upper bound of this interval is well within the planned noninferiority margin of 0.35%, and this margin is consistent with the advice given in the guidance for industry cited previously.

Table 3 shows the primary efficacy results for Study 2034, which showed the combination of dapagliflozin and metformin to be superior to either drug alone ($p < .0001$ in each case). It is also noteworthy that dapagliflozin alone was non-inferior to metformin alone. See Table 7 for the number of treated subjects in each study arm.

Table 3: Change in HbA1c from Baseline at Week 24 (LOCF) by Treatment, Study 2034

	Treatment Arm		
	Dapa. 10 mg + Metf.	Dapa. 10 mg	Metf.
Adj. Mean	-2.01 (1.08)	-1.44 (1.31)	-1.42 (1.41)
Diff. from Combin.	--	.53 (.11)**	.54 (.11)**

**p < .001 vs. the combination

Fasting Plasma Glucose (FPG)

Table 4 shows the results for the secondary FPG endpoint for the four placebo-controlled studies. Again, a fairly consistent effect was shown for both the 5 mg and 10 mg doses.

Table 4: Change in FPG from Baseline at Week 24 by Study and Dose, Placebo-Controlled Studies

Study		Dapagliflozin Dose			
		0 mg	2.5 mg	5 mg	10 mg
2013 (AM dosing)	Adj. Mean	-4.1 (3.9)	-15.2 (4.2)	-24.1 (4.3)	-28.8 (4.0)
	Diff. vs. Placebo	--	-11.1 (5.7)	-19.9 (5.8)**	-24.7 (5.6)**
2014	Adj. Mean	-6.0 (2.7)	-17.8 (2.7)	-21.5 (2.7)	-23.5 (2.7)
	Diff. vs. Placebo	--	-11.8 (3.8)*	-15.5 (3.8)**	-17.5 (3.8)**
2030	Adj. Mean	-5.5 (2.9)	N.A.	-24.9 (2.9)	-29.6 (2.9)
	Diff. vs. Placebo	--	N.A.	-19.5 (4.1)**	-24.1 (4.1)**
C00006	Adj. Mean	3.3 (3.4)	-12.5 (3.2)	-18.8 (3.1)	-21.7 (3.3)
	Diff. vs. Placebo	--	-15.8 (4.7)**	-22.1 (4.6)**	-25.0 (4.7)**

Standard error in parentheses

*p < .05 vs. placebo **p < .001 vs. placebo (Adjustment for multiplicity not applied.)

In the glipizide-controlled study (C00004), FPG was not one of the key efficacy variables and Applicant did not plan or report a noninferiority analysis. The adjusted change from baseline at Week 52 was -22.4 and -18.8 (SE = 1.6 for both) in the dapagliflozin + metformin and glipizide + metformin arms, respectively.

Table 5 shows the results for FPG for Study 2034, which showed the combination of dapagliflozin and metformin to be superior to either drug alone.

Table 5: Change in FPG from Baseline at Week 24 by Treatment, Study 2034

	Treatment Arm		
	Dapa. 10 mg + Metf.	Dapa. 10 mg	Metf.
Adj. Mean	-60.4 (2.5)	-46.4 (2.5)	-34.8 (2.5)
Diff. from Combin.	--	13.9 (3.6)**	25.5 (3.6)**

Standard error in parentheses

**p < .001 vs. the combination (Adjustment for multiplicity not applied.)

Rescue Medication

Rather than attempting to adjust the primary outcome for rescue medication, it may be more appropriate to see the proportion of subjects rescued as a separate measure of efficacy. Table 6 shows these results for the four placebo-controlled studies. The 5 mg and 10 mg arms were statistically superior to placebo in each study ($p < .05$).

Table 6: % Rescued by Week 24 by Study and Dose, Placebo-Controlled Studies

Study		Dapagliflozin Dose			
		0 mg	2.5 mg	5 mg	10 mg
2013 (AM dosing)	% Rescued (#/N)	12% (9/75)	11% (7/65)	2% (1/64)	0% (0/70)
2014	% Rescued (#/N)	16% (22/137)	4% (5/137)	4% (5/137)	4% (5/135)
2030	% Rescued (#/N)	12% (16/139)	N.A.	1% (2/141)	4% (5/140)
C00006	% Rescued* (#/N)	27% (54/197)	11% (22/202)	11% (24/212)	10% (19/196)

Note: N is the number of treated subjects. *Rescue treatment was up-titration of insulin.

Table 7 shows the results for Study 2034. The combination therapy had a significantly lower rate of rescue than either dapagliflozin or metformin alone ($p < .05$).

Table 7: % Rescued by Week 24 by Treatment, Study 2034

	Treatment Arm		
	Dapa. 10 mg + Metf.	Dapa. 10 mg	Metf.
% Rescued (#/N)	1% (3/211)	8% (17/219)	13% (27/208)

Sensitivity Analyses for HbA1c

Figure 1 compares the results from the primary analysis (LOCF) to those from three sensitivity analyses for Study 2013. (Figures are at the end of the report.) Least-square mean estimates of the change from baseline in HbA1c are shown at each time point for the placebo and dapagliflozin 10 mg arms. Note that the values shown are not raw means but rather are model-based estimates; in particular, they are adjusted for baseline HbA1c. Results of the following sensitivity analyses are included, the first two of which were proposed by the Applicant:

- 1) ANCOVA of observed cases, excluding observations after rescue,
- 2) Mixed-effects model for repeated measures (MMRM), excluding observations after rescue, and
- 3) MMRM, including observations after rescue.

Note that the estimates from the dapagliflozin 10 mg arm are fairly consistent, partly due to the fact that no patients were rescued in this arm. Hence the figure can be most easily comprehended by focusing on the placebo arm. The LOCF analysis (pink line with squares) shows a reduction in HbA1c of 0.23% at Week 24. This analysis assumes that the nine rescued patients (as well as patients who discontinued the study early) would have continued to have the same HbA1c value until the end of the trial. In contrast, the ANCOVA analysis of observed cases (pale blue with

Xs) shows a reduction of 0.62%. This analysis is particularly favorable to the placebo arm because patients who needed rescue are not included in the week 24 analysis at all. (Each time point is modeled separately). The MMRM analysis which *excludes post-rescue observations* (brown with diamonds) shows a reduction of 0.29%. Finally, the MMRM analysis which *includes post-rescue observations* (dark blue with rectangles) shows a decrease of 0.45%. This final analysis, which I prefer on theoretical grounds, yields an estimated treatment effect, i.e., difference from placebo, for the 10 mg dose of 0.45% (95% confidence interval = [0.19%, 0.72%]). In contrast, the LOCF analysis yields an estimated treatment effect of 0.66% (95% confidence interval = [0.36%, 0.96%])

Figure 2 shows the results of the same analyses for Study 2014. Note that this study included metformin as a background therapy, while Study 2013 had none. While more patients were rescued in the placebo arm (22/137), some were rescued in the 10 mg arm also (5/135). Given these differences from Study 2013, it is not surprising that the estimated treatment effect is more consistent across the various analyses. The largest estimated treatment effect, 0.54%, comes from the LOCF analysis; the smallest, 0.38%, comes from the ANCOVA of observed cases. The MMRM analysis which includes post-rescue data yields a treatment effect of 0.44%, with a 95% confidence interval of [0.24%, 0.63%].

Studies 2013 and 2014 were both placebo-controlled studies with a 24-week endpoint. In contrast, Study C00004 was active-controlled (glipizide) and the primary endpoint was assessed at Week 52. There was no rescue medication, which eliminates a major source of uncertainty about the treatment effect. Figure 3 shows the results for the primary LOCF analysis and the MMRM analysis, which were similar. Note that while dapagliflozin was non-inferior to glipizide at Week 52, it was less effective earlier in the study. (Although the figure does not show confidence limits, glipizide was statistically superior at Weeks 3 through 34.) The Applicant also conducted a per-protocol analysis at Week 52, which showed results that were similar to those from the primary analysis.

Results for Other Phase 3 Studies

As noted earlier, my review efforts have primarily focused on six out of the eleven Phase 3 studies submitted with the NDA. The results of the other studies, *as reported by the Applicant*, also support a conclusion that the 5 and 10 mg doses of dapagliflozin are an effective treatment for type 2 diabetes mellitus. All of the results in this subsection are based on LOCF imputation. Table 8 shows the reported results of three additional placebo-controlled studies which used 24-week HbA1c as their primary endpoint. In Study 2032, a monotherapy study, the 5 mg dose is reported to be superior to placebo. Study C0005 tested dapagliflozin as an add-on to glimepiride, and both the 5 and 10 mg doses are reported to be superior to placebo. Study 2029 was conducted in patients with moderate renal impairment, and did not show efficacy for either the 5 or 10 mg dose.

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

Table 8: Change in HbA1c from Baseline at Week 24 by Study and Dose, As Reported by Applicant

Study		Dapagliflozin Dose				
		0 mg	1 mg	2.5 mg	5 mg	10 mg
2032	Adj. Mean	.02 (.12)	-.68 (.12)	-.72 (.12)	-.82 (.12)	N.A.
	Diff. vs. Placebo	--	-.69 (.17)**	-.74 (.17)**	-.84 (.17)**	N.A.
C00005	Adj. Mean	-.13 (.06)	N.A.	-.58 (.06)	-.63 (.06)	-.82 (.06)
	Diff. vs. Placebo	--	N.A.	-.44 (.09)**	-.49 (.09)**	-.68 (.09)**
2029***	Adj. Mean	-.32 (.17)	N.A.	N.A.	-.41 (.17)	-.44 (.17)
	Diff. vs. Placebo	--	N.A.	N.A.	-.08 (.14)	-.11 (.15)

Standard error in parentheses

*p < .05 vs. placebo **p < .001 vs. placebo (Adjustment for multiplicity not applied.)

*** Subjects had moderate renal impairment

Finally, Table 9 shows results from Study 2021 which assessed a combination of dapagliflozin 5 mg and metformin in subjects with HbA1c \geq 7.5%. The Applicant reports that the combination was superior to each component on change in HbA1c at Week 24.

Table 9: Change in HbA1c from Baseline at Week 24 by Treatment, Study 2021, As Reported by Applicant

	Treatment Arm		
	Dapa. 5 mg + Metf.	Dapa. 5 mg	Metf.
Adj. Mean	-2.05 (.09)	-1.19 (.09)	-1.35 (.09)
Diff. from Combin.	--	-.86 (.12)**	-.70 (.12)**

**p < .001 vs. the combination

REFERENCE

National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press; 2010.

FIGURES

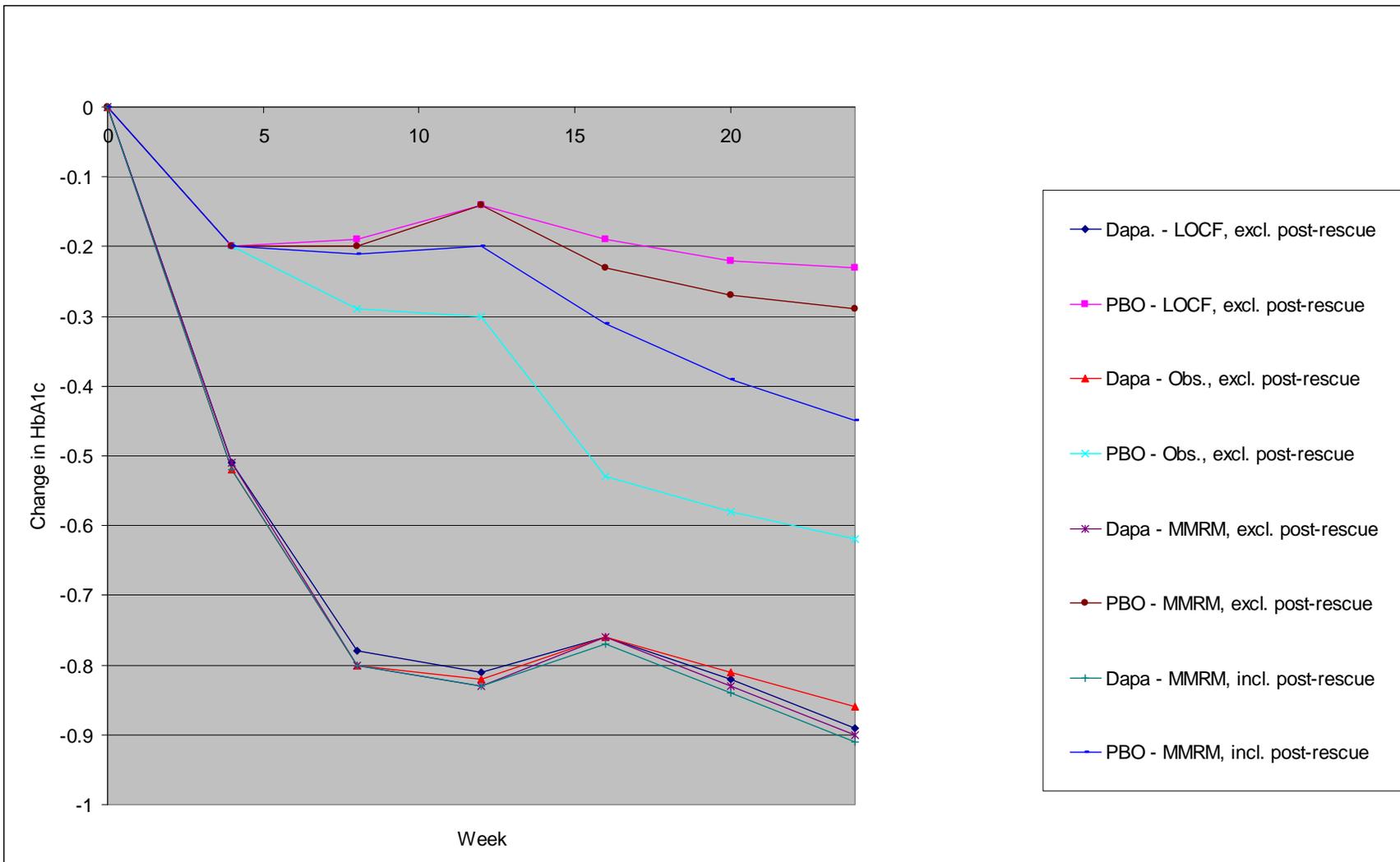


Figure 1: Study 2013, Analyses of Change in Hba1c, Dapa. 10 mg vs. Placebo

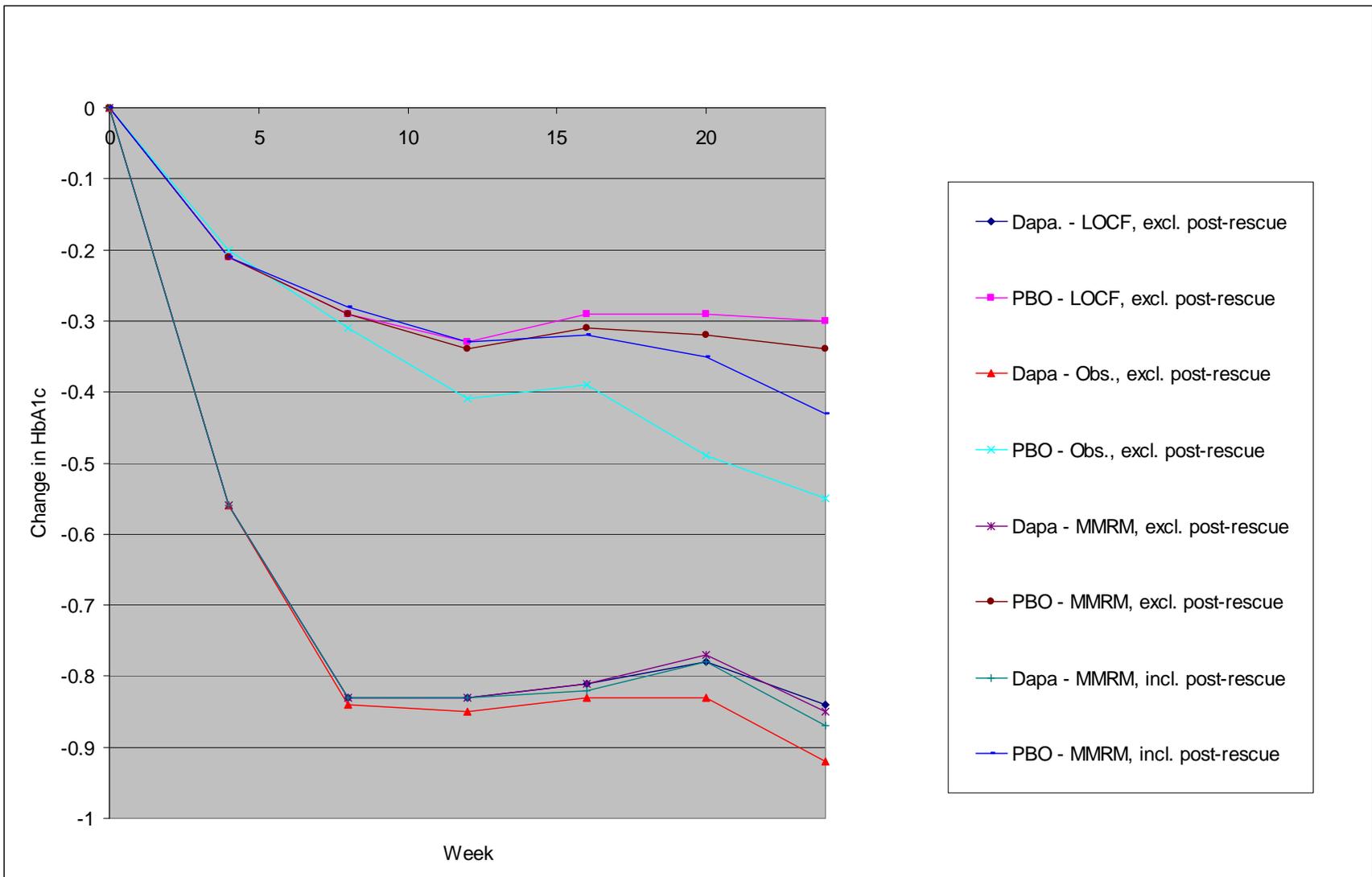


Figure 2: Study 2014, Analyses of Change in HbA1c, Dapa. 10 mg vs. Placebo

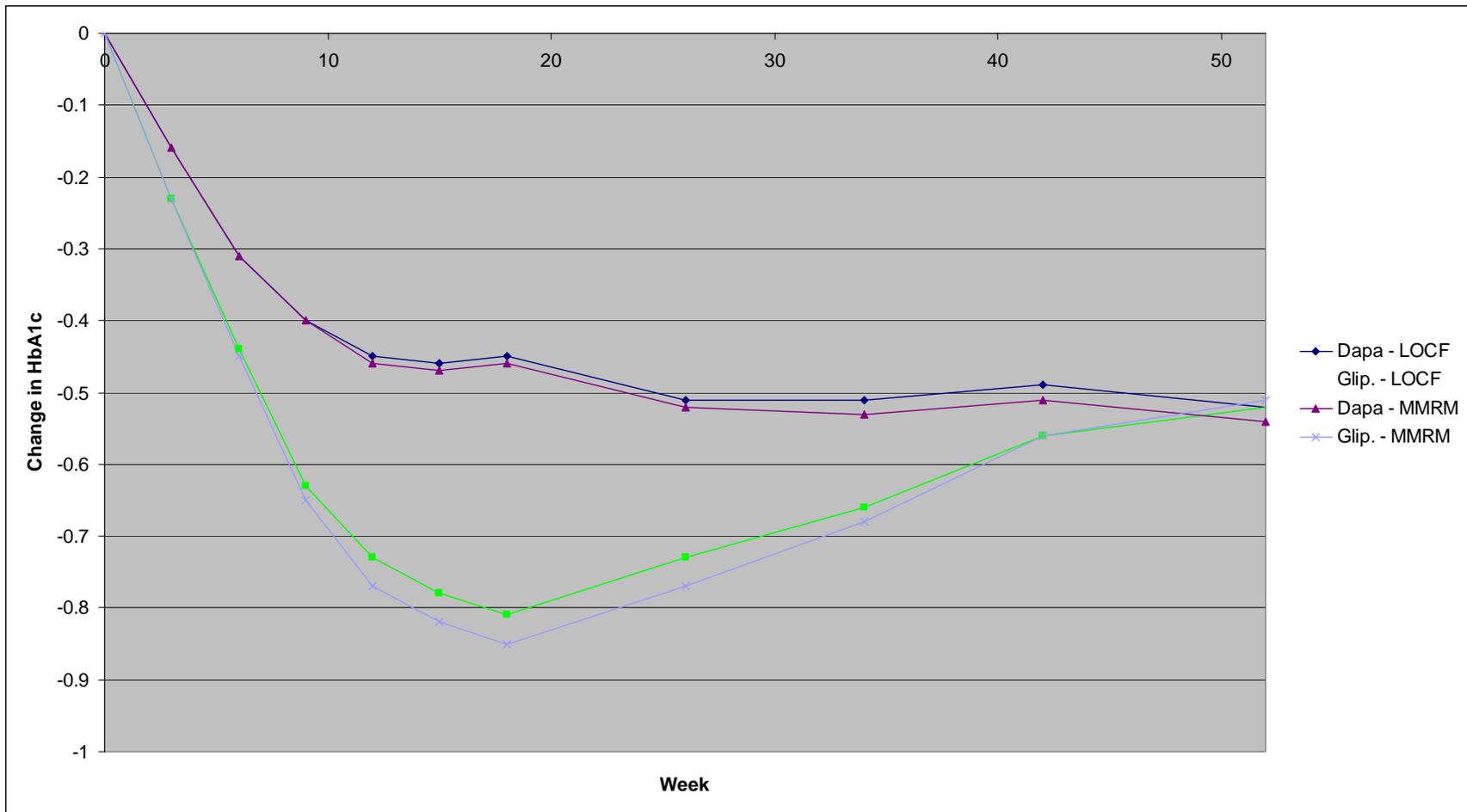


Figure 3: Study C00004, Analyses of Change in HbA1c, Dapagliflozin vs. Glipizide



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

STATISTICAL BRIEFING MATERIAL

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON DAPAGLIFLOZIN

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee,
July 19, 2011

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U.S. Food and Drug Administration

Document Date: June 16, 2011

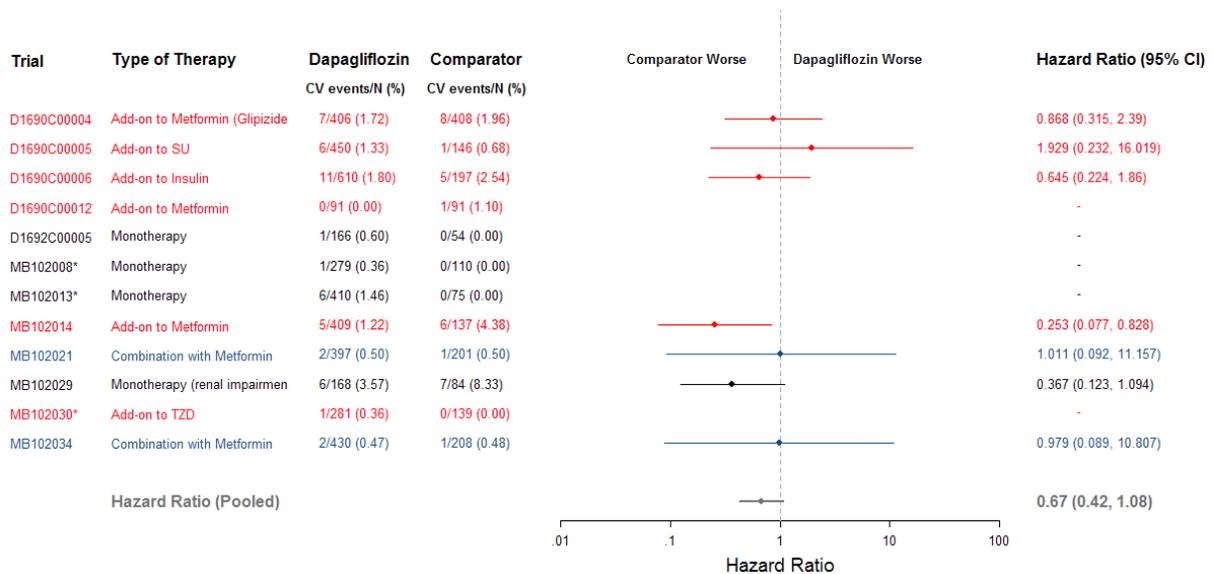
1. Summary of Cardiovascular Effects

The sponsor conducted a meta-analysis of the cardiovascular events that occurred in 14 trials using dapagliflozin (see Table 1 below). The pre-specified primary composite endpoint consisted of the following adjudicated events: CV death, MI, stroke, and hospitalization for unstable angina. Among the 6228 subjects in the database (hereby called BMS Analysis population), 78 subjects had an event that was counted in the primary composite endpoint (48 of 4287 dapagliflozin subjects and 30 of 1941 comparator subjects).

The pre-specified primary analysis was the stratified Cox proportional hazards model including trial as the stratification factor. It found that for the primary endpoint, the hazard ratio of dapagliflozin versus comparator was 0.67 with a 95% confidence interval of (0.42, 1.08). Thus, there does not appear to be an increased risk of cardiovascular events with the use of dapagliflozin over control.

A forest plot of the meta-analysis of the hazard ratios is shown in Figure 1 (note that two trials had zero events in both arms and were not included in the stratified Cox proportional hazards model). Model assumptions were verified by plotting the log-log survival curve of the data and the Schoenfeld residuals.

Figure 1: Forest plot of Hazard Ratios and 95% CI from Cox Proportional Hazards for Primary CV Composite Endpoint (BMS Analysis Population)



Source: Created by reviewer. Adaptation of Figure 2 from sponsor’s study report using adv.v.xpt

The pre-specified secondary analysis was based upon Mantel-Haenszel methods for estimating the overall incident rate ratio via Breslow and Day where the estimate was calculated by stratifying for trial. Trials with no events were excluded from the analysis. In order to include trials with zero event rates, the difference of incidence rates was calculated using Mantel-Haenszel methods. Results from these two analyses are shown below.

- Incidence Rate Ratio: 0.672 with 95% CI (0.420, 1.076).

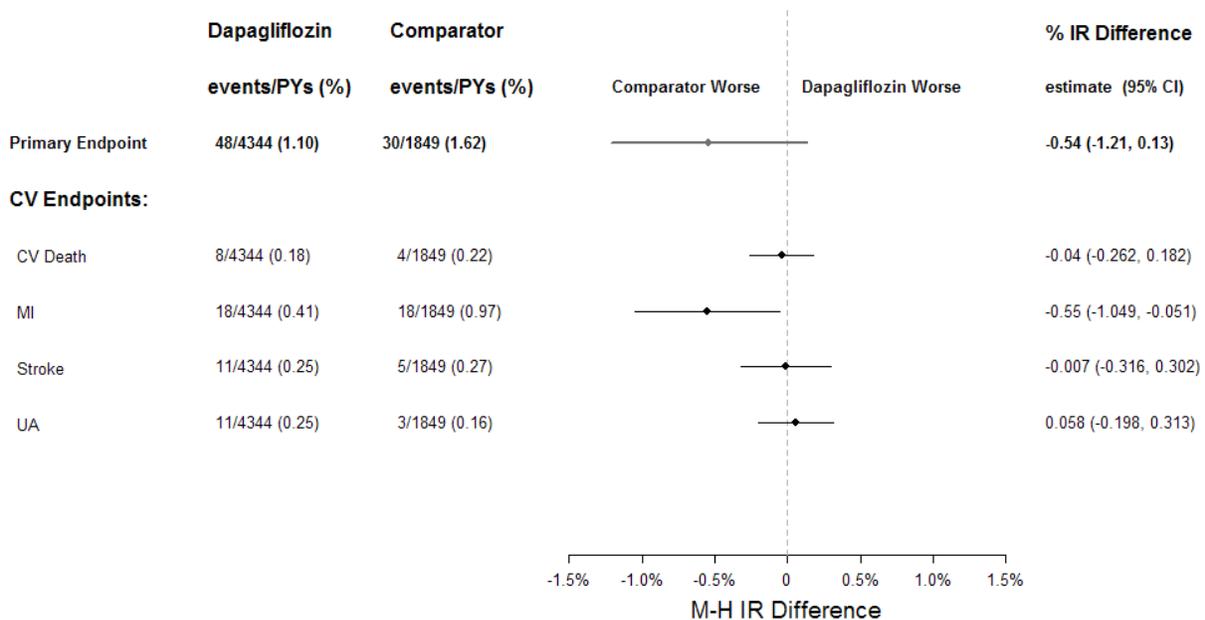
- Difference in Incidence Rates: -0.0054 with 95% CI (-0.012, 0.0013).

Thus, as with the primary analysis, there does not appear to be an increased risk of cardiovascular events with the use of dapagliflozin over control.

To further investigate the sensitivity of the primary analysis on the primary composite endpoint, the FDA conducted a sensitivity analysis excluding short-term trials (trials MB102008, MB102009, and D1692C00005) as well as the non-inferiority trial (trial D169C00004) included in the sponsor’s analysis. Using the same statistical method as in the primary analysis of the primary composite endpoint, this sensitivity analysis on an alternate analysis population also did not find a pattern of CV risk that was different from the primary analysis [hazard ratio = 0.60 with a 95% CI (0.35, 1.01)].

A forest plot of the Mantel-Haenszel incidence rate differences and the asymptotic 95% CIs for each component of the primary cardiovascular endpoint is displayed in Figure 2.

Figure 2: Forest plot of Incidence Rate Differences and 95% CI for the CV Components of the Primary Composite Endpoint (BMS Analysis Population)



*MI = myocardial infarction; UA = hospitalization for unstable angina
Source: Created by reviewer. Dataset: adcv.xpt

2. Conclusions

This document provides the Advisory Committees a summary assessment of cardiovascular (CV) related safety endpoints in the randomized phase 2b/3 clinical development program of dapagliflozin.

The sponsor conducted a meta-analysis of the cardiovascular events that occurred in 14 trials using dapagliflozin. Among the 6228 subjects in the BMS Analysis population, 78 subjects

had an event that was counted in the primary composite endpoint (48 of 4287 dapagliflozin subjects and 30 of 1941 comparator subjects). The primary analysis of the stratified Cox proportional hazards model found the hazard ratio of dapagliflozin versus comparator to be 0.67 (95% CI: 0.42, 1.08). To incorporate zero event trials in the meta-analysis, the incident rate difference was found to be -0.0054 (95% CI: -0.012, 0.0013).

A secondary composite endpoint was also evaluated which comprised of the same CV endpoints as the primary endpoint and two additional CV endpoints (unplanned coronary revascularization and hospitalization for heart failure). This endpoint also found no additional risk of CV events in the dapagliflozin group compared to the comparator group (hazard ratio (95% CI): 0.63(0.42, 0.96)).

To further investigate the sensitivity of the analysis, the FDA conducted a sensitivity analysis excluding short-term trials and the non-inferiority trial included in the sponsor's analysis. This sensitivity analysis found that there was no additional risk of CV events in the dapagliflozin group compared to comparator (hazard ratio: 0.60, 95% CI: 0.35, 1.01). Additionally monotherapy and add-on therapy trials were separately evaluated (hazard ratios (95% CI): monotherapy 0.67 (0.27, 1.68), add-on: 0.64 (0.36, 1.15)). To evaluate the proposed therapeutic dose, the 10mg dose group was separately evaluated and found to have a hazard ratio of 0.69 (95% CI: 0.39, 1.20).

An analysis of event rates was conducted by FDA to determine if the use of a different denominator (number of subjects as opposed to number of person-years of exposure) would affect the estimates. For the primary endpoint, the Mantel-Haenszel risk difference of dapagliflozin compared to comparator was found to be -0.0043 (95% CI: -0.011, -0.0020).

From the analyses performed by both the sponsor and the FDA we conclude that there does not appear to be an increased risk of cardiovascular events for dapagliflozin subjects compared to the combined comparator in this meta-analysis. The upper bound on the 95% CI for the hazard ratio comparing the primary CV composite endpoint was below the margin of 1.3.

3. References

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Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 1986; 42: 311-23.

Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Statistics in Medicine* 2010; 29: 3046-3067.

Table 1: List of trials included in BMS meta-analysis

Trial ID	Total Sample Size*	Dapa Dosage						Co-treatment				Control			Duration	Comments	
		1	2.5	5	10	20	50	Met	Glim	Ins	Pio	Met	Placebo	Glip			
D169C00004 (Phase 3)	814	.	.	.	X ²	X ²	52+156 weeks	Non-inferiority	
D1690C00005 (Phase 3)	596	.	X	X	X	.	.	.	X	.	.	.	X	.	24 + 24 weeks		
D1690C00006 (Phase 3)	807	.	X	X	X	.	.	.	X	.	.	.	X	.	24 + 80 weeks		
D1690C00012 (Phase 3)	182	.	.	.	X	.	.	.	X	.	.	.	X	.	24 + 78 weeks		
D1692C00005 (Phase 2b)	220	X	X	X	X	X	.	12 weeks	Japanese population	
MB102008 (Phase 2b)	389	.	X	X	X	X	X	X	X	.	12 weeks	
MB102009 (Phase 2b)	71	.	.	.	X	X	.	.	.	X	.	.	X	.	12 weeks		
MB102013 (Phase 3)	485	.	X	X	X	X	.	24 + 78 weeks		
MB102014 (Phase 3)	546	.	X	X	X	.	.	.	X	.	.	.	X	.	24 + 78 weeks		
MB102021 (Phase 3)	598	.	.	X	X ¹	.	.	.	X	.	24 weeks		
MB102029 (Phase 2b/3)	252	.	.	X	X	X	.	24+28+52 weeks	Renal Impairment	
MB102030 (Phase 3)	420	.	.	X	X	X	.	X	.	24 + 24 weeks		
MB102032 (Phase 3)	210	X	X	X	X	.	24 weeks		
MB102034 (Phase 3)	638	.	.	.	X	.	.	.	X ¹	.	.	.	X	.	24 weeks		

¹Trials MB102021 and MB102034 Have one arm of Dapa +Met, and one arm of Dapa alone

²Trial MB102022 Has titrated doses of Dapa from 2.5 to 10mg and Glip 5 to 20mg, Dapa dose is calculated as 10mg in analyses

*Total Sample Size indicates number of subjects included in BMS Analysis Population (excludes 1mg dose Dapagliflozin subjects)

Source: Created by reviewer. Dataset: adcv.xpt

Advisory Committee Nonclinical Briefing Document

Application: Dapagliflozin, NDA 202293

Drug Class: SGLT2 inhibitor

Clinical Indication: Type 2 Diabetes

Reviewers: Mukesh Summan, Ph.D., DABT, and Todd Bourcier, Ph.D., Division of Metabolism and Endocrinology Products

Background

The nonclinical evaluation of dapagliflozin included studies suitable to characterize the toxicology of a drug intended for chronic clinical use. Long term studies included assessment of systemic toxicity in dogs for one year and in rats for six months, assessment of carcinogenic potential in rats and mice for two years, and assessment of embryofetal and post-natal developmental toxicity in rats and rabbits. The animal species used in these studies are relevant to assessing toxicity of dapagliflozin and other SGLT2 inhibitors in general, as these compounds elicit the expected pharmacological response from inhibiting SGLT2 (e.g., glucosuria, polyuria) and, at higher doses in most cases, inhibiting SGLT1 (e.g., abdominal distension and gastrointestinal disturbances). The following discussion summarizes the key findings considered relevant to potential safety issues identified in the clinical program for dapagliflozin.

Bone Health

Monitoring of bone health in clinical studies was in part prompted by the finding that dapagliflozin increases trabecular bone in rats resulting in greater bone mass, density, and strength. No fractures were observed in the non-clinical program. Histological evidence of increased trabecular bone occurred at a drug exposure approximately 129-times higher than clinical exposure in the two-year study in rats, which is the longest duration study available in animals. The sponsor's statement that bone accretion in rats was seen only at much higher doses ($\geq 2100x$ the human dose) comes from the results of a shorter 6-month study wherein additional bone evaluations were performed. That the dose causing bone accretion in rats decreased rather markedly with increased duration of exposure (from 6 months to 2 years) suggests that emergence of this phenomenon is both dose- and time-dependent. This appears consistent with alterations in calcium homeostasis which were identified at all doses of dapagliflozin tested in rats, most prominently marked by reduced serum (1,25)-dihydroxy vitamin D, reduced urinary deoxypyridinoline (resorption marker), and increased urinary calcium excretion. Structural changes to the bone were not observed in the dog after one-year of dosing at high exposure ($\geq 130x$ human dose), though there was evidence of reduced serum (1,25)-dihydroxy vitamin D and reduced urinary deoxypyridinoline at the highest exposure and increased urinary calcium excretion at all doses. Also, there is a trend toward lower serum levels of parathyroid hormone. Regardless of the change in calcium and bone biomarkers in animals, the safety margin remains quite high to the final clinical dose for the structural change in bone in the most sensitive toxicology species (rats).

The sponsor discusses a potential role for off-target inhibition of SGLT1 in the intestines as contributing to the alterations in calcium homeostasis and bone accretion observed in rats. Because dapagliflozin was designed to selectively inhibit SGLT2, inhibition of SGLT1 would only occur at very high drug concentrations, such as those achieved in toxicology studies. In brief, the malabsorption of glucose that occurs from inhibition of SGLT1 leads to fermentation of unabsorbed sugars in the lower intestine, a decrease in intestinal pH, and an increase in absorption of dietary calcium. Mechanistic studies conducted by the sponsor indeed demonstrated that serum calcium increases within hours of dosing in rats which eventually leads to calcification of several tissues. However, among 19 investigational compounds with sufficient data, only 10 result in bone accretion in rodents despite evidence that SGLT1 is inhibited (e.g., intestinal distension, calciuria, or intentional targeting of SGLT1). Therefore, the relationship of SGLT1 inhibition to bone accretion remains controversial, and bone accretion in rodents remains a clinical concern, particularly when it occurs near clinical drug exposure, but is amenable to monitoring in trials.

As stated above, the safety margin for bone accretion with dapagliflozin remains quite high to the final clinical dose.

Neoplasms/Malignancies

As an investigational drug intended for chronic use in human subjects, dapagliflozin was evaluated for genotoxic and carcinogenic potential during the course of clinical development.

Genotoxicity: Dapagliflozin was assessed for its potential to cause mutations or structural damage to chromosomes in a standard series of *in vitro* and *in vivo* studies. Dapagliflozin was not mutagenic but did cause structural damage to chromosomes at high concentrations ($\geq 150\mu\text{g/ml}$) in a series of *in vitro* studies. The necessity of rat liver microsomes to elicit clastogenicity indicates that an unidentified metabolite or metabolites of dapagliflozin were causative, not the intact parent molecule. When tested in rats *in vivo*, dapagliflozin was not clastogenic based on evaluation of peripheral blood lymphocytes and bone marrow smears despite exposure to high drug concentrations ($\leq 70\mu\text{g/ml}$) for up to one month. The inability to reproduce the positive *in vitro* clastogenic effect in the intact rat might be explained by the presence of chromosomal reparative pathways in the intact rat, potentially absent generation of the clastogenic metabolite *in vivo*, or by an insufficient drug concentration tested in the rat study. All metabolites of dapagliflozin identified in human subjects have also been identified in mice and rats *in vivo*, and would have been evaluated for genotoxic potential in these studies. As stated above, concentrations in excess of $150\mu\text{g/ml}$ were required to elicit chromosomal damage in the *in vitro* assays and plasma drug levels up to $70\mu\text{g/ml}$ was not associated with clastogenicity *in vivo*. For comparison, the drug concentration at the maximum clinical dose of 10mg/day is approximately $\sim 0.14\text{ ug/ml}$. The weight of evidence supports the view that dapagliflozin and its identified metabolites are unlikely to be clastogenic at clinically relevant drug concentrations in human subjects.

Carcinogenicity: Dapagliflozin was assessed for its potential to induce tumors in two-year bioassays conducted in rats and mice. The two-year bioassays are intended to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action after approximately life-time exposure to an investigational drug. Dapagliflozin did not increase the incidence of any tumor in rats and mice at drug exposures reaching 129x and 70x the clinical dose, respectively. Hyperplastic lesions that could be viewed as pre-neoplastic alterations were not observed in any tissue, including the mammary and bladder tissues, with the potential exception of the kidney tubules. An increased incidence and severity of atypical hyperplasia of the renal tubules was observed at all doses of dapagliflozin in rats, though there was no increase in renal tubule adenoma or carcinoma (discussed further below).

Rodent carcinogenicity studies are sensitive assays but are not perfect predictors of human risk. It is generally accepted that the standard 2-yr studies in rodents detect all chemicals classified as known or probable human carcinogens by the International Agency for Research on Cancer (IARC class I/IIa). Conversely, certain pharmaceuticals with mechanisms of action that raise concern over human carcinogenesis, particularly immunosuppressants, have tested negative or equivocal in rodent bioassays. Limitations regarding sensitivity versus specificity of the 2 year bioassays are applicable to all investigational pharmaceuticals subjected to this assessment. An investigational compound that tests 'negative' for neoplasms in the rat and mouse two-year bioassays, particularly at the multiples of clinical exposure achieved with dapagliflozin, is typically viewed as having low or negligible carcinogenic potential in human subjects, unless factors confound the adequacy of the studies. The most common factors that would confound a negative finding in the bioassays are not present in the case of dapagliflozin. Specifically, rats and mice generate all the metabolites identified in human subjects and in sufficient quantities for an adequate evaluation, expression and function of rodent and human SGLTs 1 and 2 is similar, dapagliflozin is pharmacodynamically active in rodents, and exposure to dapagliflozin in rodents reached 129x and 70x clinical exposure.

Relatively little information regarding the carcinogenic potential of the SGLT2 inhibitor class is available, but the FDA has received preliminary reports of increased renal tubule adenoma/carcinoma with this class

of compounds. It has been proposed that malabsorption of glucose and subsequent alterations in calcium homeostasis in rats, again secondary to inhibition of intestinal SGLT1, may predispose this species to develop tumors of the renal tubules, adrenal gland, and testicular leydig cells. Part of this proposal relies on the observation that similar tumors occur in rats administered agents that result in glucose malabsorption by other means, including acarbose (α -glucosidase inhibitor) and poorly digestible sugars such as lactose and lactitol. Studies that address key events in this proposed pathway and the potential relevance to human risk are currently being conducted by some sponsors of SGLT2 inhibitors.

Pregnancy and Lactation

The sponsor has recommended against the use of dapagliflozin during the second and third trimesters of pregnancy, which in practice is compatible with a contraindication for pregnant women. The sponsor also recommends that women not take dapagliflozin during nursing. Their recommendation is based on adverse findings from exposure to dapagliflozin during the peri/post-natal and juvenile periods in rats. Exposure to dapagliflozin in rats from birth to approximately 13 weeks of age, and especially from post-natal weeks 3-6, results in dilatation of the renal pelvis and tubules and a lower rate of body growth at exposure less than 15-times the clinical dose. A 'no-effect dose' was not identified, so it is likely that exposure causing this adverse effect in rats occurs very near clinical exposure. This susceptible period in the young rats is characterized by active morphological and functional development of the kidneys. A similar period covering morphological and functional renal development in humans would be during the second/third trimesters of gestation, with functional renal development continuing until ~2yrs of age. The cause of renal pelvis and tubular dilation is not known, but the sponsor suggests that the stress of glucosuria/polyuria during a period of immature renal function may be causative. Indeed, exposure to dapagliflozin in weaning and juvenile rats (either via milk or direct administration) is sufficient to elicit pharmacodynamic effects of glucosuria/polyuria resulting from SGLT2 inhibition. For these reasons, the FDA agrees with the sponsor that dapagliflozin should not be used during pregnancy or nursing.

Hepatotoxicity

Exposure to dapagliflozin for 1 year in dogs and 2 years in rodents did not uncover evidence of liver injury considered indicative of clinical risk. Serum levels of liver enzymes and bilirubin were comparable to control animals, and there was no histological evidence of cholestatic injury, hepatocellular injury or hypertrophy, or of a chronic hepatic inflammatory state. Very high exposure in rats (~2100x clinical dose) resulted in an increased incidence of periportal hypertrophy and bile duct proliferation with a minor (1.5x) elevation in ALT and ALP. As dapagliflozin is in part excreted via the bile, these changes at high exposure are more likely secondary to the high drug concentration in the liver rather than to clinically relevant drug toxicity. Standard toxicology studies in animals present limitations in predicting drug-induced liver injury (DILI), most notably in addressing idiosyncratic mechanisms and genetic factors that may predispose humans to DILI. Species differences in potential drug interactions with hepatobiliary efflux and influx transporters may also confound a 'negative' finding in toxicology studies. This latter possibility, which is experimentally addressable, cannot be excluded because the potential interaction of dapagliflozin with human or rat/dog hepatobiliary transporters was apparently not characterized.