CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 202293	Submission Date(s): 07/11/2013
Brand Name	TBD
Generic Name	Dapagliflozin
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
Clinical Pharmacology Team Leader	Lokesh Jain, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol-Myers Squibb and AstraZeneca
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Immediate Release Tablets: 10 mg and 5 mg
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Note to the Readers: Please refer to the Clinical Pharmacology Review in DARRTs, by Dr. Ritesh Jain, dated 09/01/2011, for the clinical pharmacology assessment of this application in the first review cycle.

1 Executive Summary

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) are seeking approval of dapagliflozin for the treatment of type 2 diabetes mellitus (T2DM). Dapagliflozin is an inhibitor of sodium glucose co-transporter 2 (SGLT2), the transporter responsible for the majority of renal glucose re-absorption. Primary mechanism of action (MOA) of dapagliflozin is to increase the elimination of glucose in urine. Dapagliflozin is a new molecular entity (NME) but not a first-in-class drug (i.e., canagliflozin, another SGLT2 inhibitor, was approved on March 29, 2013). The proposed indication is to use dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The proposed commercial presentation is immediate release film coated tablets in two strengths 5 mg and 10 mg. The Sponsor's proposed clinical dose of dapagliflozin is 5 or 10 mg to be administered orally in once-a-day dosing regimen.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted under NDA 202293 in the first review cycle (dated 12/28/2010), and this review cycle (dated 07/11/2013) and recommend approval of this application with the following recommendations:

1) We recommend that 10 mg dose be approved as the starting dose in patients with normal and mild renal function, if clinical review finds the safety profile of 10 mg dose acceptable.
2) Dapagliflozin 5 mg and 10 mg doses did not provide additional benefit compared to placebo in a dedicated trial in patients with moderate renal impairment; therefore, dapagliflozin use is not recommended in this patient population.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Key Regulatory History

The initial dapagliflozin New Drug Application (NDA) was submitted on 28-Dec-2010. Dapagliflozin was presented before the Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) on 19-Jul-2011. The EMDAC voted 9 to 6 against approval of dapagliflozin due to a benefit-risk assessment of modest efficacy and concerns regarding a possible increase in cancer risk (i.e., bladder cancer), and the potential for risk of drug induced liver injury (DILI), and cardiovascular (CV) safety. On 17-Jan-2012, the FDA issued a complete response letter (CRL) and in order to address their concerns, BMS/AZ needed to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and controls.

Dapagliflozin is currently approved and available in the following countries: European Union (EU; Nov-2012), Australia (Oct-2012), Mexico (Mar-2013), New Zealand (June-2013), Brazil (July-2013), and Argentina (Sep-2013). This Application is being reviewed for a second cycle under a six-month review clock.

Current Review Cycle:

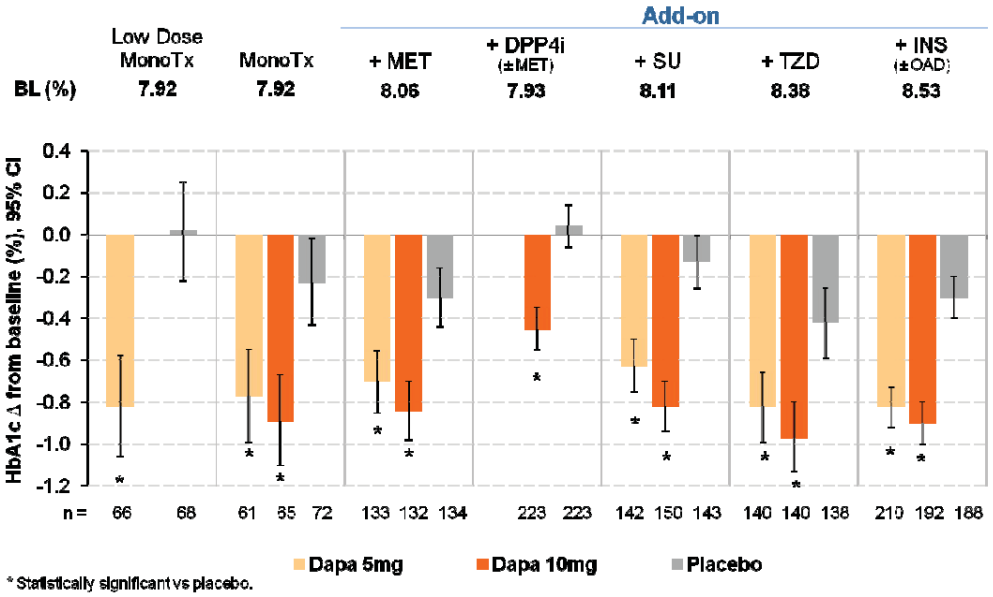
In this review cycle no new clinical pharmacology related data was submitted. The dapagliflozin clinical development program consisted of 37 Phase 1 studies (26 from the original NDA submission and eleven new studies in the 30-MU) and 26 Phase 2b and Phase 3 clinical trials (15 from the original submission, plus 6 new core studies and 5 supportive studies in the 30-MU). These data provided > 50% increase in patient-years exposure since the initial NDA.

Dose Rationale:

The Phase 1 and 2 studies for dapagliflozin established that doses of > 20 mg once daily did not result in greater glucosuria or incremental improvements of glycemic control. In the dose ranging Phase 2b study (MB102008), a clinically meaningful incremental reduction in HbA1c was not observed in doses > 10 mg. Based on the comparative pharmacodynamics, glycemic markers, and safety and tolerability findings from these studies, doses of 2.5, 5, and 10 mg dapagliflozin once daily were selected as the core doses to be studied in the Phase 3 program. Please refer to the clinical pharmacology review of the first review cycle for further details on rationale for dose selection in the Phase 3 trials.

In Phase 3 studies both the 5 and 10 mg doses were tested, the 10 mg dose consistently showed greater mean HbA1c reductions than the 5 mg dose (Figure 1). Greater reductions were also consistently seen at the 10 mg dose for FPG, postprandial glucose (PPG), and the proportion of patients achieving a target HbA1c < 7%. At the same time, the safety profiles of 5 mg and 10 mg doses appear to be similar; no risks were identified that increased in frequency or severity as the dose increased from 5 to 10 mg. Please refer to clinical review by Dr. Frank Pucino for further details.

Figure 1: HbA1c: Mean Change from Baseline at Week 24 (Primary Endpoint; Core Placebo-controlled Phase 3 Studies



* Statistically significant vs placebo.

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

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

Source: Sponsor's AC briefing document page 44.

In the first review cycle the sponsor proposed *only 10 mg dose for patients with normal to mild renal function and 5 mg dose for patients with high risk* such as volume depletion. In this resubmission sponsor changed the dosing to *5 or 10 mg for patients with normal to mild renal function*. Note that in the first review cycle, the clinical pharmacology review found the sponsor's proposal of *only 10 mg dose for patients with normal to mild renal function* acceptable; however, during the labeling negotiations, Agency asked the sponsor to make available both 5 mg and 10 mg doses for these patients. Further clarification from the sponsor in this review cycle suggests that sponsor continues to believe the 10 mg dose as the appropriate dose for patients with normal to mild renal function. The dosing was further reviewed in this review cycle. Based on the efficacy results showing that10 mg dose is comparable or better than 5 mg dose under different treatment setting and that there is no apparent increase in adverse events with 10 mg dose compared to 5 mg dose, we agree that the 10 mg should be considered as the starting dose for patients with normal to mild renal function. However, please refer to the clinical review by Dr. Frank Pucino for detailed assessment of safety for the 5 mg and 10 mg doses. In patients who are more susceptible to adverse events with use of dapagliflozin, such as patients age≥65 years and patients on loop diuretics, a starting dose of 5 mg should be considered which can be increased to 10 mg based on tolerability and need for additional glycemic control.

Reviewers Comment: In summary, of the doses studied in the Phase 3 program, 10 mg showed greater glycemic benefit than 5 mg with an apparently similar safety profile. Thus, if clinical review finds the safety of 10 mg dose acceptable, 10 mg should be approved as the starting dose of dapagliflozin, except in few specific cases such as:

In patients who are at risk of volume depletion, or elderly population who are at greater risk, dapaglifozin should be approved at the starting dose of 5 mg once-daily, which can be increased to 10 mg based on patients tolerability and need for additional glycemic control. Please refer to safety review by Dr. Frank Pucino for further details on safety in sensitive population.

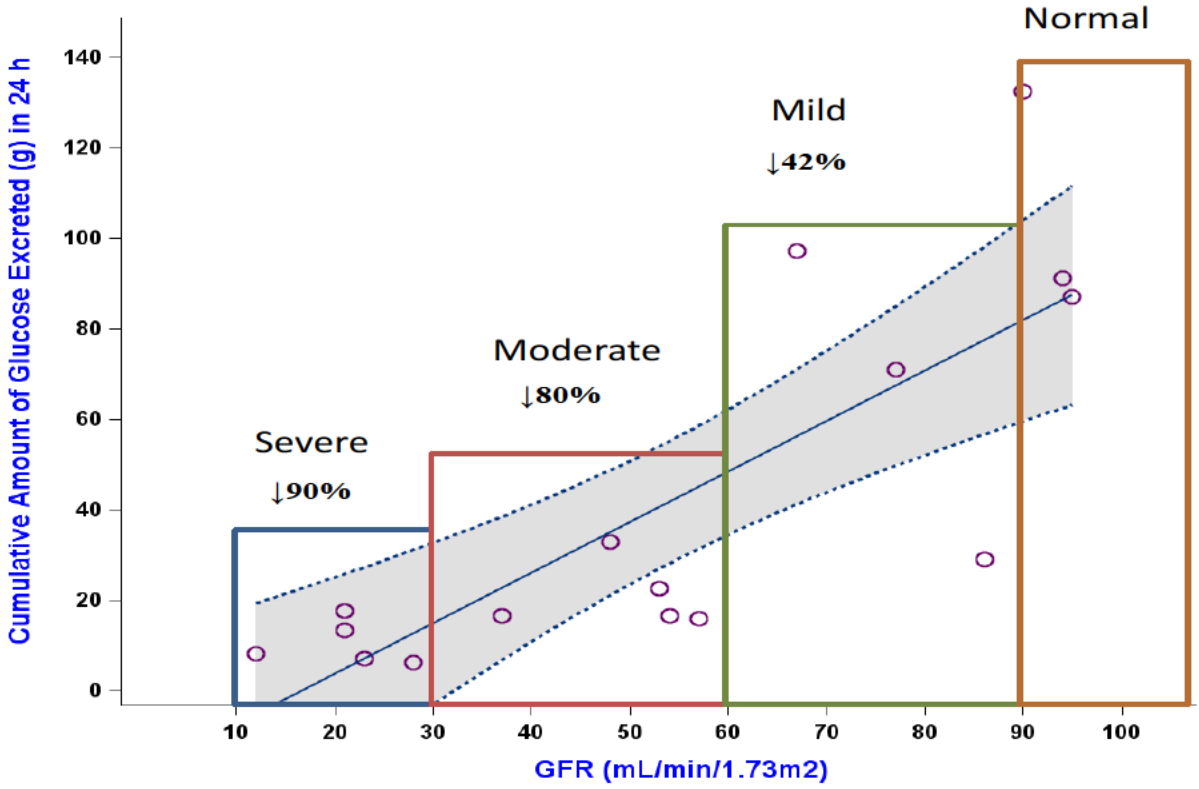
Efficacy in Moderate Renally Impaired Patients:

The Applicant is proposing that dapagliflozin not be used in patients with an eGFR <60 mL/min/1.73 m^2. The results from a PK/PD study in patients with mild, moderate, and severe renal impairment (study # MB102007) and a dedicated efficacy and safety trial in patients with moderate renal impairment (study # MB 102029) are discussed below.

- **PK/PD in Patients with Renal Impairment:**

A single- and multiple-dose PK/PD study was conducted in patients with T2DM and normal, mild, moderate, and severe renal impairment. Following multiple doses of dapagliflozin (20 mg), T2DM patients with mild, moderate, and severe renal impairment had approximately 40%, 100% and 200% higher exposures, respectively, compared to those with normal renal function. Please refer to clinical pharmacology review of the first review cycle for further details. Since the efficacy of the drug is dependent on renal function, higher systemic exposures of dapagliflozin in patients with moderate and severe renal impairment did not result in a correspondingly higher cumulative amount of glucose excretion (Figure 2).

Figure 2: Cumulative Amount of Glucose Excreted by Renal Function



- **Efficacy in Moderate Renal Impairment Patients (eGFR 30-60 mL/min/1.73 m^2)**

The Applicant evaluated the efficacy of dapagliflozin in a dedicated study (MB102029) in patients with moderate renal impairment (defined as an eGFR between 30 to <60 mL/min/1.73m2). This dedicated study in renally impaired subjects was a multicenter, double-blind, placebo-controlled, parallel group, randomized, Phase 2/3 trial to evaluate the glycemic efficacy and renal safety in patients with moderate renal function. Table 1 shows the results for the primary endpoint, change from baseline in HbA1c at Week 24. Both the 5 mg and 10 mg dapagliflozin doses were not superior to placebo, and the observed treatment effects were negligible.

The Applicant also conducted an "ad-hoc" subgroup analysis in patients with stage 3A moderate renal impairment defined as an eGFR of 45 to 59 ml/min/1.73 m^2, and 3B which was defined as a group with an eGFR of 30 to 44 ml/min/1.73 m^2. The results of the subgroup analysis showed that neither arm was significantly different from placebo (Table 2 and Table 3). Therefore, given the lack of benefit against placebo in patients with moderate renal impairment, we agree with the applicant's proposal that dapagliflozin should not be used in patients with eGFR<60 mL/min/1.73m^2.

Table 1: Results for Primary Endpoint, Study 2029
(Source: Clinical Study Report, Table 7.1)

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
PRIMARY EFFICACY ENDPOINT			
HBA1C (%) AT WEEK 24 (LOCF)			
N#	82	83	82
BASELINE MEAN (SD)	8.53 (1.285)	8.30 (1.040)	8.22 (0.973)
WEEK 24 LOCF MEAN (SD)	8.18 (1.204)	7.97 (1.150)	7.90 (0.930)
MEAN CHANGE FROM BASELINE (SD)	-0.35 (1.260)	-0.33 (0.997)	-0.32 (0.856)
ADJ. MEAN CHANGE FROM BSL. (SE)	-0.32 (0.1701)	-0.41 (0.1701)	-0.44 (0.1708)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	(-0.66, 0.01)	(-0.74, -0.07)	(-0.77, -0.10)
DIFFERENCE FROM PLACEBO (SE)		-0.08 (0.1448)	-0.11 (0.1457)
95% CI FOR DIFFERENCE FROM PLACEBO		(-0.37, 0.20)	(-0.40, 0.17)
P-VALUE VS. PLACEBO (*)		0.561	0.435

N is the number of randomized subjects who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with non-missing baseline and Week t (LOCF) values.
(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.
Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a covariate.

In subjects with baseline eGFR values included in substratum 3A, the adjusted mean change from baseline at Week 24 (LOCF) in HbA1c was -0.11 (-0.57, 0.35), -0.47 (-0.97, 0.02), and -0.44 (-0.94, 0.07) for placebo, 5 mg, and 10 mg, respectively (Table 2).

Table 2: Results for Primary Endpoint in Subjects with Stage 3A Chronic Kidney Disease at Baseline , Study 2029
(Source: Clinical Study Report, Appendix 38)

	PLACEBO N=41	DAPA 5MG N=35	DAPA 10MG N=33
SUMMARY STATISTICS			
N#	40	35	32
BASELINE MEAN (SD)	8.78 (1.318)	8.13 (0.928)	8.25 (0.892)
WEEK 24 MEAN (SD)	8.62 (1.201)	7.93 (1.086)	8.03 (1.002)
MEAN CHANGE FROM BSL (SD)	-0.16 (1.374)	-0.20 (0.941)	-0.22 (0.797)
ADJUSTED CHANGE FROM BASELINE			
MEAN (SE)	-0.11 (0.2339)	-0.47 (0.2483)	-0.44 (0.2546)
95% 2-SIDED CI	[-0.57, 0.35]	[-0.97, 0.02]	[-0.94, 0.07]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS PLACEBO			
MEAN (SE)		-0.37 (0.2322)	-0.33 (0.2376)
95% 2-SIDED CI		[-0.83, 0.10]	[-0.80, 0.14]

N is the number of randomized subjects with baseline eGFR>= 45 and <60 mL/min/1.73m^2
who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with baseline eGFR>= 45 and <60 mL/min/1.73m^2
and non-missing baseline and Week 24 (LOCF) HbA1c values.
Based on an ANCOVA model with treatment group and stratum as main effects and baseline value as a covariate.
Program Source: /gbs/test/clin/programs/mb/102/029/a0050/rpt/rt-lb-ancovabygfr-v01.sas 08SEP2010:12:09:11

In subjects with baseline eGFR values included in substratum 3B, the adjusted mean change from baseline at Week 24 (LOCF) in HbA1c was -0.52 (-1.08, 0.03), -0.47 (-1.01, 0.06), and -0.45 (-0.96, 0.05) for placebo, 5 mg, and 10 mg, respectively (Table 3).

Table 3: Results for Primary Endpoint in Subjects with Stage 3B Chronic Kidney Disease at Baseline , Study 2029
(Source: Clinical Study Report, Appendix 39)

	PLACEBO N=34	DAPA 5MG N=41	DAPA 10MG N=47
SUMMARY STATISTICS			
N#	33	41	45
BASELINE MEAN (SD)	8.23 (1.197)	8.49 (1.157)	8.12 (1.001)
WEEK 24 MEAN (SD)	7.79 (1.149)	7.97 (1.250)	7.78 (0.864)
MEAN CHANGE FROM BSL (SD)	-0.44 (1.034)	-0.52 (1.069)	-0.34 (0.931)
ADJUSTED CHANGE FROM BASELINE			
MEAN (SE)	-0.52 (0.2804)	-0.47 (0.2712)	-0.45 (0.2545)
95% 2-SIDED CI	[-1.08, 0.03]	[-1.01, 0.06]	[-0.96, 0.05]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS PLACEBO			
MEAN (SE)		0.05 (0.2107)	0.07 (0.2074)
95% 2-SIDED CI		[-0.37, 0.47]	[-0.34, 0.48]

N is the number of randomized subjects with baseline eGFR>= 30 and <45 mL/min/1.73m^2
who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with baseline eGFR>= 30 and <45 mL/min/1.73m^2
and non-missing baseline and Week 24 (LOCF) HbA1c values.
Based on an ANCOVA model with treatment group and stratum as main effects and baseline value as a covariate.
Program Source: /gbs/test/clin/programs/mb/102/029/a0050/rpt/rt-lb-ancovabygfr-v01.sas 08SEP2010:12:09:11

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/s/

RITESH JAIN
12/17/2013

LOKESH JAIN
12/17/2013

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-293 Class 2 Resubmission	**Reviewer:** Minerva Hughes, PhD	
Submission Date:	11 July 2013		
Division:	Division of Metabolism and Endocrinology Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Bristol Myers Squibb	**(Acting) Supervisor:** Richard Lostritto, PhD	
Trade Name:	Farxiga (proposed) Company code: BMS-512148	**Date Assigned:**	15 July 2013
Generic Name:	Dapagliflozin propanediol	**Date of Review:** **PDUFA:**	19 September 2013 11 January 2014
Indication:	Type 2 diabetes in adults	**Type of Submission:** Original NDA 505(b)1 (Resubmission: Class 2)	
Formulation/ strengths	Immediate Release Tablet, 5 mg and 10 mg		
Route of Administration	Oral		

SUBMISSION: Dapagliflozin is a novel small molecule inhibitior of the human renal sodium-glucose cotransporter 2 (SGLT2). This NDA is for the use of dapagliflozin in the treatment of adult Type 2 diabetes. The drug substance is a (b) (4) 1:1:1 mixture of dapagliflozin, propanediol and water (designated as BMS-512148-05). The drug product is a film-coated tablet available in two strengths: 5 mg and 10 mg. BMS manufacturing facilities located at Humacao, Puerto Rico and Mount Vernon, Indiana are proposed as drug product manufacturing sites.

The initial NDA was submitted on 28 December 2010, and FDA issued a Complete Response (CR) Letter on 17 January 2012. Product safety concerns were the main reason for FDA's CR action (e.g., increased cancer risk, liver toxicity, and cardiovascular safety). Included in the CR letter were additional comments regarding the dissolution method and financial disclosures, but these issues were not approvability issues. This NDA resubmission includes the Applicant's complete response to FDA's deficiencies and general comments outlined in the 17 January 2012 CR letter.

There was no new Biopharmaceutics and Chemistry, Manufacturing, and Controls information included in this resubmission (i.e., no Module 2.7 or 3). The Biopharmaceutics information was limited to the Applicant's response to the Biopharmaceutics comment regarding the dissolution method in the CR Letter.

This Biopharmaceutics review evaluates the Applicant's response information to the additional comment.

BIOPHARMACEUTICS INFORMATION: The dapagliflozin tablets (b) (4) immediate release tablets. As part of the initial NDA review, disintegration testing was found to be an acceptable surrogate for dissolution testing on the finished tablets. The Applicant, however, was advised that the developed dissolution method should be used to support any future post approval changes, in accordance with the SUPAC-IR guidelines.

Specifically, FDA noted the following comment in the 17 January 2012 CR Letter.

> ***FDA Comment:*** *Your proposal to use disintegration as a surrogate for dissolution testing as part of the drug product regulatory specification is acceptable. However, we remind you that in vitro dissolution will be necessary to support certain post approval changes in accordance with existing FDA guidance documents and regulations. Additionally, ongoing registration stability studies should continue to monitor tablet dissolution and disintegration through the end of the study protocol. The following dissolution method is the application method for future comparative studies.*
>
> - *USP Apparatus II (paddle), 60 rpm*
> - *Acetate buffer, pH 4.5, 1000 mL at 37°C*
> - *Limit: Q = (b) (4) in 15 min; sampling profile*

The Applicant response information, included in this resubmission, is as follows.

> **Applicant's Response:** BMS acknowledges that in vitro dissolution will be used to support certain post approval changes in accordance with existing guidance documents and regulations. The registrational stability studies have been completed and both dissolution and disintegration were performed as per the stability protocol. The dissolution method and limit stated in the question will be used for future comparative studies.

Reviewer's Comment: *The Applicant's commitment is acknowledged and satisfactorily addresses this additional Biopharmaceutics comment.*

RECOMMENDATION: There are no new biopharmaceutics issues raised in this resubmission. An approval action was recommended in the Biopharmaceutics-Quality Review dated 27 May 2011 (see DARRTS database), and that recommendation is unchanged.

From the Biopharmaceutics perspective, the Resubmission of NDA 202993 is recommended for approval.

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Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, Ph.D.
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/s/

MINERVA HUGHES
09/19/2013

ANGELICA DORANTES
09/19/2013

CLINICAL PHARMACOLOGY REVIEW

NDA: 202293	Submission Date(s): 12/27/2010
Brand Name	TBD
Generic Name	Dapagliflozin
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
Primary Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Christine Garnett, Pharm.D.
Primary Pharmacogenomics Reviewer	Hobart L. Rogers, Pharm.D., Ph.D
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm.D., M.P.H.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol-Myers Squibb and AstraZeneca
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Immediate Release Tablets: 10 mg and 5 mg
Proposed Indication	An adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes mellitus

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1 Executive Summary

Dapagliflozin is a new chemical entity developed by Bristol-Myers Squibb and Astra-Zeneca for the treatment of type 2 diabetes. Dapagliflozin belongs to a new class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors. Dapagliflozin is an orally-active inhibitor of the human renal SGLT2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin will be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin film coated tablets (5 mg and 10 mg strengths) are proposed for oral administration. The proposed clinical dose of dapagliflozin is 10 mg administered once-daily.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted under NDA 202293 (dated 12/27/2010), and finds it acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The dapagliflozin clinical development program included in this application consists of 26 clinical pharmacology studies, 3 Phase 2b studies, and 11 Phase 3 studies.

Mechanism of Action: Dapagliflozin is an orally-active inhibitor of the human renal SGLT2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary glucose excretion.

Sponsor's Clinical Pharmacology Program: Clinical Pharmacology program consists of a total of 26 Clinical Pharmacology studies (Table 5). Clinical pharmacology program also included population pharmacokinetics and exposure-response analysis using data from Phase 1 and Phase 2/3 studies.

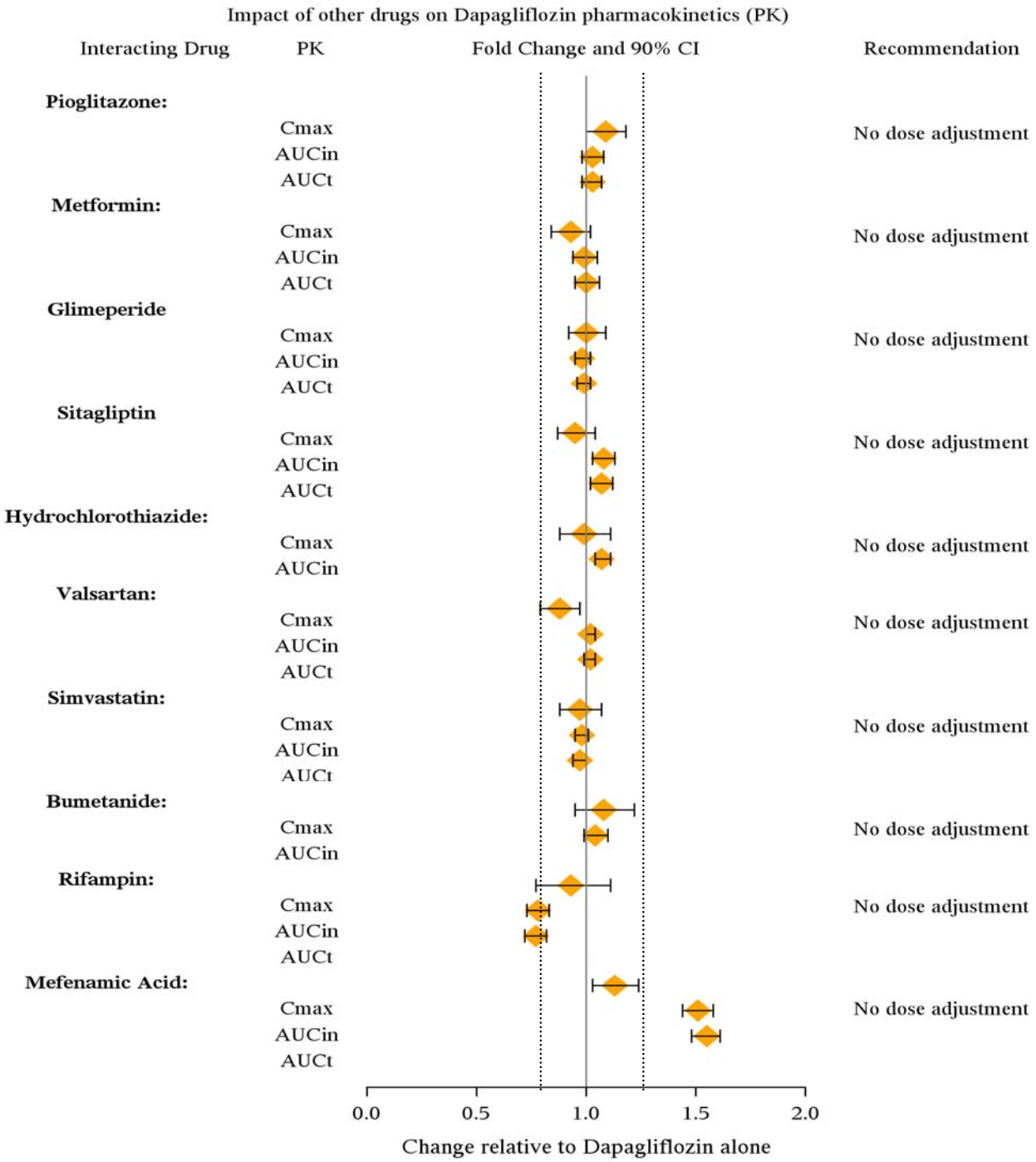
Important Pharmacokinetics Properties of Dapagliflozin: Table 1 summarizes the important pharmacokinetic properties of dapagliflozin.

Table 1: Summary of Pharmacokinetic Properties of Dapagliflozin

PK Property	PK Parameter	
Absorption	T_{max}, hour (median)	1
	$T_{1/2}$, hour (mean, SD)	12.9 (5.54)

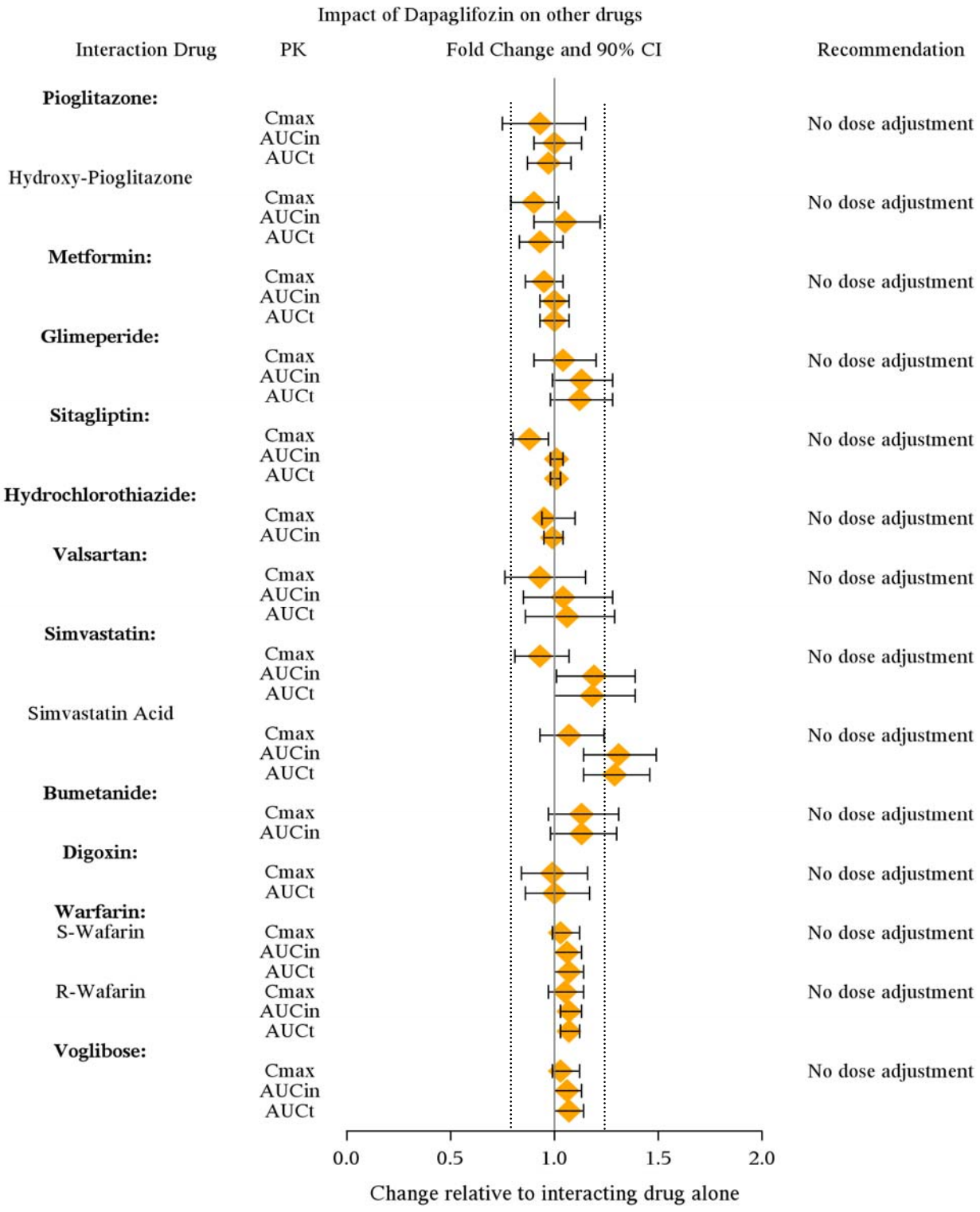
	Absolute Bioavailability (Fasted), F %; geometric mean (CV%)	77.8 (9)
	Food Effect	In presence of High Fat meal, No change in AUC, ~30% decrease in C_{max}
Distribution	Protein Binding, %	91
Metabolism	Pathways	In a mass balance study, the primary metabolite in human was dapagliflozin 3-O-glucuronide (BMS 801576) which accounted for 61% of the dapagliflozin dose. Each of the other metabolites detected in human plasma constituted < 5% of the radioactivity AUC. In vitro studies demonstrated that UGT1A9 is the major enzyme responsible for the formation of dapagliflozin 3-O-glucuronide.
Excretion		In a mass balance study, 96% of the administered dose was recovered in the urine (~75%) and feces (~21%). In urine, 1.2% of the radiolabeled dose was recovered as parent drug and 61% as dapagliflozin-3-O-glucuronide. In feces, 15.4% of the radioactivity is because parent drug.
Dose-Proportionality		Exposures of dapagliflozin were slightly greater than proportional to dose while C_{max} values were less than proportional to dose
Accumulation Index following Multiple Dose in Healthy and T2DM subjects		~1.3

Drug-Drug Interaction: Figure 1 summarizes the effect of co-administered drugs on the pharmacokinetics of dapagliflozin. Figure 2 summarizes the impact of dapagliflozin on the pharmacokinetics of co-administered drugs. In summary, there were no clinically meaningful drug-drug interaction observed in the all the DDI studies conducted.



Dashed line indicate the 80%-125% limit

Figure 1: Effect of Drugs on the Pharmacokinetics of Dapagliflozin



Dashed line indicate the 80%-125% limit

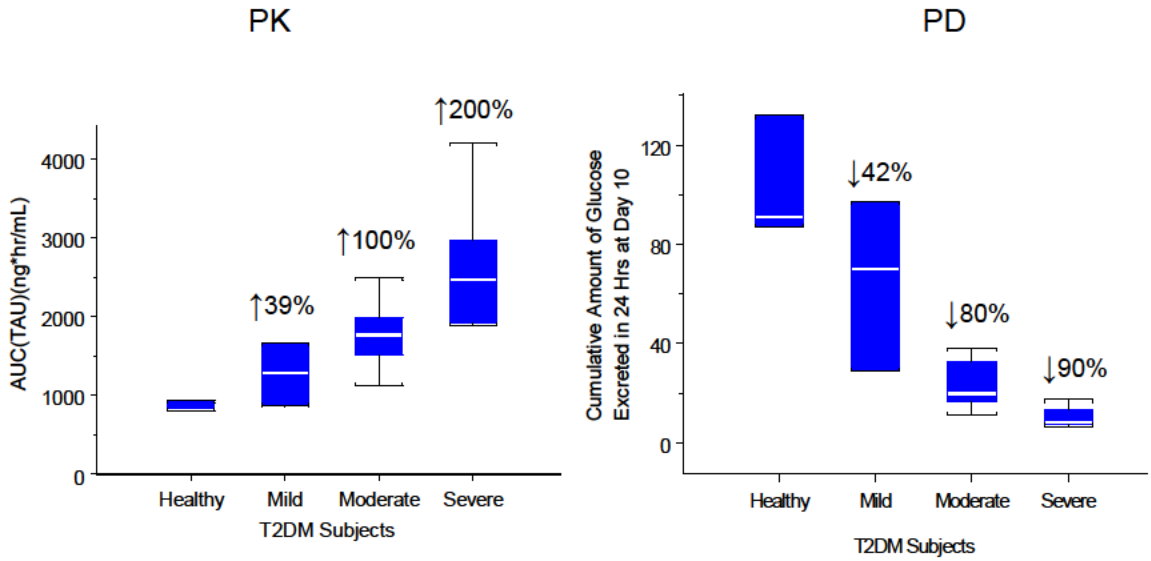
Figure 2: Effect of Dapagliflozin on the Pharmacokinetics of other Drugs

Specific Populations

➢ **Renal Impairment:**

Following administration of 20-mg dapagliflozin given once daily for 7 days, T2DM 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 (Figure 3). Furthermore, higher systemic exposures of dapagliflozin in subjects with moderate, and severe renal impairment did not result in higher cumulative amount of glucose excretion (Figure 3). This is consistent with dapagliflozin's glomerular filtration rate-dependent mechanism of action where it is not expected to provide clinically meaningful benefit in these populations.

Sponsor's proposals of no dose adjustment in mild renal impaired patients and that the drug not be used in moderate to severe renal impairment, is acceptable.



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

Figure 3: Effect of Renal Impairment on PK and PD of Dapagliflozin (N=3 For healthy, N=3 for mild, N=6 moderate, N=5 for severe).

➢ **Hepatic Impairment:**

In subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B), Cmax and AUC of dapagliflozin were increased by 22% and 36%, respectively, compared to healthy subjects. In subjects with severe hepatic impairment (Child-Pugh Class C), dapagliflozin Cmax and AUC were up to 40% and 67% higher than matched healthy controls, respectively. Sponsor's proposal for no dose adjustment in hepatic impaired patients is acceptable.

➢ **Genetic Variation:**

Dapagliflozin is primarily metabolized by the polymorphic uridine diphosphate glucuronosyltransferase (UGT1A9). The sponsor conducted a retrospective genetic

substudy of the Phase 2b trial, MB102008, to investigate the role of the UGT1A9 variants on the clearance of dapagliflozin (based on population PK parameters). No significant effects of UGT1A9 genotype on dapagliflozin clearance were identified. The results of this study coupled with the scarcity of UGT1A9 variants indicate that these variants are unlikely to play a clinically significant role in the exposure to dapagliflozin.

Sponsor's Phase 3 Program: Phase 3 program for dapagliflozin consists of 11 studies to evaluate the efficacy and safety of dapagliflozin as monotherapy, add-on combination therapy (to metformin, sulfonylurea (SU), thiaozolidinedione (TZD), and insulin), and initial combination therapy with metformin.

- **Dose/Exposure-Response Safety:**

The major safety issues associated with dapagliflozin were bladder and breast cancer, marked elevation in liver enzymes, genital infections, urinary tract infections, bone related adverse events, renal safety and adverse events related to volume depletion. Dose-response analysis was not conducted for the effect of dapagliflozin on bone safety because the overall fracture rate was low (1.4%) and was balanced between dapagliflozin and the control groups. Incidence of breast and bladder cancers is low to perform meaningful dose-response analysis. No significant trend for increasing proportion of subjects with safety events such as genital or urinary tract infections, liver enzyme elevations, volume depletion with increasing dose observed. However, in the development program one case of probable Hy's law has been identified in association with dapagliflozin.

- **Dose/Exposure-Response Efficacy:**

The dose-response relationship for effectiveness supports the proposed dose of 10 mg QD because higher response was observed at the 10 mg dose compared to the lower doses of 5 and 2.5 mg in combination therapy trials.

Dose response relationship was observed in MB102014 and D1690C00005, where three doses of dapagliflozin (2.5, 5 and 10 mg) were administered as an add-on to metformin and glimepiride (a sulfonylurea) respectively (Figure 4). There is a larger decline in HbA1c with increasing doses. At week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.84) compared to the 5 mg dose group (-0.7) in MB102014. Similarly in D1690C00005, at week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.82) compared to the 5 mg dose group (-0.63) in MB102014.

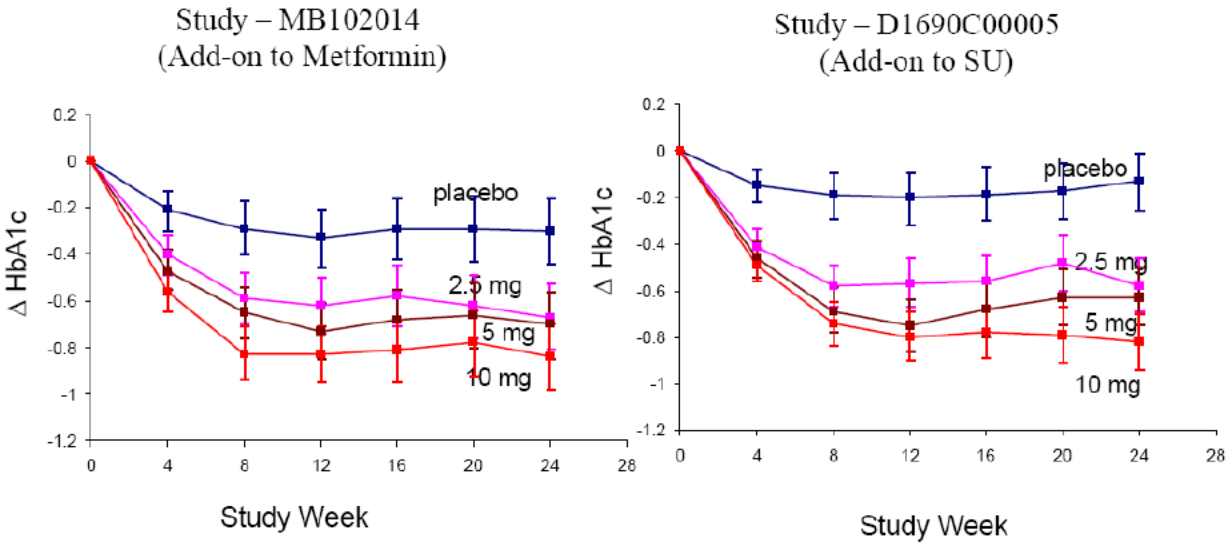


Figure 4: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 combination therapy trials MB102014 (left) and D1690C0005 (right) upon administration of placebo (blue), 2.5 mg (pink), 5 mg (brown) and 10 mg (orange) QD of dapagliflozin as an add-on to metformin and glimepiride (SU) respectively.

Source: Sponsor's Tables S.5.1 and S.5.2 in study reports mb102014. Sponsor's Table 11.2.2.1.5 in study report D1690C00005.

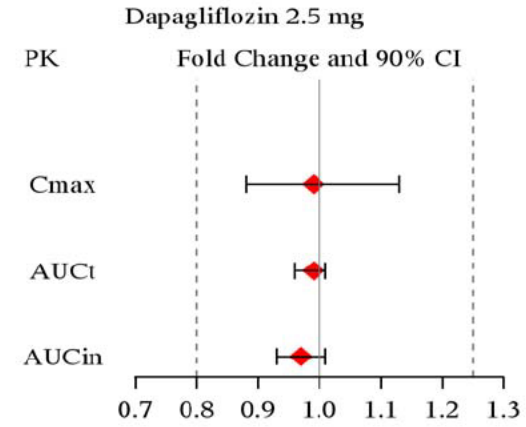
➢ **Pivotal BE Studies :**

There were no pivotal BE studies in this application. The film-coated tablets proposed for commercialization are similar to the tablets used in the Phase 3 clinical trials except that there were minor modifications of [(b) (4)] shape, embossing [(b) (4)] for which a biowaiver was requested.

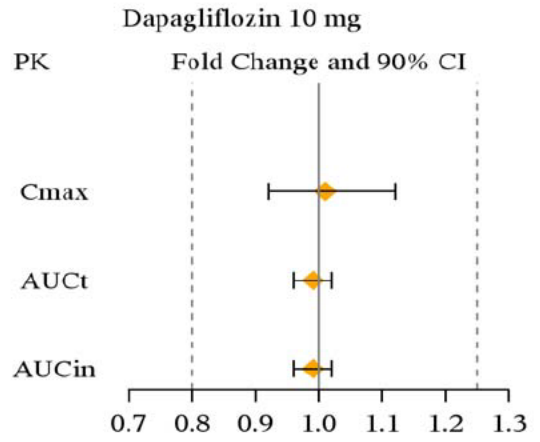
➢ **Drug Substance** [(b) (4)]

During the stability studies, it was found that dapagliflozin [(b) (4)] for 4 weeks. To assess the impact of [(b) (4)], bioequivalence studies were conducted from a [(b) (4)] tablet formulation relative to [(b) (4)] tablet formulation. Figure 5 shows that geometric mean ratio and 90% CI for AUC_t, AUC_{inf} and C_{max} were within 80% to 125% criterion limits following administration of [(b) (4)] and [(b) (4)] tablets at 2.5 mg and 10 mg dose strengths.

Study:MB102090



Study: MB102062



(b) (4)

Figure 5: Bioequivalence between (b) (4) Tablets with 2.5 and 10 mg Proposed Commercial Tablet Formulation

In conclusion, overall there were no major clinical pharmacology issues and this NDA 202293 is acceptable.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

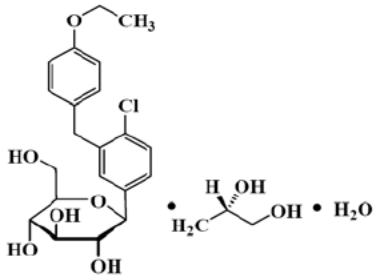
Dapagliflozin is an orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin film coated tablets, 5 mg and 10 mg are the proposed commercial strengths for oral administration. The proposed clinical dose of dapagliflozin is 10 mg administered once-daily.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Dapagliflozin is a new chemical entity developed by Bristol-Myers Squibb and Astra-Zeneca for the indication of treatment of type 2 diabetes. Dapagliflozin is a first in class drug that belongs to a new class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitor.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Table 2: Chemistry and Physicochemical Properties of the Drug Substance

	Dapagliflozin
Description	white to off-white powder
Chemical Name (IUPAC)	(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, (2*S*)-propane-1,2-diol (1:1) monohydrate
Molecular Formula	C21H25ClO6 •C3H8O2 •H2O
Molecular Weight	408.87 (Dapagliflozin)
Structural Formula	

Solubility	(b) (4)
Melting Point/Range:	
***n*-Octanol/Water Partition Coefficients (Po/w) at 24°C ± 3°C at pH 7.4**	
Isomerism	

Formulation: Dapagliflozin film-coated tablets containing dapagliflozin propanediol drug substance are manufactured in strengths of 5 mg and 10 mg (as dapagliflozin). Table 3 shows the composition of the to-be-marketed dapagliflozin film tablets.

Table 3: Composition of Dapagliflozin Film-Coated Tablets, 5 mg and 10 mg

Component	Quality Standard	Function	Quantity per Unit Dose (mg/tablet)	
			5-mg tablet	10-mg tablet
CORE TABLET				(b) (4)
Dapagliflozin Propanediol (BMS-512148-05)[a]	In-house[b]	Active		
Microcrystalline Cellulose[d]	NF/Ph.Eur.	(b) (4		
Anhydrous Lactose	NF/Ph.Eur.			
Crospovidone	NF/Ph.Eur.			
Silicon Dioxide	NF			
Magnesium Stearate	NF/Ph.Eur.			
				(b) (4)
FILM COAT				
				(b) (4)
Film-Coated Tablet Weight			**130.000**	**260.00**

(b) (4)

2.1.3 What is the mechanism of action and therapeutic indication?

Dapagliflozin is an orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption.

SGLT2 is the major luminal glucose transporter responsible for reabsorption of glucose from the glomerular filtrate, and is selectively expressed in the kidney. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary glucose excretion (glucuresis). In cell-based assays of human SGLT2 and SGLT1 activity, dapagliflozin inhibited human SGLT2 activity with an half-maximal effective concentration (EC_{50}) value of 1.12 ± 0.065 nM, and inhibited human SGLT1 with an EC50 value of 1391 ± 7 nM, leading to a selectivity estimate of 1200 fold for SGLT2 vs. SGLT1.

2.1.4 What are the proposed dosage and route of administration?

Dapagliflozin was developed for use in the treatment of type 2 diabetes mellitus (T2DM) by Bristol-Myers Squibb and AstraZeneca. The proposed clinical dose of dapagliflozin is 10 mg to be administered orally once-daily. A 5 mg dapagliflozin tablet is also available if needed for patients at risk of volume depletion. Due to the diuretic effect of dapagliflozin, volume depletion is a potential concern. In patients at high risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg dose of dapagliflozin is recommended. This recommendation is supported by observations of fewer adverse events of hypotension, dehydration, or hypovolemia among the dapagliflozin 5 mg group in the small subgroup of subjects who received loop diuretics.

2.1.5 Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

No, DSI inspection was not requested from clinical pharmacology standpoint.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The dapagliflozin clinical development program included in this application consists of 26 pharmacology studies, 3 Phase 2b studies, and 11 Phase 3 studies.

Efficacy and Safety Program (Phase 2b/3 Program):

The Phase 2b program included 3 studies in drug-naïve and insulin-treated subjects with T2DM and evaluated the dose ranging from 1 to 50 mg of dapagliflozin. Improvement in glycemic parameters were evident throughout this dose range, with efficacy observed in the range of 2.5 and 10 mg. Adverse events (e.g. genital or urinary tract infections (UTIs), hyperphosphatemia) were more common in the 20 and 50 mg dose groups compared to lower doses. Based on these observations the dapagliflozin 2.5, 5, and 10 mg doses were chosen for further evaluation in the Phase 3 program. Also based on FDA's advice, dapagliflozin 1 mg was also evaluated in a Phase 3 trial.

Phase 3 program for dapagliflozin consist of 11 studies to evaluate the efficacy and safety of dapagliflozin as monotherapy, add-on combination (to metformin, SU, TZD, and insulin) therapy, and initial combination therapy with metformin. **Table 4** presents the summary of Phase 3 program.

Table 4: List of Phase 2b and Phase 3 studies

Study number/ Duration	**Subject population**	**Treatment groups N per group/N treated with dapagliflozin/Total**
Phase 2b studies		
MB102008 12 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, 10, 20, and 50 mg, placebo and metformin XR 750/1500 mg 47-59/279/389
MB102009 12 weeks	Insulin-dependent subjects with HbA1c ≥7.5% and ≤10.0%	Dapa 10 or 20 mg and placebo 23-24/48/71
D1692C00005 12 weeks	Japanese subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, 5, and 10 mg and placebo 54-59/225/279
Phase 3 studies		
Monotherapy		
MB102013 24 plus 78 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0% Open treatment group with HbA1c ≥10.1% and ≤12.0%	Dapa 2.5, 5, and 10 mg and placebo 64-76/410/485 Dapa 5, 10 mg 34-39/73/73
MB102032 24 weeks	Drug-naive subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, and 5 mg and placebo 68-74/214/282
Add-on combination therapy with metformin		
MB102014 24 plus 78 weeks	Subjects on metformin ≥1500 mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 135-137/409/546
D1690C00012 24 plus 78 weeks	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10 mg and placebo 91/91/182

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Add-on combination therapy with insulin		
D1690C00006 24 plus 24 plus 56 weeks	Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%	Dapa 2.5, 5, and 10 mg and placebo 196-212/610/807
Add-on combination therapy with TZD		
MB102030 24 plus 24 weeks	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10 mg and placebo 139-141/281/420
Add-on combination therapy with SU		
D1690C00005 24 plus 24 weeks	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596
Initial combination therapy with metformin		
MB102021 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638
Active comparator		
D1690C00004 52 plus 156 weeks	Subjects on metformin >1500 mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814
Special populations		
MB102029 24 plus 28 plus 52 weeks	Subjects with moderate renal impairment (GFR >30 to <60 mL/min/1.73m^2 on a stable anti-diabetic regimen with HbA1c ≥7% and ≤11%	Dapa 5 and 10 mg and placebo 83-85/168/252

Dapa Dapagliflozin; GFR glomerular filtration rate; HbA1c Hemoglobin A1c; IU International units; OAD Oral antidiabetic drug; SU Sulfonylurea; vs Versus; XR Extended release.

Clinical Pharmacology Program:

Clinical Pharmacology program consists of a total of 26 Clinical Pharmacology studies. The clinical pharmacology profile of dapagliflozin has been characterized based on the results of 26 clinical pharmacology studies as well as population pharmacokinetic (PPK)

and exposure-response (E-R) analyses that incorporated data from Phase 1 and Phase 2/3. In general, clinical pharmacology program consists of SD and MD dose PK/PD studies in healthy and T2DM subjects, mass balance study, absolute oral bioavailability study, drug-drug interaction, renal impairment and hepatic impairment study, relative bioavailability (b) (4) study, food effect study, bioequivalence study of (b) (4) tablets, thorough QTc study. Clinical pharmacology program also included population pharmacokinetics and exposure-response analysis from Phase 1 and Phase 2/3 studies. Table 5 summarizes the list clinical pharmacology studies.

Table 5: List of Clinical Pharmacology Studies

Study Description [Dapagliflozin Dose(s) Used in the Study]	Study Number
Safety/Pharmacokinetics/Pharmacodynamics	
Single ascending doses in healthy subjects [2.5 - 500 mg]	MB102001[1,2]
Multiple ascending doses in healthy subjects [2.5 to 100 mg]	MB102002[3,4]
Multiple doses in subjects with T2DM [5 - 100 mg]	MB102003[5,6]
Low dose pharmacokinetics/pharmacodynamics in healthy subjects [0.001 to 2.5 mg]	MB102088[7]
^{14}C-ADME and Mass Balance [50 mg/~12 µCi]	MB102006[8,9]
Absolute Oral Bioavailability [Intravenous: 80 µg/~160 µCi. Oral: 10 mg]	MB102059[10]
Thorough QTc study [20 and 150 mg]	D1690C00001[11,12]
Exposure-response modeling [2.5-500 mg single dose, 2.5-100 mg QD]	Multiple studies[13]
Specific Populations	
Renal impairment [20 mg and 50 mg]	MB102007[14,15]
Hepatic impairment [10 mg]	MB102027[16,17]
Race, Age, T2DM, Gender, Body Weight (pooled analysis of Clinical Pharmacology studies and population pharmacokinetic analysis)	Section 3 and Multiple studies[13]
Single ascending doses in healthy Japanese subjects [2.5 - 50 mg]	MB102010[18]
Multiple ascending doses in Japanese subjects with T2DM [2.5 - 20 mg]	MB102025[19]
Drug-Drug Interactions	
Antidiabetic Agents	
Pioglitazone (45 mg QD) + Dapagliflozin [50 mg]	MB102017[20,21]
Metformin (1000 mg) + Dapagliflozin [20 mg]	MB102026[22,23]

Study Description [Dapagliflozin Dose(s) Used in the Study]	Study Number
Glimepiride (4 mg) + Dapagliflozin [20 mg]	MB102037[24,25]
Sitagliptin (100 mg) + Dapagliflozin [20 mg]	MB102037[24]
Voglibose (0.2 mg TID) + Dapagliflozin [10 mg]	D1692C00002[26,27]
Potentially Co-Prescribed Cardiovascular Disease Agents	
Hydrochlorothiazide (25 mg)) + Dapagliflozin [50 mg]	MB102004[28,57]
Valsartan (320 mg) + Dapagliflozin [20 mg]	MB102036[29,30]
Simvastatin (40 mg) + Dapagliflozin [20 mg]	MB102036[29]
Bumetanide (1 mg) + Dapagliflozin [10 mg]	MB102057[31,32]
Digoxin (0.25 mg) + Dapagliflozin [10 mg]	MB102058[33]
Warfarin (25 mg) + Dapagliflozin [10 mg]	MB102058[33]
Metabolic Enzyme Inducer	
Rifampin (600 mg) + Dapagliflozin [10 mg]	MB102074[34]
Biopharmaceutics	
Relative bioavailability ((b) (4) [50 mg]	MB102005[35,36]
Food effect study [10 mg, (b) (4)	MB102019[37,38]
Bioequivalence of (b) (4) in tablets and food effect on the (b) (4) [10 mg]	MB102062[39]
Bioequivalence & food effect of (b) (4) in tablets [2.5 mg]	MB102090[40]

Source: Sponsor's summary of clinical pharmacology report.
Drug-Drug Interaction study (MB102093) with UGT1A9 inhibitor Mefenamic acid is submitted after the initial NDA submission and hence not shown in the list.

2.2.2 *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?*

The American Diabetes Association (ADA) recommends the use of HbA1c levels as an indicator of glycemic control. The sponsor has used the change from baseline in HbA1c as the primary efficacy variable in all key efficacy studies. In addition, to other glycemic parameters, PD parameter based on the mechanism of action of drug was measured in some clinical pharmacology studies. These include urinary glucose excretion, fasting plasma glucose, and postprandial glucose.

2.2.3 *Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes. Please refer to the analytical section for details.

2.3 Exposure-Response

2.3.1 What are the characteristics of the exposure-response relationship for effectiveness?

The dose-response relationship for effectiveness supports the proposed dose of 10 mg QD. In Phase 2B monotherapy trial, MB102008 a dose-related increase was observed in change from baseline in HbA1c, FPG and urinary glucose (Figure 6). However, there was no significant improvement in HbA1c levels beyond 10 mg dose group. At week 12, the mean change from baseline in HbA1c was -0.85, -0.55 and -0.9 for the 10, 20 and 50 mg dose groups respectively.

Phase 2B – MB102008

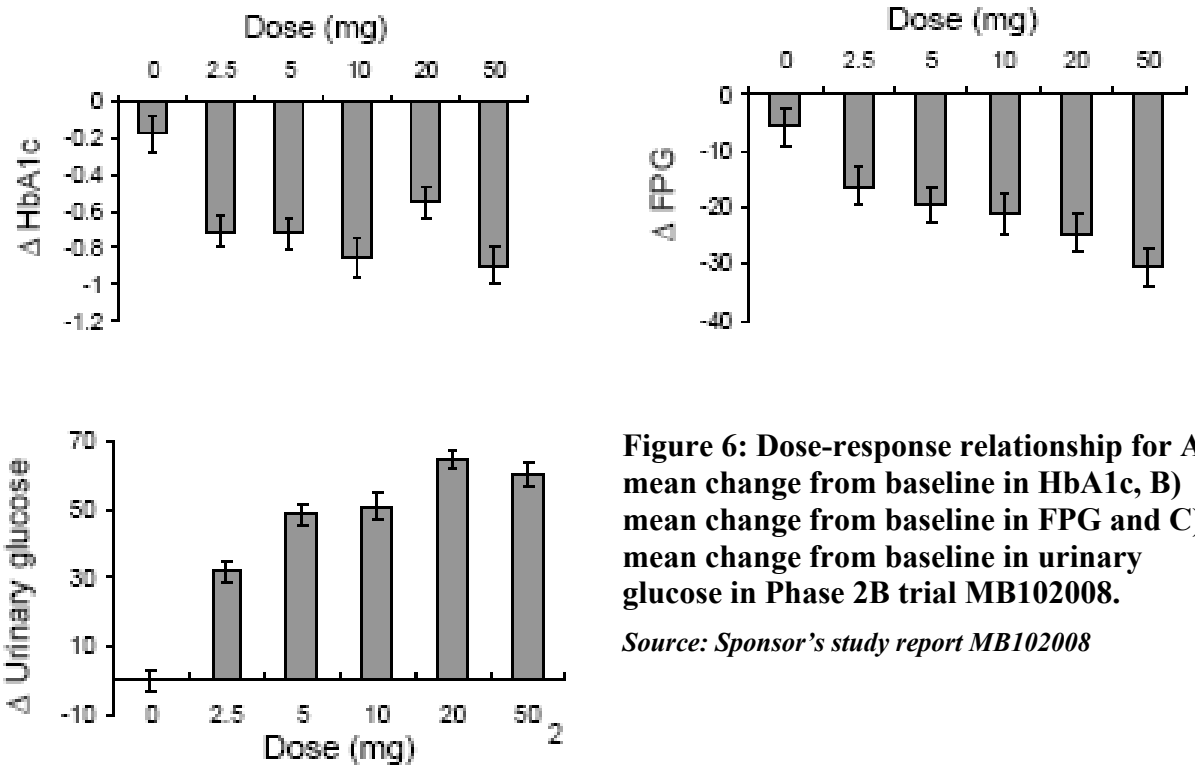


Figure 6: Dose-response relationship for A) mean change from baseline in HbA1c, B) mean change from baseline in FPG and C) mean change from baseline in urinary glucose in Phase 2B trial MB102008.

Source: Sponsor's study report MB102008

In two Phase 3 monotherapy trials (study MB102013 and MB102032), a clear separation between the time-profiles of the adjusted mean change in HbA1c for the treatment arms and placebo is observed (Figure 7). There is a larger decline in the adjusted mean change from baseline in HbA1c for the treatment arms compared to placebo at all time points. However, in the trial MB 102013 decline in HbA1c in the 10 mg dose group is similar to the decline observed for the 5 mg dose group. There is no clear separation between the 5 and 10 mg dose groups (Figure 7).

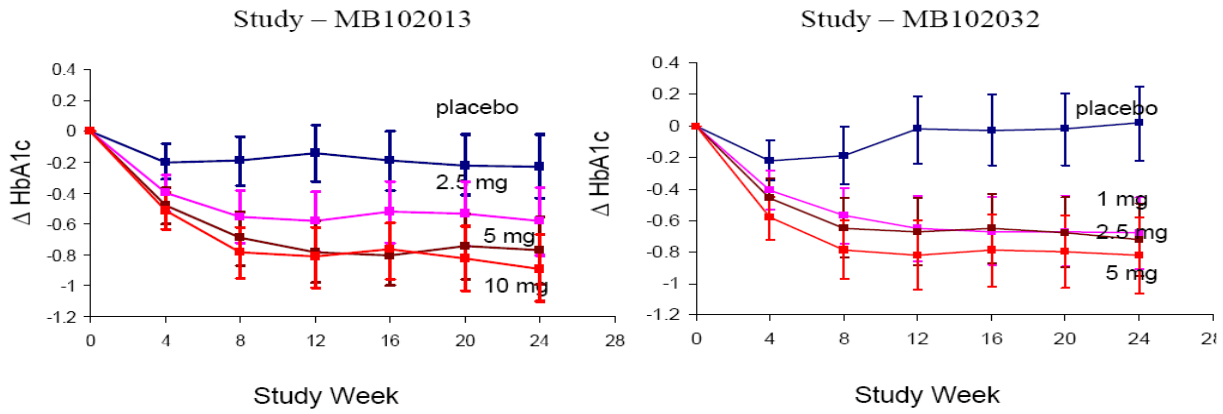


Figure 7: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 monotherapy trials MB102013 (left) and MB102032 (right) upon administration of placebo (blue), 2.5 mg (pink), 5 mg (brown) and 10 mg (orange) QD of dapagliflozin.

Source: Sponsor's Tables S.5.1 and S.5.2 in study reports mb102013 and mb102032.

Also, an increase in response was observed with increasing doses in Phase 3 combination therapy trials. A clear separation was observed between the treatment arms and the placebo group in MB102014 and D1690C00005, where three doses of dapagliflozin (2.5, 5 and 10 mg) were administered as an add-on to metformin and glimepiride (SU) respectively (Figure 8).

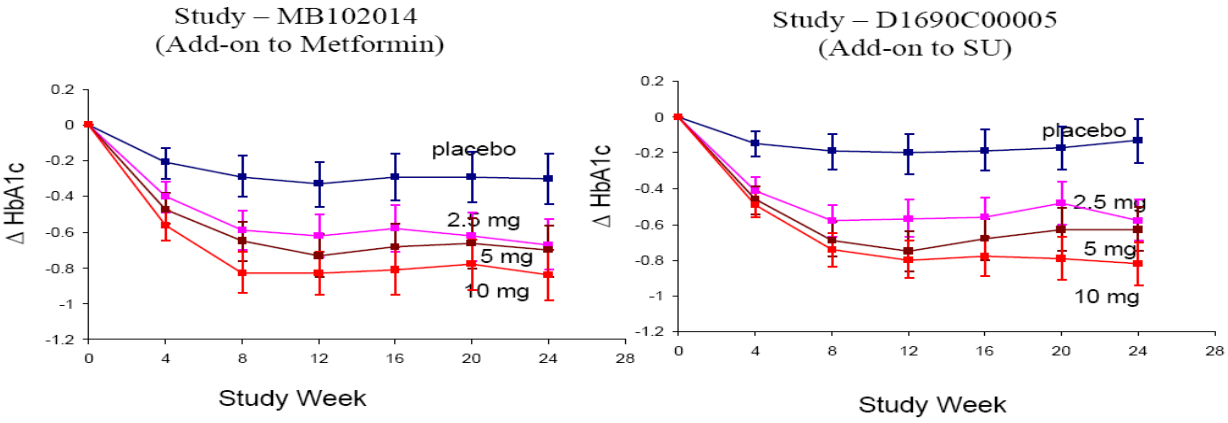


Figure 8: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 combination therapy trials MB102014 (left) and D1690C0005 (right) upon administration of placebo (blue), 2.5 mg (pink), 5 mg (brown) and 10 mg (orange) QD of dapagliflozin as an add-on to metformin and glimepiride (SU) respectively.

Source: Sponsor's Tables S.5.1 and S.5.2 in study reports mb102014. Sponsor's Table 11.2.2.1.5 in study report D1690C00005.

There is a larger decline in HbA1c with increasing doses. At week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.84) compared to the 5 mg dose group (-0.7) in MB102014. Similarly in D1690C00005, at week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.82) compared to the 5 mg dose group (-0.63) in MB102014. Thus based on effectiveness, the 10 mg dose group seems appropriate in combination therapy as an increase in response was observed with increasing doses. Please refer to Pharmacometrics Review by Dr. Anshu Marathe (Appendix 4.4) for further details.

2.3.2 What are the characteristics of the exposure-response relationships for safety?

The major safety issues associated with dapagliflozin were bladder and breast cancer, marked elevation in liver enzymes, genital infections, urinary tract infections, bone related adverse events, renal safety and adverse events related to volume depletion (Please refer to review by Dr. Somya Dunn for details on safety).

- **Genital and Urinary Tract Infection:** In the Phase 2 dose finding study, genitourinary tract infections were more common in the 20 and 50 mg dose groups (17% and 16%) compared to the 2.5, 5, and 10 mg dapagliflozin groups (7%, 10%, and 11%).In the short term treated pooled analysis of Phase 3 trials, no significant trend for increasing proportion of subjects with genital or urinary tract infections with increasing dose (2.5 mg-10 mg) was observed. The proportion of subjects with genital infections was 5.8%, 7% and 7% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arms, respectively. The proportion of subjects with urinary tract infections were 4.2 %, 7.3% and 6.5% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm.

- **Breast and Bladder Cancer:** Numeric imbalances in breast cancer and bladder cancer were observed in the clinical development program. Nine (0.4%) patients treated with dapagliflozin vs. 1 (0.09%) with placebo were reported with breast cancer. Nine (0.3%) patients treated with dapagliflozin vs. 1 (0.05%) with placebo were reported with bladder cancer (Please refer to review by Dr. Somya Dunn for further information). Incidence of these cancers is low to perform meaningful dose-response analysis.

- **Liver Injury:** The proportion of subjects with elevated liver tests was 3.9%, 3.5% and 3.6% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm. Overall, a trend for increasing proportion of subjects with liver enzyme elevations with increasing dose is not observed. However, in the development program one case of probable Hy's law has been identified in association with dapagliflozin (Please refer to review by Dr. Somya Dunn for further information).

- **Bone Safety:** Dose-response analysis was not conducted for the effect of dapagliflozin on bone safety because the overall fracture rate was low (1.4%) and was balanced between dapagliflozin and the control groups.

- **Renal Safety and Volume Depletion:** There was no evidence of any impact on estimated glomerular filtration rate (eGFR) in patients with normal or mild renal impairment (Figure 9). There was a small initial decrease in eGFR that was stable and did not appear to progress in a dedicated study in patients with T2DM with moderate renal impairment (Appendix 4.4)

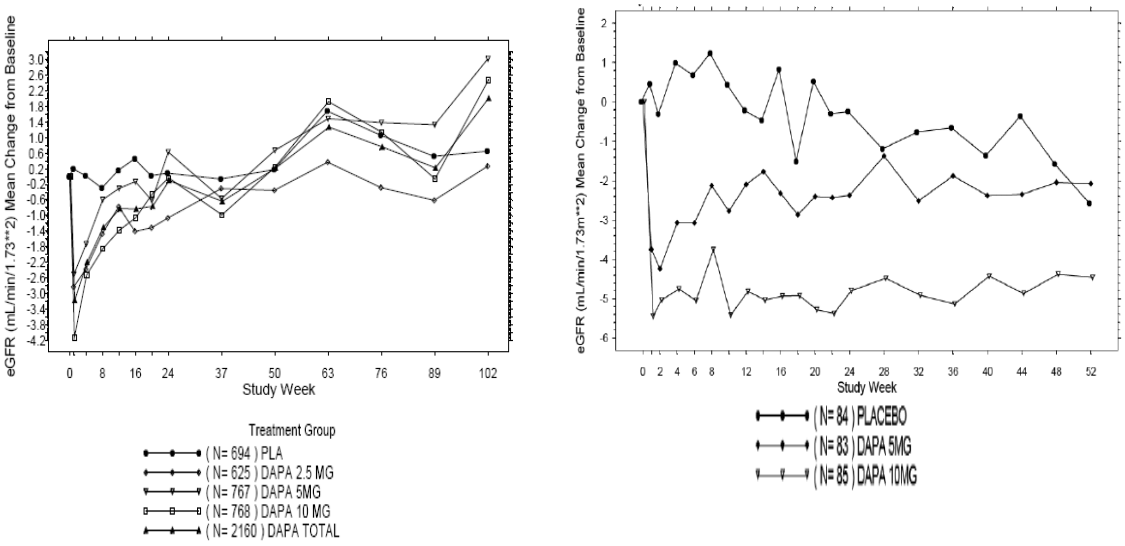


Figure 9: Time-profiles for mean change in GFR from baseline in A) pooled analysis and B) renal impairment trial MB102029.

Source: Sponsor's Figure 4 and Figure 5 in summary of clinical safety.

- **Volume Depletion:** There was no trend of increased AE related to volume depletion with increasing dose. The incidence these adverse events were low. In 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. The sponsor has proposed a lower dose of 5 mg in these patients at higher risk for volume depletion.

- **Cardiovascular Safety:** The cardiovascular risk profile was evaluated through a meta-analysis of major cardiovascular events in a pool of Phase 2b and Phase 3 trials. In the meta-analysis there was no 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 which meets the December 2008 Guidance, ruling out the unacceptable cardiovascular risk (Please refer to Dr. Anita Abraham's Review for further detail).

2.3.3 Does this drug prolong QT/QTc Interval?

The effect of dapagliflozin on the QT interval was assessed in a single centre, 4-period, 4-treatment, double-blind, double-dummy, placebo-controlled, crossover study in 50

healthy males randomized to receive one of the following 4 treatments in 4 separate periods, separated by a minimum 7-day washout interval:

- Treatment A: 150-mg dapagliflozin
- Treatment B: 20-mg dapagliflozin
- Treatment C: 400-mg moxifloxacin
- Treatment D: placebo

Moxifloxacin (400 mg) was used as a positive control. Based on Sponsor's analysis, no significant effect of Dapagliflozin was detected in this 'thorough QT' study. No significant QT prolongation effect of dapagliflozin (20 mg and 150 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between dapagliflozin (20 mg and 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms.

The C_{max} of dapagliflozin and its metabolite BMS-801576 after supratherapeutic dose (150 mg) was approximately 8- and 7-fold those of the therapeutic dose (20 mg), respectively. The maximum proposed clinical dose of dapagliflozin is 10 mg daily which is 15 times less than the supratherapeutic dose (150 mg single oral dose). The relationship between ΔΔ QTcF and dapagliflozin concentrations is visualized in Figure 10 with no evident exposure-response relationship. Please see QT-IRT review under IND 68,652 (DARRTs dated 4 April 2009) for more details.

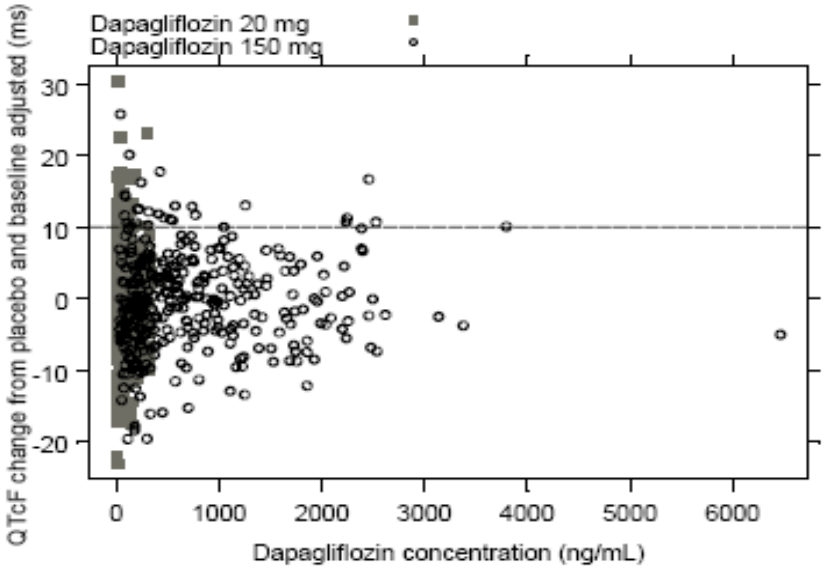


Figure 10 : ΔΔQTcF vs. Dapagliflozin Concentration

Source: QTIRT Review by Dr. Joanne Zhang DARRTs dated 04/02/2009

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

- **Single Dose:**

The single dose PK of dapagliflozin was characterized in double-blind, placebo-controlled, sequential, ascending, single-dose study in healthy subjects. Single oral dose range from 2.5 mg- 500 mg were administered in healthy volunteers. Dapagliflozin was rapidly absorbed after oral administration with maximum plasma concentrations (C_{max}) observed within 2 h after administration in the fasted state. T_{max} ranged from 0.5 – 2.0 h and elimination phase half-life values (T-HALF) ranged from 1.7 to 19 h. Figure 11 presents the pharmacokinetic profile and Table 6 summarizes the pharmacokinetic parameter of dapagliflozin following single dose administration in healthy subjects.

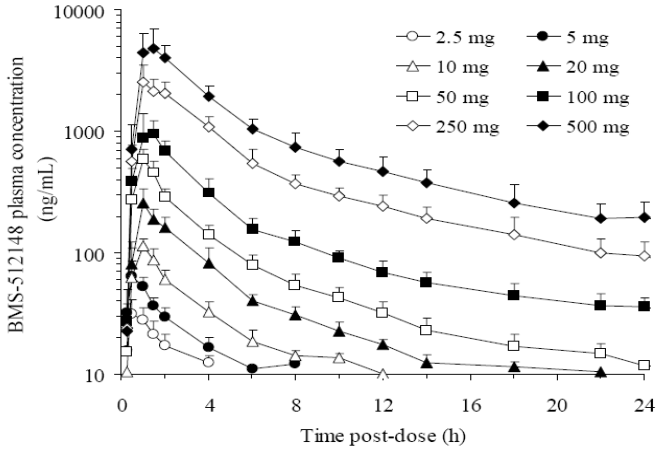


Figure 11: Plasma Concentration-Time Profiles Over the First 24 h Following Administration of Single Oral Doses of Dapagliflozin (b) (4) * to Fasted Healthy Subjects

Source: MB102001 Clinical Study Report;
**** (b) (4) formulation was used in the early clinical trial. Phase 3 studies used tablet formulation. Refer to section General Biopharmaceutics for further details.***

Table 6: Summary Statistics for Dapagliflozin PK Parameters Following Single Dose Administration is Fasted State

PK Parameter	Dapagliflozin Dose (mg)	n	Statistic
Cmax (ng/mL) Geometric Mean (CV%)	2.5	6	32 (24)
	5	6	67 (21)
	10	6	116 (17)
	20	6	269 (18)
	50	6	600 (21)

	100 250 500	6 5 6	1112 (32) 2510 (31) 4734 (40)
AUC(INF) (ng•h/mL) Geometric Mean (CV%)	2.5 5 10 20 50 100 250 500	5 6 6 6 6 6 5 6	81 (46) 185 (20) 368 (20) 977 (23) 2004 (16) 4363 (15) 13337 (28) 25518 (24)
Tmax (h) Median (Min, Max)	2.5 5 10 20 50 100 250 500	6 6 6 6 6 6 5 6	0.50 (0.50, 1.50) 0.50 (0.50, 1.00) 1.00 (0.50, 1.50) 1.00 (1.00, 2.00) 1.00 (0.50, 1.50) 1.25 (1.00, 1.50) 1.50 (1.00, 2.00) 1.50 (1.00, 2.00)
T-HALF (h) Mean (SD)	2.5 5 10 20 50 100 250 500	5 6 6 6 6 6 5 6	1.67 (0.69) 2.52 (0.74) 3.00 (0.87) 8.51 (6.92) 11.96 (7.36) 15.93 (15.80) 17.33 (19.75) 19.04 (7.01)
%UR (%) Mean (SD)	2.5 5 10 20 50 100 250 500	4 6 6 6 6 6 6 4	1.54 (0.89) 0.46 (0.19) 3.20 (1.39) 0.61 (0.16) 0.72 (0.17) 1.04 (0.21) 1.54 (0.40) 1.17 (0.54)
CLR (mL/min) Mean (SD)	2.5 5 10 20 50 100 250 500	3 6 6 6 6 6 6 4	4.99 (3.41) 2.08 (0.90) 13.93 (4.84) 2.17 (0.78) 3.03 (0.78) 4.03 (0.96) 4.99 (0.91) 4.06 (1.28)

Reviewer's Comment: *The increase in dapagliflozin half-life with increasing dose is likely related to the analytical limit of quantitation that is higher than the plasma concentration in the terminal elimination phase at the lower doses. In these initial studies the lower limit of quantification for dapagliflozin was 10 ng/mL.*

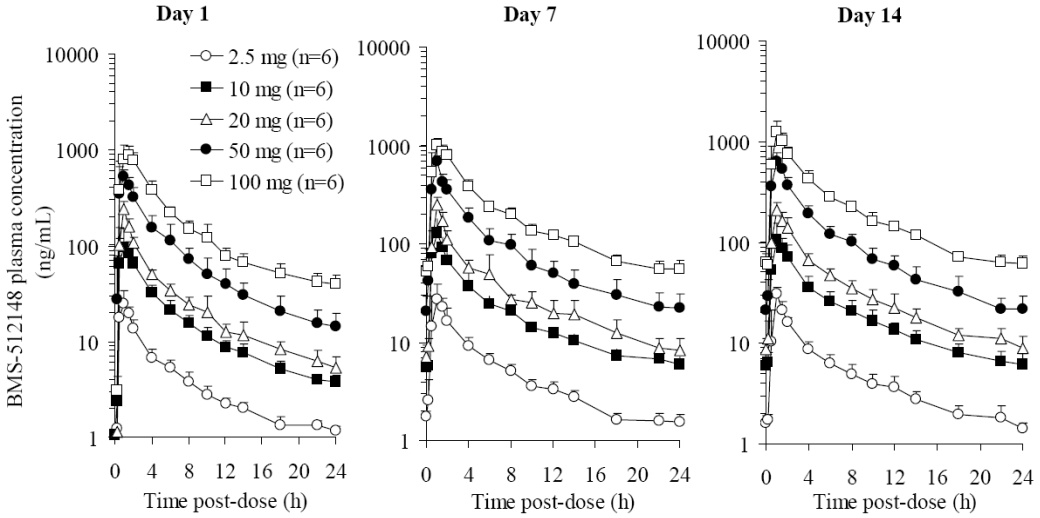
The amount of dapagliflozin recovered in the urine was low. Less than 5% of the dose was excreted unchanged in the urine (%UR) and renal clearance (CLR) values were less than 5 mL/min for all dose groups except the 10-mg panel. The reason(s) for the higher

mean %UR for dapagliflozin and consequently the corresponding CLR values in the 10 mg panel relative to the lower and higher dose panels within this study remain unknown. The mean %UR does not appear to be influenced by outlier value(s).

- **Multiple Dose:**

The multiple dose PK of dapagliflozin was characterized in double-blind, placebo-controlled, sequential, ascending multiple-dose study in healthy subjects. Subjects receive once daily oral dose of dapagliflozin ranging from 2.5 mg to 100 mg for 14 days. Dapagliflozin was rapidly absorbed after oral administration with a T_{max} of 1 h (range: 0.5 to 2.0 h). Dapagliflozin $T_{1/2}$ ranged from 11.2 to 16.6 h. After multiple doses, dapagliflozin PK parameters were similar on Days 7 and 14 indicating that steady-state was reached by at least the 7th day of dosing. The accumulation index is ~ 1.25.

Figure 12 presents the pharmacokinetic profile and Table 7 summarizes the pharmacokinetic parameter of dapagliflozin following single dose administration in healthy subjects.



Source: MB102002 Clinical Study Report; * (b) (4) formulation was used in the early clinical trial. Phase 3 studies used tablet formulation. Refer to section General Biopharmaceutics for further details.

Figure 12: Mean Plasma Concentration-Time Profiles of Dapagliflozin on Days 1, 7, and 14 Following Multiple Dose Oral Administration ((b) (4) to Fasted Healthy Subjects

Table 7: Summary Statistics for Dapagliflozin PK Parameters After Oral administration of Single and Multiple Oral Doses in Healthy Subjects				
PK Parameter	**Dapagliflozin Dose (mg)**	**Study Day**		
		Day 1 (n=6)	**Day 7 (n=6)**	**Day 14 (n=6)**
Cmax (ng/mL) Geometric Mean (CV%)	2.5 mg 10 mg 20 mg 50 mg 100 mg	27 (23) 106 (32) 236 (20) 582 (30) 977 (10)	31 (26) 120 (39) 246 (20) 707 (14) 1072 (11)	30 (16) 119 (21) 202 (22) 728 (19) 1237 (23)
AUC(TAU) (ng·h/mL) Geometric Mean (CV%)	2.5 mg 10 mg 20 mg 50 mg 100 mg	98 (22) 420 (21) 725 (12) 2013 (24) 4299 (10)	126 (13) 516 (21) 854 (17) 2386 (24) 5018 (10)	126 (15) 506 (20) 910 (15) 2543 (16) 5599 (9)
Tmax (h) Median (Min, Max)	2.5 mg 10 mg 20 mg 50 mg	1.00 (0.50, 1.50) 1.00 (0.50, 2.00) 1.00 (1.00, 1.00) 1.00 (0.50, 1.50)	1.00 (0.50, 1.50) 1.00 (1.00, 1.50) 1.00 (1.00, 1.50) 1.00 (0.50, 1.00)	1.00 (1.00, 1.00) 1.00 (0.50, 2.00) 1.00 (0.50, 1.00) 1.00 (0.50, 1.50)
T-HALF (h) Mean (SD)	2.5 mg 10 mg 20 mg 50 mg 100 mg	N/A	N/A	11.21 (5.67) 15.77 (6.23) 13.72 (6.35) 14.38 (5.74) 16.55 (8.05)
Accumulation Index (AI) Geometric Mean (CV%)	2.5 mg 10 mg 20 mg 50 mg 100 mg	N/A	1.29 (12.81) 1.23 (6.60) 1.18 (11.94) 1.19 (7.63) 1.17 (5.86)	1.28 (10.40) 1.20 (8.07) 1.25 (9.06) 1.26 (9.75) 1.30 (11.02)

Source: MB102002 Clinical Study Report. T-HALF values on Days 1 and 7 could not be adequately characterized because plasma samples were not collected at time points greater than 24 h post-dose

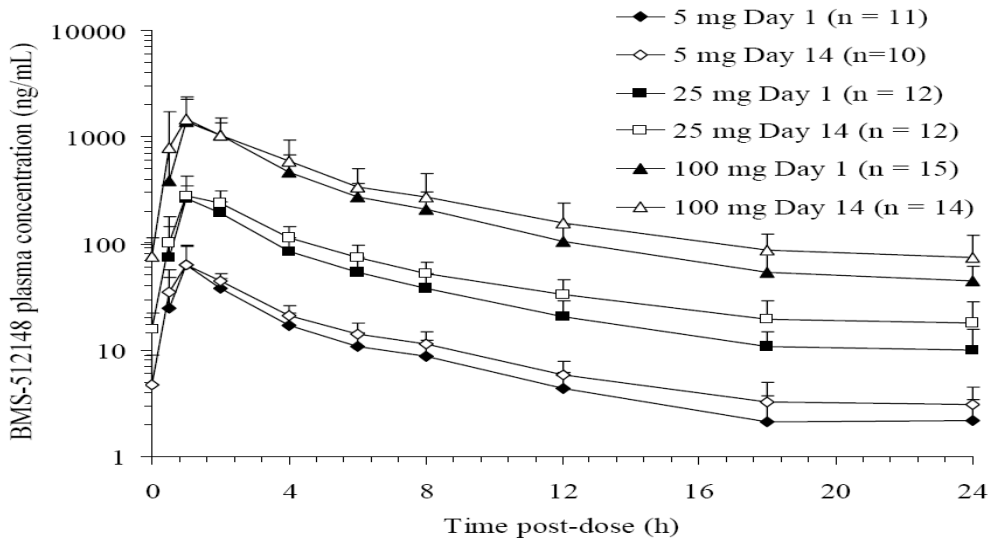
Reviewer's Comment: *Dapagliflozin-3-O-glucuronide which is the major inactive metabolite of dapagliflozin was not monitored in these early Phase 1 single dose and multiple dose studies. In these studies active minor metabolite BMS-511926 was monitored which was not a major metabolite (molar ratio in plasma of 0.01).*

2.4.2 How does the PK of Dapagliflozin in T2DM patients compared to that in healthy volunteers?

The PK characteristics of dapagliflozin were similar in healthy subjects and T2DM patients.

The multiple dose PK of dapagliflozin was characterized in double-blind, placebo-controlled, multiple-dose study in type-2 diabetic subjects. Subjects received once daily oral dose of dapagliflozin ranging from 2.5 mg -100 mg (2.5, 10 mg, 100 mg) for 14 days. Dapagliflozin was rapidly absorbed after oral administration with a T_{max} of 1 h (range: 0.5 to 4.0 h). The accumulation index is ~ 1.3. Figure 13 presents the

pharmacokinetic profile and Table 8 summarizes the pharmacokinetic parameter of dapagliflozin following single and multiple oral dose administration in type-2 diabetic subjects.



Source: MB102003 Clinical Study Report

Figure 13: Plasma Concentration-Time Profiles for Dapagliflozin on Days 1 and 14 Following Daily Administration of 5, 25, and 100 mg of BMS-512148 to Type 2 Diabetic Subjects.

Table 8: Summary Statistics for Dapagliflozin PK Parameters After Oral administration of Single and Multiple Oral Doses in Type-2 Diabetic Subjects

Pharmacokinetic Parameter	BMS-512148 Dose	Study Day	
		Day 1	Day 14
Cmax (ng/mL)	5 mg (n=11)	66 (37)	68[c] (32)
Geometric Mean	25 mg (n=12)	279 (19)	288 (41)
(C.V. %)	100 mg (n=16)	1490 (40)	1617[b] (46)
AUC(TAU) (ng·h/mL)	5 mg (n=11)	220 (32)	281[c] (28)
Geometric Mean	25 mg (n=12)	1037 (25)	1373 (31)
(C.V. %)	100 mg (n=16)	5427 (30)	7070[b] (36)
A.I.	5 mg (n=11)	-- --	1.23[c] (16)
Geometric Mean	25 mg (n=12)	-- --	1.32 (17)
(C.V. %)	100 mg (n=16)	-- --	1.33[b] (11)
Tmax (h)	5 mg (n=11)	1.00 (0.50, 2.00)	1.00[c] (0.50, 2.00)
Median	25 mg (n=12)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
(Min, Max)	100 mg (n=16)	1.00 (1.00, 4.00)	1.00[b] (0.50, 4.00)
%UR	5 mg (n=11)	1.44 (0.75)	2.02[c] (1.21)
Mean	25 mg (n=12)	0.83 (0.34)	1.28 (0.66)
(S.D.)	100 mg (n=16)	1.49 (0.80)	2.41[b] (0.90)
CLR (mL/min)	5 mg (n=11)	5.88 (4.07)	6.37[c] (3.91)
Mean	25 mg (n=12)	3.44 (1.83)	3.95 (2.47)
(S.D.)	100 mg (n=16)	4.41 (1.89)	5.50[b] (1.89)

Source: MB102003 Clinical Study Report

2.4.3 What are the characteristics of drug absorption?

The absolute bioavailability of dapagliflozin from the Phase 3 tablet formulation is 78% under fasting condition (Table 9). Please refer to section 2.8.5 for further details.

Table 9: Summary Statistics for Dapagliflozin PK Parameters following IV and Oral Administration.

Dapagliflozin Pharmacokinetic Parameters		
	Treatment A (n=7)	Treatment B (n=7)
AUC_{inf} (ng.h/mL) Geom. Mean (CV %)	628 (17)	6.78 (22)
AUC_{0-t} (ng.h/mL) Geom. Mean (CV %)	598 (17)	6.43 (23)
C_{max} (ng/mL) Geom. Mean (CV %)	143 (29)	10.2 (49)
$T_{1/2}$ (h) Mean (s.d.)	13.7 (3.44)	12.2 (5.25)
T_{max} (h) Median (Min, Max)	1.03 (0.50, 1.50)	0.03 (0.03, 0.08)
CL (mL/min) Geom. Mean (CV %)	NA	207 (23)
V_{ss} (L) Mean (s.d.)	NA	118 (31.6)
F (%) Geom. Mean (CV %)	77.8 (9)	NA

Trt: A = dapagliflozin 10 mg po dose
Trt: B = [14C]-dapagliflozin 80µg iv dose
Note: NA = Not applicable

2.4.4 What are the characteristics of drug distribution?

The in vitro protein binding of dapagliflozin (BMS-512148) and its inactive metabolite dapagliflozin 3-O-glucuronide (BMS 801576) in human, rat, dog, mouse, and rabbit plasma was determined by equilibrium dialysis. The results are summarized in the Table 10 below. The *in vitro* plasma protein binding of dapagliflozin was 91% in humans. The *ex vivo* plasma protein binding of dapagliflozin in healthy human subjects was ~92%, and was similar to that in diabetic subjects with or without renal impairment and in subjects with hepatic impairment. After IV administration the volume of distribution of dapagliflozin is 118 L.

Table 10: Percent Binding of BMS-512148 and BMS-801576 to Protein in Rat, Dog, Mouse, Mouse, Rabbit and Human Plasma at 500 and 5000 ng/mL (Mean ± SD)

	Rat	Dog	Mouse	Rabbit	Human
BMS-512148	95.1 ± 0.77	93.1 ± 0.96	92.8 ± 1.20	94.2 ± 0.52	91.0 ± 0.65
BMS-801576	93.4 ± 1.08	91.9 ± 0.83	91.2± 1.38	94.7 ± 0.56	89.1 ±1.88

2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The elimination of dapagliflozin involves multiple pathways including metabolism, biliary and/or intestinal clearance, and renal clearance, with metabolic clearance being the predominant mechanism. During the collection interval of 13 days, 96% of the administered dose was recovered in the urine (~75%) and feces (~21%). In urine, 1.2% of the radiolabeled dose was recovered as parent drug and 61% as dapagliflozin-3-O-glucuronide. In feces, 15.4% of the radioactivity is because parent drug.

Table 11: Summary Statistics for Radioactivity Pharmacokinetic Parameters

Pharmacokinetic Parameter	50 mg [^{14}C]BMS-512148 (n=6)
Cmax (ng.eq/mL) Geometric Mean (C.V.%)	1761 (16)
AUC(INF) (ng.eq·h/mL) Geometric Mean (C.V. %)	6952 (22)
Tmax (h) Median (Min, Max)	1.00 (0.75, 1.00)
T-HALF (h) Mean (S.D.)	5.39 (2.86)
CLR (mL/min) Mean (S.D.)	107.73 (22.01)
%UR Mean (S.D.)	75.16 (9.19)
%FE Mean (S.D.)	20.99 (8.81)
%Total Mean (S.D.)	96.16 (1.69)
Blood Cmax (ng.eq/mL) Geometric Mean (C.V. %)	1105 (17)
Blood AUC(INF) (ng.eq·h/mL) Geometric Mean (C.V. %)	4029 (19)
Blood Tmax (h) Median (Min, Max)	0.88 (0.75, 1.00)
Blood T-HALF (h) Mean (S.D.)	3.95 (1.66)

Source: MB102006 Clinical Study Report

2.4.6 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Dapagliflozin 3-O-glucuronide was the predominant drug-related component in human plasma, accounting for 42% [based on AUC (0-12 h)] of total plasma radioactivity, similar to the 39% contribution by parent drug. No other metabolite detected in human plasma constituted > 5% of plasma radioactivity.

2.4.7 What are the characteristics of drug metabolism?

Dapagliflozin is extensively metabolized. In humans ^{14}C ADME study, < 10% of a dapagliflozin dose was eliminated via pathways involving oxidative metabolism, making it unlikely that CYP enzymes play a major role in the disposition of dapagliflozin in humans. The primary metabolite in human was dapagliflozin 3-O-glucuronide (BMS 801576) which accounted for 61% of the dapagliflozin dose. All other metabolites detected in human plasma each constituted < 5% of the radioactivity AUC. In vitro studies demonstrated that UGT1A9 is the major enzyme responsible for the formation of dapagliflozin 3-O-glucuronide. Figure 14 shows the proposed metabolic pathway of dapagliflozin.

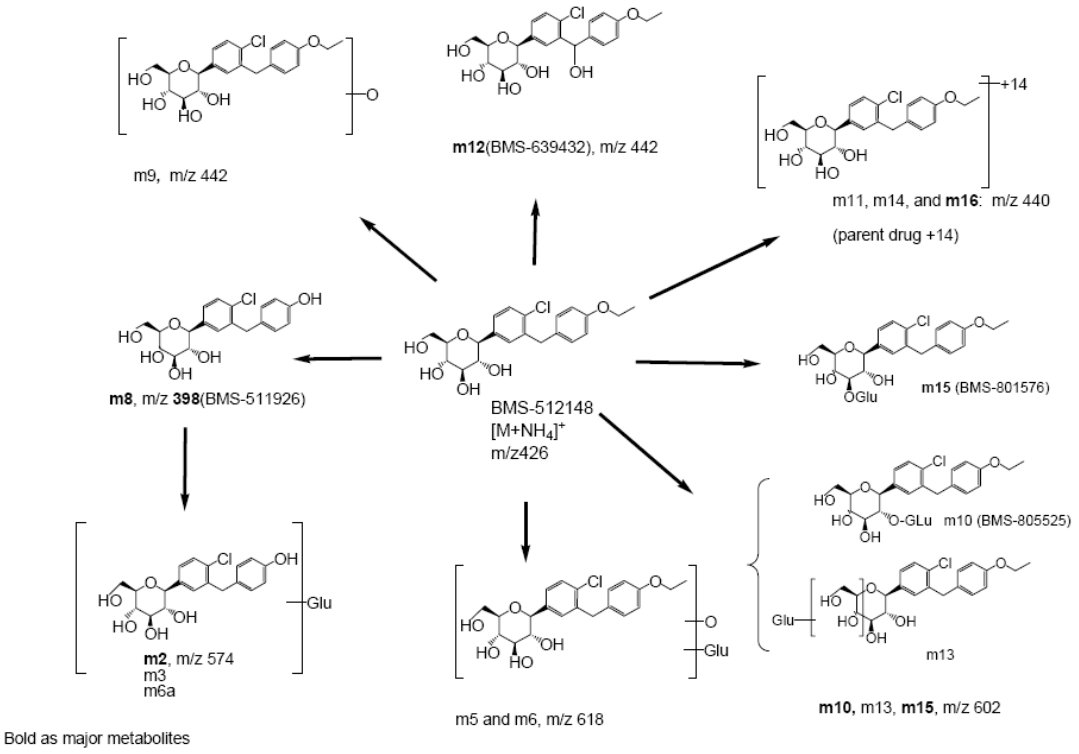


Figure 14: Proposed pathways for the *in vivo* biotransformation of [^{14}C] dapagliflozin in mouse, rats, dogs, mice and humans

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2.4.8 ***Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?***

Dose proportionality was estimated using the power model, ($Y = \alpha * Dose^{\beta}$ where Y, α and β correspond to the PK parameter (AUC or Cmax), proportionality constant and an exponent, respectively). If the 90% CI for the exponent, β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional.

Dose proportionality was evaluated using dapagliflozin AUC and Cmax obtained from the single dose ascending studies in fasted healthy subjects (MB102001) (Figure 15). Even though the C_{max} and AUC appear to increase approximately double with doubling of dose, strict dose proportionality in this dose range could not be established since the 90 % confidence intervals for slopes excluded 1.

The results slope (90%CI) for Ln Dose Vs. Ln (AUCinf) or Ln(Cmax) are as follows:
-Cmax: 0.89 (0.85 – 0.93)
- AUCinf: 1.07 (1.04 – 1.10)

In multiple dose study in healthy subjects the results slope (90%CI) for Ln Dose Vs. Ln (AUC0-tau) or Ln(Cmax) are as follows:
-Cmax: 1.02 (0.96 – 1.08)
- AUC0-tau: 1.02 (0.98 – 1.06)

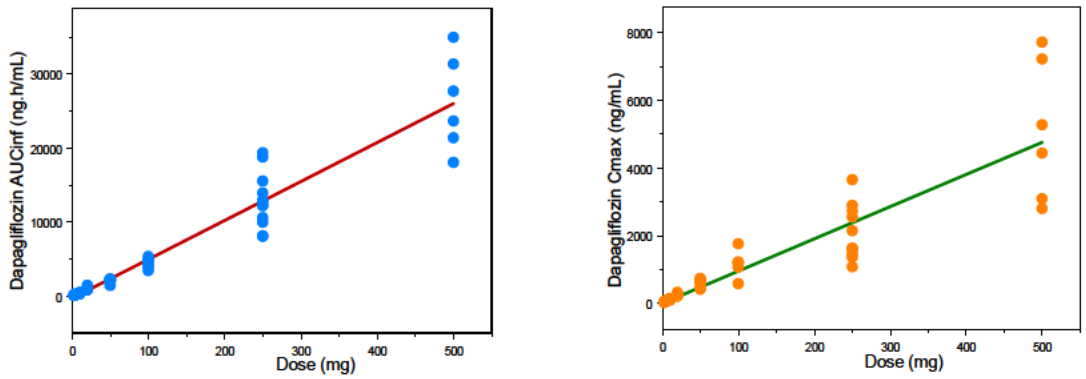


Figure 15: Dapagliflozin AUCinf and Cmax following Single Dose Administration in Healthy Subjects.

Reviewer's Comments: *Dapagliflozin PK parametes, C_{max} and AUC, appear to increase approximately double with doubling of dose. However, the strict dose proportionality in single dose study, in this dose range studied, could not be established since the 90 % confidence intervals for slopes excluded 1. In multiple dose study, Cmax and AUCtau appear to be dose proportional. Sponsor also conducted a pooled analysis of all the doses used in the clinical program. The results of the pooled analysis followed the similar trend as single dose study where dapagliflozin C_{max} appeared to increase slightly less*

than proportionally with dose, while AUC_{inf} appeared to increase slightly more than proportionally to dose.

2.4.9 How do the PK parameters change with time following chronic dosing?

PK does not vary with time. Refer to **Section 2.4.1 and 2.4.2** Multiple Doses

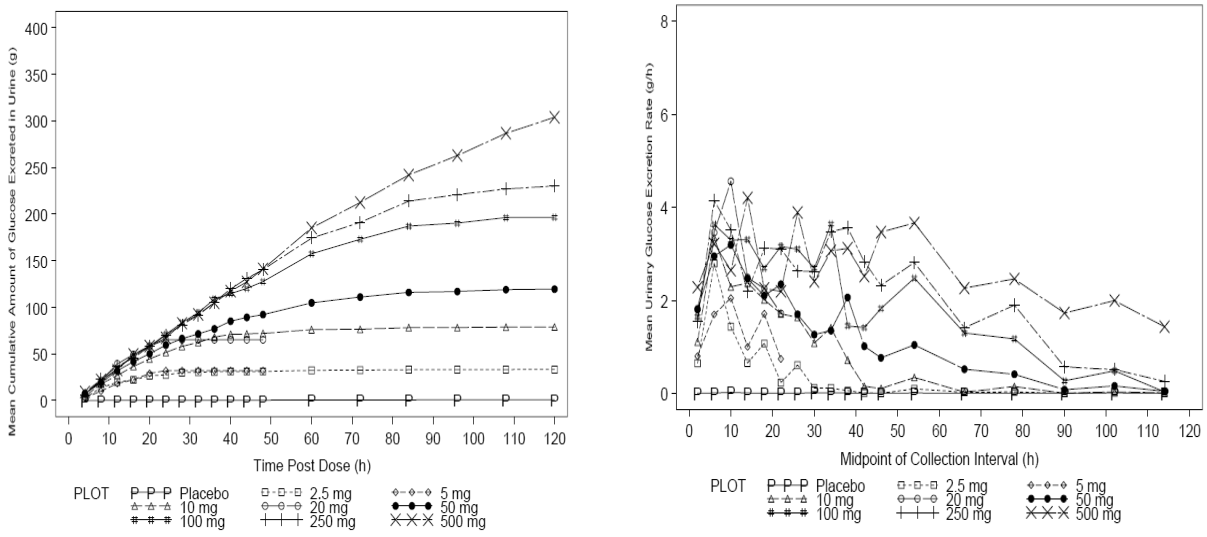
2.5 What are the PD characteristics of the drug?

2.5.1 What are the PD characteristics of Dapagliflozin following single and multiple dose in healthy adults?

- **Single Dose:**

Following administration of a single oral dose of 2.5 to 500 mg of dapagliflozin (BMS-512148) in healthy subject healthy subjects, the cumulative amount of glucose in the urine over the 0 to 120 h interval increased in a dose-dependent manner (Figure 16). However, there was no substantial difference in the cumulative amount of glucose eliminated in the urine over the 0 to 24 hr interval. The maximal rate of urinary glucose elimination was similar at BMS-512148 doses of 10 mg and higher. However, the duration at which the maximal rate of glucose elimination was maintained was apparently longer with increasing doses of BMS-512148 (Figure 16).

A **B**



Source: MB102001 Clinical Study Report

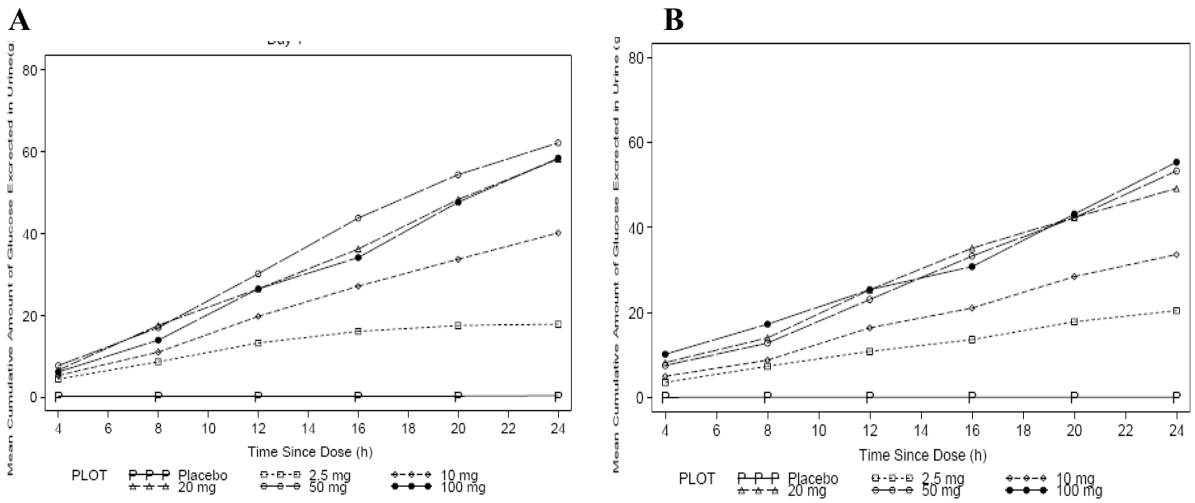
Figure 16: A) Mean Cumulative Amount of Glucose Excreted in Urine Over 120 Hours following Single Dose Administration of Dapagliflozin in Healthy Subjects.; B) Mean Urinary Glucose Excretion Rate following Single Dose Administration of Dapagliflozin in Healthy Subjects

- **Multiple Dose**

In a multiple dose study of dapagliflozin (2.5 mg, 10 mg, 20 mg, 50 mg or 100 mg), the daily amount of glucose eliminated in the urine was similar after a single dose and after 14 days of dosing (Figure 17**)**. Subjects administered 20 to 100 mg of dapagliflozin for 1, 7 and 14 days appeared to have greater daily urinary glucose excretion (47 to 62 g/24 h) than subjects administered 2.5 and 10 mg (~40 g/24 h) BMS-512148.

The mean daily absolute amount of glucose eliminated in the urine at doses of 20 to 100-mg dapagliflozin is around 47 to 62 g/24 h. Cumulative 24-h urine glucose excretion following 2.5 and 10-mg dapagliflozin was approximately 50 and 70%, respectively, of that excreted following doses of 20 mg and higher.

The ratio of the amount of glucose eliminated in the urine in a collection interval to the amount of renally filtered glucose (calculated by multiplying the estimated GFR by the mean serum glucose concentration over the urine collection interval) on that same interval showed that approximately 25 to 30% of glucose resorption was inhibited at doses greater than 20 mg. This study suggests that even with maximal inhibition of SGLT2, approximately 70 % of filtered glucose is reabsorbed by the kidney.



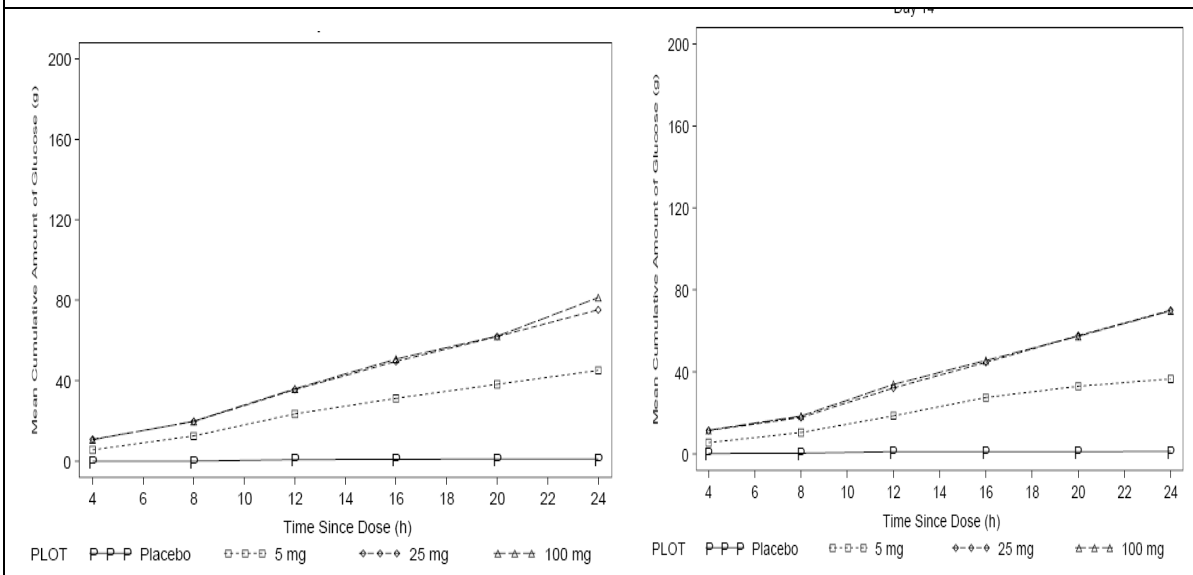
Source: MB102002 Clinical Study Report

Figure 17: A) Mean Cumulative Amount of Glucose Excreted in Urine Over 24 Hours on Day 1.; B) Mean Cumulative Amount of Glucose Excreted in Urine Over 24 Hours on Day 14 following Multiple Dose Administration of Dapagliflozin in Healthy Subjects

2.5.2 How does the PD of Dapagliflozin in T2DM patients compared to that in healthy volunteers?

Following multiple dose administration of dapagliflozin to subjects with T2DM mean cumulative amount of glucose excreted was similar on Day 1 and Day 14 of dosing. Subjects administered 25 or 100 mg BMS-512148 for 1 and 14 days have greater

cumulative 24 h urinary glucose excretion compared to subjects administered 5 mg BMS-512148 for 1 and 14 days (Figure 18).



Source: MB102003Clinical Study Report

Figure 18: A) Mean Cumulative Amount of Glucose Excreted in Urine Over 24 Hours on Day 1.; B) Mean Cumulative Amount of Glucose Excreted in Urine Over 24 Hours on Day 14 following Multiple Dose Administration of Dapagliflozin in T2DM subjects

Percent inhibition of renal glucose resorption over each collection interval is shown in Table 12**.** Dosing with 25 and 100 mg BMS-512148 appeared to have a greater effect on the percent inhibition of renal glucose resorption following both a single dose and 14 days of dosing compared to 5 mg BMS-512148. Within dose groups, there was no apparent difference between Day 1 and Day 14 for the percent inhibition of renal glucose resorption.

Table 12: Summary Statistics for Glucose Resorption

Parameter	BMS-512148 Dose	Study Day		
		Day -1	Day 1	Day 14
% Inhibition of Renal Glucose Resorption (0-4h) Mean (SD)	Placebo	0.09 (0.04)	0.06 (0.05)	0.88 (1.86)
	5mg	0.09 (0.09)	19.49 (13.21)	19.77 (15.47)
	25 mg	0.05 (0.04)	33.56 (10.06)	40.88 (18.99)
	100 mg	0.09 (0.14)	36.15 (9.53)	44.01 (15.65)
% Inhibition of Renal Glucose Resorption (4-8h) Mean (SD)	Placebo	0.45 (1.09)	0.04 (0.02)	0.07 (0.07)
	5mg	0.04 (0.03)	21.37 (11.01)	14.67 (12.97)
	25 mg	0.04 (0.04)	24.37 (10.30)	19.02 (8.21)
	100 mg	0.04 (0.03)	27.36 (9.47)	23.12 (9.55)

Source: Sponsors study report MB102003, page 139.

2.6 Intrinsic Factors

2.6.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

- **Renal Impairment:**

Impact of renal impairment on the pharmacokinetics and pharmacodynamics of dapagliflozin was studied in a single (50 mg) and multiple dose (20 mg) PK/PD study (MB102007) in type 2 diabetic patients with normal, mild, moderate, and severe renal impairment. In this study subjects were recruited into the following 5 groups according to degree of renal function at screening as determined by Cockcroft- Gault (C-G) calculated creatinine clearance (CLcr):

A: Healthy subjects with normal renal function (CLcr > 80 mL/min)
B: Subjects with T2DM and normal renal function (CLcr > 80 mL/min)
C: Subjects with T2DM and mild renal impairment (50 < CLcr ≤ 80 mL/min)
D: Subjects with T2DM and moderate renal impairment (30 ≤ CLcr ≤ 50 mL/min)
E: Subjects with T2DM and severe renal impairment (CLcr < 30 mL/min) (not receiving dialysis)

Reanalysis of the sponsor data for dapagliflozin and its metabolite dapagliflozin 3-O-glucuronide following single dose of dapagliflozin (50 mg) are presented in Table 13 and Table 14, respectively. The reanalysis was based on the estimated GFR values using MDRD equation and the cutoff values and grouping of subjects according to the latest guidance renal impairment (e.g, normal = estimated GFR ≥ 90 mL/min/1.73 $m^{2;}$ mild = estimated GFR ≥ 60 and ≤ 89 mL/min/1.73 m^2; mod = estimated GFR ≥ 30 and ≤ 59 mL/min/1.73 m^2; and severe = estimated GFR ≥29 mL/min/1.73 m^2 and ≤ 15 mL/min /1.73 m^2).

Compared to subjects with T2DM and normal renal function, subjects with T2DM and mild, moderate or severe renal impairment had:
− 17%, 20% and 33% higher geometric mean C_{max} values of dapagliflozin, respectively,
− 30%, 60% and 131% higher geometric mean AUC_{inf} values of dapagliflozin, respectively,

The higher systemic exposures to parent dapagliflozin with declining GFR may be due to a meaningful contribution by the kidney to the metabolism of dapagliflozin and not an outcome of decreased renal clearance with decreasing GFR (since renal clearance is only a small percentage of total body clearance)

Table 13: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters (Phase A, Single Dose of 50 mg Dapagliflozin)

Renal Function	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean(SD)	AUC(inf) (ng·h/mL) Geom. Mean (CV%)	Total Clearance (CLT/F) (mL/min) Geom. Mean (CV%)	Renal Clearance CLR(mL/min) Geom. Mean (CV%)
Healthy Normal (n=5)	745 (29)	1.5 (0.5 1.5)	13.0 (7.1)	2888 (27)	288 (54)	3.43 (35)
Diabetic Normal (n=9)	674 (51)	1.0 (0.5 2.0)	12.6 (5.5)	2632(34)	316(67)	3.30(47)
Diabetic Mild(n=9)	788 (34)	1.5 (0.5 2.0)	15.6 (7.2)	3433(32)	242(36)	3.34 (51)
Diabetic Moderate (n=8)	814 (33)	1.0 (0.5 2.9)	17.6 (7.1)	4215(21)	197(49)	2.35 (71)
Diabetic Severe(n=6)	901 (39)	1.0 (0.5 1.5)	35.5 (46.5)	6082(29)	137(28)	0.96 (55)

Source: Reviewer's Reanalysis of data based on estimated GFR values using MDRD. The cutoff values and grouping of subjects was according to the latest guidance renal impairment (e.g, normal = estimated GFR ≥ 90 mL/min/1.73 $m^{2;}$ mild = estimated GFR ≥ 60 and ≤ 89 mL/min/1.73 m^2; mod = estimated GFR ≥ 30 and ≤ 59 mL/min/1.73 m^2; and severe = estimated GFR ≥29 mL/min/1.73 m^2 and ≤ 15 mL/min /1.73 m^2).

Compared to subjects with T2DM and normal renal function, subjects with T2DM and mild, moderate or severe renal impairment had:
− 23%, 31% and 38% higher geometric mean C_{max} values of BMS-801576, respectively,
− 42%, 98% and 221% higher geometric mean AUC_{inf} values of BMS-801576, respectively,

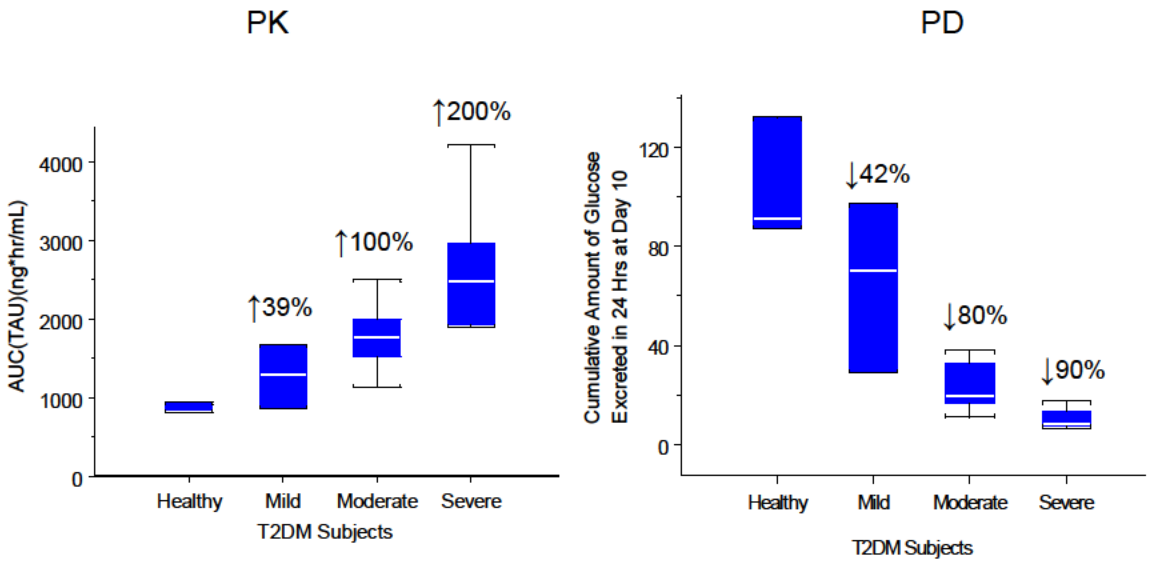
The relatively higher systemic exposure to dapagiflozin 3-O-glucuronide (compared to parent dapagliflozin) with declining GFR is likely due to the high dependence of dapagliflozin 3-O-glucuronide renal excretion for its elimination.

Table 14: Summary Statistics for Dapagliflozin 3-O-glucuronide Pharmacokinetic Parameters (Phase A, Single Dose of 50 mg Dapagliflozin)

Renal Function	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-Half (h) Mean(SD)	AUC(inf) (ng·h/mL) Geom. Mean (CV%)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)
Healthy Normal (n=5)	904 (28)	2.0 (1.0 2.0)	13.3 (6.6)	4133 (14)	161 (54)	56.3 (21.5)
Diabetic Normal (n=9)	1381 (18)	2.0 (1.0 3.0)	11.9 (4.1)	6530(22)	80(67)	53.3 (32.9)
Diabetic Mild(n=9)	1708 (37)	2.0 (1.0 3.0)	14.5 (6.7)	9285(38)	77(36)	67.3 (28.5)
Diabetic Moderate(n=8)	1815 (32)	1.5 (1.0 2.9)	15.7 (6.4)	12959(40)	50(49)	57.5 (21.2)
Diabetic Severe(n=6)	1905 (25)	2.0 (1.5 4.0)	19.9 (12.7)	21007(70)	14(28)	26.7 (15.5)

Source: Reviewer's Reanalysis of data based on estimated GFR values using MDRD. The cutoff values and grouping of subjects was according to the latest guidance renal impairment (e.g, normal = estimated GFR ≥ 90 mL/min/1.73 m^2; mild = estimated GFR ≥ 60 and ≤ 89 mL/min/1.73 m^2; mod = estimated GFR ≥ 30 and ≤ 59 mL/min/1.73 m^2; and severe = estimated GFR ≥29 mL/min/1.73 m^2 and ≤ 15 mL/min /1.73 m^2).

Following administration of 20-mg dapagliflozin given once daily for 7 days, T2DM 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 (Figure 19). Further, higher systemic exposures of dapagliflozin in subjects with moderate, and severe renal impairment did not result in a correspondingly higher cumulative amount of glucose excretion (Figure 19). This is consistent with dapagliflozin's glomerular filtration rate-dependent mechanism of action where it is not expected to provide clinically meaningful benefit in these populations.



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

Figure 19: Effect of Renal Impairment on PK and PD of Dapagliflozin (N=3 For healthy, N=3 for mild, N=6 moderate, N=5 for severe).

Reviewer's Comment:

- *The results presented above are based on the reanalysis of the study results. In this re-analysis, classification of subjects for renal function was based on estimated GFR values. The cutoff values and grouping of subjects was according to the latest guidance on "Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling" (e.g, normal = estimated GFR ≥ 90 mL/min/1.73 $m^{2;}$ mild = estimated GFR ≥ 60 and ≤ 89 mL/min/1.73 m^2; mod = estimated GFR ≥ 30 and ≤ 59 mL/min/1.73 m^2; and severe = estimated GFR ≥29 mL/min/1.73 m^2 and ≤ 15 mL/min /1.73 m^2). In contrast, sponsor in their analysis grouped the subjects based on the numbers from old guidance (e.g., normal = CLcr > 80 mL/min; mild= 50 < CLcr ≤ 80 mL/min etc).*

- *Reviewer's results for renally impaired patients are based on ratio of geometric mean values of **observed data** in renal impaired patients to that in healthy subjects. In contrast, sponsor used **linear regression analysis to fit the observed data** to estimated **creatinine clearance. Then they used the regression model to predict the exposures in healthy and renally impaired patients**. Linear regression model might not be appropriate in this study because of the poor goodness of fit (R^2=0.439).*

- *Sponsor proposed no dose adjustment for mild renal impaired patients and that this not be used in moderate to severe renal impaired patients, which is acceptable.*

- *Sponsor conducted a dedicated safety and efficacy study in patients with moderate renal impairment (Study MB102029). Efficacy of dapagliflozin in this Phase 3 trial was not demonstrated to be better than placebo.*
- *The impact of hemodialysis on dapagliflozin exposure is not studied.*

Effect of renal impairment was also assessed in the population PK analysis. There is an increase in clearance with increasing creatinine clearance (Figures 20). The clearance in patients with moderate and mild renal impairment is 42% and 29% lower than patients with normal renal function (Figure 20).

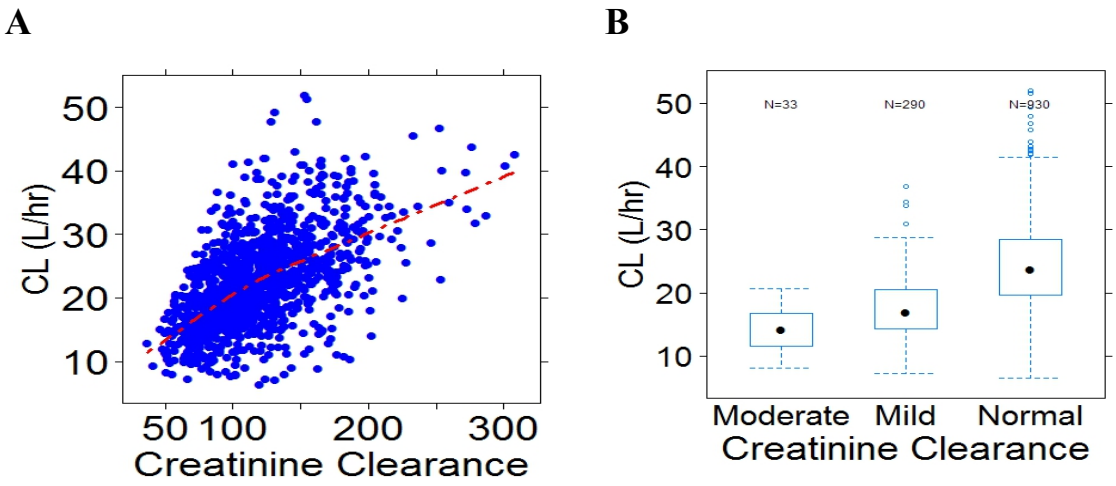


Figure 20: A) Scatter plot of clearance vs. creatinine clearance, B) Boxplot of clearance vs. creatinine clearance

Reviewer's Comment: *The eGFR of most of the subjects with moderate renal impairment (eGFR between 30-59 mL/min/1.73m2) in the PPK analysis dataset are in the range of 50-59 mL/min/1.73m2. Conclusion based on the exposure of these subjects may not be applicable to the subjects with lower eGFR in the moderate renal impairment category.*

- **Hepatic Impairment:**

Impact of hepatic impairment on the pharmacokinetic of dapagliflozin was studied in an open-label, parallel-group, single-dose study in fasted hepatic impaired subjects and healthy subjects (MB102027). Six (6) subjects were enrolled each in Child Pugh Class A, B or C group and 6 healthy subjects were enrolled. Subjects were matched to the extent possible with regard to age (± 10 years), body weight (± 20%), gender, and smoking status.

In subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B), C_{max} and AUC of dapagliflozin were increased by up to 22% and 36%, respectively, compared to healthy subjects following administration of a single oral 10-mg dose of

dapagliflozin (Table 15**).** Subjects with severe hepatic impairment (Child-Pugh Class C), dapagliflozin C_{max} and AUC were up to 40% and 67% higher than matched healthy controls, respectively (Table 15). There were no differences in the plasma protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects.

Table 15: Statistical Analyses on Dapagliflozin PK Parameters in Hepatic Impaired Subjects

Pharmacokinetic Variable	Hepatic Group	Geometric Mean	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	Healthy	136	-	-	-
	Child-Pugh Class A	120	CPA[a] *vs* Healthy	0.882	(0.598, 1.301)
	Child-Pugh Class B	153	CPB[b] *vs* Healthy	1.122	(0.761, 1.654)
	Child-Pugh Class C	190	CPC[c] *vs* Healthy	1.395	(0.946, 2.056)
AUC(INF) (ng·h/mL)	Healthy	465	-	-	-
	Child-Pugh Class A	480	CPA[a] *vs* Healthy	1.033	(0.765, 1.396)
	Child-Pugh Class B	632	CPB[b] *vs* Healthy	1.359	(1.007, 1.836)
	Child-Pugh Class C	776	CPC[c] *vs* Healthy	1.669	(1.236, 2.255)
AUC(0-T) (ng·h/mL)	Healthy	438	-	-	-
	Child-Pugh Class A	443	CPA[a] *vs* Healthy	1.011	(0.750, 1.363)
	Child-Pugh Class B	614	CPB[b] *vs* Healthy	1.401	(1.040, 1.889)
	Child-Pugh Class C	762	CPC[c] *vs* Healthy	1.739	(1.291, 2.345)

a CPA = Child-Pugh Class A
b CPB = Child-Pugh Class B
c CPC = Child-Pugh Class C

Pharmacokinetic of dapagliflozin 3-O-glucuronide, the major metabolite of dapagliflozin is summarized in Table 16. Compared to healthy subjects, mean dapagliflozin 3-O-glucuronide C_{max} for subjects with mild, moderate, and severe hepatic impairment were 4% higher, 58% higher and 14% lower, respectively. Compared to healthy subjects, mean dapagliflozin 3-O-glucuronide AUC_{inf} for subjects with mild, moderate, and severe hepatic impairment were 6%, 100% and 29% higher, respectively.

Table 16: Statistical Analyses on Dapagliflozin 3-O-Glucuronide PK Parameters

Pharmacokinetic Variable	Hepatic Group	Geometric Mean	Ratio of Geometric Means		
			Ratio	Point Estimate	90% CI
Cmax (ng/mL)	Healthy	196	-	-	-
	Child-Pugh Class A	203	CPA[a] *vs* Healthy	1.035	(0.651, 1.646)
	Child-Pugh Class B	310	CPB[b] *vs* Healthy	1.582	(0.995, 2.515)
	Child-Pugh Class C	168	CPC[c] *vs* Healthy	0.857	(0.539, 1.362)
AUC(INF) (ng·h/mL)	Healthy	837	-	-	-
	Child-Pugh Class A	889	CPA[a] *vs* Healthy	1.062	(0.705, 1.600)
	Child-Pugh Class B	1670	CPB[b] *vs* Healthy	1.996	(1.325, 3.007)
	Child-Pugh Class C	1082	CPC[c] *vs* Healthy	1.293	(0.858, 1.947)
AUC(0-T) (ng·h/mL)	Healthy	803	-	-	-
	Child-Pugh Class A	853	CPA[a] *vs* Healthy	1.063	(0.699, 1.617)
	Child-Pugh Class B	1650	CPB[b] *vs* Healthy	2.055	(1.351, 3.126)
	Child-Pugh Class C	1049	CPC[c] *vs* Healthy	1.307	(0.859, 1.988)

a CPA = Child-Pugh Class A
b CPB = Child-Pugh Class B
c CPC = Child-Pugh Class C

In summary, mean dapagliflozin exposures were < 2-fold higher in the most severe hepatically-impaired subjects.

Reviewer's Comment:

- *Metabolism is the primary elimination pathway for dapagliflozin. Dapagliflozin is predominantly metabolized via uridine diphosphate glucuronyl transferase (UGT) 1A9. Less than 2% of the administered dapagliflozin dose was recovered in the urine as unchanged drug.*

- *Higher exposures of dapagliflozin 3-O-glucuronide in moderate and severe hepatic impaired paired patients were observed. The exact cause of this in not known. According to sponsor higher exposure of dapagliflozin 3-O-glucuronide in moderate and severe hepatic impaired patients may be because of the fact that dapagliflozin 3-O-glucuronide is cleared mainly via renal excretion and the estimated creatinine clearance values were not balanced between the groups in this study. The moderate hepatic impairment group had the widest range of estimated creatinine clearance of any group (69-232 mL/min in the moderate hepatic impairment group compared to 91-200 mL/min in all of the other groups combined) and this group also had several subjects clustered at the lower end of*

the estimated creatinine clearance range. Therefore differences between the groups in GFR are likely to have contributed to the large variability and relatively higher metabolite exposures in the moderate hepatic group. The reviewer does not concur with the sponsor's conclusion that renal function might have played a role in the higher systemic exposure of dapagliflozin 3-O-glucuronide. There was only one subject in the moderate hepatic impairment group which had GFR less than 90 otherwise in all subjects were with normal renal function (GFR>90 mL/min).

- *The lack of a large effect of hepatic impairment on the elimination of dapagliflozin may be, in part, related to the distribution and expression of UGT1A9. UGT1A9 is expressed in multiple tissues including the liver, kidney.*

- *Reviewer agree with the sponsor's conclusion on no dose adjustment is needed in hepatic impaired patient. Dapagliflozin exposure increased less than 2-fold in hepatic impaired patients and that dapagliflozin has a favorable safety profile in long term studies with higher exposures (study with moderate renal impairment).*

Age: In the population PK analysis, age was not identified as a significant covariate on the apparent clearance of dapagliflozin. There is a trend for decrease in clearance with increasing age specifically beyond 50 years of age (Figure 21 A). However, age was found to be highly correlated to cCrCL (correlation coefficient > 0.5) and thus inclusion of creatinine clearance in the model resulted in no systematic trend between inter-individual variability on clearance and age (Figure 21 C). The effect of age on dapagliflozin PK is not considered clinically meaningful because the decrease in clearance in subjects greater than 65 years of age is 22% compared to subjects less than 65 years of age.

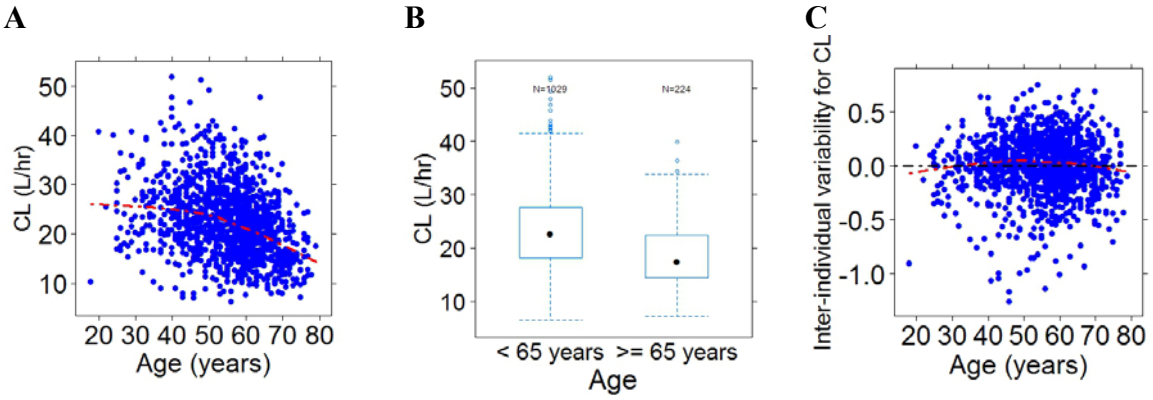


Figure 21: A) Scatter plot for clearance vs. age B) Boxplot of clearance vs. age and C) Inter-individual variability on clearance vs. age

- **Body Weight:** In the population pharmacokinetic analysis, body weight was not identified as a significant covariate on the apparent clearance of dapagliflozin. There is a trend for increasing clearance with increase in body weight (Figure 22

A). However, body weight was found to be highly correlated to cCrCL (correlation coefficient > 0.5) and thus inclusion of creatinine clearance in the final model resulted in no systematic trend between inter-individual variability on clearance and body weight as observed in Figure 22 C. The effect of body weight is not considered clinically meaningful as there is only a 38% increase in clearance from the lowest quartile of body weight to the highest quartile.

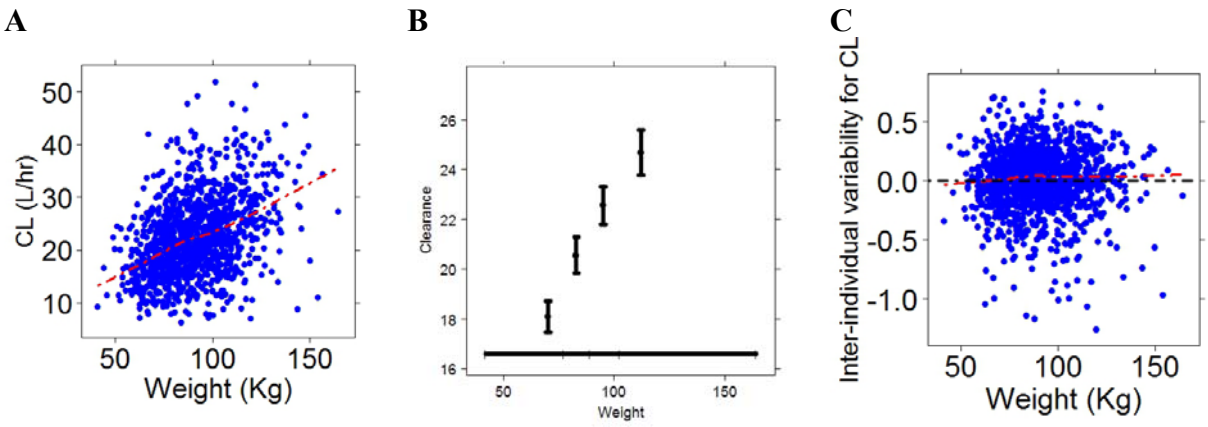


Figure 22: A) Scatter plot for clearance vs. weight B) Quartile plot of clearance vs. weight and C) Inter-individual variability on clearance vs. weight

- **Gender:** In population PK analysis gender was identified as a significant covariate on the apparent clearance of dapagliflozin. Males have a 23% higher clearance than females which is considered not to be clinically meaningful (Figure 23). No systematic trend between inter-individual variability on clearance and gender is observed after inclusion of gender as a covariate on clearance (Figure 23).

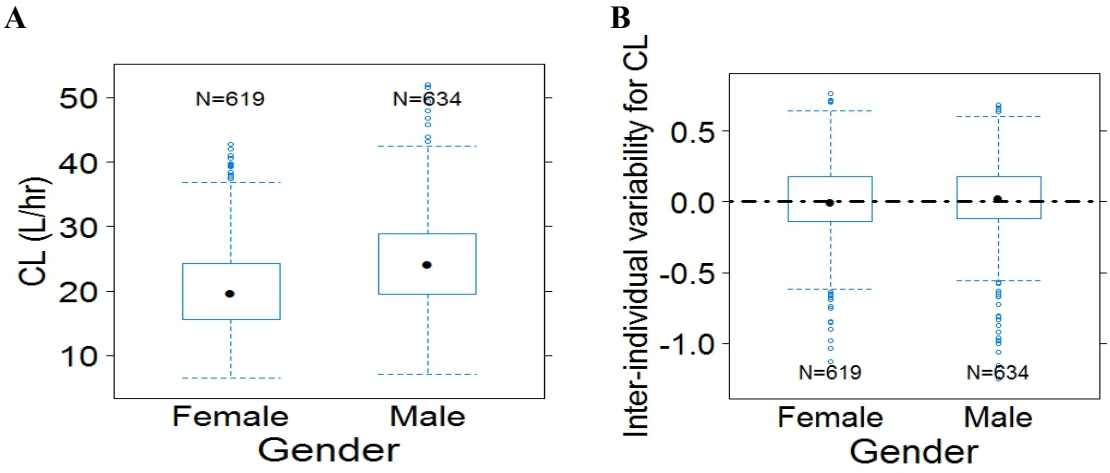


Figure 23: A) Clearance and B) Inter-individual variability on clearance vs. gender

Race/Ethnicity: In the population pharmacokinetic analysis race does not significantly affect the pharmacokinetics of dapagliflozin. Figure 24 shows that the clearance was similar between white (1), African American (2) and Asian (3). There were very few subject of American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander race to make any conclusions on changes in clearance in these populations.

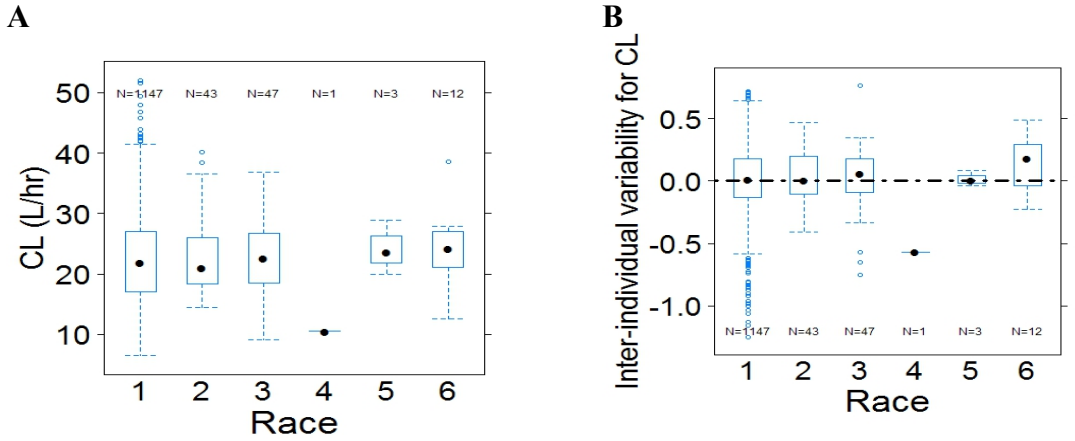


Figure 24: A) Clearance and B) Inter-individual variability on clearance vs. race. 1=White, 2=African American, 3=Asian, 4=American Indian/Alaska Native, 5=Native Hawaiian/Other Pacific Islander, 6=Others

- **Pediatric Patients:**

No studies in pediatric patients have been conducted to date. However, the sponsor has requested for a waiver for the use of dapagliflozin in pediatric patients with T2DM who are less than 10 years of age. Also, sponsor is requesting a deferral for the use of dapagliflozin in pediatric patients with T2DM who are 10 to 17 years of age until a positive benefit/risk is established in adults. Sponsor's proposed timeline for pediatric assessment is shown in Table 17.

Table 17: Sponsor's Proposed Timeline for Pediatric Assessment.

D1690C00016: A randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of dapagliflozin in children, 10 to <18 years of age with T2DM receiving one of the three dose levels of dapagliflozin over the range of 2.5 to 10 mg.	Submit full protocol	3Q2011
	Planned FPFV[a]	4Q2011
	Planned LPLV[b]	By Sep-2012
	Submit Final Clinical Study report	By Sep-2013
D1690C00017: A double-blind, randomised, placebo controlled Phase III study to evaluate dapagliflozin versus placebo in pediatric subjects with T2DM who are inadequately controlled on metformin monotherapy	Submit full protocol	By Sep-2013
	Planned FPFV[c]	After NDA approval
	Planned LPLV[d]	By Sep-2017
	Submit Final Clinical Study report	By Sep-2018

[a] FPFV=First patient first visit

[b] LPLV=Last patient last visit

2.6.2 What pregnancy and lactation use information is available?

There is no pregnancy and lactation use information in the application.

2.6.3 Does genetic variation impact exposure and/or response?

No. The results of a genetic substudy of MB102008 showed no major difference in dapagliflozin clearance across eight UGT1A9 polymorphisms. The functional, but rare UGT1A9*2 and *3 variants were included in this analysis. Known UGT1A9 variants such as *2 and *3, considering their rarity and the limited observed PK variability, are unlikely to be clinically relevant (Table 18**).** Please refer Pharmacogenomics review by Dr. Rogers Hobart for further details (APPENDIX 4.1).

Table 18: Observed Geometric Mean Clearance (CL) and Ratios by Genotype

SNP ID	N (AA/Aa/aa)	N, Geo Mean CL (95%CI) AA	Aa	aa	GMR (95%CI) Aa vs AA	aa vs AA
*2, C3Y (rs72551329)	183/0/0	---	---	---	---	---
*3, M33T (rs72551330)	182/3/0	---	---	---	---	---
I399C>T (rs2741049)	53/93/37	19.2 (16.7,21.9)	20.6 (18.6,22.8)	22 (18.7,25.8)	0.93 (0.79,1.10)	0.87 (0.71,1.08)
rs2011404	118/42/1	19.7 (17.9,21.6)	22.8 (19.4,26.7)	---	0.87 (0.72,1.04)	---
rs1105880	80/61/20	22.4 (20.0,25.1)	19.1 (16.8,21.8)	17.7 (14.1,22.2)	1.17 (0.99,1.39)	1.27 (0.98,1.63)
rs6759892	65/72/24	22 (19.4,25.0)	20.4 (18.1,22.9)	17.1 (13.9,21.1)	1.08 (0.91,1.29)	1.29 (1.01,1.64)
rs7577677	71/72/16	22.1 (19.7,24.9)	19.5 (17.3,21.9)	16.9 (13.2,21.7)	1.13 (0.96,1.34)	1.31 (0.99,1.73)
rs4148323	156/4/0	---	---	---	---	---

A=major allele, a=minor allele

2.7 Extrinsic Factors

2.7.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of various drugs on the exposure of dapagliflozin (and vice versa) are discussed in section 2.7.7. The effect of different types of meals on the bioavailability of dapagliflozin is discussed in section 2.8. The effect of smoking, herbal products, and alcohol use were not evaluated by the sponsor.

2.7.2 Is the drug a substrate of CYP enzymes?

Yes. In vitro metabolism of dapagliflozin with recombinant human enzymes showed multiple CYP enzymes, including CYP1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A4, and CYP3A5, demonstrated some degree of activity against dapagliflozin. However, in humans ^{14}C ADME study, < 10% of a dapagliflozin dose was eliminated via pathways involving oxidative metabolism, making it unlikely that CYP enzymes play a major role in the disposition of dapagliflozin in humans. The primary metabolite in human was dapagliflozin 3-O-glucuronide which accounted for 61% of the dapagliflozin dose. All other metabolites detected in human plasma each constituted < 5% of the radioactivity AUC. In vitro studies demonstrated that UGT1A9 is the major enzyme responsible for the formation of dapagliflozin 3-O-glucuronide.

2.7.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

- **Inhibition of CYP Enzymes:**

Incubation of dapagliflozin (0.0045-45 μM) in human liver microsomes showed that dapagliflozin has no direct inhibition effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Based on *in vitro* data, it is unlikely that dapagliflozin will inhibit the metabolism of CYP substrates IC50> 45 μM. Overall, IC_{50} values are well in excess of the steady-state plasma C_{max} value in humans receiving 10-mg dapagliflozin daily (~0.3 μM), indicating that it is unlikely that dapagliflozin will affect the metabolism of CYP substrates.

- **Induction of CYP Enzymes:**

In vitro, at concentrations up to 25 μM, dapagliflozin did not transactivate the human pregnane-X receptor in HepG2/C3A cells. In addition, at concentrations ranging from 0.2 μM to 20 μM, dapagliflozin failed to induce CYP1A2, CYP2B6, or CYP3A4/5 activity in human hepatocytes. Overall, IC_{50} values are well in excess of the steady-state plasma C_{max} value in humans receiving 10-mg dapagliflozin daily (~0.3 μM), indicating that it is unlikely that dapagliflozin will affect the metabolism of CYP substrates.

Reviewer's Comment: *In the in vitro studies dapagliflozin did not inhibit or induce CYP enzymes. These in vitro results are in consistent with the in vivo DDI studies where dapagliflozin when co-administered with several drugs showed has no effect on the pharmacokinetics of the co-administered drug. Sponsor did not investigate the effect of major glucuronidated metabolite (dapagliflozin 3-O-glucuronide) on the induction inhibition potential of CYP enzymes. However, sponsor did conduct several in vivo DDI studies with several agents which are metabolized by CYP isozymes. In vivo drug-drug interaction studies suggests that major metabolite of dapagliflozin has no inhibition potential on CYP enzymes.*

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

- **P-Glycoprotein:**

Dapagliflozin demonstrated active efflux in Caco-2 cells assays with an observed efflux ratio greater than 3 (range ~ 2.5-4.3). No saturation of efflux was observed up to a maximally achieved test concentration of ~ 70μM. Also, co-incubation of dapagliflozin with cyclosporine A (20μM) or ketoconazole (20μM) inhibited the efflux of dapagliflozin (efflux ratio ~1.5-1.7), suggesting it's a substrate of P-glycoprotein. *In vitro* studies suggests that neither dapagliflozin nor dapagliflozin 3-O glucoronide demonstrate any ability to inhibit P-gp mediated efflux of digoxin with IC_{50} values of >57.6μM and >20.1μM for dapagliflozin and dapagliflozin 3-O glucoronide, respectively.

- **Other transporters:**

In vitro substrate studies with dapagliflozin 3-O glucoronide (BMS-801576) were performed using cell-based model systems expressing a single transporter (hOCT2, hOAT1, and hOAT3). BMS-801576 was not a substrate of hOCT2 and hOAT1. However, it was a substrate of hOAT3 and its K_m value for hOAT3-mediated uptake was 115 μM. In the inhibition studies, dapagliflozin was an inhibitor of hOAT3 with IC_{50} value of 33 μM, but not hOAT1 and hOCT2. BMS-801576 inhibited hOAT3 (IC_{50}: 100 μM) and minimally hOAT1 (29% inhibition at 100 μM), but not hOCT2. Based on C_{max} (<1 μM) of dapagliflozin and BMS-801576 in clinical studies, the transporters inhibition potential of dapagliflozin and BMS-801576 are not likely to be clinical relevant($C_{max}/IC_{50}<0.001$).

Reviewer's Comment: *The C_{max} values after 10 mg dose in clinical study were ~0.27 μM for dapagliflozin and ~0.34 μM for dapagliflozin 3-O glucoronide. Based on IC_{50} values from in vitro results for P-gp inhibition, it is unlikely that dapagliflozin will inhibit P-gp mediated efflux. This is further confirmed by in vivo DDI study where dapagliflozin has no effect on the pharmacokinetics of digoxin. In vitro studies suggest that dapagliflozin is a substrate for P-gp. However, with high absolute oral bioavailability (~78%) it is unlikely that it will have any clinical significance when administered with P-gp inhibitors. Also, based on the in vitro results it is unlikely that dapagliflozin and dapagliflozin 3-O glucoronide is an inhibitor for renal transporters (hOAT1, hOAT3, hOCT2).*

2.7.5 Are there other metabolic/transporter pathways that may be important?

In humans ^{14}C ADME study, < 10% of a dapagliflozin dose was eliminated via pathways involving oxidative metabolism, making it unlikely that CYP enzymes play a major role in the disposition of dapagliflozin in humans. The primary metabolite in human was dapagliflozin 3-O-glucuronide which accounted for 61% of the dapagliflozin dose. *In vitro* studies in 12 different recombinant human UGT enzymes suggest that UGT1A9 exhibited the most activity for the formation of dapagliflozin 3-O-glucuronide. *In vitro* inhibition with of UGT1A9 enzyme with inhibitors such as niflumic acid and mefenamic acid resulted in inhibition of dapagliflozin 3-O-glucuronide formation. Thus, these *in*

vitro results suggests that UGT1A9 plays and important role in the metabolism of dapagliflozin.

2.7.6 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In vitro assessments indicate that dapagliflozin has no biologically-significant potential to inhibit or induce CYP, and is unlikely to affect the metabolism of co-administered CYP substrates. Dapagliflozin was shown to be a substrate for UGT1A9 enzymes. In vivo drug-drug interaction with mefenamic acid (UGT1A9 inhibitor) showed slight increase in exposure of dapagliflozin. However, the increase in exposure does not warrant any dose adjustment.

2.7.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

In the application several drug-drug interaction studies were carried with anti-diabetic agents (pioglitazone, metformin, glimepiride, sitagliptin, voglibose), several potential co-prescribed cardiovascular agents (hydrochlorothiazide, valsartan, simvastatin, bumetanide, digoxin, warfarin), metabolic enzyme inducer rifampin, and UGT1A9 inhibitor mefenamic acid. Table 19 summarizes the effect of co-administered drugs on the pharmacokinetics of dapagliflozin. Table 20 summarizes the impact of dapagliflozin on the pharmacokinetics of co-administered drugs. In summary, there were no clinically meaningful drug-drug interaction observed in the all the DDI studies conducted.

Table 19: Effect of Co-administered Drug on the Pharmacokinetics of Dapagliflozin

Co-administered Drug (Dose Regimen)	Dapagliflozin(Dose Regimen)	Major Clearance Pathways of Co-administered Drug	Effect on Dapagliflozin Exposure GMR (90% CI)	
			AUC_{inf}	C_{max}
Pioglitazone (45 mg)	Dapagliflozin (50 mg)	Metabolism by CYP2C8 (major) and CYP3A4 minor)	1.03 (0.98, 1.08)	1.09 (1.00, 1.18)
Metformin (1000 mg)	Dapagliflozin (20 mg)	Renal excretion by hOCT-1 and OCT-2	0.995 (0.94, 1.05)	0.932 (0.84, 1.02)
Glimepiride (4 mg)	Dapagliflozin (20 mg)	Metabolism by CYP2C9	0.989 (0.95, 1.02)	1.006 (0.92, 1.09)
Sitagliptin (100 mg)	Dapagliflozin (20 mg)	Renal excretion by	1.081 (1.03, 1.13)	0.958 (0.87, 1.04)

		hOAT-3		
Voglibose (0.2 mg TID for at least 8 weeks)	Dapagliflozin (10 mg)	Poorly absorbed from the Gastrointestinal tract, minimal metabolism	1.009 (0.95, 1.06)	1.040 (0.89, 1.20)
Hydrochlorothiazide (25 mg)	Dapagliflozin (50 mg)	Mainly renally excreted unchanged	1.07 (1.04, 1.11)	0.99 (0.88, 1.11)
Simvastatin (40 mg)	Dapagliflozin (20 mg)	Metabolism by CYP3A4	0.986 (0.95, 1.01)	0.978 (0.88, 1.07)
Valsartan (320 mg)	Dapagliflozin (20 mg)	Mainly renally excreted unchanged	1.024 (1.00, 1.04)	**0.881 (0.79, 0.97)**
Bumetanide (Days 8-14, 1 mg QD)	Dapagliflozin (Days 1-7, 10 mg QD)	Mainly renally excreted unchanged	1.047‡ (0.99, 1.10)	1.080 (0.95, 1.22)
Rifampin (Days 4-9, 600 mg QD)	Dapagliflozin (Days 1, 10 mg QD; Day 9, 10 mg QD)	Metabolizing enzyme inducer	**0.780 (0.73, 0.83)**	**0.931 (0.77, 1.11)**
Mefenemic Acid (Days 4-7, 500 mg loading dose, 250 mg q6h)	Dapagliflozin (Day 1, 10 mg QD; Day 5, 10 mg QD)	UGT1A9 inhibitor	**1.51 (1.44, 1.58)**	1.13 (1.03, 1.24)

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

Table 20: Effect of Dapagliflozin on the Pharmacokinetics of Co-administered Drugs

Co-administered Drug (Dose Regimen)	Co-administered Drug (Dose Regimen)	Major Clearance Pathways of Co-administered Drug	Effect on Co-administered Drug Exposure GMR (90% CI)	
			AUC_{inf}	C_{max}
Dapagliflozin (50 mg)	Pioglitazone (45 mg)	Metabolism by CYP2C8 (major) and CYP3A4 minor)	1.00 (0.90, 1.13)	0.93 (0.75, 1.15)
	Hydroxy-Pioglitazone		1.05 (0.90, 1.22)	**0.90 (0.79, 1.02)**
Dapagliflozin (20 mg)	Metformin (1000 mg)	Renal excretion by hOCT-1 and OCT-2	1.00 (0.933, 1.07)	0.95 (0.866, 1.04)
Dapagliflozin (20 mg)	Glimepiride (4 mg)	Metabolism by CYP2C9	**1.13 (0.996, 1.28)**	1.04 (0.905, 1.20)
Dapagliflozin (20 mg)	Sitagliptin (100 mg)	Renal excretion by hOAT-3	1.01 (0.985, 1.04)	0.88 (0.807, 0.97)
Dapagliflozin (50 mg)	Hydrochlorothiazide (25 mg)	Mainly renally excreted unchanged	0.99 (0.95-1.04)	0.95 (0.94-1.05)
Dapagliflozin (20 mg)	Simvastatin (40 mg)	Metabolism by CYP3A4	**1.19 (1.01, 1.39)**	0.93 (0.81, 1.07)
	Simvastatin Acid		**1.311 (1.14, 1.49)**	1.07 (0.93, 1.24)
Dapagliflozin (20 mg)	Valsartan (320 mg)	Mainly renally excreted unchanged	**1.04 (0.85, 1.28)**	**0.93 (0.76, 1.15)**
Dapagliflozin (Days 1-7, 10 mg QD)	Bumetanide (Days 8-14, 1 mg QD)	Mainly renally excreted unchanged	**1.13 (0.98, 1.30)**	**1.13 (0.97, 1.31)**
Dapagliflozin (Days 1, 20 mg QD; Days 2-8 10 mg)	Digoxin (Day 2, 0.25 mg)	Mainly renally excreted unchanged via P-gp transport	1.00 (0.86, 1.16)	0.99 (0.84, 1.16)
Dapagliflozin (Days 1, 20 mg QD; Days 2-8, 10 mg)	Warfarin (Day 2, 25 mg)	Metabolism by CYP2C9 (*S*-warfarin)		
	S-Warfarin		1.06 (1.00, 1.13)	1.03 (0.99, 1.12)
	R-Warfarin		1.07 (1.03, 1.13)	1.05 (0.97, 1.14)

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

Reviewer's Comment:

- *Dapagliflozin is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A9 to a glucoronidated metabolite, dapagliflozin 3-O-glucuronide (also known as BMS-801576), which is not a meaningful inhibitor of SGLT2 at the proposed dose of dapagliflozin of 10 mg. Based on the UGT1A9 mediated metabolic pathway of dapagliflozin, there was a low potential for drug-drug interactions.*

- *Pioglitazone, metformin, glimepiride, sitagliptin, voglibose, hydrochlorothiazide, simvastatin, valsartan, and bumetanide have no effect on the pharmacokinetics of dapagliflozin.*

- *Co-administration of dapagliflozin and rifampin, an inducer of various active transporters and metabolizing enzymes resulted in a decrease in dapagliflozin C_{max} and AUC_{inf} by 7 and 22 %, respectively. The mean amount of glucose excreted in the urine over 24 h following administration of dapagliflozin alone (51 g) was not markedly affected by rifampin [rifampicin] co-administration (45 g) and, based on this PD endpoint and modest PK effects of rifampin on dapagliflozin, no dose adjustment of dapagliflozin is needed.*

- *A drug-drug interaction study with a UGT1A9 inhibitor (mefenamic acid) showed a 51% increase in AUC_{inf} with no change in C_{max}. This increase in systemic exposure does not warrant a dose adjustments based on long term safety in moderate renally impaired patients, where 100 % increase in systemic exposure is observed.*

- *A slight increase in exposure of glimepiride, simvastatin, simvastatin acid, valsartan, and bumetanide were observed when dapagliflozin is co-administered with these agents. These changes are not clinically meaningful and no dose adjustment is needed.*

2.7.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions for dapagliflozin. However, dapagliflozin causes glucosuria which may lead to increased urine volumes due to enhanced osmotic diuresis. Since bumetanide, a loop diuretic, also exhibit diuretic properties a drug interaction study was conducted to see if there is any PD interaction when both dapagliflozin and bumetanide are co-administered. Co-administration of dapagliflozin and bumetanide, a loop diuretic, did not meaningfully change the PD effect of dapagliflozin to increase urinary glucose excretion in healthy subjects. Furthermore, co-administration of dapagliflozin did not meaningfully alter the steady-state PD responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Drug interaction studies with warfarin showed no changes in pharmacokinetics of S- and R-warfarin. Similar to the PK results, the PD of warfarin was not affected by co-administration of dapagliflozin. INR values after treatment with warfarin alone were essentially identical to from those seen after combination treatment with dapagliflozin and warfarin. The 90% CI for the ratio of INR_{max} and $AUC_{(INR)}$ between treatments fell within the usual equivalence interval from 0.80 to 1.25 (Table 21).

Table 21: Summary Statistical Analysis on INR parameters

INR Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt A / Trt B)	
	Trt A	Trt B	Point Estimate	90% CI
INRmax	1.648	1.641	1.004	(0.967, 1.043)
AUC(INR)	267	265	1.007	(0.989, 1.025)

Treatments: A=Dapagliflozin 20 mg + Dapagliflozin 10 mg QD + Warfarin 25 mg
B=Warfarin 25 mg

2.7.9 Are there any other questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Dapagliflozin is a chiral molecule with 5 defined stereocenters. Therefore, if formed, there are 32 potential diastereomers that are theoretically possible. Sponsor synthesized chemical standards for four diastereomers of dapagliflozin and tested any inference with bioanalytical method. A clarification was sought from the sponsor for their rationale of studying only 4 diastereomers. Sponsor justified that 4 diastereomers studied represents 4 of the 5 single chiral center inversion products of dapagliflozin. Also, the possibility of formation of diastereomers with two or more chiral center inversions would be a sequential set of events and, therefore, their formation would require the detectable presence of one of the 4 single chiral center inversions.

To further investigate the potential for formation of diastereomers of dapagliflozin under biological conditions, pooled clinical samples from trial MB102093 at predose, 1 hour, 36 hours and 72 hour were analysed using chiral chromatography. There was no evidence in these chromatograms of any additional peaks related to dapagliflozin epimers or other diastereomers **(**Figure 25**)**

2.8 General Biopharmaceutics

In the early Phase 1 ascending dose studies (MB102001 and MB102002) and the Phase 2a study (MB102003) (b) (4) formulations were used. Tablet formulations were used in the Phase 2b studies (MB102008 and MB102009). Subsequently, film-coated tablet formulations were developed for the Phase 3 program (1-, 2.5-, 5-, and 10-mg dose strengths).

A (b) (4) was used for the 5- and 10-mg strengths of the Phase 3 tablets, and the tablets proposed for commercialization. However, 1- and 2.5-mg strengths of the Phase 3 tablets (b) (4) are not planned to be marketed. .

The film-coated tablets proposed for commercialization are similar to the tablets used in the Phase 3 clinical trials except that there were minor modifications of (b) (4) shape, embossing (b) (4) Figure 26 summarizes the studies that were carried out by the sponsor to link formulations used during development program.

Figure 26: Formulation Development and Bridging in the Dapagliflozin Development Program.

2.8.1 What is relative bioavailability between the (b) (4) formulation used in early phase 1 trials to the tablet formulation used in phase 2b trials?

A relative bioavailability study (MB102005) was conducted to bridge the (b) (4) formulation (5 x 10-mg) used in Phase 1 with the Phase 2b (b) (4) tablet formulation (1 x 50 mg). The study was an open-label, randomized, 2-period, 2-treatment, crossover study. 14 subjects were randomized to receive a single oral dose of BMS-512148 5 x 10 mg (b) (4) (Treatment A) or BMS-512148 1 x 50 mg tablet (Treatment B). There was at least a 7-day washout interval between each dose. In healthy subjects, following oral administration (b) (4) formulation and tablet formulation has similar exposure in terms of AUC_{inf}, AUC_{0-t} and C_{max} (Table 22).

Table 22: Summary of Pharmacokinetics Parameters of Dapagliflozin following Oral Administration of (b) (4) and Tablet Formulation.

Pharmacokinetic Parameter	Treatment	
	A ((b) (4) Formulation, n=13)	B (Tablet Formulation, n=13)
C_{max} (ng/mL) Geometric Mean (CV %)	548 (27)	512 (32)
$AUC_{(INF)}$ (ng/mL·h) Geometric Mean (CV %)	2235 (25)	2308 (25)
$AUC_{(0-T)}$ (ng/mL·h) Geometric Mean (CV %)	2160 (25)	2241 (25)
$AUC_{(0-T)}/AUC_{(INF)}$ Ratio Geometric Mean (CV %)	0.97 (3.81)	0.97 (2.21)
T_{max} (h) Median (Min, Max)	0.98 (0.75, 1.50)	1.00 (0.73, 3.00)
T-HALF (h) Mean (S.D.)	19.89 (18.05)	16.79 (7.48)

***Reviewer's Comment**: The results of this study showed that the bioavailability of 50-mg dapagliflozin was comparable between 5 x 10-mg Phase 1 (b) (4) and 50-mg Phase 2b tablet formulation. Although the study was not powered to demonstrate bioequivalence, the 5 × 10 mg BMS-512148 (b) (4) and the 1 × 50 mg BMS-512148 tablet have also met the usual criteria for bioequivalence with respect to BMS-512148 C_{max}, AUC_{inf} and AUC_{0-t}. The ratio of adjusted geometric means (90% CI) for the 5 × 10 mg (b) (4) to the 1 × 50 mg tablet for BMS-512148 C_{max}, AUC_{inf}, and AUC_{0-t} were 0.94 (0.82, 1.09), 1.03 (1.0, 1.07) and 1.04 (1.0, 1.08), respectively*

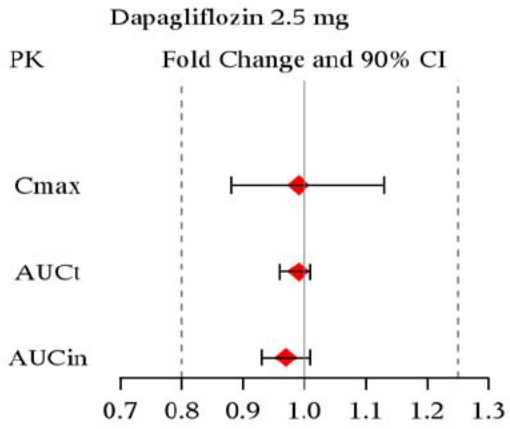
2.8.2 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

The film-coated tablets proposed for commercialization are similar to the tablets used in the Phase 3 clinical trials except that there were minor modifications of (b) (4) shape (diamond or round), and embossing (identification numbering/lettering stamped into the tablet (b) (4) Sponsor claims that these small changes in the proposed to-be-marketed formulation will not affect the product performance and thus a biowaiver requested was made at the NDA submission. Biowaiver request is reviewed by ONDQA and for further details please refer to Biopharmaceutics review by Dr. Minerva Hughes.

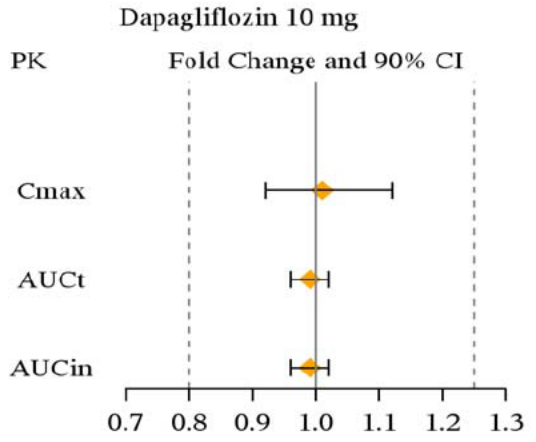
2.8.3 *Are the* [redacted] *tablets bioequivalent?*

During the stability studies, it was found that dapagliflozin [redacted] for 4 weeks. To assess the impact [redacted] bioequivalence studies were conducted from a [redacted] tablet formulation relative to [redacted] tablet formulation. Study MB102090 investigated the effect [redacted] on *in vivo* performance of the tablet at 2.5-mg dose strength and study MB102062 at 10-mg dose strength. Both studies were randomized cross over studies with at-least 4 days washout period, and used the proposed commercial formulation (Please refer to individual study review for further details). [redacted] Figure 27 shows that geometric mean ratio and 90% CI for AUC_t, AUC_{inf} and C_{max} were within 80% to 125% criterion limits following administration of [redacted] tablets at 2.5 mg and 10 mg dose strengths.

Study:MB102090



Study: MB102062



[redacted]

Figure 27: Bioequivalence between [redacted] Tablets with 2.5 and 10 mg Proposed Commercial Tablet Formulation

Reviewer's Comment: *Based on the similarity in systemic exposures of dapagliflozin administered as [redacted] tablets, there is no impact [redacted] on the in vivo performance of 2.5 and 10 mg proposed commercial dapagliflozin tablets.*

2.8.4 *What is the effect of food on the bioavailability of the [redacted] tablets?*

Study MB102090 investigated the effect of high-fat, high-calorie meal on the pharmacokinetics of dapagliflozin from a [redacted] 2.5 mg dapagliflozin tablet formulation. Studies MB102062 and MB102019 investigated the effect of high-fat, high-calorie meal on the pharmacokinetics of dapagliflozin from a

(b) (4) 10 mg dapagliflozin tablet formulation. In all studies subjects were given high-fat (>50% fat) high-calorie meal (~950kcal). Subjects were fasted for at least 10 hours before the drug dosing. Figure 28 shows that the geometric mean ratio and 90% CI for AUC_t and AUC_{inf} were within 80% to 125% criterion limits following administration of (b) (4) tablets at 2.5 mg and 10 mg dose strengths in fed and fasted state. The geometric mean ratio and 90% CI for C_{max} were outside the 80% to 125% criterion limits in fed and fasted state at both 2.5 mg and 10 mg dose strengths. Following a single dose oral administration of dapagliflozin 10 mg tablet, the C_{max} value was 31% lower with a high-fat meal (Table 23). Results from these studies indicate that food has no effect on systemic exposure of dapagliflozin. However, this reduction seen in C_{max} when administered with food does not seem to be clinically relevant based on the efficacy observed in the pivotal Phase 3 monotherapy trials (MB102032 and MB102013), where dapagliflozin was administered with meal. Therefore, sponsor's claim that dapagliflozin can be administered regardless of food is acceptable.

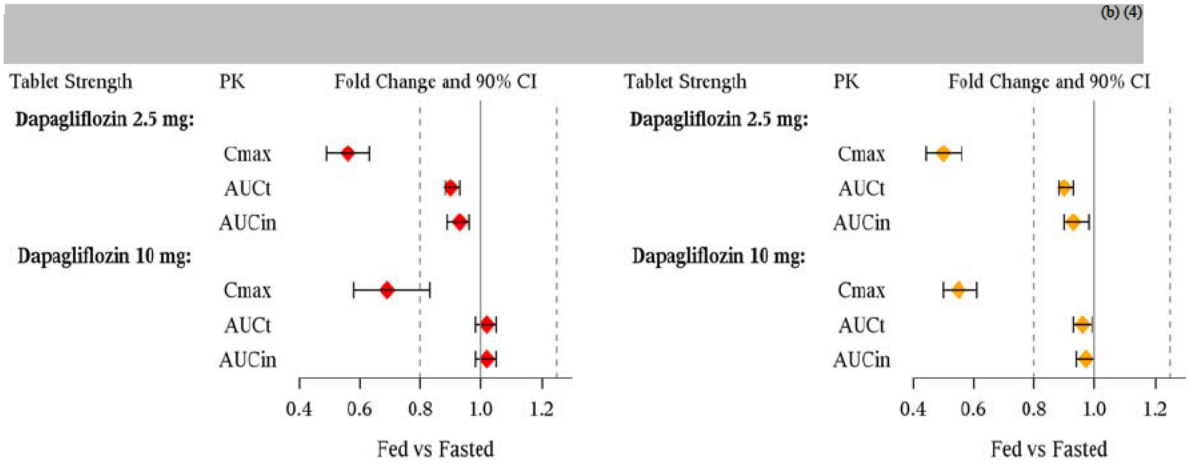


Figure 28: Effect of High-Fat Meal on the Pharmacokinetics of Dapagliflozin from A (b) (4) Formulation. The Studies were Conducted with both 2.5 mg Dose and 10 mg Dose Strengths.

Table 23: Summary for Dapagliflozin Pharmacokinetic Parameters Following Administration of 10 mg Tablet in Fed and Fasted State

	Study MB102019		Study MB102062	
Dapagliflozin Pharmacokinetic Parameter	**(b) (4) Dapagliflozin 10-mg (fasted) (n=14)**	**(b) (4) Dapagliflozin 10-mg (fed) (n=14)**	**(b) (4) Dapagliflozin 10-mg (fasted) (n=29)**	**(b) (4) Dapagliflozin 10-mg (fed) (n=29)**
C_{max} (ng/mL) Geometric Mean (CV %)	136 (22)	94 (33)	176 (30)	97 (28)
AUC_{inf} (ng.h/mL) Geometric Mean (CV %)	497 (19)	507 (16)	650 (24)	635 (25)

AUC_{0-t} (ng·h/mL) Geometric Mean (CV %)	470 (20)	478 (16)	629 (25)	604 (25)
T_{max} (h) Median (Min, Max)	0.98 (0.48, 1.50)	1.98 (0.98, 3.98)	0.75 (0.50,1.50)	2.00 (0.75,4.00)
T-Half (h) Mean (SD)	12.0 (4.62)	14.0 (4.38)	13.1 (4.2)	13.2 (3.8)

2.8.5 What is absolute oral bioavailability of Dapagliflozin following oral administration?

An absolute bioavailability study (MB102059), comparing the bioavailability of dapagliflozin from the Phase 3 tablet formulation to an intravenous dose, was conducted in healthy fasted subjects (n=7). On Day 1, subjects received a 10-mg oral dose of dapagliflozin followed on hour later by an 80µg dose of ^{14}C-dapagliflozin infused intravenously over 1 minute. PK samples were collected at selected time points up to 49 hours post oral dose. The absolute bioavailability of dapagliflozin from the Phase 3 tablet formulation was 78% (Table 24).

Table 24: Summary Statistics for Dapagliflozin PK Parameters following IV and Oral Administration.

Dapagliflozin Pharmacokinetic Parameters		
	Treatment A (n=7)	Treatment B (n=7)
AUC_{inf} (ng.h/mL) Geom. Mean (CV %)	628 (17)	6.78 (22)
AUC_{0-t} (ng.h/mL) Geom. Mean (CV %)	598 (17)	6.43 (23)
C_{max} (ng/mL) Geom. Mean (CV %)	143 (29)	10.2 (49)
$T_{1/2}$ (h) Mean (s.d.)	13.7 (3.44)	12.2 (5.25)
T_{max} (h) Median (Min, Max)	1.03 (0.50, 1.50)	0.03 (0.03, 0.08)
CL (mL/min) Geom. Mean (CV %)	NA	207 (23)
V_{ss} (L) Mean (s.d.)	NA	118 (31.6)
F (%) Geom. Mean (CV %)	77.8 (9)	NA

Trt: A = dapagliflozin 10 mg po dose
Trt: B = [14C]-dapagliflozin 80µg iv dose
Note: NA = Not applicable

2.9 Analytical

2.9.1 How are the active moieties identified and measured in the plasma/serum?

In this NDA, a number of validated liquid chromatography tandem mass spectrometry (LC-MS/MS) bioanalytical methods were developed for the analysis of plasma and urine sample of dapagliflozin (BMS-512148), its minor hydroxylated metabolite (BMS-511926), and inactive major metabolite (BMS-801576). Plasma and urine samples were analyzed at various sites and companies. BMS, (b) (4) and (b) (4) were involved with sample analysis.

2.9.2 What bioanalytical methods are used to assess concentrations?

BMS initially developed and validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods for the analysis of dapagliflozin and its metabolite BMS-511926 in plasma and urine. The plasma and urine LC-MS/MS methods were then transferred and validated (b) (4) to measure dapagliflozin and BMS-511926. The plasma and urine LC-MS/MS methods were subsequently transferred and validated (b) (4) where several LC-MS/MS methods were developed to measure dapagliflozin, BMS-511926 and BMS-801576, either together in one assay or in separate assays, for both plasma and urine to support several Phase 1, 2 and 3 studies. Ultimately, the plasma and urine LC-MS/MS methods were transferred and validated (b) (4) In the BMS (b) (4) methods the lower limit of quantification (LLOQ) for dapagliflozin and BMS-511926 in both the plasma and urine methods was 10.0 ng/mL. For all other methods developed at contract research organizations (CRO), the LLOQ was 0.1 or 1.0 ng/mL for dapagliflozin, 1.0 ng/mL for BMS-511926 and 0.2, 1.0 or 5.0 ng/mL for BMS-801576 in plasma and 10.0 ng/mL for BMS-801576 in urine.

Summary of Validation Method for the Analysis of Plasma Samples at BMS:
Dual analyte bioanalytical LC-MS/MS assays were developed and validated by BMS to quantitatively measure dapagliflozin and BMS-511926 in human EDTA plasma samples. The first method (Document number 930007482, see Table 25), with an LLOQ of 10.00 ng/mL for both analytes, used solid phase extraction and stable labeled internal standards prior to gradient elution chromatographic separation on a reversed phase C18 column. MS/MS detection of the analytes and internal standard was accomplished using positive electrospray ionization and selective reaction monitoring (SRM) mode with unique transitions for each analyte. In the second method (Document number 930012389, see Table 25), the ionization was changed to negative ionization mode which allowed for better ionization efficiency and a more sensitive assay; which achieved an LLOQ of 1 ng/mL.

Table 25: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Plasma at BMS

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930007482	BMS-512148	Plasma EDTA	LCMS/MS	10-2000	≤0.0	≤9.7	±5.0/	RT = 24 h, F/T = 3 cycles, LTS =14 days @ -20 C	MB102001; MB102002
	BMS-511926	Plasma EDTA	LCMS/MS	10 - 2000	≤6.8	≤8.6	±4.0		
930012389	BMS-512148	Plasma EDTA	LCMS/MS	1-1000	≤8.4	≤7.5	±7.7	RT = 24 h, F/T = 4 cycles, LTS = 414 days @ -20 C	MB102003
	BMS-511926	Plasma EDTA	LCMS/MS	1 - 1000	≤7.2	≤5.4	±8.0	RT = 24 h, F/T = 4 cycles, LTS = 416 days @ -20 C	

Summary of Validation Method for the Analysis of Plasma Samples (b) (4) (b) (4) developed and validated one LC-MS/MS plasma method to measure dapagliflozin and BMS-511926 with an LLOQ of 1.00 ng/mL for both the analytes (Table 26). The sample treatment, HPLC and the MS detection were similar to the BMS method.

Table 26: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Plasma (b) (4)

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930016101	BMS-512148	Plasma EDTA	LCMS/MS	1-1000	≤3.3	≤9.8	±5.1	RT = 24 h, F/T = 3 cycles, LTS =414 days @ -20 C	MB102004; MB102005 MB102006
	BMS-511926	Plasma EDTA	LCMS/MS	1 - 1000	≤1.1	≤3.4	±9.3		

Summary of Validation Method for the Analysis of Plasma Samples (b) (4) (b) (4) developed and validated four LC-MS/MS plasma methods (Table 27). They include one method to measure dapagliflozin only, and three methods to simultaneously measure dapagliflozin and BMS-80157. The LLOQs established were 1.00 ng/mL for dapagliflozin and 1.00 or 5.00 ng/mL for BMS-801576.

Table 27: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Plasma (b) (4)

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930028632	BMS-512148	Plasma EDTA	LCMS/MS	1-500	≤2.9	≤4.1	±8.3	RT = 192 h, F/T = 3 cycles, LTS =498 days @ -20oC	MB102009, MB102013, MB102017, MB102026, D1690C00006, D1692C00002, D1692C00005, MB102032
930028226	BMS-512148	Plasma EDTA	LCMS/MS	1-500	≤4.3	≤3.6	±4.0	RT =72 h, F/T = 3 cycles, LTS = 119 days @ -20 C	MB102007, MB102010, MB102017, MB102019, MB102025, MB102027, MB102029
	BMS-801576	Plasma EDTA	LCMS/MS	1 - 500	≤5.6	≤7.3	±5.2		
930046065	BMS-512148	Plasma EDTA	LCMS/MS	1-500	≤2.1	≤6.6	±10.4	RT = 192 h, F/T = 3 cycles, LTS = 498 days @ -20oC	MB102062, MB102074
	BMS-801576	Plasma EDTA	LCMS/MS	5 - 500	≤4.0	≤7.5	±1.3	RT = 192 h, F/T = 4 cycles, LTS = 280 days @ -20oC	
930033156	BMS-512148	Plasma Li Heparin	LCMS/MS	1-500	≤7.7	≤7.5	±6.8	RT = 24 h, F/T = 3 cycles, LTS = 324 days @ -20oC	D1690C0000
	BMS-801576	Plasma Li Heparin	LCMS/MS	2 - 500	≤5.0	≤12.7	±8.8	RT = 24 h, F/T = 2 cycles, LTS = 323 days @ -20oC	

Summary of Validation Method for the Analysis of Plasma Samples (b) (4) LC-MS/MS assays to measure dapagliflozin only, and dapagliflozin and BMS-801576 in a simultaneous assay were developed and validated (b) (4) using Ultra Pressure Liquid Chromatography (UPLC). The LLOQ established were 1.00 or 0.1 ng/mL for dapagliflozin and 0.2 ng/mL for BMS-801576 (Table 28).

Table 28: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Plasma (b) (4)

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930039480	BMS-512148	Plasma EDTA	LCMS/MS	1-200	≤6.4	≤3.0	±5.8	RT = 191 h, F/T = 7 cycles, LTS = 31 days @ -20oC	MB102036, MB102037
930041398	BMS-512148	Plasma EDTA	LCMS/MS	1-200	NA	≤3.0	±2.3	F/T = 11	MB102057, MB102058, MB102059,
930046422	BMS-512148	Plasma EDTA	LCMS/MS	0.1-50	≤10.5	≤10.5	±6.7	RT = 24 h, F/T = 5 cycles, LTS = 19 days @ -20oC	MB102088, MB102090
	BMS-801576	Plasma EDTA	LCMS/MS	0.2-100	≤8.5	≤8.9	±4.3		

Summary of Validation Method for the Analysis of Urine Samples at BMS:
In order to support the urine analysis in clinical studies, a dual analyte LC-MS/MS urine method for measuring dapagliflozin and its metabolite, BMS-511926 was developed and validated at BMS with an LLOQ of 10.0 ng/mL for both analytes (Table 29). The method used solid phase extraction, gradient chromatography using a reversed phase C18 column, negative electrospray ionization in SRM mode with unique transitions for each analyte.

Table 29: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Urine at BMS

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930013236	BMS-512148	Urine	LCMS/MS	10-2000	≤4.1	≤9.3	±4.4	RT = 24 h, F/T = 3 cycles, LTS = 445 days @ -20oC	MB102001, MB102002, MB102003
	BMS-511926	Urine	LCMS/MS	10-2000	≤4.1	≤9.6	±4.3		

Summary of Validation Method for the Analysis of Urine Samples (b) (4)
The BMS dual analyte, dapagliflozin and BMS-511926, urine method was transferred (b) (4) and a validated LC-MS/MS method were developed with an LLOQ of 10.0 ng/mL for both analytes (Table 30).

Table 30: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Urine (b) (4)

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930017657	BMS-512148	Urine	LCMS/MS	10-2000	≤2.3	≤6.6	±5.7	RT = 24 h, F/T = 4 cycles	MB102006
	BMS-511926	Urine	LCMS/MS	10-2000	≤3.1	≤5.5	±5.3		

Summary of Validation Method for the Analysis of Urine Samples (b) (4) (b) (4) developed and validated two separate LC-MS/MS methods to measure dapagliflozin and BMS-801576 in urine with LLOQs of 1.00 ng/mL and 10.0 ng/mL, respectively. The methods utilized solid phase extraction for the dapagliflozin method and direct urine sample workup for the BMS-801576 method (Table 31).

Table 31: Summary of Bioanalytical Validation Reports for the Analysis of Dapagliflozin and its Metabolite in Urine (b) (4)

Document Control Number	Analyte	Sample Matrix	Method	Standard Curve Range (ng/mL)	Assay Precision (%CV)		Accuracy (% Deviation)	Stability (RT, F/T, LTS)	Study No
					Inter	Intra			
930027978	BMS-512148	Urine	LCMS/MS	1-1000	≤4.7	≤5.4	±7.2	RT = 24 hr, F/T = 3 cycles, LTS = 132 days @ -20oC	MB102007, MB102010, MB102025, MB102074
930027982	BMS-801576	Urine	LCMS/MS	10-5000	NA	≤3.0	±2.3	RT = 24 hr, F/T = 3 cycles, LTS = 252 days @ -20oC	MB102007, MB102010, MB102025, MB102074

Reviewer's Comment: *Accepted validation indicates that method met the FDA guidance "Bioanalytical Method Validation" recommendations, and was therefore acceptable.*

3 DETAILED LABELING RECOMMENDATION

No labeling recommendations at this time. A separate memo will address the labeling comments later.

4 APPENDIX

4.1 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY

GENOMICS GROUP REVIEW

NDA Number	202,293
Submission Date	December 28, 2010
Drug Name	Dapagliflozin
Sponsor	Bristol Myers Squibb
Submission Contents	1 Clinical Study Report
Review Date	February 1, 2011
Primary Reviewer	Hobart L. Rogers, Pharm.D., Ph.D
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

Executive Summary

Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that is being reviewed for an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is primarily metabolized by the polymorphic uridine diphosphate glucuronosyltransferase (UGT1A9). The sponsor conducted a retrospective genetic substudy of the Phase 2b trial, MB102008, to investigate the role of the UGT1A9 variants on the clearance of dapagliflozin (based on population PK parameters). No significant effects of UGT1A9 genotype on dapagliflozin clearance were identified. The results of this study coupled with the scarcity of UGT1A9 variants indicate that these variants are unlikely to play a clinically significant role in the exposure to dapagliflozin. No additional pharmacogenetic studies related to PK are indicated at this time from the perspective of the Genomics Group.

1 Background

The current submission is a NDA for dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is an orally active inhibitor of the renal sodium-glucose co-transporter type 2 (SGLT2). By inhibiting the SGLT, dapagliflozin lowers plasma glucose via blocking glucose absorption in the proximal tubule, which increases glucose excretion in the urine.

Dapagliflozin is primarily metabolized by hepatic and renal uridine diphosphate glucuronosyltransferase (UGT1A9). In European populations, polymorphisms in the

UGT1A9 gene include the C3Y (*2) and M33T (*3), the latter of which has been shown to decrease the metabolism of UGT1A9 substrates. The *3 variant has an allele frequency of approximately 3%. Additional reduced activity variants are present in Asian (Japanese) populations, including Y242X (*4) and D256N (*5), but are also rare. (http://www.pharmacogenomics.pha.ulaval.ca/sgc/ugt_alleles; Villeneuve 2003, PMID 12944498; Saeki 2003, PMID 15618729; Jinno 2003, PMID 12730278)

In the current submission, the sponsor submitted a pharmacogenetic study report that evaluated *UGT1A9* variant effects on dapagliflozin pharmacokinetics. The purpose of this review is to evaluate the sponsor's findings and whether labeling related to the pharmacogenetic interaction, or lack thereof, is warranted.

2 Submission Contents Related to Genomics

The sponsor submitted one report entitled "Analysis of Human Uridine Diphosphate Glucuronosyltransferase (UGT) 1A9 Single Nucleotide Polymorphisms and Dapagliflozin Systemic Exposure in Patients with Type 2 Diabetes Mellitus in Study. MB102008." MB102008 was a phase 2b dose-finding study in previously untreated patients with type 2 diabetes. Genotyping was performed for UGT1A9*2 and UGT1A9*3 and 6 common polymorphisms (I.399C>T, rs2011404, rs1105880, rs6759892, rs7577677, and rs4148323). The primary endpoint for this analysis was dapagliflozin clearance as estimated from a population-based modeling approach. Only summary results were reviewed; individual subject data listings were not provided or requested.

3 Key Questions and Summary of Findings

3.1 Are UGT1A9 variants associated with higher exposure to dapagliflozin?

*No. The results of a genetic substudy of MB102008 showed no major difference in dapagliflozin clearance across eight UGT1A9 polymorphisms. The functional, but rare UGT1A9*2 and *3 variants were included in this analysis. Known UGT1A9 variants such as *2 and *3, considering their rarity and the limited observed PK variability, are unlikely to be clinically relevant.*

Subjects voluntarily signed informed consent and provided DNA samples for pharmacogenetic analysis. Of 389 subjects who agreed to provide a sample for genetic analysis, 187 subject samples had clearance values that could be merged with the DNA genotyping results. Of the 187 subjects, 3 subjects carried the *UGT1A9*3* allele and none carried the *2 allele. Other variants that were genotyped were well-represented in the substudy population; genotype frequencies are summarized in Table 1 below.

*Comment: The *2 and *3 alleles are relatively uncommon in white and African-American populations. The *2 allele is present in 5% of African Americans (heterozygous) and is*

*rare in whites, while the *3 allele is present in 4% of Caucasians and is rare in African Americans. The I.399C>T polymorphism has previously been shown to increase the enzyme activity and SN-39 glucuronidation in vitro and in vivo. The remaining 5 SNPs are intronic SNPs and their functional relevance has not been established; presumably they were selected to tag halplotypes of UGT1A9, but the rationale for SNP selection was not provided by the sponsor.*

Descriptive statistics for dapagliflozin clearance by *UGT1A9* genotype and the results of ANCOVA modeling are summarized in the following table. The clearance values were consistent across all the studied SNPs. Trends toward lower clearance (approximately 30%) were observed among variant allele homozygotes for rs7577677, rs6759892, and rs1105880 compared to common allele homozygotes. Notably, the lowest clearance (6.01 L/hr) of any of the subjects was in a *3 carrier. However the next lowest clearance (6.20 L/hr) was found for a common allele homozygote (*1/*1).

Table 1. Observed Geometric Mean Clearance (CL) and Ratios by Genotype

SNP ID	N	N, Geo Mean CL (95%CI)			GMR (95%CI)	
	(AA/Aa/aa)	AA	Aa	aa	Aa vs AA	aa vs AA
*2, C3Y (rs72551329)	183/0/0	---	---	---	---	---
*3, M33T (rs72551330)	182/3/0	---	---	---	---	---
I399C>T (rs2741049)	53/93/37	19.2 (16.7,21.9)	20.6 (18.6,22.8)	22 (18.7,25.8)	0.93 (0.79,1.10)	0.87 (0.71,1.08)
rs2011404	118/42/1	19.7 (17.9,21.6)	22.8 (19.4,26.7)	---	0.87 (0.72,1.04)	---
rs1105880	80/61/20	22.4 (20.0,25.1)	19.1 (16.8,21.8)	17.7 (14.1,22.2)	1.17 (0.99,1.39)	1.27 (0.98,1.63)
rs6759892	65/72/24	22 (19.4,25.0)	20.4 (18.1,22.9)	17.1 (13.9,21.1)	1.08 (0.91,1.29)	1.29 (1.01,1.64)
rs7577677	71/72/16	22.1 (19.7,24.9)	19.5 (17.3,21.9)	16.9 (13.2,21.7)	1.13 (0.96,1.34)	1.31 (0.99,1.73)
rs4148323	156/4/0	---	---	---	---	---

A=major allele, a=minor allele

*Comment: Given the low prevalence of both the *2 and *3 alleles in the population studied, a larger retrospective study or prospective pharmacogenetic study would be necessary in order to fully characterize effects of UGT1A9 variants on dapagliflozin clearance. Considering the totality of the clinical pharmacology database, dapagliflozin does not exhibit highly variable pharmacokinetics (CV% ~ 25-35% for Cmax, and AUC; see Office of Clinical Pharmacology review), or racial/ethnic differences in PK. Consequently, additional studies to characterize genetic effects of UGT1A9 or other PK-related variants are likely to be of limited utility.*

4 Summary and Conclusions

4.1 Overall, the *UGT1A9* genotyping study results suggest that *UGT1A9* genetic variations with known functional effects do not impact dapagliflozin clearance to a clinically relevant extent.

4.2 Out of 187 individuals, only 3 individuals carried the functional *UGT1A9*3* allele. Given the low prevalence of these two alleles in the Caucasian population (*2 < 1%, *3 ~ 4%), the study was underpowered to identify smaller effects and the findings of this study are not conclusive.

4.3 Considering the low prevalence of these variants and the limited pharmacokinetic variability of dapagliflozin, UGT1A9 or other genetic factors that affect dapagliflozin PK are not likely to be clinical relevant.

4.4 Clearance tended to be reduced in individuals with variant alleles other than *2 and *3. The consistency in the effect across multiple alleles suggests the potential for underlying linkage disequilibrium, supporting that *UGT1A9* variants that have not been fully characterized may indeed affect dapagliflozin clearance. However, the effect size was still relatively small. Thus, additional studies or consideration of a genotype guided strategy are not warranted.

5 Recommendations

The Genomics Group reviewed the UGT1A9 pharmacogenetics report. At this time UGT1A9 polymorphisms do not appear to contribute significantly to variability in the metabolism of dapagliflozin. Exploratory pharmacogenetic studies may be possible for efficacy or safety issues if necessary given the availability of DNA samples from dapagliflozin clinical trials. From the perspective of the Genomics Group, no additional action is indicated at this time.

4.2 INDIVIDUAL STUDY REVIEWS

Individual will be DARRTed separately as attachment to this review.

9 Page(s) has been Withheld in Full as duplicate copy of OCP Filing Memo (dated 03/01/2011) immediately following this page

4.4 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	202293
Submission Number (Date)	December 27, 2010
Compound (Dosing regimen)	Dapagliflozin Immediate Release Tablets: 10 mg and 5 mg
Clinical Division	DMEP
Primary PM Reviewer	Ritesh Jain, Ph.D.
Secondary PM Reviewer	Anshu Marathe, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the dose-response relationship for effectiveness and safety support the proposed dose of 10 mg QD?

Yes, the dose-response relationship for effectiveness supports the proposed dose of 10 mg QD because an increase in response was observed with increasing doses in Phase 3 combination therapy trials. Additionally, an increase in genitourinary tract infections was observed at doses higher than 10 mg in Phase 2B trial without significant increase in response.

The time-profiles for the adjusted mean change from baseline in HbA1c in combination therapy trials is shown in Figure 1. A clear separation was observed between the treatment arms and the placebo group in MB102014 and D1690C00005, where three doses of dapagliflozin (2.5, 5 and 10 mg) was administered as an add-on to metformin and glimepride (a sulphonylurea) respectively (Figure 1). There is a larger decline in HbA1c with increasing doses. At week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.84) compared to the 5 mg dose group (-0.7) in MB102014. Similarly in D1690C00005, at week 24, the adjusted mean change from baseline in HbA1c is higher for the 10 mg dose group (-0.82) compared to the 5 mg dose group (-0.63) in MB102014. Thus based on effectiveness, the 10 mg dose group seems appropriate in combination therapy as an increase in response was observed with increasing doses.

In Phase 2B monotherapy trial, MB102008 a dose-related increase was observed in change from baseline in HbA1c, FPG and urinary glucose (Figure 2). However, there was no significant improvement in HbA1c levels beyond 10 mg dose group. At week 12, the mean change from baseline in HbA1c was -0.85, -0.55 and -0.9 for the 10, 20 and 50 mg dose groups respectively. However, genitourinary tract infections were more common in the 20 and 50 mg dose groups (17% and 16%) compared to the 2.5, 5, and 10 mg dapagliflozin groups (7%, 10%, and 11%).

In Phase 3 monotherapy trial MB102013, a clear separation between the time-profiles of the adjusted mean change in HbA1c for the treatment arms (2.5, 5 and 10 mg) and placebo is observed (Figure 3). There is a larger decline in the adjusted mean change from baseline in HbA1c for the treatment arms compared to placebo at all time points. However, the decline in HbA1c in the 10 mg dose group is similar to the decline observed for the 5 mg dose group. There is no clear separation between the 5 and 10 mg dose groups in MB102013. In MB102032, again a clear separation is observed between the placebo and treatment arms (Figure 3). The decline in HbA1c in the 5 mg dose group is comparable with the decline observed in the 5 and 10 mg groups in MB102013. While in monotherapy trials the response is similar for the 5 and 10 mg dose groups, this finding is not supported by the combination therapy trials where higher response was observed in the 10 mg dose group.

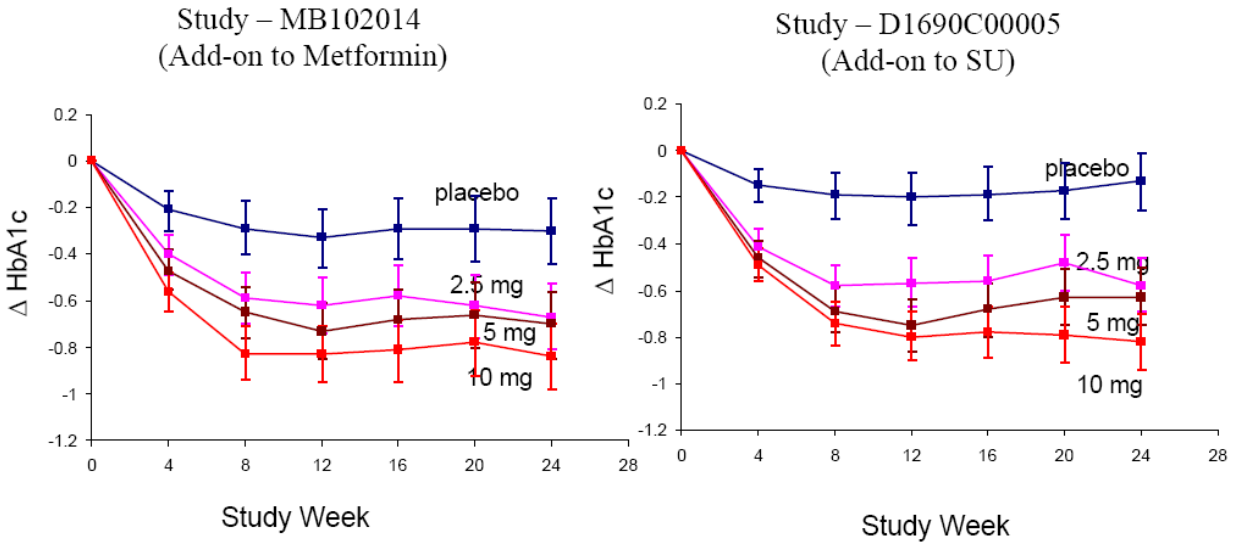


Figure 1: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 combination therapy trials MB102014 (left) and D1690C0005 (right) upon administration of placebo (blue), 2.5 mg (pink), 5 mg (brown) and 10 mg (orange) QD of dapagliflozin as an add-on to metformin and glimepride (a sulphonylurea) respectively. ***Source: Sponsor's Tables S.5.1 and S.5.2 in study reports mb102014. Sponsor's Table 11.2.2.1.5 in study report D1690C00005.***

Phase 2B – MB102008

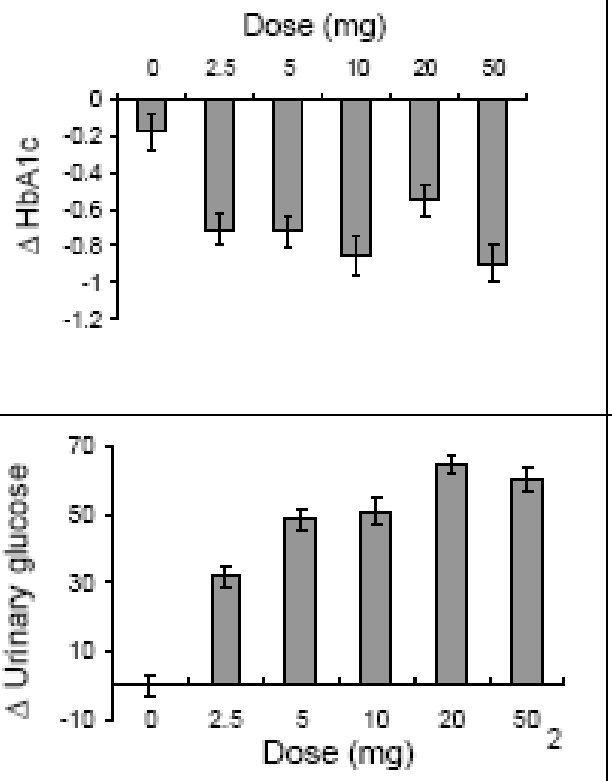


Figure 2: Dose-response relationship for A) mean change from baseline in HbA1c, B) mean change from baseline in FPG and c) mean change from baseline in urinary glucose in Phase 2B trial MB102008.

Source: Sponsor's table 7.1 in study report MB102008

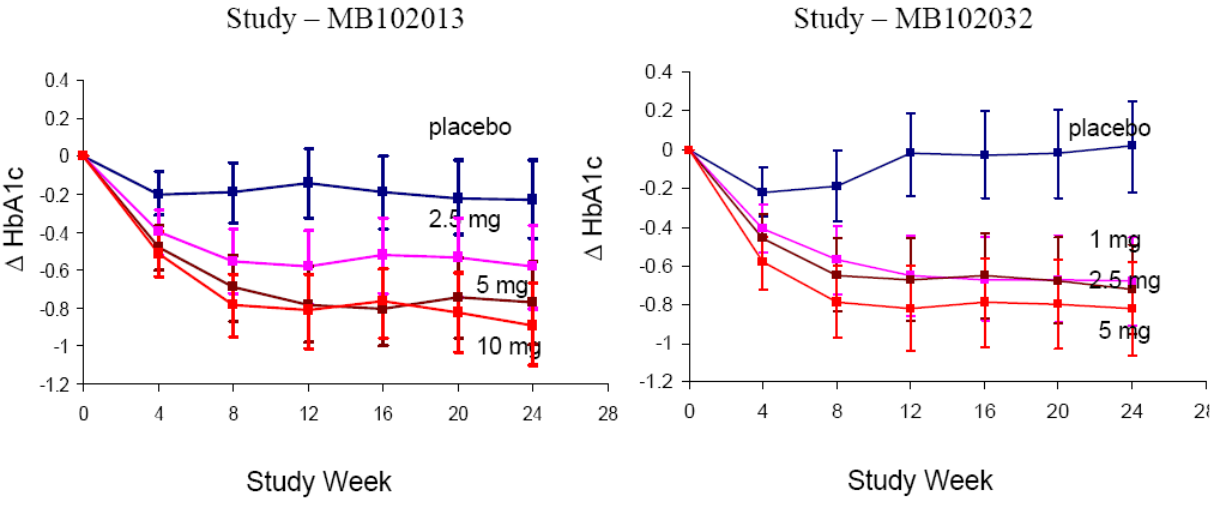


Figure 3: Time-profiles for adjusted mean change from baseline in HbA1c in Phase 3 monotherapy trials MB102013 (left) and MB102032 (right) upon administration of placebo (blue), 2.5 mg (pink), 5 mg (brown) and 10 mg (orange) QD of dapagliflozin.
Source: Sponsor's Tables S.5.1 and S.5.2 in study reports mb102013 and mb102032.

1.1.2 Is there impact of renal impairment on the efficacy of dapagliflozin?

Yes, there appears to be significantly less reduction in HbA1c levels in patients with moderate renal impairment compared to normal patients and patients with mild renal impairment (Figure 4).

The time-profiles for the adjusted mean change from baseline in HbA1c in studies MB102013 and MB102029 are shown in Figure 4. MB102013 was a placebo-controlled Phase 3 study to evaluate the effect of 3 different doses (2.5 mg, 5 mg, and 10 mg) of dapagliflozin in patients with Type 2 diabetes. This study included patients with normal renal function (estimated GFR $\geq$ 90 mL/min/1.73m^2) and mild renal impairment (estimated GFR between 60 and 90 mL/min/1.73m^2). MB102029 was a placebo-controlled Phase2/3 trial to evaluate the efficacy, renal safety and PK-PD of 2 different doses (5mg and 10mg) of dapagliflozin in Type 2 diabetes patients with moderate renal impairment (estimated GFR between 30 and 59 mL/min/1.73m^2). There is a clear separation between the time-profiles for the treatment arms (5 and 10 mg) and placebo in MB102013. For both 5 and 10 mg doses, there is a larger decline in the adjusted mean change from baseline in HbA1c compared to placebo at all time points In MB102029, a clear separation between the placebo and treatment arms (5 and 10 mg) is not observed. A slight separation between the placebo and treatment arms is observed between weeks 8 and 12. However, beyond week 16, there is no separation. The magnitude of effect of the 5 and 10 mg doses in patients with moderate renal impairment (MB102029) is much lower compared to patient with normal renal function or mild renal impairment (MB102013). At week 24, the adjusted mean change from baseline in HbA1c for the 10 mg dose is -0.89 in MB102013. In MB102029, the adjusted mean change from baseline is -0.41 for the 10 mg dose group at week 24. Overall, consistent with the known mechanism of action of the drug, there appears to be significantly less reduction in HbA1c levels in patients with moderate renal impairment.

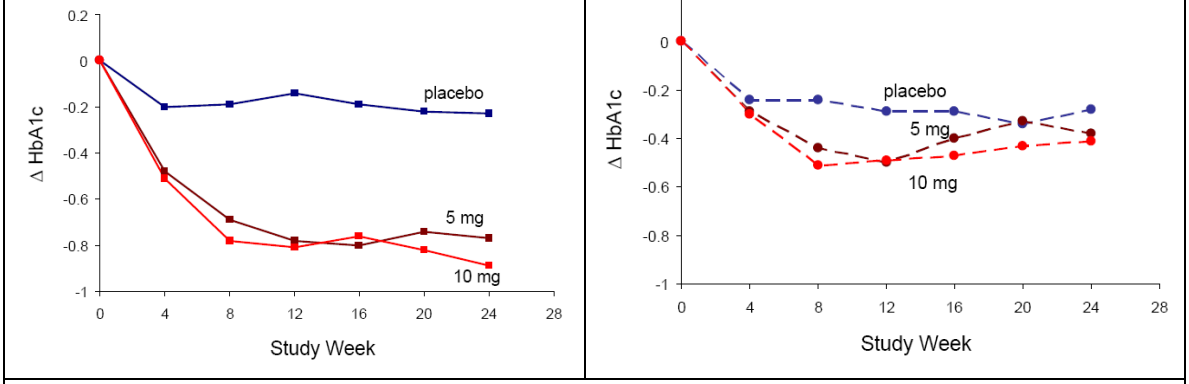


Figure 4: Time-profiles for adjusted mean change from baseline in HbA1c in A) Study MB102013 and B) Study MB102029 upon administration of placebo (blue), 5 mg QD of dapagliflozin (brown) and 10 mg QD of dapagliflozin. Data from 2.5 mg dapagliflozin treatment arm in MB102013 is not shown. *Source: Sponsor's Tables S.5.1 and S.5.3 in study reports mb102013 and mb102029*.

1.1.3 Is there dose-response relationship for adverse events?

The major safety issues associated with dapagliflozin as identified by Dr. Dunn (medical reviewer) and discussed at the advisory committee for dapagliflozin are bladder and breast cancer, marked elevation in liver enzymes, genital infections, urinary tract infections, bone related adverse events, renal safety and adverse events related to volume depletion.

Based on Dr. Hampp's review (see review in DAARTS dated 07/20/2011), ten subjects were diagnosed with bladder cancer in Phase 2B and 3 clinical trials on dapagliflozin. Nine of these cases occurred in the treatment arm and one on the placebo arm. Nine cases of breast cancer were diagnosed in the treatment arm versus none in the comparator group (See Dr. Ju's review in DAARTS dated 06/07/2011). Incidence of these cancers is low to perform meaningful dose-response analysis.

The proportion of subjects with elevated liver tests were 3.9%, 3.5% and 3.6% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm (see Table 82 in sponsor's summary of clinical safety). Overall, a trend for increasing proportion of subjects with liver enzyme elevations with increasing dose is not observed.

No significant trend for increasing proportion of subjects with genital or urinary tract infections with increasing dose was observed. The proportion of subjects with genital infections were 5.8%, 7% and 7% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm (see Table 49 in sponsor's summary of clinical safety). The proportion of subjects with urinary tract infections were 4.2%, 7.3% and 6.5% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm (see Table 57 in sponsor's summary of clinical safety).

Dose-response analysis was not conducted for the effect of dapagliflozin on bone safety because the overall fracture rate was low (1.4%) and was balanced between dapagliflozin and the control groups.

In a pooled analysis including patients with normal renal function and mild renal impairment, a transient decline from baseline in eGFR was observed by week 1 and then increase towards or above baseline over time (Figure 5A). There was no clear trend for this decline to be dose-dependent. In trial MB102029 that included patients with moderate renal impairment, a dose-dependent decline from baseline in eGFR was observed and then the levels stabilized (Figure 5B). The proportion of subjects with events characterized as renal impairment or failure were 2.4%, 1.8% and 2.0% in the 2.5 mg, 5 mg and 10 mg dapagliflozin arm (see Table 70 in sponsor's summary of clinical safety). These events appear similar between dose groups.

No trend for increasing proportion of subjects with adverse events related to volume depletion with increasing dose was observed. The incidence these adverse events were low (Table 1).

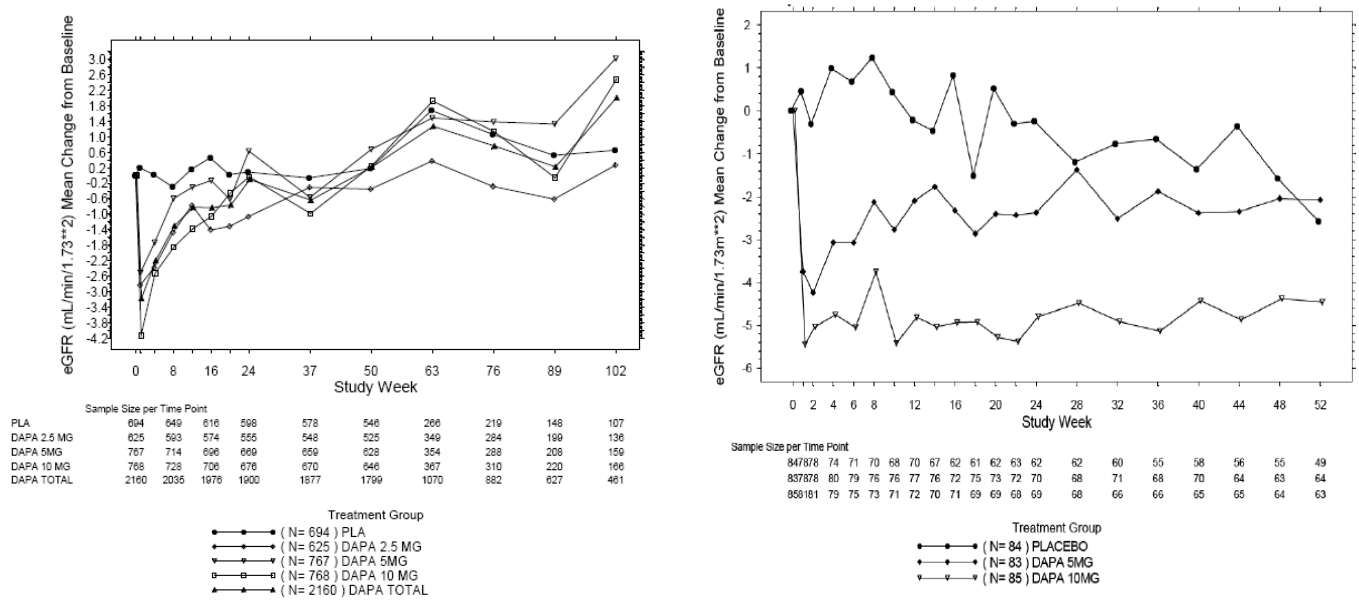


Figure 5: Time-profiles for mean change in GFR from baseline in A) pooled analysis and B) renal impairment trial MB102029. ***Source: Sponsor's Figure 4 and Figure 5 in summary of clinical safety.***

Table 1: Adverse events related to volume depletion in short-term, double-blind treatment period

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: Sponsor's Table 72 in Summary of Clinical Safety

1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective.

1.3 Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for NDA 202293. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12.3 Pharmacokinetics

Effects of Age, Body weight, Gender and Race

Based on a population PK analysis (b) (4) gender, race, age, and body weight do not have a clinically meaningful effect on (b) (4) of dapagliflozin and thus no dose adjustment is recommended.

(b) (4)

Reviewer's comments:

- *Sponsor's labeling claims that there is no clinically meaningful effect of age, race, weight and gender on exposure is acceptable. However, (b) (4) have been removed to keep the label concise.*
- (b) (4) *Labeling claims for renal function are based on the dedicated renal impairment study (MB102007) and Phase 3 trial in patients with moderate renal impairment (MB102029). Renal function measurement by calculated creatinine clearance, cCrCL, was identified as a statistically significant covariate on the apparent clearance of dapagliflozin. In this population PK analysis majority of the subject were normal renal function subjects or subject with mild renal functions. Efficacy in Phase 3 trials were comparable between patients with mild renal function to that of subjects with normal renal function.*
- *Sponsor conducted a dedicated Phase 3 study in patients with moderate renal function. Results of this Phase 3 trial showed efficacy of dapagliflozin in terms of lowering of HbA1c is not statistically significant different than the placebo.*

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from five clinical studies that includes one Phase 1 trial in healthy subjects (MB102002), one Phase 2 study in T2DM subjects (MB102003), and three Phase 3 trials in T2DM subjects (MB102013, MB102032, D1690C00006). Primary objective of the population PK analysis was to identify patient factors (age, race, gender, renal function, body weight etc.) that may affect PK and therefore may require dose adjustment.

2.1.1 Methods

PK Data from a total of 1243 subjects (8011 samples) from Phase 1 study (MB102002), 1 Phase 2 study (MB102003), two Phase 3 monotherapy studies (MB102013, MB102032), and one Phase 3 add-on to insulin study (D1690C00006). Description of the studies with other relevant information is provided in Table 2.

Table 2: Studies Used for the Population PK Model

Study Description	Study Number	Subject Population	Source Data for
Phase 1 study, Multiple Ascending Dose	MB102002	Healthy	PPK
Phase 2 study, proof-of-concept	MB102003	T2DM	PPK
Phase 3 study[a], Efficacy and safety of dapagliflozin monotherapy	MB102013	T2DM, drug naive	PPK, efficacy and safety
Phase 3 study[a], Efficacy and safety of dapagliflozin monotherapy	MB102032	T2DM, drug naive	PPK, efficacy and safety
Phase 3 study[a], Efficacy and safety of dapagliflozin and insulin	D1690C00006	T2DM with inadequate glycemic control on insulin	PPK, safety

Abbreviations: T2DM = type 2 diabetes mellitus; PPK, population pharmacokinetic modeling

[a]: Data from short-term duration only.

Source: Sponsor's Population PK Report, Page 3

PK data were then fitted using NONMEM Version VI Level 1.1 (Icon US, Hanover, MD). The PPK model was developed in 3 stages. First, a base model was developed to describe the PK without consideration of covariate effects. Second, a full-covariate model was developed by incorporating the effects of all potentially significant covariate-parameter relationships, and lastly the final model was developed by retaining only the statistically significant covariate-parameter relationships by step-wise backward elimination. Model building and covariate assessments were conducted using standard methods. The final model for the PK database was evaluated for performance using visual predictive check (VPC) and quantitative predictive check evaluation.

2.1.2 Final Model

To arrive at the final model, the full model was subjected to a step-wise backward elimination procedure. After the backwards elimination procedure was completed, 4 covariate-parameter relationships were retained in the final model: cCrCL and gender (female/male) on *CL/F*, and body mass index on *V2/F*. The IIV parameters of the base model were specified by a lognormal distribution. The residual error (intra-individual variability) parameters of the final model were described by combined error model.
The NONMEM output for the base model is presented in Table 3.

Table 3: Parameter Estimates of Final Model (Final)

Name [Units]	Symbol	Estimate	Standard Error (RSE%)[b]	95% Confidence Interval[c]
Fixed Effects				
KA [1/hr]	θ_1	2.97	0.429 (14.4)	2.13 - 3.81
CL/F [L/hr]	θ_2	22.9	0.404 (1.76)	22.1 - 23.7
V2/F [L]	θ_3	73.9	1.19 (1.61)	71.6 - 76.2
V3/f [L]	θ_4	113	5.45 (4.82)	102 - 124
Q/F [L/hr]	θ_5	8.85	0.267 (3.02)	8.33 - 9.37
CRC1~CL/F	θ_6	0.552	0.0368 (6.67)	0.480 - 0.624
GENDER~CL/F	θ_8	-0.161	0.0223 (13.9)	-0.205 - -0.117
BWT~V2/F	θ_{10}	0.705	0.0753 (10.7)	0.557 - 0.853
EP1	θ_{12}	0.725	0.0275 (3.79)	0.671 - 0.779
Random Effects[a]				
KA	$\omega_{1,1}$	8.68 (2.95)	0.723 (8.33)	7.26 - 10.1
CL	$\omega_{2,2}$	0.106 (0.326)	0.00516 (4.87)	0.0959 - 0.116
V3	$\omega_{4,4}$	0.147 (0.383)	0.0360 (24.5)	0.0764 - 0.218
Residual Error				
err.1	$\sigma_{1,1}$	0.197 (0.444)	0.00175 (0.888)	0.194 - 0.200
err.2	$\sigma_{2,2}$	0.0979 (0.313)	0.0123 (12.6)	0.0738 - 0.122

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the [c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)
[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)
[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Source: Sponsors Population PK Report, Pages 101

Basic goodness of fit plots for the Sponsor's final model is shown in Figure 6.

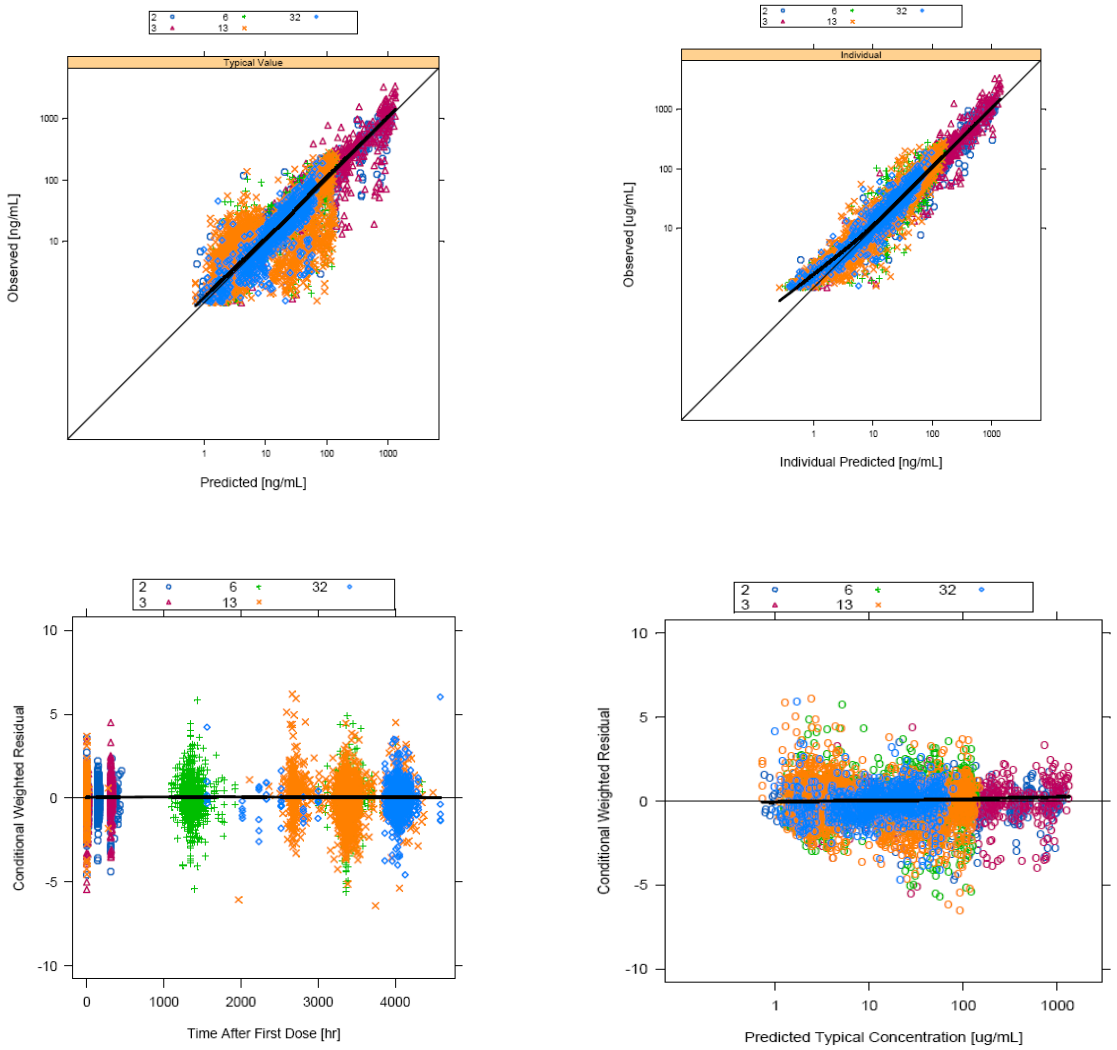


Figure 6: Basic goodness of fit plots for the Sponsor's final model

Source: Sponsors Population PK Report, Pages 103-107

2.1.2.1 Dapagliflozin Covariate Effects

Exposures (steady state AUC) in relevant sub-populations based on age, gender, renal function, race and weight were calculated using the final population PK model and the results are summarized in Table 4. These simulations utilized 5000 subjects each treated with 10 mg QD dose of dapagliflozin. The mean dapagliflozin systemic exposure (AUC) in young patients (<40 years) was estimated to be 10.4% lower compared to the reference group (≤ 40 years and < 65 years) and 25% higher in elderly patients (≥ 65 years) compared to the reference group. Females have 22% higher exposure as compared to males. Compared to whites, there was no difference in systemic exposures in Asians. Compared to whites, African-American subjects had 4.9% lower systemic exposures. Systemic exposures in high body weight subjects (≥120 kg) were estimated to be 78.3% of those of reference subjects with body weight between 75 and 100 kg. Exposures in low

body weight (<50 kg) subjects were estimated to be 29% higher than subjects with the reference group body weight. These differences in systemic exposure were considered not to be clinically meaningful. In the renally impaired patients mild renal impaired subjects have 19% higher exposure and moderate have 52 % higher exposure as compared to subjects with normal renal function. However, sponsor also conducted a dedicated renal impairment study where mild subjects have 39% higher exposure and moderate have 100 % higher exposure as compared to subject with normal renal function.

Table 4: Summary of Predicted Dapagliflozin Steady State Exposures in Subjects with T2DM Normalizing to 10 mg QD

COVARIATE	Number of Subjects	AUCss (ng.hr/mL) Geometric mean [90% CI] [b]	AUCss relative to Subgroup Reference (%) Geometric mean [90% CI] [b]
Age			
40≤Age<65 years[a]	924	454 [446, 462]	
Age>=65 years	224	568 [548, 588]	125 [123, 129]
Age<40 years	105	407 [388, 428]	89.6 [87.9, 92.2]
Body Weight			
75≤BWT<100 kg[b]	614	469 [459, 478]	
BWT<50 kg	4	699 [442, 1110]	149 [146, 156]
BWT>=120 kg	91	367 [346, 390]	78.3 [78.2, 83.2]
Renal Function			
Mild (30<=eGFR<60 mL/min/1.73m^2)	692	484 [474, 493]	119 [117, 123]
Moderate (60<=eGFR<90 mL/min/1.73m^2)	135	620 [594, 647]	152 [149, 158]
Normal[a] (eGFR>90 mL/min/1.73m^2)	426	407 [397, 417]	
Gender			
Female	619	518 [507, 529]	122 [117, 124]
Male[a]	634	425 [416, 434]	
Race			
Asian	47	469 [432, 509]	100 [96.3, 101]
Black	43	446 [417, 477]	95.1 [92.3, 96.3]
White[a]	1147	469 [462, 477]	

Source: /global/pkms/data/MB/102/C01/prd/pk/sp/plotscripts/pkall.nm.new/splots.Final.ssc

[a] Subgroup reference in each covariate category

[b] 90% confidence interval obtained by simulating a population with number of subjects equal to the reference group

Source: Sponsors Population PK Report, Pages 116

2.2 Sponsor's Conclusions

- The pharmacokinetics of dapagliflozin can be characterized adequately by a 2-compartment linear model with first-order absorption and no time-variant parameters.

- There are no meaningful differences in systemic exposures based on body weight, gender, age, race and mild renal impairment suggesting no dosage adjustment on the basis of these covariates.

***Reviewer's comments on Sponsor's Population PK Analysis**:*

- *Sponsor's population PK analysis is generally adequate and acceptable.*

- *The covariates that were identified in the final model are likely not to be significant as the inclusion of all the covariates did not reduce the inter-individual variability on clearance significantly.*

- *Sponsor's conclusion that no dose adjustment based on age, gender, body weight and race is acceptable. See reviewer's independent analysis in section 3.3.*

- (b) (4) *Renal function measurement by calculated creatinine clearance, cCrCL, was identified as a statistically significant covariate on the apparent clearance of dapagliflozin. In this population PK analysis majority of the subject were normal renal function subjects or subject with mild renal functions. Efficacy in Phase 3 trials were comparable between patients with mild renal function to that of subjects with normal renal function. Sponsor conducted a dedicated Phase 3 study in patients with moderate renal function. Results of this Phase 3 trial showed efficacy of dapagliflozin in terms of lowering of HbA1c is not statistically significant different than the placebo.*

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Objectives

The primary objective was to confirm sponsor's claim that there are no meaningful differences in systemic exposures based on body weight, gender, age, race and mild renal impairment.

3.2 Methods

3.2.1 Data Sets

Data set used are summarized in Table

Table : Analysis Data Set

Study Number	Name	Link to EDR
MB102002 MB102003 MB102013 MB102032 D1690C00006	pkall.xpt	\\Cdsesub1\evsprod\NDA202293\0000\m5\datasets\pop-pk\analysis

3.2.2 Software

R and NONMEM were used for reviewer's analysis.

3.3 Results

There is an increase in clearance with increasing creatinine clearance (Figures 7A and B). The clearance in patients with moderate and mild renal impairment is 42% and 29% lower than patients with normal renal function. After inclusion of creatinine clearance in sponsor's final model, no systematic trend between inter-individual variability on clearance and creatinine clearance is observed (Figure 7C).

There is a trend for increasing clearance with increase in body weight (Figure 8A). However, body weight was found to be highly correlated to cCrCL (correlation coefficient > 0.5) and thus inclusion of creatinine clearance in the final model resulted in no systematic trend between inter-individual variability on clearance and body weight as observed in Figure 8C. The effect of body weight is not considered clinically meaningful as there is only a 38% increase in clearance from the lowest quartile of body weight to the highest quartile.

There is also a trend for decrease in clearance with increasing age specifically beyond 50 years of age (Figure 9A). Age was found to be highly correlated to cCrCL (correlation coefficient > 0.5) and thus inclusion of creatinine clearance in the model resulted in no systematic trend between inter-individual variability on clearance and age (Figure 9C). The effect of age on dapagliflozin PK is not considered clinically meaningful because the decrease in clearance in subjects greater than 65 years of age in 22% compared to subjects less than 65 years of age.

Males have a 23% higher clearance than females which is considered not to be clinically meaningful (Figure 10A). No systematic trend between inter-individual variability on clearance and gender is observed after inclusion of gender as a covariate on clearance (Figure 10B).

Race does not significantly affect the pharmacokinetics of dapagliflozin. Figure 11 shows that the inter-individual variability in clearance cannot be explained by race.

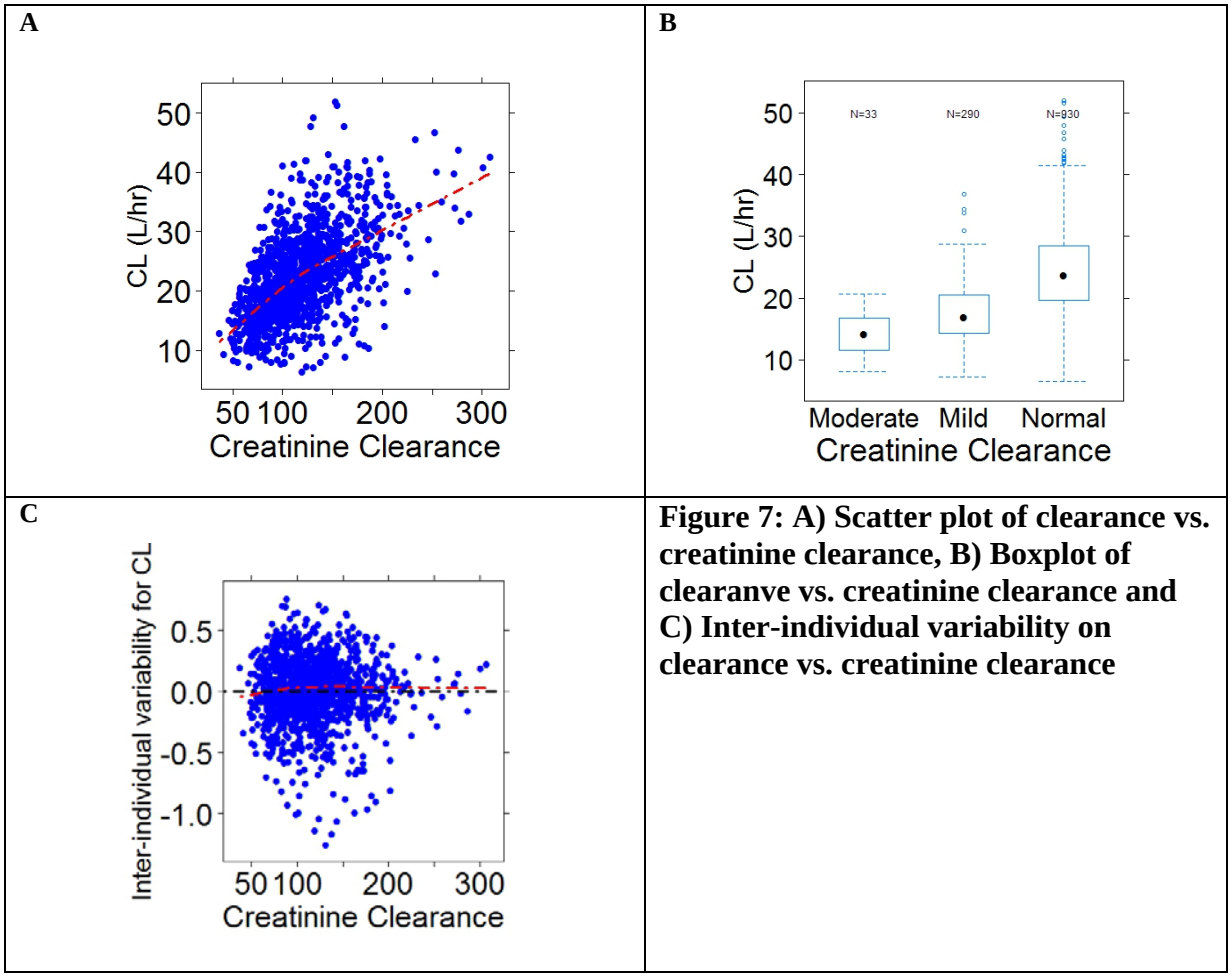


Figure 7: A) Scatter plot of clearance vs. creatinine clearance, B) Boxplot of clearanve vs. creatinine clearance and C) Inter-individual variability on clearance vs. creatinine clearance

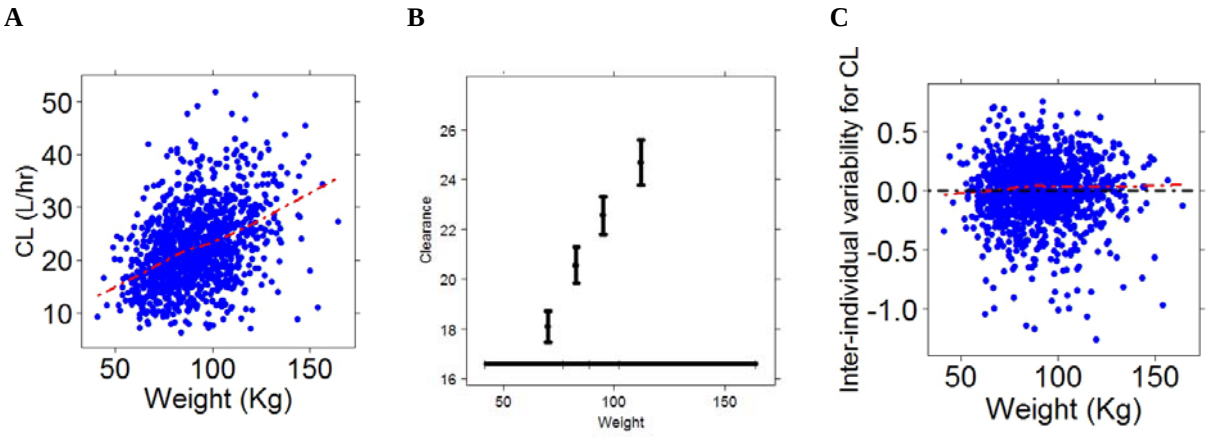


Figure 8: A) Scatter plot for clearance vs. weight B) Quartile plot of clearance vs. weight and C) Inter-individual variability on clearance vs. weight

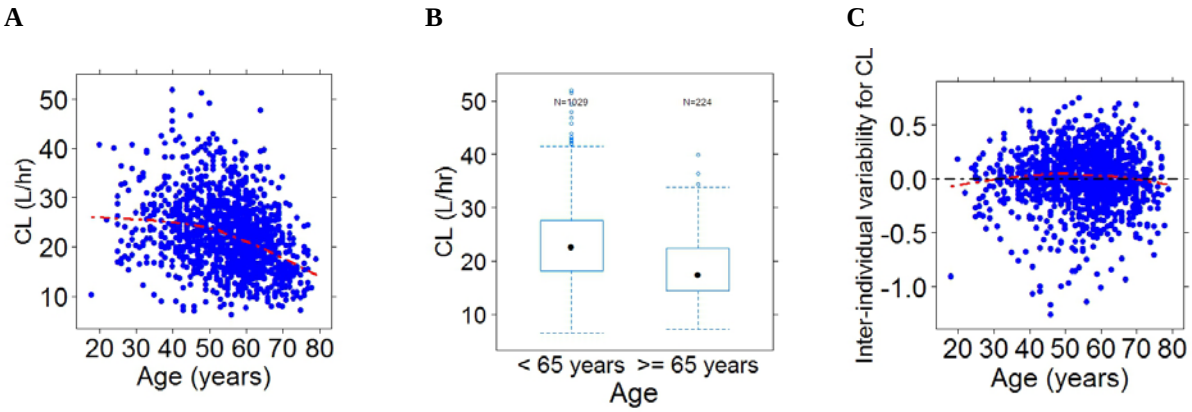
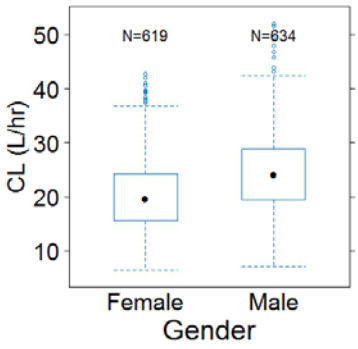


Figure 9: A) Scatter plot for clearance vs. age B) Boxplot of clearance vs. age and C) Inter-individual variability on clearance vs. age

A



B

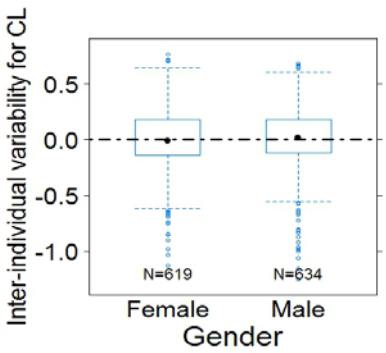
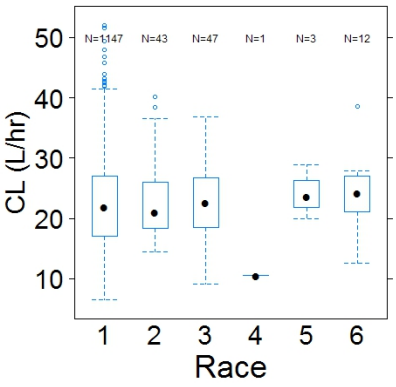


Figure 10: A) Clearance and B) Inter-individual variability on clearance vs. gender

A



B

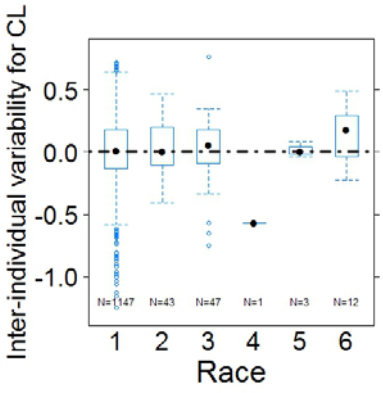


Figure 11: A) Clearance and B) Inter-individual variability on clearance vs. race. 1=White, 2=African American, 3=Asian, 4=American Indian/Alaska Native, 5=Native Hawaiian/Other Pacific Islander, 6=Others

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/s/

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BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-293	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	27 December 2011		
Division:	Division of Metabolism and Endocrinology Products	**Team Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Bristol Myers Squibb	**Supervisor:** Patrick Marroum, Ph.D.	
Trade Name:	None proposed Company code: BMS-512148	**Date Assigned:**	27 December 2010
Generic Name:	Dapagliflozin propanediol	**Date of Review:**	26 May 2011
Indication:	Type 2 diabetes in adults	**Type of Submission:** Original NDA 505(b)1	
Formulation/strengths	Tablet, 5 mg and 10 mg		
Route of Administration	Oral		

SUBMISSION: NDA 202-293 was submitted in accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the use of dapagliflozin in the treatment of type 2 diabetes in adults as an adjunct to diet and exercise to improve glycemic control. Dapagliflozin is a novel small molecule inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), which is the major transporter responsible for renal glucose reabsorption. The drug substance is a (b) (4) propanediol and water in a 1:1:1 ratio. The drug product is a yellow, biconvex, round, film-coated tablet with identifiers debossed on each side. The formulation is comprised of the excipients microcrystalline cellulose, lactose, crospovidone, silicon dioxide, magnesium stearate, (b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol (b) (4) talc and iron oxide yellow (b) (4) Two strengths are proposed for the commercial market, 5 mg and 10 mg. The proposed daily dose is 10 mg taken one daily; however, for patients at risk for volume depletion due to coexisting conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose may be appropriate.

Bristol-Myers Squibb utilized Quality-by-Design (QbD) concepts in the formulation/process development of the drug product.

BIOPHARMACEUTIC INFORMATION: The applicant requested approval for the use of disintegration testing as a surrogate for dissolution for routine quality control.

The proposed disintegration method is as follows.

- USP<701>, pH 4.5 acetate buffer, with disks
- Limit = (b) (4)

The developed dissolution test method is as follows.

- USP Apparatus II (paddle), 60 rpm
- Acetate buffer pH 4.5, 1000 mL @ 37°C
- Sampling at 5, 15, 30 and 60 minutes.
- Limit – none. ***Note:*** *Specific tolerance not specified in NDA as disintegration is proposed in lieu of dissolution, profile data were collected for registration stability batches and QbD studies employing this method.*
- HPLC Analysis – (b) (4)

The dissolution method development, applicant's justification for the using disintegration testing in lieu of dissolution, and supporting product release and stability data were reviewed. Full details are provided in the appended Review Notes Section.

RECOMMENDATION: From a biopharmaceutics perspective, the application is recommended for approval; however, the following comment should be conveyed to the applicant.

- Your proposal to use disintegration as a surrogate for dissolution testing as part of the drug product regulatory specification is accepted. However, you are reminded that in vitro dissolution will be necessary to support certain post approval changes in accordance with existing FDA guidance documents and regulations. Additionally, ongoing registration stability studies should continue to monitor tablet dissolution and disintegration through the end of the study protocol. The following dissolution method is the application method for future comparative studies.
    - USP Apparatus II (paddle), 60 rpm
    - Acetate buffer pH 4.5, 1000 mL @ 37°C
    - Limit: Q = (b) (4) in 15 min; sampling profile at 5, 15, 30 and 60 minutes

Minerva Hughes
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick Marroum
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

Cc: List electronically filed in DARRTS

REVIEWER'S NOTES

1.0 INTRODUCTION

Dapagliflozin is a novel small molecule inhibitior of the human renal sodium-glucose cotransporter 2 (SGLT2). This NDA is for the use of dapagliflozin in the treatment of adult Type 2 diabetes. The drug substance is a [(b) (4)] 1:1:1 mixture of dapagliflozin, propanediol and water (designated as BMS-512148-05). The drug product is a film-coated tablet available in two strengths: 5 mg and 10 mg. BMS manufacturing facilities located at Humacao, Puerto Rico and Mount Vernon, Indiana are proposed as drug product manufacturing sites. Relevant Agency interactions regarding biopharmaceutics are summarized below:

- 26 Sept 2008 – In FDA's response to questions raised in the 5 Sept 2008 End-of-Phase 2 Meeting Package (IND 68,652 SN 144) the Agency considered (1) the proposed dissolution method using USP Apparatus 2, [(b) (4)] pH 4.5 50 mM acetate medium (1000 mL) to be adequate, (2) bridging Phase 3 and commercial product by using in vitro dissolution for changes in tablet shape and color was acceptable (*Reviewer's note:* [(b) (4)]).
- 6 Oct 2008 – FDA memorandum on file. The Agency stated that comparative dissolution testing would be acceptable to bridge changes [(b) (4)] between formulations.
- 26 Nov 2008 - BMS submitted a change to the dissolution method paddle speed [(b) (4)] to 60 rpm [(b) (4)] (IND 68,652 SN 155).
- 22 April 2010 – Additional biopharmaceutics data were submitted to the IND on 3 March 2010 in response to FDA's request for BMS to justify changes to the dissolution method. FDA commented that [(b) (4)] the 60 rpm method was deemed acceptable. The Agency commented further that disintegration testing may be more discriminative and requested that BMS consider disintegration testing for quality control.

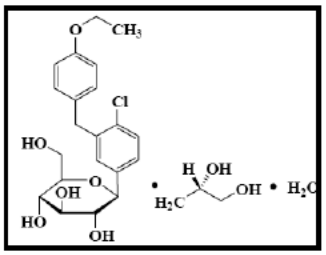
This submission provides for the use of disintegration testing in lieu of dissolution testing. Data in support of this request are reviewed in the subsequent sections.

2.0 BIOPHARMACEUTICS QUALITY ASSESSMENT

2.1 GENERAL PROPERTIES

2.1.1 Structure

The structure of the drug substance is as follows.



Molecular Formula: $C_{21}H_{25}ClO_6*C_3H_8O_2*H_2O$
Molecular Weight: 408.87 g/mol (dapagliflozin) 502.98 g/mol [(b) (4)]

Reviewer's Comment: *Dapagliflozin is a new molecular entity. Although the active moiety is the dapagliflozin molecule, solubility and bioavailability may be influenced* (b) (4) *The applicant conducted relative bioavailability studies using* (b) (4) *tablets (Study MB102062 and MB102090) to address this issue. (Refer to Clinical Pharmacology Review)*

2.1.2 Solubility and Other Relevant Characteristics

The applicant stated that dapagliflozin is a BCS Class 3 product. The pH-solubility profile and pKa data are provided below.

(b) (4)

2.2 DISSOLUTION AND DISINTEGRATION METHOD DEVELOPMENT

2.2.1 Drug Product Composition

Throughout the clinical development program, the applicant explored different investigational drug products and used comparative dissolution or clinical studies to bridge the different formulations. An illustrative overview was provided in NDA Module 2.7.1, Figure 1.4.

The drug product is manufactured (b) (4) The proposed to-be-marketed formulation is summarized below.

Component	Function	5- mg Tablet	10-mg Tablet
Dapagliflozin propanediol	Active	(b) (4)	(b) (4)
Microcrystalline cellulose	(b) (4)		
Anhydrous lactose			
Crospovidone			
Silicon dioxide			
Magnesium stearate			
(b) (4)			
Total Tablet Weight		130.00 mg	260.00 mg

2.2.2 Dissolution Method Development

The dissolution method evolved throughout the clinical development program. The initial method optimized for commercial product quality control is summarized below.

(b) (4)

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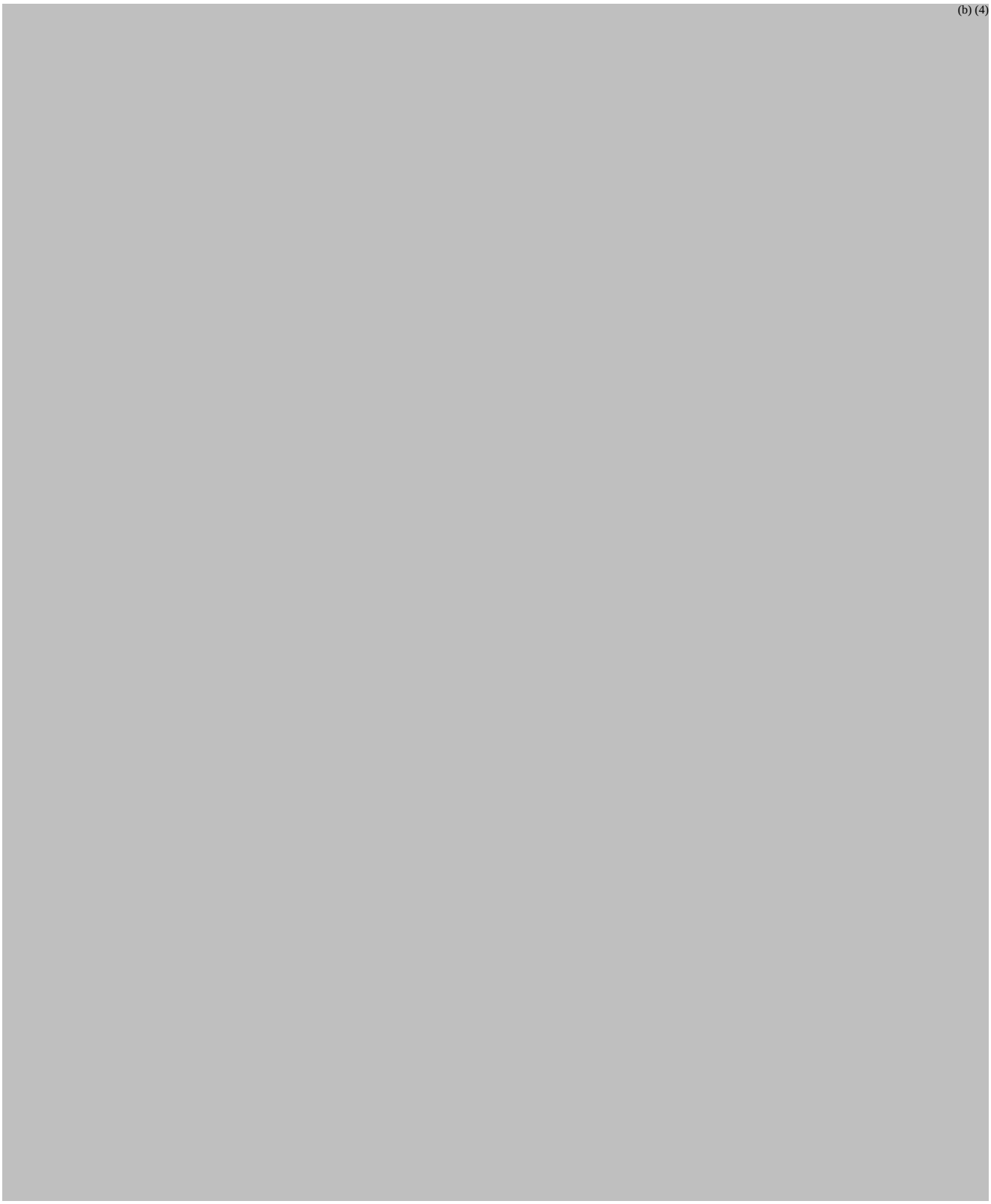
(b) (4)



3.0 REGULATORY ISSUES

- Disintegration testing in lieu of dissolution is accepted.

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/s/

MINERVA HUGHES
05/26/2011

PATRICK J MARROUM
05/27/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202293**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCPII**	**Generic Name**	**Dapagliflozin**
Medical Division	**DMEP**	**Drug Class**	**SGLT2 Inhibitor**
OCP Reviewer	**Ritesh Jain**	**Indication(s)**	**Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
OCP Team Leader	**Sally Choe**	**Dosage Form**	**Immediate Release Tablets: 10 mg and 5 mg**
Pharmacometrics Reviewer	**Anshu Marathe Christine Garnett (Team Leader)**	**Dosing Regimen**	**10 mg once daily taken at anytime of the day regardless of meals.**
Date of Submission	**12/27/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**09/09/2011**	**Sponsor**	**Bristol-Myers Squibb and AstraZeneca**
Medical Division Due Date	**10/07/2011**	**Priority Classification**	**S**
PDUFA Due Date	**10/28/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study: MB102006**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**2**		**Studies: MB102027a, MB102007a**
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**	**2**		**Studies: MB102001, MB102088**
multiple dose:	**X**	**1**		**Study: MB102002**
Patients-				
single dose:				
multiple dose:	**X**	**1**		**Study: MB102003**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Drug-drug interaction studies -	**X**	**10**		**Studies: MB102017, MB102026, MB102037, D1692C00002, MB102004, MB102036, MB102057, MB102058, MB102074, MB102016**
In-vivo effects on primary drug:	**X**			
In-vivo effects of primary drug:	**X**			
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**2**		**Studies: MB102010, MB102025 Single and multiple dose study in Japanese Subjects**
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		**Study: MB102007**
hepatic impairment:	**X**	**1**		**Study: MB102027**
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		**Study: MB102008**
Phase 3 clinical trial:	**X**	**3**		**Studies: MB102013, MB102032, D1690C00006**
Population Analyses -				
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		**Study: MB102059**
Relative bioavailability -	**X**			
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Study: MB102005 comparing tablet vs (b) (4) formulation**
Bioequivalence studies -	**X**	**2**		**Studies MB102062 and MB102090. These studies compared the effect (b) (4) on the formulation**
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**Study: MB102019**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**1**		**Study: MB102008**
Chronopharmacokinetics				
Pediatric development plan	**X**			
Literature References				
Total Number of Studies		**31**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence				Sponsor used the same formulation

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		in their pivotal clinical trial as to be marketed formulation except that there are some changes in color and debossing for which a biowaiver request is made.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Waiver for pediatric patient less than 10 years of age. Deferral for pediatric patient between 10 to 17 years of age
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____YES__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

From Clinical Pharmacology there are no comments for 74-day letter

Ritesh Jain 02/23/2011

Reviewing Clinical Pharmacologist Date

Sally Choe 02/23/2011

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo (Internal Memo)

1. Background

Dapagliflozin (BMS-512148) is an active inhibitor of the human renal sodium glucose co-transporter type 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose in the proximal tubule, thereby promoting its urinary excretion. Dapagliflozin was developed for use in the treatment of type 2 diabetes mellitus (T2DM) by Bristol-Myers Squibb and AstraZeneca. Only the oral route of administration is proposed for dapagliflozin. The proposed clinical dose of dapagliflozin is 10 mg administered once-daily. Sponsor used the same formulation in their pivotal clinical trial as to be marketed formulation except that there are some changes in color and debossing for which a biowaiver request is made.

From Clinical Pharmacology there are no comments for 74-day letter. Also, no DSI inspection is requested by Clinical Pharmacology.

2. Clinical Pharmacology Studies:

The clinical pharmacology profile of dapagliflozin has been characterized based on the results of 26 clinical pharmacology studies as well as population pharmacokinetic (PPK) and exposure-response (E-R) analyses that incorporated data from Phase 1 and Phase 2/3 studies.

Below is the summary of some of the highlights of Dapagliflozin related to clinical pharmacology from the sponsor:

- Absolute Oral Bioavailability following Oral Administration: ~78%.
- Cmax ~ 2 hours, t1/2 ~ 12.5 h, and protein binding ~90%
- PK was similar between single dose and multiple dose administrations.
- No drug accumulation following multiple dose for 14 days (AI-1.25)
- Dapagliflozin PK parameters were similar on Days 7 and 14 indicating that steady-state was reached by at least the 7th day of dosing.
- Dose-proportional increase in systemic exposures for doses ranging from 0.1 to 500 mg.
- Food had relatively modest effects on dapagliflozin PK (↓ AUC 7%, ↓ Cmax 50%).
  - Dosing recommendation: Can be taken with or without food.
- Dapagliflozin is metabolized by UGT1A9, an enzyme present in the liver and kidney, to a glucoronidated metabolite dapagliflozin 3-O-glucuronide, which is not an inhibitor of SGLT2.
- CYP-mediated metabolism was a minor clearance pathway in humans
- After administration of a 50-mg [U-14C]dapagliflozin dose to healthy subjects,
  - 96% of TRA was recovered,
  - 75% in urine and 21% in feces over a collection period of 14 days.
  - In feces, approximately 15% of the dose was eliminated as parent drug.
  - Renal excretion of dapagliflozin is minimal (<2%).
  - Dapagliflozin 3-O-glucuronide accounted for 61% of a 50-mg [U-14C]-dapagliflozin dose in urine.

- **Renal Impairment:** Compared to subjects with T2DM and normal renal function, the mean steady-state systemic exposures of dapagliflozin in subjects with T2DM and mild, moderate or severe renal impairment were 32%, 60% or 87% higher, respectively.
    - **Dosing Recommendation: The efficacy of TRADENAME is dependent on renal function**. TRADENAME should 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)

- **Hepatic Impairment:** In subjects with mild or moderate and severe hepatic impairment the exposure of dapagliflozin were increased by 22% and 67% respectively.
    - **Dosing Recommendation:** No dosage adjustment for TRADENAME is necessary for patients with mild, moderate, or severe hepatic impairment

- Pharmacogenetic analysis showed no conclusive evidence for a meaningful difference in dapagliflozin clearance across genotypes for any single nucleotide polymorphisms
- PPK modeling does not suggest dose adjustment on the basis of age, race, gender, body weight, mild renal function impairment, duration of T2DM or dosing time (morning vs. evening) in adult subjects with T2DM.

Table 1 list the clinical pharmacology studies submitted with this NDA:

Table 1: List of clinical pharmacology studies

Study Description [Dapagliflozin Dose(s) Used in the Study]	Study Number
Safety/Pharmacokinetics/Pharmacodynamics	
Single ascending doses in healthy subjects [2.5 - 500 mg]	MB102001[1,2]
Multiple ascending doses in healthy subjects [2.5 to 100 mg]	MB102002[3,4]
Multiple doses in subjects with T2DM [5 - 100 mg]	MB102003[5,6]
Low dose pharmacokinetics/pharmacodynamics in healthy subjects [0.001 to 2.5 mg]	MB102088[7]
^{14}C-ADME and Mass Balance [50 mg/~12 µCi]	MB102006[8,9]
Absolute Oral Bioavailability [Intravenous: 80 µg/~160 µCi. Oral: 10 mg]	MB102059[10]
Thorough QTc study [20 and 150 mg]	D1690C00001[11,12]
Exposure-response modeling [2.5-500 mg single dose, 2.5-100 mg QD]	Multiple studies[13]
Specific Populations	
Renal impairment [20 mg and 50 mg]	MB102007[14,15]
Hepatic impairment [10 mg]	MB102027[16,17]
Race, Age, T2DM, Gender, Body Weight (pooled analysis of Clinical Pharmacology studies and population pharmacokinetic analysis)	Section 3 and Multiple studies[13]
Single ascending doses in healthy Japanese subjects [2.5 - 50 mg]	MB102010[18]
Multiple ascending doses in Japanese subjects with T2DM [2.5 - 20 mg]	MB102025[19]
Drug-Drug Interactions	
Antidiabetic Agents	
Pioglitazone (45 mg QD) + Dapagliflozin [50 mg]	MB102017[20,21]
Metformin (1000 mg) + Dapagliflozin [20 mg]	MB102026[22,23]

Study Description [Dapagliflozin Dose(s) Used in the Study]	Study Number
Glimepiride (4 mg) + Dapagliflozin [20 mg]	MB102037[24,25]
Sitagliptin (100 mg) + Dapagliflozin [20 mg]	MB102037[24]
Voglibose (0.2 mg TID) + Dapagliflozin [10 mg]	D1692C00002[26,27]
Potentially Co-Prescribed Cardiovascular Disease Agents	
Hydrochlorothiazide (25 mg)) + Dapagliflozin [50 mg]	MB102004[28,57]
Valsartan (320 mg) + Dapagliflozin [20 mg]	MB102036[29,30]
Simvastatin (40 mg) + Dapagliflozin [20 mg]	MB102036[29]
Bumetanide (1 mg) + Dapagliflozin [10 mg]	MB102057[31,32]
Digoxin (0.25 mg) + Dapagliflozin [10 mg]	MB102058[33]
Warfarin (25 mg) + Dapagliflozin [10 mg]	MB102058[33]
Metabolic Enzyme Inducer	
Rifampin (600 mg) + Dapagliflozin [10 mg]	MB102074[34]
Biopharmaceutics	
Relative bioavailability ((b) (4) [50 mg]	MB102005[35,36]
Food effect study [10 mg, (b) (4)	MB102019[37,38]
Bioequivalence of (b) (4) in tablets and food effect on the (b) (4) 10 mg]	MB102062[39]
Bioequivalence & food effect of (b) (4) in tablets [2.5 mg]	MB102090[40]

3. Phase 2b/3 Studies

The Phase 2b program consists of 3 studies and Phase 3 program of 11 studies evaluated the efficacy and safety of dapagliflozin as monotherapy, add-on combination (to metformin, SU, TZD, and insulin) therapy, and initial combination therapy with metformin. Table 2 presents the summary of Phase 3 program.

Table 2: List of Phase 2b and Phase 3 studies conducted in this NDA

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Phase 2b studies		
MB102008 12 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, 10, 20, and 50 mg, placebo and metformin XR 750/1500 mg 47-59/279/389
MB102009 12 weeks	Insulin-dependent subjects with HbA1c ≥7.5% and ≤10.0%	Dapa 10 or 20 mg and placebo 23-24/48/71
D1692C00005 12 weeks	Japanese subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, 5, and 10 mg and placebo 54-59/225/279
Phase 3 studies		
Monotherapy		
MB102013 24 plus 78 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0% Open treatment group with HbA1c ≥10.1% and ≤12.0%	Dapa 2.5, 5, and 10 mg and placebo 64-76/410/485 Dapa 5, 10 mg 34-39/73/73
MB102032 24 weeks	Drug-naive subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, and 5 mg and placebo 68-74/214/282
Add-on combination therapy with metformin		
MB102014 24 plus 78 weeks	Subjects on metformin ≥1500 mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 135-137/409/546
D1690C00012 24 plus 78 weeks	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10 mg and placebo 91/91/182

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Add-on combination therapy with insulin		
D1690C00006 24 plus 24 plus 56 weeks	Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%	Dapa 2.5, 5, and 10 mg and placebo 196-212/610/807
Add-on combination therapy with TZD		
MB102030 24 plus 24 weeks	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10 mg and placebo 139-141/281/420
Add-on combination therapy with SU		
D1690C00005 24 plus 24 weeks	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596
Initial combination therapy with metformin		
MB102021 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638
Active comparator		
D1690C00004 52 plus 156 weeks	Subjects on metformin >1500 mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814
Special populations		
MB102029 24 plus 28 plus 52 weeks	Subjects with moderate renal impairment (GFR >30 to <60 mL/min/1.73m^2 on a stable anti-diabetic regimen with HbA1c ≥7% and ≤11%	Dapa 5 and 10 mg and placebo 83-85/168/252

Dapa Dapagliflozin; GFR glomerular filtration rate; HbA1c Hemoglobin A1c; IU International units; OAD Oral antidiabetic drug; SU Sulfonylurea; vs Versus; XR Extended release.

Potential Key Review Questions

- What are PK and PD features of dapagliflozin?
- What is the exposure-efficacy relationship?
- What is exposure-safety relationship?
- Is there any need for dose adjustment based on intrinsic factors?
- Is there any need for dose adjustment based on extrinsic factors?

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/s/

RITESH JAIN
03/01/2011

SALLY Y CHOE
03/01/2011

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-293	**Reviewer:** Minerva Hughes, PhD	
Submission Date:	27 Dec 2010		
Division:	Division of Metabolism and Endocrinology Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Bristol Myers Squibb	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	None proposed Company code: BMS-512148	**Date Assigned:**	27 Dec 2010
Generic Name:	Dapagliflozin	**Date of Review:**	31 Jan 2011
Indication:	Type 2 diabetes in adults	**Type of Submission:** Original NDA 505(b)(1)	
Formulation/strengths	Tablet, 5 mg and 10 mg		
Route of Administration	Oral		

SUBMISSION: Bristol-Myers Squibb has submitted NDA 202-293 in accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the use of dapagliflozin in the treatment of type 2 diabetes in adults as an adjunct to diet and exercise to improve glycemic control. Dapagliflozin is a novel small molecule inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), which is the major transporter responsible for renal glucose reabsorption. The drug substance is (b) (4) propanediol and water in a 1:1:1 ratio. The drug product is formulated as a yellow, biconvex, round, film-coated tablet with identifiers debossed on each side. The formulation is comprised of the excipients microcrystalline cellulose, lactose, crospovidone, silicon dioxide, magnesium stearate, (b) (4) (i.e., polyvinyl alcohol, titanium dioxide, polyethylene glycol (b) (4) talc and iron oxide yellow) (b) (4) Two strengths are proposed for the commercial market, 5 mg and 10 mg. The proposed daily dose is 10 mg taken one daily; however, for patients at risk for volume depletion due to coexisting conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose may be appropriate.

Bristol-Myers Squibb utilized Quality-by-Design (QbD) concepts in the manufacturing process development for the drug substance and formulation/process development for the drug product.

BIOPHARMACEUTIC INFORMATION: The applicant purports that dapagliflozin is a BCS Class III drug exhibiting high solubility and low permeability (b) (4) As such, the applicant proposes to use tablet disintegration as a surrogate for dissolution testing for routing quality control.

The proposed disintegration test method and specification is as follows.

- Test Method = Method No. 0121(G)
- Limit = (b) (4)
- Reference was made to the principles of USP <701>, using disks in acetate buffer, pH 4.5

(b) (4)

(b) (4)

In support of the applicant's QbD considerations for in vitro tablet performance and proposed specification, the NDA contains the following biopharmaceutics data.

- Drug substance solubility data
- Dissolution and disintegration method development report (Section 3.2.P.2)
- Dissolution Method 11724 Report (b) (4) (Section 3.2.P.8.3)
- Method validation report for Method 11724 (Section 3.2.P.8.3)
- Representative stability data for each strength, which includes multi-point dissolution and disintegration results
- Bioequivalence study reports for (b) (4) tablets (b) (4) (Report MB102062 and MB102090) – *Reviewed by Clinical Pharmacology*
- Comparative dissolution profile data using 3 different media (b) (4) to support formulation changes (Section 2.7.1)
- QbD process development studies: Impact of process changes on dissolution/disintegration (Section 3.2.P.2 Manufacturing Process Development Report)

RECOMMENDATION: From a biopharmaceutics perspective, the NDA is recommended for filing; however, the following comment should be conveyed to the applicant.

1. Please provide the complete disintegration method report (Method 0121) and supporting validation data.

Minerva Hughes
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum
Biopharmaceutics Supervisor
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Xavier Ysern, Raymond Chiang

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/s/

MINERVA HUGHES
01/31/2011

PATRICK J MARROUM
01/31/2011