CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s000

SUMMARY REVIEW

Class 1 Re-submission Memorandum

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Memorandum for Regulatory Action
NDA/BLA # **Supplement #**	204629
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	June 3rd 2014
PDUFA Goal Date	August 1st 2014
Proprietary Name / **Established (USAN) Name**	Jardiance Empaglifozin
Dosage Forms / Strength	Tablet/ 10 mg and 25 mg
Proposed Indication(s)	1. To improve glycemic control in adult patients with diabetes mellitus.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer/CDTL Review	William Chong, MD
Chemistry, Manufacturing and Controls	Joseph Leginus, PhD

On June 3rd, 2014 Boehringer Ingelheim Pharmaceuticals, Inc. submitted a Class 1 resubmission of the new drug application for Jardiance under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. The resubmission is a complete response to the Complete Response Letter issued by the Agency on March 4th 2014. The application received a complete response due to product quality issues. In brief, FDA inspections revealed violations of current good manufacturing practices (cGMP) at the empagliflozin drug substance and product manufacturing site. Drug substances (i.e., APIs) and finished pharmaceutical products manufactured at Boehringer-Ingelheim Pharma GmbH & Co. KG in Ingelheim am Rhein, Germany were deemed adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, 21 USC 351(s)(2)(B) as a result of these violations. Boehringer Ingelheim Pharma GmbH & Co. KG was issued a Warning Letter on May 6th 2013. The firm took corrective action and FDA re-inspected this facility during the period of February 24th-March 7th 2014. The FDA agreed that corrective actions addressed the violations listed in the May 6th 2013 Warning Letter and re-classified the manufacturing site as acceptable on May 28th 2014. Refer to Dr. Leginus' memorandum for details. This resolves the deficiency listed in the Complete Response Letter.

As part of the re-submission, the applicant also provides an update to the major safety information from the original NDA with data derived from one recently completed trial and extensions of parent trials previously reviewed. Dr. Chong has reviewed the newly submitted safety information in detail in his CDTL memorandum and concludes that the additional safety data does not change the favorable benefit risk profile established with data from the original NDA. I have reviewed his memorandum and I am in agreement with his conclusion.

I recommend approval of the application pending final agreement on labeling. The applicant has addressed the manufacturing issues adequately and the additional safety data do not change the favorable benefit-risk profile established with data in the original submission. For a full discussion of benefit risk with Jardiance refer to my previous memorandum dated March 4th 2014. The following post-marketing studies will be required under Sections 505(o)(3) or Sections 505B(a) of the Federal Food, Drug and Cosmetic Act. Refer to the PMR development template for details.

- Completion of an ongoing cardiovascular outcomes trial to assess the cardiovascular risk associated with Jardiance use and to monitor for the following events of interest: renal failure, specific malignancies [lung, bladder, breast and melanoma], drug induced liver injury, complicated genital and urinary tract infections, hypotension, fractures, and serious hypersensitivity reactions.
- A pediatric pharmacokinetic/pharmacodynamic study, and a pediatric safety and efficacy study. As part of the safety and efficacy study, the effect on bone health and development will be evaluated.
- A nonclinical juvenile toxicity study with a particular focus on renal development, bone development, and growth.

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/s/

JEAN-MARC P GUETTIER
07/31/2014

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MDCM
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	204629
Applicant Name	Boehringer Ingelheim
Date of Submission	March 5, 2013
PDUFA Goal Date	March 5, 2014
Proprietary Name / **Established (USAN) Name**	Jardiance Empagliflozin
Dosage Forms / Strength	Tablet/ 10 mg and 25 mg
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	William Chong, MD
Statistical Review	Dongmei Liu, PhD
Pharmacology Toxicology Review	Mukesh Summan, PhD
CMC Review/OBP Review	Joseph Leginus, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Manoj Khurana, PhD; Lokesh Jain, Ph.D; Nitin Mehrota, PhD
OPDP	Kendra Y. Jones
DSI	Cynthia Kleppinger, MD
CDTL Review	Karen Mahoney, MD
OSE/DMEPA	Reasol Agustin, PharmD
OSE/DRISK	Amarilys Vega, M.D., M.P.H
Others	John Senior, MD (liver injury risk), Jennie Chang, Pharm.D. (malignancy risk)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Memorandum

1. Introduction

On March 5, 2013 Boehringer Ingelheim submitted a 505(b)(1) new drug application (NDA) for Jardiance. The applicant is seeking to indicate Jardiance as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Jardiance is a tablet containing either 10 or 25 mg of empagliflozin [i.e., a selective sodium glucose co-transporter 2 (SGLT-2) inhibitor]. If approved, Jardiance will be the third SGLT-2 inhibitor indicated for use in the management of patients with type 2 diabetes mellitus in the United States.

This document serves as the division director's memorandum for the application.

2. Background

The sodium glucose cotransporter 2 (SGLT-2) is a low-affinity, high-capacity, active sodium glucose symporter expressed at the apical membrane of epithelial cells lining the proximal renal tubule. SLGT-2 is responsible for reabsorbing the majority of the glucose filtered at the glomerulus. Inhibition of SGLT-2 by empagliflozin decreases glucose reabsorption and promotes urinary glucose excretion. Urinary glucose loss is the primary mechanism by which empagliflozin lowers blood glucose.

The glucose lowering effect of agents that work by inhibiting SGLT-2 wanes as renal function deteriorates. Invokana and Farxiga, the two approved products in the class, did not provide clinically meaningful glucose lowering in patients with estimated glomerular filtration rate below 45 and 60 mL/min/1.73 m^2 respectively.

Inhibition of glucose reabsorption induces an osmotic diuresis resulting in polyuria and intravascular volume contraction. Adverse reactions associated with volume contraction identified in clinical trial datasets for the two approved products include hypotension and impairment in renal function. Advanced age, impairment in renal function and use of specific diuretics at baseline were identified as risk factors for volume contraction related adverse reactions in these programs.

Promotion of glucosuria, as a result of SGLT-2 inhibition, increases the risk for male and female genital mycotic infections. These class-related adverse reactions were observed with use of both Invokana and Farxiga products.

The development program for empagliflozin was discussed with the Division of Metabolism and Endocrinology Products (DMEP). Records of these interactions can be found in an End of Phase II Advice letter issued December 8, 2009, End of Phase II Meeting Minutes issued June

3, 2010, Written Responses to proposed analyses issued May 22, 2012 and pre-NDA Meeting Minutes issued December 17, 2012. The development program included a prospective proposal to assess cardiovascular risk associated with empagliflozin use to satisfy the requirements stipulated in the 2008 FDA Guidance for Industry entitled: *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* The acceptability of the proposed plan was reviewed by DMEP as reflected in an advice letter issued on April 9th 2012.

3. CMC/Device

I concur with the conclusions reached by Dr. Leginus regarding the acceptability of the proposed manufacturing processes for the drug substance and drug product. Stability testing supports an expiry of 36 months when the product is stored at room temperature.

The drug substance and finished products will be manufactured by Boehringer-Ingelheim Pharma GmbH & Co. KG., in Ingelheim am Rhein, Germany. Manufacturing site inspections performed in November 2012 identified significant violations of current good manufacturing practices (cGMP) for the manufacture of active pharmaceutical ingredients (API) and finished pharmaceutical products at that site. Drug substances (i.e., APIs) and finished pharmaceutical products manufactured at Boehringer-Ingelheim Pharma GmbH & Co. KG. were deemed adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, 21 USC 351(s)(2)(B) as a result of these violations. Boehringer Ingelheim Pharma GmbH & Co. KG. was issued a Warning Letter on May 6th 2013 detailing these violations.

Since issuance of the Warning letter, the firm has taken corrective actions and notified the Division that they were ready for re-inspection on January 8th 2014. The re-inspection will be extensive and will include a full cGMP inspection and multiple pre-approval inspections. It is scheduled to take place between February 24th and March 7th 2014. The re-inspection, and preparation of the Establishment Inspection Report will not be completed until after the Prescription Drug User Fee Act goal date of March 5th 2014. Compliance will make a withhold approval recommendation until they can establish that drug substances and finished products manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG. are no longer deemed adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, 21 USC 351(s)(2)(B)s.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Drs. Summan and Bourcier that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

To support the indication of improved glycemic control, the long term glucose lowering effect of empagliflozin was evaluated in 4 pivotal phase 3 clinical trials. These trials were multi-center, multi-national, randomized, double blind and placebo-controlled. The variable used in the primary efficacy assessment was the difference in the change in hemoglobin A1c (i.e., HbA1c) from baseline to trial end between empagliflozin-treated subjects and placebo-treated subjects. Efficacy was assessed at 24-weeks in each of these trials. Inclusion and exclusion criteria were similar between trials and these are reviewed in Drs. Chong and Liu's reviews. The design features, primary endpoint and timing of the efficacy assessment in the empagliflozin phase III pivotal trials conform with the Guidance for Industry entitled "*Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention"* and are appropriate to support an indication of improved glycemic control.

The efficacy of empagliflozin was assessed in various, relevant, clinical use settings that included;

- Empagliflozin used as monotherapy in drug naïve adult subjects with type 2 DM not optimally controlled[1] on diet and exercise alone.
    - **Trial 1245.20 – Efficacy assessment at 24 weeks**
    - Compared empagliflozin (10 and 25 mg) to placebo (primary objective) and sitagliptin (100 mg dose and secondary objective)
    - Eligible[2] completers were asked to re-consent to enter trial **1245.31** a double-blind controlled extension of at least 52 weeks beyond the primary endpoint[3]

- Empagliflozin used as add-on therapy to background metformin in adult subjects with type 2 DM not optimally controlled[1] on ≥ 1500 mg/day of metformin
    - **Trial 1245.23 met – Efficacy assessment at 24 weeks**

[1] HbA1c >7.0% and <10.0%
[2] As an example, completers with ALT or AST > 3X the ULN, with eGFR < 30 mL/min or < 60 mL/min (China), or who were known to have hypersensitivity to product (Ireland) at trial end were excluded.
[3] database cutoff for NDA submission May 29th 2012

- Compared empagliflozin (10 and 25 mg) to placebo
- Eligible completers were asked to re-consent to enter trial **1245.31** a double-blind controlled extension of at least 52 weeks beyond the primary endpoint[3]

- Empagliflozin used as add-on therapy to background metformin and sulfonylurea in adult subjects with type 2 DM not optimally controlled[1] on ≥ 1500 mg/day of metformin and at least 4 mg of glimepiride.

  - **Trial 1245.23 met + SU – Efficacy assessment at 24 weeks**
  - Compared empagliflozin (10 and 25 mg) to placebo
  - Eligible completers were asked to re-consent to enter trial **1245.31** a double-blind controlled extension of at least 52 weeks beyond the primary endpoint[3]

- Empagliflozin used as add-on therapy to background pioglitazone or piolitazone and metformin in adult subjects with type 2 DM not optimally controlled[1] on ≥ 30 mg/day of pioglitazone alone or in combination with metformin.

  - **Trial 1245.19 - Efficacy assessment at 24 weeks**
  - Compared empagliflozin (10 and 25 mg) to placebo
  - Eligible completers were asked to re-consent to enter trial **1245.31** a double-blind controlled extension of at least 52 weeks beyond the primary endpoint[3]

The primary efficacy results for these four pivotal trials, reproduced from Table 3 in Dr. Liu's statistical review are shown below. Improvement in glycemic control was demonstrated for both doses across all four trials. The observed placebo adjusted least square mean reduction in HbA1c across doses and trials at 24-weeks ranged from -0.48% to -0.83%. In three of the four trials the 25 mg dose provided numerically greater HbA1c reduction than the 10 mg dose though the magnitude of the added reduction gained by more than doubling the dose was small. Dr. Liu performed a number of sensitivity analyses to test the robustness of the primary analysis model and found the results to be robust.

Table 1: Summary of Primary Efficacy Endpoints in the 4 Pivotal Trials (Source Table 3 in Dr. Liu's review)

Trial/ Treatment Group	Number of subjects	Baseline HbA1c Mean (SE)	Change Froom Baseline at Week 24	Adjusted Mean Difference	97.5% CI	P-value
1245.20 (monotherapy)						
Placebo	228	7.91 (0.05)	0.06 (0.05)	---	---	---
Empagliflozin 10 mg	224	7.87 (0.06)	-0.66 (0.05)	-0.72	(-0.89, -0.56)	<0.0001
Empagliflozin 25 mg	224	7.86 (-.06)	-0.77 (0.06)	-0.83	(-0.99, -0.68)	<0.0001
Sitagliptin	223	7.85 (0.05)	-0.65 (0.05)	-0.70	(-0.86, -0.54)	<0.0001
1245.23 *(met)* (metformin background)						
Placebo	207	7.90 (0.06)	-0.13 (0.05)	---	---	---
Empagliflozin 10 mg	217	7.94 (0.05)	-0.72 (0.05)	-0.57	(-0.72, -0.42)	<0.0001
Empagliflozin 25 mg	213	7.86 (0.06)	-0.75 (0.06)	-0.64	(-0.79, -0.48)	<0.0001
1245.23 *(met+SU)* (metformin + sulphonylurea background)						
Placebo	225	8.15 (0.06)	-0.18 (0.05)	---	---	---
Empagliflozin 10 mg	225	8.07 (0.05)	-0.80 (0.05)	-0.64	(-0.79, -0.49)	<0.0001
Empagliflozin 25 mg	216	8.10 (0.06)	-0.77 (0.05)	-0.60	(-0.76, -0.44)	<0.0001
1245.19 (pioglitazone ± metformin background)						
Placebo	165	8.16 (0.07)	-0.14 (0.08)	---	---	---
Empagliflozin 10 mg	165	8.07 (0.07)	-0.57 (0.07)	-0.48	(-0.70, -0.26)	<0.0001
Empagliflozin 25 mg	168	8.06 (0.06)	-0.70 (0.07)	-0.63	(-0.85, -0.41)	<0.0001
The primary analysis was performed using an analysis of covariate model (ANCOVA) with baseline HbA1c as covariate, treatment and stratification factors for randomization as fixed effects. Missing data was imputed using LOCF.						

Five additional trials were deemed supportive of the indication by the applicant. For details refer to Drs. Chong's and Liu's reviews. Briefly, improvement in glycemic control was designated as a primary, secondary or tertiary objective in the following five trials and was assessed after a variable duration of exposure shown in parentheses.

- **Trial 1245.36 (24-weeks)-** Randomized, double-blind, PLACEBO-controlled trial to establish the efficacy and safety of 10 and 25 mg of empagliflozin subjects with type 2 DM and renal impairment at baseline (all with eGFR < 90mL/min/1.73 m^2).
- **Trial 1245.48 (12-weeks)**- Randomized, double-blind, PLACEBO-controlled trial to establish the efficacy and safety of 10 and 25 mg of empagliflozin in adult subjects with type 2 DM and hypertension.
- **Trial 1245.25 (12, 52 and once yearly)**-Randomized, double-blind, PLACEBO-controlled cardiovascular outcomes trial in adult subjects with type 2 DM at risk of CV-events. Assessment of glycemic control was a tertiary objective in a trial not primarily designed to assess glycemic control.
- **1245.28 (52-weeks)**-Randomized, double-blind, ACTIVE-controlled trial comparing the efficacy and safety of 25 mg of empagliflozin to 1 to 4 mg of glimepiride in adults with type 2 DM inadequately controlled on background metformin.

- **1245.33 (18-weeks)-**Randomized, double-blind, PLACEBO-controlled efficacy trial to establish the efficacy and safety of 10 and 25 mg of empagliflozin used as add-on to a fixed dose background basal insulin therapy in adult subjects with type 2 DM.

Dr. Liu verified the primary analyses in trials **1245.28** and **1245.33**. Empagliflozin 10 and 25 mg added to basal insulin (1245.33) resulted in a placebo adjusted mean change (97.5%) in HbA1c from baseline of -0.62 (-0.82, -0.42) and-0.74 (-0.93, -0.56) respectively at 18 weeks when used as an-add on to a fixed dose of basal insulin. Improvement in glycemic control was similar between 25 mg of empagliflozin and glimepiride at the end of 52-weeks in trial **1245.33** [i.e., adjusted mean difference between treatment groups in the change in HbA1c from baseline at Week 52 was -0.07% with a 97.5% CI of (-0.16, 0.02); pre-specified non-inferiority margin 0.3%].

For each trial, changes in pre-specified key glycemic (fasting plasma glucose, responder analyses) and non-glycemic secondary endpoints (change in systolic and diastolic blood pressure, weight and insulin dose) were analyzed. Secondary endpoints were tested according to pre-specified hierarchical testing sequences to control type-1 error across multiple comparisons and two doses of empagliflozin. Results for analyses based on secondary glycemic endpoints confirmed the findings based on HbA1c. Results for analyses of non-glycemic endpoints confirm what is known about the class of SGLT-2 inhibitors. That is, glucose lowering through this mechanism is associated with modest reductions in body weight (~2.0 kg at 24-weeks) and systolic (~-3 to 4 mmHg) but not diastolic blood pressure. It is unknown whether these changes meaningfully impact morbidity and mortality. Results for these analyses are detailed in Dr. Liu's and Chong's reviews.

Dr. Liu integrated data across the four pivotal placebo-controlled trials and repeated the primary efficacy analysis across various subgroups for the two empagliflozin doses. Responses across the subgroups for race (refer to Figure 8 in Dr. Liu's review) and geographic region (refer to Figure 10 in Dr. Liu's review) were similar to the overall response. Of note, participants in the four pivotal trials were predominantly enrolled in Asia (~54%) and Asians (56%) were the most represented racial group in these trials. Results of subgroup analyses by geographical regions and race do not indicate differences in response across these characteristic and suggest overall response is reasonably likely to reflect response for a US population treated to US standard of care.

A significant interaction was noted between efficacy and baseline renal function for one of the empagliflozin dosing group (i.e., 25 mg refer to Figure 14 in Dr. Liu's review). Lesser glucose lowering was observed for patients with higher degree of renal impairment at baseline. This is expected from the drug's mechanism of action which relies on renal function and is similar to observations made in the Invokana and Farxiga programs.

Efficacy in Patients with Moderately Impaired Renal Function

The renal function subgroup analysis findings were confirmed in a dedicated trial (**1245.36**) designed to compare the glycemic lowering effect of empagliflozin 25 mg against placebo at the end of 24-weeks in subjects with type 2 DM and renal impairment at baseline. The LS mean change in HbA1c from baseline was -0.6%, -0.5% and -0.2% for patients with an eGFR between 60 to 90, 45 to 60 and 30 to 45 mL/min/1.73 m2 at baseline respectively. The results shown below are modified from Table 25 in Dr. Chong's review.

Table 2: Placebo Adjusted Change in HbA1c (%) from baseline to end-of-treatment (mITT population using LOCF) in Subjects with eGFR < 90 mL/min/1.73 m^2

Study (Weeks)	Treatment Arm	n	Baseline Mean (SE)	LS Mean Change (SE)	LS mean difference (95% CI)	p-value
eGFR ≥ 60 mL mL/min/1.73 m^2	Empa 25 mg Placebo	97 95	7.96 (0.07) 8.09 (0.08)	-0.63 (0.07) 0.06 (0.07)	**-0.68 (-0.49, -0.88)**	<0.0001
eGFR 45 to < 60 mL/min/1.73 m^2	Empa 25 mg Placebo	91 89	8.12 (0.09) 8.08 (0.09)	-0.54 (0.07) -0.08 (0.08)	**-0.46 (-0.28, -0.56)**	<0.0001
eGFR 30 to < 45 mL/min/1.73 m^2	Empa 25 mg Placebo	96 98	7.95 (0.08) 8.01 (0.08)	-0.21 (0.07) 0.17 (0.07)	**-0.39 (-0.19, -0.58)**	<0.0001

8. Safety

Please refer to safety reviews by Drs. Chong, Charles and Senior for full details of the safety findings in the empagliflozin application. Dr. Mahoney's CDTL memorandum summarizes the key safety findings in the application and the reader is referred to it for a synopsis. I agree with the reviewers that the analyses of safety in the empagliflozin program do not raise concerns that would preclude approval of the product. The major safety findings were consistent with known and expected class-related adverse reactions. Adverse reactions associated with empagliflozin use included adverse reactions related to volume contraction in (e.g., hypotension and renal impairment), genital mycotic infections, increased urination, and increased thirst. Some of these adverse reactions were more frequent and more pronounced in specific patient subgroups. These adverse reactions are mitigated through product labeling in the two approved products in the class.

Size of the Database Used in Safety Analyses:

For the review of overall safety Drs. Chong and Mahoney focused on a pool of 16 phase I, II and III trials and their extensions (i.e., 1245.31 extensions of four pivotal studies and 1245.24 extensions of two phase-2 dose ranging studies) referred to as SAF-5. This pool includes all studies and trials carried out in individuals with type-2 diabetes mellitus. Studies in this pool differed significantly in design, size, empagliflozin dose evaluated, duration (8 days to time to event) and population enrolled (e.g., drug naïve, add-on to background therapy and enriched for co-morbid conditions such as hypertension, renal impairment and high CV risk). SAF-5 is

the largest pool in terms of numbers and exposure duration. The 10 and 25 mg empagliflozin doses account for most of the exposure in this pool. The trial contributing the most to the pool in terms of numbers exposed and exposure duration was trial 1245.25 (CVOT trial). At the time of submission all trials in SAF-5, were completed except for extensions of the four pivotal trials (1245.31), trial 1254.28 (comparison to glimepiride) and trial 1245.25 (CVOT). Database lock for the original submission was August 31st 2012. Dr. Chong also presents data for the SAF-3 pool which is a subset of trials included SAF-5 and is limited to data from the four placebo controlled pivotal efficacy trials and from their ongoing extensions.

Data in SAF-5 reflect exposure of 8400 patients to various doses of empagliflozin and a mean empagliflozin exposure duration of 340 days. Demographic, anthropometric and disease characteristics were balanced between empagliflozin and placebo treated patients. The mean age of the entire SAF-5 population was 60 years and 6% were older than 75 years of age. Sixty three percent (63%) of the subjects in SAF-5 were male; 62% were White, 34% were Asian, and 4% were Black or African American. At baseline, 65% of the population had had diabetes for 5 years or more. The mean HbA1c (SD) at baseline was 8.0% (0.84). Baseline renal function based on estimated GFR was normal or mildly impaired in 83% of patients and moderately impaired in 16% of patients (mean eGFR at baseline was 80 mL/min/1.73 m2).

Table 2: Exposure in SAF-5 pool (Source: Modified from Table 51 in Dr. Chong's review).

	SAF-5 Pool: ALL TYPE 2 DM TRIALS (16 trials + 2 extension trials)
Subjects	
Empagliflozin (all doses)	8400
10 mg	3630
25 mg	4602
Comparators (all)	4676
Placebo-only	3522
Patient-Years	
Empagliflozin	7828
Comparators	4184
Placebo-only	2758

Deaths, Serious Adverse Events and Events Leading to Discontinuations:

Fewer incident deaths occurred on patients treated with empagliflozin (0.52 deaths per 100 patient years) than on placebo (1.04 deaths per 100 patient years) or comparator (0.78 deaths per 100 patient years). Dr. Chong reviewed narratives for all deaths in the program. Drs. Chong and Mahoney conclude that clinical descriptions of the events in narratives do not raise concerns for a drug-related specific cause of death.

The overall incidence of nonfatal serious adverse events was lower in empagliflozin-treated patients (10.79 events per 100 patient-years) compared to placebo (16.54 events per 100 patient-years) and all comparators (12.78 events per 100 patient-years) (refer to Table 60 in Dr. Chong's review). More serious adverse events in the "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" and "Reproductive system and breast disorders" organ classes were reported in empagliflozin-treated patients than in the placebo or comparator-treated patients. Dr. Chong performed a causality assessment for events which were seen more commonly in empagliflozin-treated patients. Drs. Chong and Mahoney both conclude that narrative review do not raise concerns with regards to a potential causal relationship between empagliflozin use and any specific serious adverse event identified in SAF-5.

The proportion of patients who discontinued due to occurrence of an adverse event was similar between empagliflozin-treated (4.9%), placebo-treated (5.3%) and all comparator-treated (4.8%) patients. More patients on empagliflozin (>2-fold) discontinued due to the specific events of urinary tract infection and weight decreased (refer to Table 64 in Dr. Chong's review). A causal relationship to the drug is very likely in light of the marketed observed imbalance, mechanism of action of the drug and observation of similar findings in other members of the class.

Common Adverse Reactions

Adverse reactions attributed to empagliflozin use included events related to thirst, increased urination and genital mycotic infections (refer to tables 124-127 in Dr. Chong's review). For the purpose of labeling none of the sponsor's proposed pools are ideal. The applicant should present pooled placebo-controlled data for the four pivotal trials up to the primary efficacy endpoint as these were similar in design, duration, and dose and least subject to confounding due to differential dropouts and use of rescue medication. In addition, preferred terms that represent similar medical concepts (polyuria, polakiuria) should be combined for an accurate representation of drug related adverse reactions.

Application Specific Concerns

Cardiovascular Risk Assessment:

Please refer to Drs. Chong and Charles reviews for details. To assess whether empagliflozin use is associated with an unacceptable increased in cardiovascular (CV) risk, the applicant

performed a meta-analysis of clinical trials. This assessment of cardiovascular risk was prospective, pre-specified, reviewed by the Agency and carried out in accordance with the general principles laid out in the December 2008 FDA Guidance for Industry *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The cardiovascular meta-analysis was based on data from six completed randomized double-blind phase II and phase III trials (1245.19, 1245.20, 1245.23 $_{met}$, 1245.23$_{met+su}$, 1245.36, 1245.33) with treatment duration at least 12 weeks as well as data from ongoing randomized double-blind phase III trials (1245.25, 1245.28 and 1245.31).

The primary comparison for the meta-analysis was between all empagliflozin doses and all comparators. The primary safety endpoint was MACE+, a composite endpoint comprising CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina. A key secondary endpoint was MACE, a composite endpoint comprising CV death, non-fatal MI, or non-fatal stoke. All events included in the meta-analysis were based on positively adjudicated events determined by a blinded Clinical Event Committee using accepted standardized event definitions. The pre-specified primary statistical analysis used a Cox proportional hazards model, stratified by trial.

Results of the meta-analysis exclude the 1.8 pre-marketing CV-risk margin for MACE+ (b) (4) events) and MACE-only (b) (4) events). Analyses of the individual components of MACE+ were consistent with overall conclusions. For full details of these analyses the reader is referred to Tables 12, 13 and 14 of Dr. Charles's review.

Dr. Charles also performed subgroup analyses to explore CV-risk across baseline characteristics including: gender, race, age, geographic region, BMI, smoking status, renal function, duration of diabetes, and empagliflozin dose. Results of these analyses were consistent with results based on overall data.

Liver Injury Risk Assessment:

Drs. Chong and Senior reviewed liver injury risk associated with empagliflozin use. To assess liver injury risk, Dr. Chong considered reported adverse events in SAF-5, safety laboratory monitoring in SAF-5 and performed a review of case narratives for participants with laboratory evidence of hepatocellular injury severe enough to cause jaundice (e.g., alanine amino transferase (ALT) ≥ 3 above the upper limit of normal (ULN) and total bilirubin (T.Bili) ≥ 2-fold above the ULN or ALT ≥ 5 times the ULN).

Rates of reporting for adverse events preferred terms associated with abnormal liver enzymes, jaundice, hepatitis, and hepatic failure were compared. No significant imbalance in any preferred terms was observed with the exception of more frequent reporting of the term 'hyperbilirubinemia' (8/8400 vs. 0/4676) in patient using empagliflozin (refer to Table 94 in Dr. Chong's review).

Rates of significant hepatocellular injury defined as occurrence of a central laboratory monitored ALT value ≥ 3, 5, 10 and 20 times the ULN detected at any time were compared in SAF-5. A greater proportion of patients experienced an ALT ≥ 3 times the ULN in the comparator group (0.51% versus 0.79% for empagliflozin versus all comparators). A greater proportion of patient had an ALT ≥ 5 (0.19% versus 0.06%), 10 (0.08% versus 0) and 20 (0.01% versus 0) times the upper limit of normal in the empagliflozin group (Refer to Table 96 in Dr. Chong's review).

All patients meeting central laboratory criteria suggestive of significant hepatic injury defined as an ALT > 5 times the ULN or an ALT ≥ 3 times the ULN and a T.Bili > 2 times the ULN within 30 days of the noted ALT abnormality were reviewed by an independent adjudication committee consisting of three hepatologists with expertise in drug induced liver injury (Drs. Freston, Lewis and Watkins). These cases were also reviewed by Drs. Chong and Senior. For the majority of cases an etiology other than empagliflozin was judged a more likely cause of the liver event (refer to Table 95 in Dr. Chong's review and Dr. Senior's review). Many cases identified as severe ALT elevation were not accompanied by a T.Bili rise, were not associated with symptomatic complaints and therefore not investigated and resolved spontaneously in spite of continued treatment. After review of these cases and the data above Drs. Chong, Senior and Mahoney conclude that empagliflozin is unlikely to cause serious liver injury or dysfunction but recommend continued evaluation in prospective ongoing studies.

Malignancy:

In the SAF-5 dataset, the proportion of participants who reported a malignant event (any type) after at least six months of exposure to drug was balanced between groups (0.58% versus 0.53%). Two specific malignant events (lung and melanoma) were reported more frequently in patients exposed to empaglifozin for greater than six months.

In non-clinical studies empagliflozin was not mutagenic, clastogenic or carcinogenic at clinically relevant exposures. In distribution studies, empagliflozin concentrations were not elevated in lungs after oral dosing and clearance studies did not suggest drug accumulation in any organs examined. Finally, non-clinical studies did not suggest a phototoxic risk associated with oral empagliflozin use.

Seven patients exposed to empagliflozin for at least six months (0.08%) were reported to have had a malignant lung neoplasm event compared to none in the comparator group. Time between first exposure to empagliflozin and diagnosis ranged from 6 to 16 months. A causality assessment performed by both Drs. Jennie Chang (Oncology consultant) and William Chong revealed miscoding for one case (metastatic colon cancer), presence of confounders (asbestos exposure, prior or current significant smoking exposure) for five cases, and recurrence of a known cancer in one case. No dose response relationship was identified and pathology reports do not indicate presence of a predominant cell type. The observed incidence (150 cases per 100,000) observed in the empagliflozin arm is between the estimated incidence for the general population (61 cases per 100,000) and high-risk

population (600 cases per 100,000). In totality, these data does not suggest a causal relationship between empagliflozin use and lung cancer occurrence. Drs. Chong and Mahoney do not believe this signal precludes approval and recommend continued follow-up of lung neoplasm in long term clinical trials.

Six patients exposed to empagliflozin (0.07%) for at least six months were reported to have had a melanoma event compared to none in the comparator group (0). Time between first exposure to empagliflozin and diagnosis ranged from 7 to 12 months. Of these six patients, two had a prior melanoma, one had multiple prior skin carcinomas, and one had "sun damaged skin". All patients were White. Non-melanoma skin cancer occurred more frequently in comparators. No dose response was seen. Presence of prior disease and risk factors in the majority of cases are not consistent with a drug related etiology. Drs. Chong and Mahoney do not believe this signal precludes approval but recommend continued follow-up of melanoma in long term clinical trials.

Other Significant Class-Related Adverse Reactions:

Adverse reactions related to volume contraction, impairment in renal function, increases in hematocrit and increases in total and LDL cholesterol were observed with empagliflozin use. Refer to Drs. Chong and Mahoney's reviews for details. These are known class related adverse reactions and magnitude of observed changes were consistent with what was observed for the two other member of the class. Of note and in contrast to other programs, acute change to serum creatinine (i.e., Week 1-3) after drug initiation was not captured in the dedicated renal impairment study (first safety lab was evaluated at 12-weeks). These reactions were for the most part not severe, would not preclude approval and can be mitigated through product labelling.

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Pediatrics

A pediatric study plan was submitted with the application. Pediatric studies required for empagliflozin will be similar to pediatric studies required for other members of the class. The applicant requests a waiver for children under 10 as type 2 DM rarely occurs in this age group and a deferral for children 10 to 18 until a pediatric study plan is agreed to. The plan and scientific rationale for waivers and deferrals were discussed with the Pediatric Review Committee on February 12th 2014. The sponsor has proposed to carry out a PK/PD study (1245.87) and an efficacy and safety study (1245.56). The Agency comments on the acceptability of the plan have been issued.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

The proprietary name of Jardiance has been found acceptable (Refer to OSE/DMEPA review in DARRTS July 25th, 2013). This name will need to be subject to review when the application is filed again.

Approval is not recommended and labeling negotiations will continue on the next cycle of review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

I recommend a Complete Response until the manufacturing site for both the drug substance and product are determined to be compliant with current good manufacturing practices.

Otherwise, the applicant has demonstrated in adequate and well controlled trials that 10 and 25 mg of empagliflozin result in clinically meaningful improvement in long-term glycemic control in patients with type 2 DM inadequately controlled with diet and exercise, metformin, metformin and sulfonylurea and pioglitazone. Glucose lowering through SGLT-2 inhibition was noted to be associated with a small placebo-adjusted reduction in weight and systolic blood pressure. These effects were observed for the two approved products in the class and are related to urinary glucose loss caused by SGLT-2 inhibition. Finally, the benefit of glucose lowering using empagliflozin in patients with an eGFR ≤ 45 mL/min/1.73 m^2 does not outweigh the increased risk associated with volume contraction (e.g., hypotension and worsening renal function).

Glucose lowering with empagliflozin is not associated with an inherently high risk of hypoglycemia. The risk of hypoglycemia increases when empagliflozin is added to drugs known to cause hypoglycemia (e.g., sulfonylurea and insulin). Drug-related risks identified in the application (genital mycotic infection, hypovolemia related adverse reactions, increased thirst and urination) are known risks associated with this class of glucose lowering agent. Hypovolemic risks are expected to be dose-dependent as these results from urinary glucose excretion (osmotic diuresis) and this pharmacodynamics effect was shown to be dose-

dependent at the two proposed doses in clinical pharmacology studies. Similar to observations made in the canagliflozin and dapagliflozin programs, the elderly, patients with renal impairment and patients on diuretics were particularly vulnerable to hypovolemia related adverse reactions. The applicant's pre-marketing CV-risk analysis excludes an excess CV-risk of 1.8. Empagliflozin was found unlikely to cause significant liver dysfunction or injury. The probability of a causal relationship between lung neoplasm, melanoma and empagliflozin use was judged to be low after considering all available non-clinical and clinical data.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

These are deferred until the applicant resolves the above listed manufacturing deficiencies.

- Recommendation for other Postmarketing Requirements and Commitments

These are deferred until the applicant resolves the above listed manufacturing deficiencies.

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/s/

JEAN-MARC P GUETTIER
03/04/2014