CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204353Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	204353
Submission Date	February 10, 2014
Submission Type	Resubmission of application; Response to Complete response
Brand Name	INVOKAMET
Generic Name	Canagliflozin/Metformin FDC tablets
Dosage Form	Immediate Release Fixed Dose Tablet;
Dosage Strengths	50/500, 50/1000, 150/500, 150/1000 mg/mg of canagliflozin and metformin respectively
Sponsor	Janssen Research and Development.
Proposed Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin. It can also be used in patients who are already treated with both canagliflozin and metformin
Sponsor's Proposed Dosing regimen	Individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 150 mg canagliflozin / 1,000 mg metformin hydrochloride twice daily with meals
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D
Clinical Pharmacology Team Leader	Lokesh Jain, Ph.D
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.
OCP Division	DPM, DCP II
OND Division	Metabolism and Endocrinology Products

1 EXECUTIVE SUMMARY

Modeling and simulation strategy was utilized to bridge efficacy between QD and BID dosing regimens for canagliflozin to support approval of canagliflozin/metformin fixed dose combination (FDC) product for treatment of adult patients with type 2 diabetes. Exposure-response analysis was used to demonstrate that the efficacy of canaglifozin is similar following QD or BID dosing regimen.

Canagliflozin (NDA 204042) is an approved sodium-glucose co-transporter 2 (SGLT2) inhibitor for type 2 diabetes mellitus (T2DM) and is currently marketed as immediate-release tablets of 100 mg and 300 mg dose strengths as once daily (QD) dosing regimen. In order to develop a FDC with metformin immediate release (IR) formulation which is administered as twice daily (BID), canagliflozin is required to be administered as a BID regimen i.e. either 50 or 150 mg BID.

In the original NDA 204353 dated 12/12/2012, sponsor developed an immediate release (IR) fixed dose combination of canagliflozin/ metformin oral tablets for twice daily administration (BID). The sponsor relied on the efficacy and safety findings from NDA 204042 to support their FDC application. Since, the dosing frequency of canagliflozin in the FDC (BID regimen) differs from the daily dosing frequency of the single entity (QD regimen), in order to justify the appropriateness of reliance of data from NDA 204042, it was pivotal for the sponsor to demonstrate that the difference in administration schedules for canagliflozin would not impact efficacy.

As part of NDA 204353, sponsor submitted data from a Phase 2 study (DIA 2003) that evaluated the efficacy (change from baseline in HbA1c at week 18) of 50 mg and 150 mg BID of canagliflozin as an add-on to stable doses of metformin against placebo in T2DM patients who were inadequately controlled on metformin. However, the sponsor did not include the corresponding QD regimens and thus could not establish that BID regimen resulted in similar efficacy as the QD regimen.

Furthermore, a cross-trial comparison showed that the efficacy (placebo-subtracted change from baseline in HbA1c) was lower in canagliflozin BID dosing regimen (-0.44% and -0.60% with 50 and 150 mg BID doses) compared to efficacy observed in the QD regimens (-0.59% and -0.67% with 100 and 300 mg QD doses) in earlier conducted Phase 3 trial (NDA 204042). The sponsor attributed difference in baseline HbA1c between the trials as a possible reason for the observed discrepancy and used a bootstrap analysis to explain the same. The analysis was reviewed and deemed to be inadequate (see complete response letter in DAARTs dated 12/11/2013). Sponsor did not utilize exposure-response analysis to bridge the efficacy between QD and BID as part of their original NDA 204353 application. During the review cycle, the sponsor was encouraged to bridge the efficacy between QD and BID dosing regimen through exposure-response (ER) analysis but was unable to provide an adequate ER analysis within the previous cycle (see clinical pharmacology review by Dr. Ritesh Jain in DAARTs dated 11/15/2013). Based on these deficiencies, a complete response letter was issued by the Agency.

The complete response letter stated that the sponsor can address the deficiency and demonstrate an adequate QD to BID bridge, through a robust modeling and simulation strategy or choose to conduct a clinical trial. This application is a response to the complete response letter where the sponsor has used a modeling and simulation strategy to bridge the QD and BID regimens.

Additionally, an inspection by DSI (Division of Scientific Investigation) was requested for the pivotal BE study (DIA 1038) and Phase 1 PK/PD study (DIA1032) in the previous cycle. The outcome of the inspection was not captured in the review during the first cycle. The inspection concluded that the clinical and analytical portions of these studies are acceptable and data from these studies are acceptable to be used for Agency's review. Please refer to the DSI review by Dr. Dasgupta in DARRTs dated 0/17/2013 for further details.

1.1 Recommendation

The Office of Clinical Pharmacology (Divisions of Pharmacometrics and Clinical Pharmacology II) has reviewed the resubmission of NDA 204353 dated 02/10/2014 and recommends approving the canagliflozin/metformin FDC product as the sponsor has adequately addressed the deficiency in the complete response letter and demonstrated similar efficacy between the QD and BID dosing regimens through exposure-response analysis.

Sponsor's simulation using population PK and exposure-response models (under similar baseline covariate values, including $HbA_{1c,}$ the same study effect), demonstrated that $HbA1_c$ change from baseline for BID and QD dosing regimens are fairly similar. The differences between the BID and QD mean profiles are small and are not considered clinically meaningful. The difference up to week 26 was at most 0.03% between the 50 mg BID and 100 mg QD regimens and 0.02% between the 150 mg BID and 300 mg QD regimens, with BID regimen showing slightly greater reduction in HbA1c (Figure 6).

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The purpose of this application, (NDA 204353) is to address if the modeling and simulation strategy utilized by the sponsor is adequate to address the deficiency (lack of evidence to bridge efficacy between QD and BID regimens of canagliflozin) that was communicated in the complete response letter issued by the Agency. Based on the reviewer's assessment, sponsor has successfully implemented modeling and simulation to bridge the QD and BID regimens for canagliflozin to seek marketing approval for the immediate release fixed dose combination (FDC) tablets of canagliflozin/metformin.

Population PK Model

Sponsor developed the population PK model for canagliflozin using pooled data from nine Phase 1, two Phase 2, and three Phase 3 studies. Sponsor externally validated the population PK model and demonstrated that the model could predict the mean concentration profiles reasonably well for the QD (100 and 300 mg) and BID regimens (50 and 150 mg) for a Phase 1 study that was not used in the model development) (Figure 2). This was considered important as PK data was only collected from ~30% of the subjects in the treatment arm used for developing the population PK-PD model and the population PK model was used to predict the PK profiles in the remaining subjects. This external validation was recommended to the sponsor by the Agency as a method to evaluate the robustness of the PK model. Overall the sponsor's population PK model is adequate to predict the PK profiles for population PK-PD modeling (exposure-response analysis).

Population PK-PD Model

Sponsor developed a dynamic PK-PD model linking the time profile of canagliflozin concentrations to the time profiles for HbA1c. Please note that in this review, the terms population PK-PD model and exposure-response model have been used interchangeably. For the development of the model, data from DIA 2001, DIA 3006, the placebo arm from DIA 2003 and the baseline characteristics from the treatment arms in DIA 2003 were used. In all these studies canagliflozin was added on to the background monotherapy of metformin. Sponsor externally validated the population PK-PD model by predicting the post-baseline HbA1c values from the treatment arms 50 mg and 150 mg BID in the DIA2003 study (i.e. data not used for model development) reasonably well (Figure 5 and Table 2). This external validation was recommended to the sponsor by the Agency as a method to evaluate the robustness of the population PK-PD model. Additionally, after inclusion of post-baseline HbA1c values from the treatment arms in the data for model refinement showed that the final model predicts the placebo-subtracted LS mean changes from baseline in HbA1c at week 18 in studies DIA 2003 and DIA 3006 reasonably well (Table 4).

Simulations to Bridge Efficacy Between QD and BID Dosing Regimens

Sponsor's simulation using population PK and exposure-response models (under similar baseline covariate values, including $HbA_{1c,}$ the same study effect), demonstrated that $HbA1_c$ change from baseline for BID and QD dosing regimens are fairly similar. The differences between the BID and QD mean profiles are small and are not considered clinically meaningful. The difference up to week 26 was at most 0.03% between the 50 mg BID and 100 mg QD regimens and 0.02% between the 150 mg BID and 300 mg QD regimens, with BID regimen showing slightly greater reduction (Figure 6). Sponsor addressed the Agency's question that the 300 mg QD dose could have an additional effect on HbA1c lowering through the SGLT-1 besides the SGLT-2 in the model. Inclusion of an additional parameter was found to be statistically insignificant suggesting minimal effect of the SGLT-1 pathway (Table 6).

2 QUESTION BASED REVIEW

In this application, the sponsor has used a modeling and simulation strategy to bridge the efficacy for the QD and BID regimens of canagliflozin. Figure 1 outlines the overall approach that was utilized by the sponsor after discussion with the Agency. The details of each step of the methodology are discussed later as part of key questions in section 2.1. Broadly, the first step involved development of a population PK model, followed by prediction of PK profiles of subjects in studies DIA 2001, DIA 3006 and DIA 2003. Subsequently, a dynamic population PK-PD model was developed that linked the PK profile in subjects with their HbA1c profile. In order to evaluate the robustness of the population PK and population PK-PD models, the Agency recommended the sponsor to externally validate these models. The Agency also recommended the sponsor to conduct a sensitivity analysis to ascertain that deviations in the PK profile will have minimal impact on the HbA1c profiles. Following a reasonable internal and external validation of the PK-PD model, the model was further refined by combining the data used for external validation with the data used for model development and re-estimating the parameters of the model. Next, the final PK-PD model was used in simulations to predict the HbA1c response under similar demographics and baseline conditions for both QD and BID regimens with the purpose of bridging the efficacy of the two regimens.

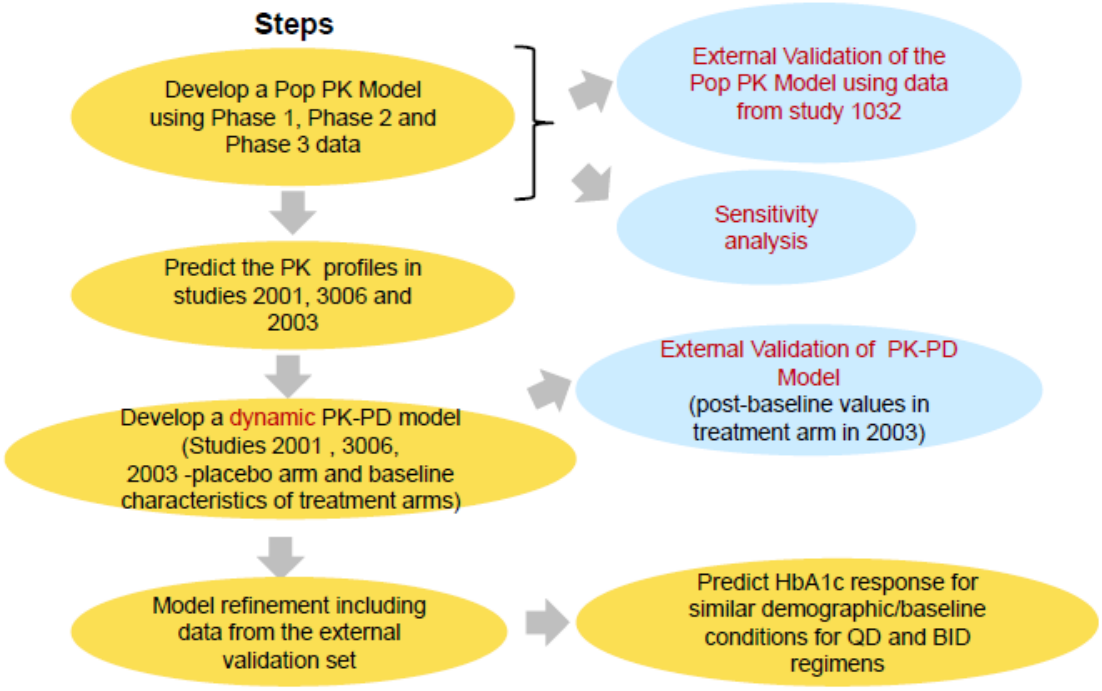


Figure 1: Modeling and simulation approach for bridging the efficacy of QD and BID regimens

2.1 Key Review Questions

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

2.1.1 Is the population PK model adequate to predict the pharmacokinetics of canagliflozin?

Yes, the sponsors' population PK model is adequate to predict the concentration-time profiles of canagliflozin at a mean level upon multiple dose administration of canagliflozin. An external validation of the model showed that the model could predict the mean concentration profiles for the QD (100 and 300 mg) and the BID regimens (50 and 150 mg) for a Phase 1 study (DIA 1032, study that was not used in the model development) reasonably well (Figure 2). This was considered critical as PK data was only collected from ~30% of the subjects in the treatment arm used for developing the population PK-PD model and the population PK model was used to predict the PK profiles in the remaining subjects. The lack of PK data in this analysis was a critical review issue as the Division/FDA advocates adequate PK sampling from sufficient number of patients for informing the exposure-response analysis. Therefore, a thorough evaluation of the model was conducted and external validation and sensitivity analysis were recommended by the Agency to evaluate the robustness of the model. Generally, if population PK and exposure-response is deemed pivotal for regulatory decision, it is in sponsor's best interest to collect PK data from sufficient number of patients for adequate PK characterization in order to avoid uncertainty at the review stage.

The population PK analysis for canagliflozin included pooled data from nine Phase 1, two Phase 2 and three Phase 3 studies. A total of 5,715 PK samples from 245 subjects from Phase 1 studies were used for model and covariate model development. The parameter estimates from the Phase 1 analysis are shown in Table 7. Once the structural model and statistically significant covariates on absorption (ka and Tlag) and distribution (Vc/F) parameters, were identified, the dataset was combined with data from Phase 2 and Phase 3 studies. 8,813 PK samples from 1,526 subjects were included in the analysis. The parameters of the structural model in the final population PK model were fixed based on the initial analysis of Phase 1 data and are shown in Table 8.

During the review of the population PK analysis in the previous cycle, the reviewer identified that inter-individual variability (IIV) on the absorption parameters were high. Since the development of the PK-PD model relied on the predicted concentration profiles in DIA3006 study (as PK samples were not collected in the study), constituting ~70% of subjects used in the development of the exposure-response model, the high IIV on absorption parameters could potentially impact the predictions around the C_{max} of the drug. This concern was conveyed to the sponsor and during further interactions, it was agreed upon that the sponsor would externally validate the model and predict the concentration profiles of subjects in a study DIA 1032 that was not used for model development. DIA1032 was a Phase 1 study where the steady state PK of once daily versus twice daily dosing was assessed in healthy subjects. Additionally sponsor agreed to conduct sensitivity analysis to show that the deviations in the PK profile will have minimal effect on the HbA1c profiles,

Figure 2 shows that the model could predict the mean concentration profiles for the QD (100 and 300 mg) and the BID regimens (50 and 150 mg) for DIA 1032 study reasonably well. Figure 3 shows the prediction error (%PE_1) of the plasma concentrations at different time points along the PK profile. %|PE_1| was defined as $[C(t)_{obs}-C(t)_{pred}]*100/C(t)_{pred}$. The median values of %|PE_1| at each time point were typically <30%, although values of approximately 50% were observed at a couple of time points near T_{max}. These deviations are not likely to have a significant effect on HbA1c profiles because plasma exposure is well above the EC_{50} for efficacy during times near T_{max}, making the PD responses largely insensitive to differences in exposure of 30% to 50%. The estimated EC_{50} from the exposure-response model is 61.6 ng/ml (= exp(4.12) from Table 3). The second reason is that the HbA1c-lowering response is likely dependent on the full 24-hour PK profile and therefore errors associated with times near T_{max} do not translate into large errors in the overall predicted efficacy when the remainder of the 24-hour PK profile is predicted reasonably well. This was confirmed by sponsor's sensitivity analysis. Sensitivity analysis demonstrated that variations in PK due to varying absorption parameters (20% and 80% percentiles of the respective estimated population distributions) had minimal impact on HbA1c (mostly between ±0.005%) predictions (data not shown, for details see section 5.3.5 of sponsor's exposure-response analysis report).

Overall, the reviewer's assessment is that for this application where the main purpose is to compare the mean HbA1c response between the QD and BID regimens for the same total daily dose, the sponsor's population PK model is adequate for PK predictions as the model predicted the mean concentration profiles for DIA1032 reasonably well.

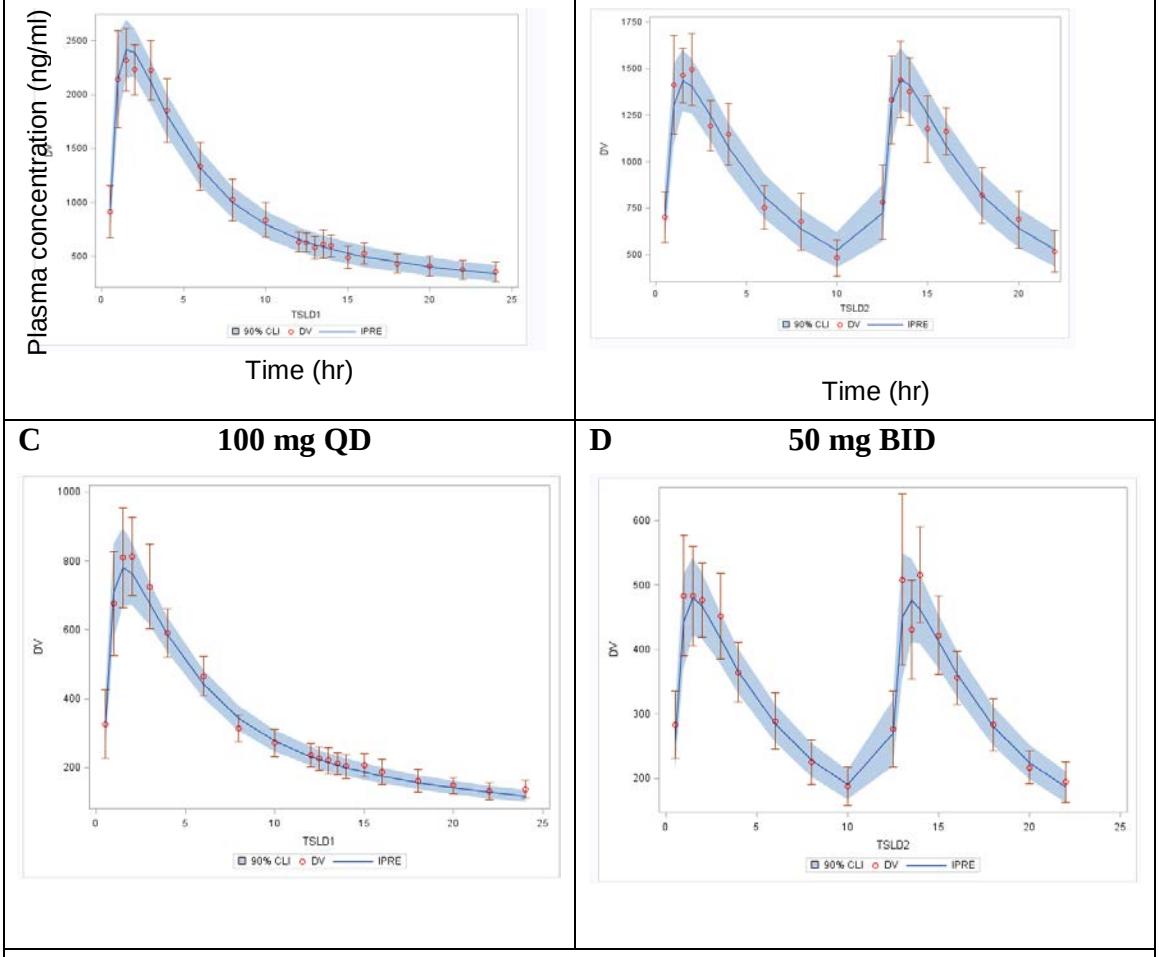


Figure 2: Concentration-time profiles of canagliflozin at steady state (on day 5) upon administration of A) 300 QD, B) 150 mg BID, C) 100 mg QD and D) 50 mg BID dosing regimens in healthy subject in study DIA 1032. The red symbols represent the mean (90 % CI) of the observed data. The blue line and the shaded region represent the mean and 90 % CI of the model predictions.

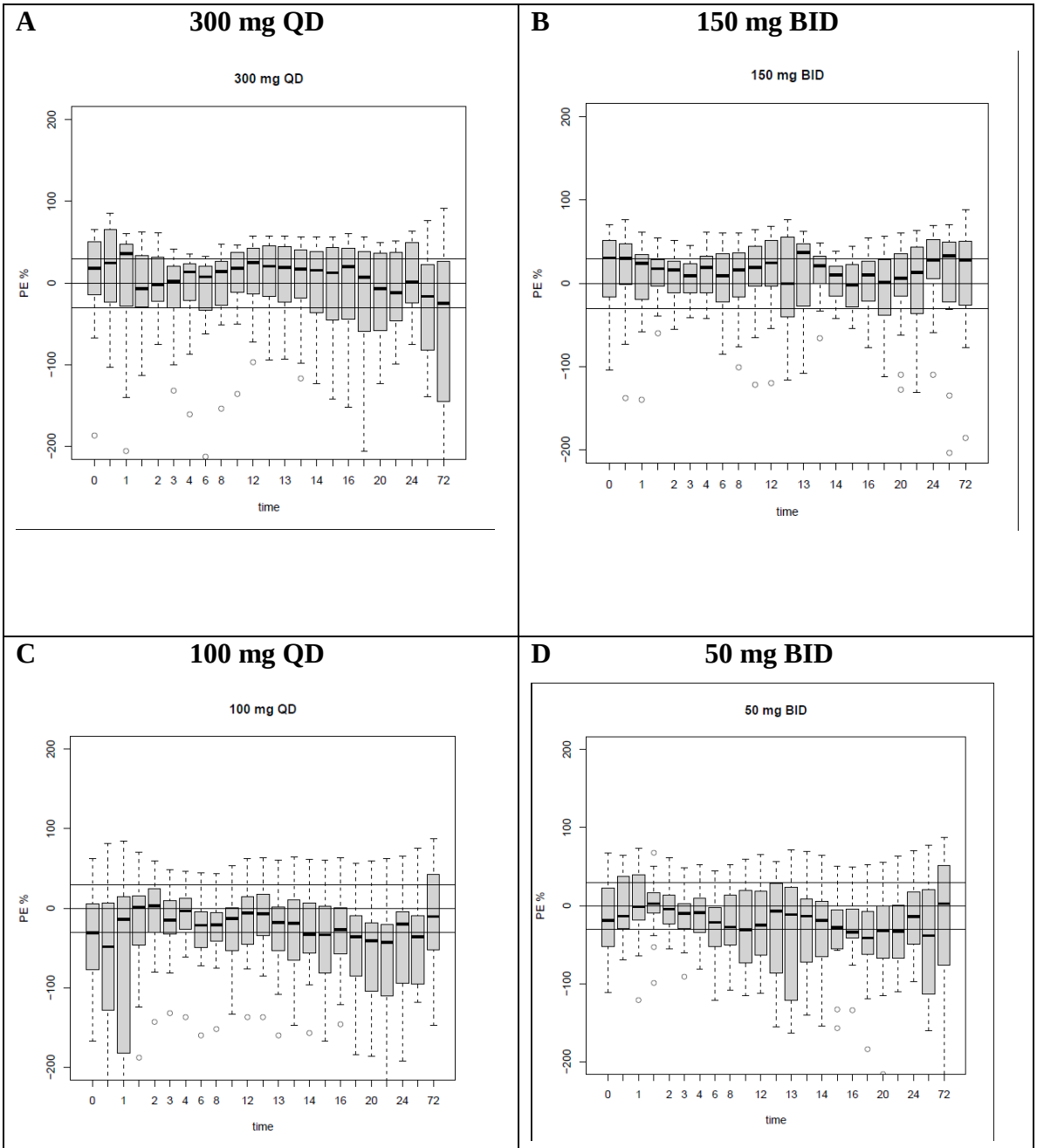


Figure 3: Prediction Error (%PE1) of the plasma concentrations at different time points along the PK profile of canagliflozin on day 5 in DIA 1032, stratified by dose and by dose regimen. The horizontal lines represent prediction errors of -30%, 0% and 30%.

2.1.2 Is the population PK-PD model adequate to characterize the HbA1c response upon administration of canagliflozin in T2DM subjects?

Yes, the sponsor's population PK-PD model adequately characterizes the HbA1c response for patients in studies DIA 2001 and DIA 3006 reasonably well. Additionally, the external validation of the model showed that the model could predict the post-baseline HbA1c values (i.e. data not used for model development) for patients in DIA 2003 in the treatment arm reasonably well.

The population PK-PD model was developed using data from studies DIA2001, DIA3006, placebo arm in DIA 2003 and baseline characteristics from all treatment arms in DIA2003 (Table 9 and Table 10 in section 4.2). Post-baseline values from the treatment arm in DIA 2003 were used for external validation of the PK-PD model. Placebo arm was included during model development as the placebo response varied significantly among studies (Table 11). HbA1c observations after initiation of antihyperglycemic agents (AHAs) to rescue subjects from hyperglycemia are confounded by the HbA1c-lowering effect of the AHA used for glycemic rescue and thus were excluded from the current analysis. Since in DIA2001 and DIA2003, only subjects on metformin monotherapy were eligible to be randomized, subjects in DIA3006 on sulfonyl urea (SU) therapy at the time of screening were excluded from the analysis. This was considered adequate as difference in HbA1c-lowering between subjects discontinuing the SU therapy relative to subjects not on SU therapy was observed. Dataset consisted of data from 1,347 subjects (1046 in treatment arm; 301 in placebo arm) with T2DM. The details of the PK-PD model are provided in section 4.2.

Table 1 shows the parameter estimates from sponsor's PK-PD model. The parameters were estimated with reasonable precision. The estimated EC_{50} from the model is 58.6 ng/ml (=exp (4.07)). The observed HbA1c versus individual predicted HbA1c goodness of fit plot shows that the model fits the data used for model development reasonably well (Figure 4). The observed HbA1c versus individual predicted HbA1c goodness of fit plot for the post-baseline values in DIA 2003 shows that the model could predict the data used for external validation reasonably well (Figure 5). Additionally, Table 2 shows that the model predicts the placebo-subtracted LS mean changes from baseline in HbA1c at Week 18 for the BID regimen in study 2003 (external validation) reasonably well.

Since the external validation of the model proved satisfactory, the model was refined by refitting the full dataset that included the post-baseline HbA1c values in the canagliflozin arm. The parameter estimates of the final model from the fitting of the full dataset are shown in Table 3. The parameters are very similar to the parameters obtained earlier during model development. The comparison between the predicted placebo-subtracted LS mean changes from baseline in HbA1c at Week 18 from the final model and observed data in studies DIA 3006 and DIA 2003 are shown in Table 4. The model predicted the observed data reasonably well.

Overall, based on the internal and external validation of the population PK-PD model described above, the reviewer's assessment is that the sponsor's population PK-PD model adequately characterizes the HbA1c response both for QD and BID regimens and can be subsequently used to bridge the efficacy between the regimens through simulations.

Table 1: Sponsor's parameter estimates from population PK-PD model as fitted to model development dataset

Parameter	Estimate	Std. Error
$t_{1/2}$ HbA_{1c} (days)	29.7	2.6
Baseline HbA_{1c} (%)	7.72	0.024
Variance of random effect on baseline (ETA(1))	0.011	0.00045
Ef_p (%HbA_{1c} @ steady-state, DIA2001)	−0.495	0.07
Ef_p (%HbA_{1c} @ steady-state, DIA2003)	−0.140	0.081
Ef_p (%HbA_{1c} @ steady-state, DIA3006)	−0.328	0.059
Variance of random effect on placebo (ETA(2))	0.385	0.029
E_{max} (%HbA_{1c} @ steady-state)	−0.744	0.08
Log(EC_{50}) (Log(ng/mL))	4.07	0.59
Residual error variance (Variance of EPS(1))	0.00188	0.00015

$t_{1/2}$ HbA_{1c} = half-life of HbA_{1c} turnover = $\log(2)/k_{out}$
Ef_p = effect of placebo + diet & exercise on HbA_{1c} at steady-state for a typical subject (HbA_{1c} at baseline 8.0%)
E_{max} = maximum placebo-corrected HbA_{1c}-lowering effect of canagliflozin at steady-state for a typical subject with HbA_{1c} at baseline of 8.0%
EC_{50} = exposure (C(t)) at which half-maximal effect is reached
ETA(1), ETA(2), and EPS(1) are defined in Attachment 5

Source: Table 2 of sponsor's exposure response analysis report.

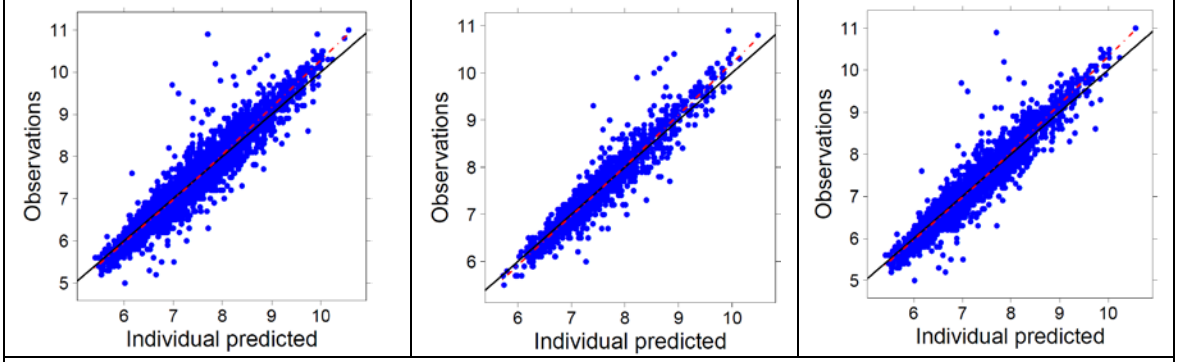


Figure 4: Observed versus individual predicted concentrations.

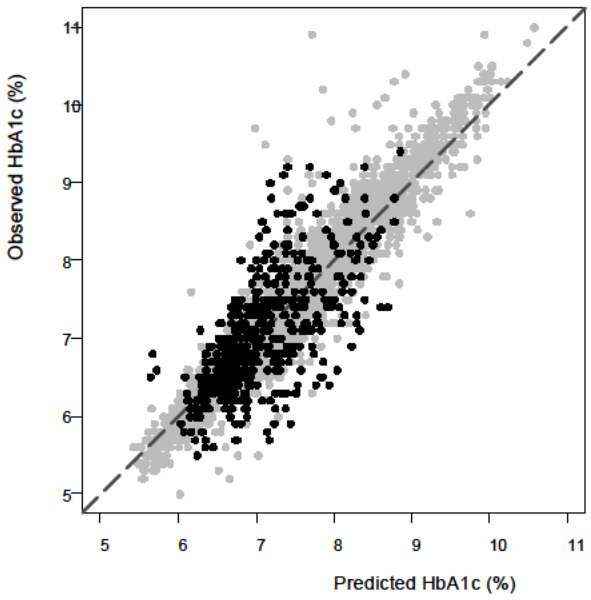


Figure 5: External validation of the population PK-PD model. Observed versus individual predicted concentrations of the canagliflozin arms in DIA 2003 on the fitted background of data used for model development. Black symbols represent post-baseline values from canagliflozin arm in DIA 2003. Gray symbols represent the data used for model development.

Table 2: Comparison of Observed and Model-predicted Placebo-Subtracted LS Mean Changes from Baseline in HbA1c at Week 18 inDIA2003

Study	Comparison	Observed changes in HbA1c LS Means (95% CI)	Model-predicted changes in HbA1c LS Means (95% CI)
DIA 2003	50 mg BID - Placebo	-0.43 (-0.62, -0.23)	-0.50 (-0.60, -0.41)
	150 mg BID - Placebo	-0.59 (-0.78, -0.39)	-0.54 (-0.64, -0.45)

*The analysis included only subjects who had HbA1c values at week 18. ANCOVA model was used with treatment and baseline HbA1c as covariate.

Table 3: Sponsor's parameter estimates from population PK-PD model as fitted to full dataset

Parameter		Estimate	Std. Error
$t_{1/2}$ HbA_{1c} (days)		28.2	2.24
Baseline HbA_{1c} (%)		7.72	0.024
Variance of random effect on baseline (ETA(1))		0.011	0.00044
Ef_p	(%HbA_{1c} @ steady-state, DIA2001)	–0.483	0.062
Ef_p	(%HbA_{1c} @ steady-state, DIA2003)	–0.137	0.057
Ef_p	(%HbA_{1c} @ steady-state, DIA3006)	–0.330	0.051
Variance of random effect on placebo (ETA(2))		0.369	0.026
E_{max}	(%HbA_{1c} @ steady-state)	–0.738	0.070
Log(EC_{50})	(Log(ng/mL))	4.12	0.54
Residual error variance (Variance of EPS(1))		0.00182	0.00014

$t_{1/2}$ HbA_{1c}= half-life of HbA_{1c} turnover = log(2)/k_{out}
Ef_p = effect of placebo + diet & exercise on HbA_{1c} at steady-state for a typical subject (HbA_{1c} at baseline 8.0%)
E_{max} = maximum placebo-corrected HbA_{1c}-lowering effect of canagliflozin at steady-state for a typical subject with HbA_{1c} at baseline of 8.0%
EC_{50} = exposure (C(*t*)) at which half-maximal effect is reached
ETA(1), ETA(2), and EPS(1) are defined in Attachment 5

Source: Table 8 of sponsor's exposure response analysis report.

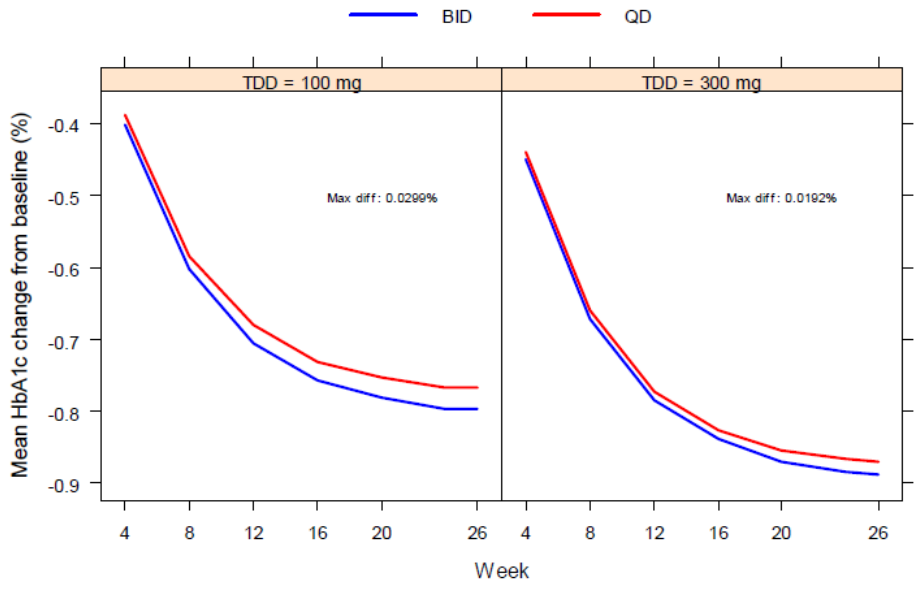
Table 4: Comparison of Observed and Model-predicted Placebo-Subtracted LS Mean Changes from Baseline in HbA1c at Week 18 for Studies DIA2003 and DIA3006 Using Parameter Estimates Derived by Fitting the Model to the Full Data Set Including Post-baseline Values in Treatment Arm in DIA 2003.

Study	Comparison	Observed changes in HbA1c LS Means (95% CI)	Model-predicted changes in HbA1c LS Means (95% CI)
DIA 3006	100 mg QD-Placebo	-0.53 (-0.69, -0.36)	-0.52 (-0.65, -0.39)
	300 mg QD-Placebo	-0.60 (-0.76, -0.44)	-0.59 (-0.72, -0.45)
DIA 2003	50 mg BID - Placebo	-0.43 (-0.62, -0.23)	-0.48 (-0.64, -0.33)
	150 mg BID - Placebo	-0.59 (-0.78, -0.39)	-0.62 (-0.78, -0.46)

*The analysis included only subjects who had HbA1c values at week 18. ANCOVA model was used with treatment and baseline HbA1c as covariate.

2.1.3 Does the population PK-PD model adequately bridge the efficacy of canagliflozin from once-daily administration (QD) to twice-daily administration (BID)?

Yes, the population PK-PD model adequately bridges the efficacy of canagliflozin from once-daily administration (QD) to twice-daily administration (BID). Sponsor's simulation using population PK and exposure-response models (under similar baseline covariate values, including HbA_{1c}, the same study effect), demonstrated that HbA_{1c} change from baseline for BID and QD dosing regimens are fairly similar. Figure 6 shows the simulated mean HbA1c change from baseline profiles for total daily doses of 100 mg and 300 mg administered as QD and BID regimens. The differences between the BID and QD mean profiles are small and are not considered clinically meaningful. The difference up to week 26 was at most 0.03% between the 50 mg BID and 100 mg QD regimens and 0.02% between the 150 mg BID and 300 mg QD regimens, with BID regimen showing a slightly greater HbA1c reduction. The patient demographics and baseline HbA1c conditions utilized for QD-BID bridging simulations are shown in Table 5. The demographics correspond to the canagliflozin treated subjects in DIA 2001. See section 4.3 for details of the simulation methodology. Additionally several sensitivity analyses were conducted by the sponsor that confirmed the results shown in Figure 6 (see section 4.3 for details).



Note: Max diff=maximum difference in mean HbA_{1c} change from baseline up to Week 26 between QD and BID dosing for the same TDD.
Key: BID=twice daily; QD=once daily; HbA_{1c}=glycated hemoglobin; TDD=total daily dose

Figure 6: Simulated mean HbA1c change from baseline profiles for total daily doses of 100 mg and 300 mg administered as QD and BID regimens. The blue and red line represents BID and QD regimen. Source: Figure 3 of sponsor's response to information request submitted on July 3rd, 2014

Table 5: Demographics and baseline characterized utilized for simulations

	N	Mean	Median	SD	Range
Sex, n (%)	287				
Male	151 (53)				
Female	136 (47)				
Age (year)	287	53	54	8.0	(29 ; 65)
Weight (kg)	287	87.3	85.2	16.88	(50.8 ; 140)
BMI (kg/m^2)	287	31.61	30.66	4.94	(24.16 ; 44.38)
eGFR ($mL/min/1.73m^2$)	287	95	93	19.5	(35 ; 166)
HbA_{1c} (%)	287	7.7	7.6	0.94	(5.9 ; 10.5)

Key: BMI=body mass index; eGFR=estimated glomerular filtration rate; HbA_{1c}=glycated hemoglobin; N=total number of subjects; n=number of subjects in each subgroup; SD=standard deviation

*The demographics correspond to the canagliflozin treated subjects in DIA 2001. Source: Table 1 of sponsor's response to information request submitted on July 3rd, 2014

2.1.4 Does the model address the question of an additional effect on HbA1c lowering through the SGLT-1 pathway for the 300 mg QD regimen compared to the 150 mg BID regimen?

Yes, the model addresses Agency's question that the 300 mg QD dose could have an additional effect on HbA1c lowering through the SGLT-1 besides the SGLT-2. The sponsor evaluated the additional effect of the 300 mg dose strength on efficacy and inclusion of an additional parameter was found to be statistically insignificant (Table 6). This suggested no significant effect of inclusion of an additional pathway on HbA1c response. This implies that the HbA1c difference observed between the 300 mg and lower dose levels is not significantly driven by the SGLT-1 pathway and primarily driven by systemic exposure through the SGLT-2 pathway. Using a very conservative approach, the sponsor included this additional effect in the model, despite it not statistically improving model fits and conducted simulations to assess the SGLT-1 contribution. This would represent a worst-case scenario that was simulated by the sponsor. With the inclusion of this additional parameter, the model predicted the maximum difference of 0.07% at Week 26 for the 300 mg QD and 150 mg BID doses, with QD regimen showing slightly greater reduction in HbA1c (Figure 7). It should be noted that the difference between the two regimens is small.

Further circumstantial experimental data (i.e., FPG comparison between two doses, see Figure 8) suggested that the additional HbA1c lowering effect for the 300 mg QD dose was not entirely driven by SGLT-1 inhibition. The effect of SGLT-1 inhibition will be primarily reflected in the reduction in post-prandial glucose (PPG), while the effect of SGLT-2 inhibition will be primarily reflected in the reduction in fasting-plasma glucose (FPG). The observation that on an average additional 7 unit of FPG reduction was

observed for the 300 mg dose compared to the 100 mg dose, indicate that SGLT-2 inhibition contributes to the added benefit for 300 mg dose.

Table 6: Evaluation of an additional effect on PD for the 300 mg dose strength

Model	Description	p^a	OFV[b]	ΔOFV[c]
A	Model A as fitted to Dataset 1: base exposure-response model	10	-22292.483	-
B	Model A plus additional PD effect for 300 mg dose strength	11	-22294.227	1.744

[a] Number of parameters in the model to be estimated
[b] NONMEM objective function value (~-2log(likelihood)
[c] Difference in OFV between nested models

Source: Table 3 of sponsor's exposure-response analysis report

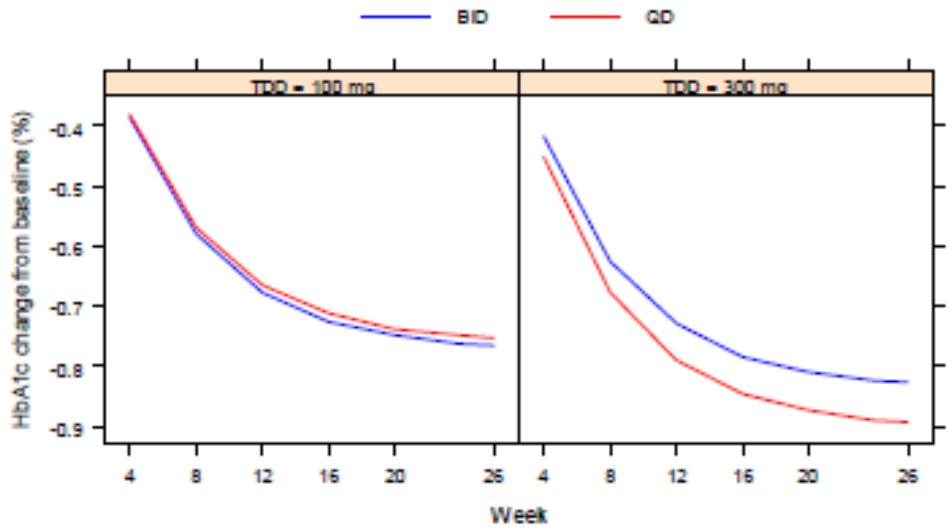


Figure 7: Simulated mean HbA1c change from baseline profiles for total daily doses of 100 mg and 300 mg administered as QD and BID regimens with an additional PD effect on lowering HbA1c for the 300 mg QD dose included in the model. The blue and red line represents BID and QD regimen. Source: Figure 1 in Appendix 2 of sponsor's exposure response analysis report.

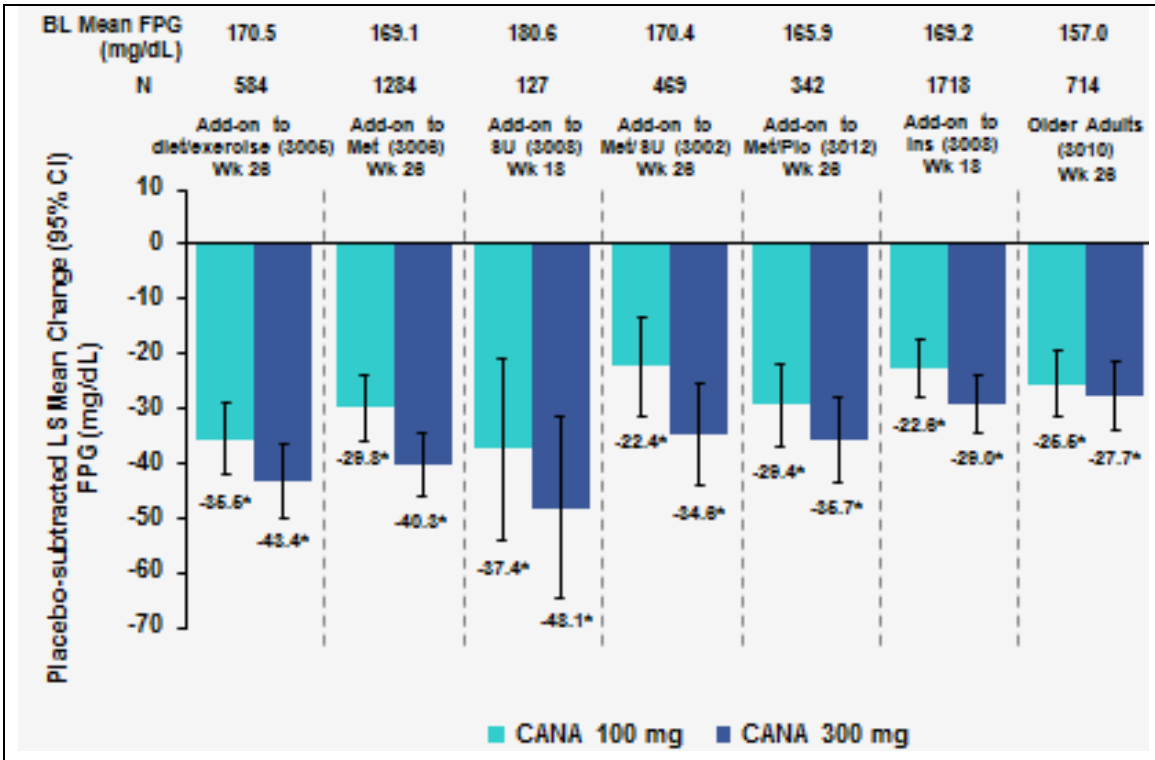


Figure 8: Placebo adjusted mean change in FPG from Phase 3 trials evaluating canagliflozin 100 mg (teal color) and 300 mg (blue color) doses. Source: Sponsor's presentation on December 19th, 2013.

3 PRELIMINARY LABELING RECOMMENDATIONS

The following are the labeling recommendations relevant to dosing and administration section for NDA 204353. 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. The complete labeling recommendations will be DARRTed separately.

2.1 (b) (4)

- Individualize the starting dose of INVOKAMET based on the patient's current regimen:
  - In patients on metformin, switch to INVOKAMET containing 50 mg canagliflozin with a similar total daily dose of metformin;
  - In patients on canagliflozin, switch to INVOKAMET containing 500 mg metformin with a similar total daily dose of canagliflozin;
  - In patients already treated with canagliflozin and metformin, switch to INVOKAMET containing the same total daily doses of each component.
- Take INVOKAMET twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin. For available dosage forms and strengths, see *[Dosage Forms and Strengths (3)]*.
- In patients with volume depletion not previously treated with canagliflozin, correct this condition before initiating INVOKAMET *[see Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.
- Adjust dosing based on effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 2000 mg metformin and 300 mg canagliflozin in patients with eGFR of 60 mL/min/1.73m^2 or greater *[see Dosage and Administration (2.2)]*.

(b) (4)

4 APPENDIX - SPONSOR'S ANALYSIS

4.1 Population PK Analysis

The final population PK analysis for canagliflozin included pooled data from nine Phase 1 studies (i.e., DIA1001, DIA1002, DIA1003, DIA1007, DIA1008, DIA1019, DIA1023, DIA1030, and TA7284-02), two Phase 2 studies (i.e., DIA2001, OBE2001) and three Phase 3 studies (i.e., DIA3004, DIA3005, and DIA3009). Total of 5,715 PK samples from 245 subjects across the nine richly sampled Phase 1 studies was used for model and covariate model development on Phase 1. Once the structural model and statistically significant covariates on absorption (ka and Tlag) and distribution (Vc/F) parameters, were identified, the dataset was combined with data from two sparsely sampled Phase 2 studies and three sparsely sampled Phase 3 studies. This combined dataset included 8,813 PK samples from 1,526 subjects. This combined dataset included only PK samples collected up to the primary endpoint (i.e. week 26 for DIA3004 and DIA3005 and week 52 for DIA3009).

A 2-compartment population PK model with sequential zero- and first order absorption and first order elimination, with IIV on Vc/F, ke, ka, k32 and Tlag was selected as the structural model to describe canagliflozin PK. To arrive at the final model, the full model was subjected to a stepwise backward elimination procedure. The parameter estimates from the Phase 1 analysis are shown in Table 7. The parameters of the final population PK model were fixed based on the initial analysis of Phase 1 data and are shown in Table 8. For details see sponsor's population PK report and the clinical pharmacology review in DARRTS dated 02/06/2013 for NDA 204042.

Table 7: Parameter Estimates of Population PK Model for Phase 1

Parameter		Population Mean Estimate	Relative Standard Error (RSE%)	Inter-Individual Variability (%CV)
V_c/F	(L) (males)	99.3	2.0	15
k_e	(hr^{-1})	0.150	2.1	20
k_a	(hr^{-1})	3.68	13.7	123
T_{lag}	(hr) (non-encaps. tablet)	0.147	9.0	79
D_1	(hr)	0.604	8.9	
k_{23}	(hr^{-1})	0.101	4.8	
k_{32}	(hr^{-1})	0.0856	3.9	35
V_c/F	(L) (females)	82.6	2.7	
T_{lag}	(hr) (over-encaps. tablet)	0.262	14.0	
Body Weight on V_c/F		0.583	8.5	
Age on V_c/F		-0.167	21.3	
Body mass index on k_a and T_{lag}		1.41	21.6	
Residual variability (%)		22.9	9.7	

V_c/F = apparent volume of distribution of central compartment
k_a = absorption rate constant
k_e = elimination rate constant
T_{lag} = lag-time
D_1 = duration of zero-order input into gut compartment
k_{23}, k_{32} = distribution rate constants to and from peripheral compartment

Source: Table 5 of sponsor's population PK modeling report

Table 8: Parameter Estimates of Population PK Model for Phase 1, 2 and 3

Parameter		Population Mean Estimate	Relative Standard Error (RSE%)	Inter-Individual Variability (%CV)
V_c/F	(L) (males)	99.3 FIX		15 FIX
k_e	(hr^{-1})	0.145	1.0	23
k_a	(hr^{-1})	3.68 FIX		123 FIX
T_{lag}	(hr) (non-encaps. tablets)	0.147 FIX		79 FIX
D_1	(hr)	0.604 FIX		
k_{23}	(hr^{-1})	0.101 FIX		
k_{32}	(hr^{-1})	0.0856 FIX		35 FIX
V_c/F	(L) (females)	82.6 FIX		
T_{lag}	(hr) (over-encaps. tablets)	0.262 FIX		
Body weight on V_c/F		0.583 FIX		
Age on V_c/F		-0.167 FIX		
Body mass index on k_a and T_{lag}		1.41 FIX		
eGFR on k_e		0.261	9.0	
Dose on k_e		-0.0631	16.2	
Residual variability (%) Phase 1		20.2	4.9	
Residual variability (%) Phase 2 and 3		55.9	6.0	

V_c/F = apparent volume of distribution of central compartment
k_a = absorption rate constant
k_e = elimination rate constant
T_{lag} = lag-time
D_1 = duration of zero-order input into gut compartment
k_{23}, k_{32} = distribution rate constants to and from peripheral compartment
eGFR = estimated glomerular filtration rate
CL/F = apparent total clearance
FIX = absorption (k_a, T_{lag} and D_1) and distribution (V_c/F, k_{23} and, k_{32}) parameters, including covariate and random effects, were fixed to the values obtained from the model built on Phase 1 data

Source: Table 9 of sponsor's population PK modeling report

4.2 Population PK-PD Analysis

Data

The PK-PD analysis included studies having subject populations with metformin monotherapy as background AHA medication. Table 9 shows the studies that were included in the analysis where patients received canagliflozin or placebo as add-on therapy to metformin monotherapy. For the development of the model, data from DIA 2001, DIA 3006, the placebo arm from DIA 2003 and the baseline characteristics from the treatment arms in DIA 2003 were used. Post-baseline values from the treatment arm in DIA 2003 were used for external validation of the PK-PD model. Placebo arm was

included during model development as the placebo response varied significantly among studies (Table 11). HbA1c observations after initiation of AHAs to rescue subjects from hyperglycemia are confounded by the HbA1c-lowering effect of the AHA used for glycemic rescue and thus were excluded from the analysis. In DIA 3006, subjects on metformin and sulfonyl urea (SU) therapy at screening were excluded. Based on the DIA3006 protocol, subjects on metformin and sulphonylurea (SU) therapy at the screening visit were allowed to discontinue the SU therapy and undergo a glycemic stabilization phase prior to randomization. In DIA2001 and DIA2003, only subjects on metformin monotherapy were eligible to be randomized. The rationale to exclude subjects in DIA3006 on SU therapy at the time of screening from the current analysis is based on differences in HbA1c-lowering between subjects discontinuing the SU therapy relative to subjects not on SU therapy at the screening visit. Full dataset consisted of data from 1,347 subjects (1046 in treatment arm; 301 in placebo arm) with T2DM (Table 10).

Table 9: Studies used for PK-PD analysis

Clinical Studies	**Treatment arms**	**Use**
DIA2001	Placebo, 50 mg QD, 100 mg QD, 200 mg QD, 300 mg QD, 300 mg BID	Model development
DIA3006	Placebo, 100 mg QD, 300 mg QD	
DIA2003	Placebo Baseline characteristics from treatment arm i.e. 50 mg BID and 150 mg BID	
DIA2003	Post baseline values from treatment arm i.e. 50 mg BID and 150 mg BID	External Validation

Table 10: Demographics of subjects used for PK-PD analysis

		Placebo	50 QD	50 BID	100 QD	200 QD	150 BID	300 QD	300 BID	Total
N		**301**	**60**	**93**	**346**	**55**	**93**	**339**	**60**	**1347**
Sex, n(%) :	Male	146 (48.5)	31 (51.7)	40 (43)	171 (49.4)	29 (52.7)	44 (47.3)	158 (46.6)	26 (43.3)	645 (47.9)
	Female	155 (51.5)	29 (48.3)	53 (57)	175 (50.6)	26 (47.3)	49 (52.7)	181 (53.4)	34 (56.7)	702 (52.1)
Race, n(%)										
White, Not Hispanic or Latino		171 (56.8)	39 (65)	64 (68.8)	182 (52.6)	35 (63.6)	69 (74.2)	173 (51)	29 (48.3)	762 (56.6)
Black, of African heritage or African American		7 (2.3)	2 (3.3)	5 (5.4)	12 (3.5)	1 (1.8)	1 (1.1)	7 (2.1)	2 (3.3)	37 (2.7)
White, Hispanic or Latino		46 (15.3)	9 (15)	11 (11.8)	54 (15.6)	8 (14.5)	14 (15.1)	67 (19.8)	13 (21.7)	222 (16.5)
Asian		45 (15)	5 (8.3)	3 (3.2)	45 (13)	8 (14.5)	6 (6.5)	55 (16.2)	8 (13.3)	175 (13)
Native Hawaiian or Other Pacific Islander		1 (0.3)	0	0	0	0	1 (1.1)	0	0	2 (0.1)
American Indian or Alaskian Native		5 (1.7)	1 (1.7)	1 (1.1)	7 (2)	0	0	5 (1.5)	2 (3.3)	21 (1.6)
Other		26 (8.6)	4 (6.7)	9 (9.7)	46 (13.3)	3 (5.5)	2 (2.2)	32 (9.4)	6 (10)	128 (9.5)
Age (year)	Mean (SD)	55.5 (9.3)	53.0 (8.5)	58.5 (8.9)	54.1 (9.4)	54.0 (8.9)	56.6 (10.4)	54.3 (8.8)	54.8 (7.2)	54.9 (9.2)
	Median	57.0	53.5	58.0	54.0	55.0	58.0	55.0	56.5	56.0
	Range	(26.0;80.0)	(33.0;65.0)	(33.0;80.0)	(27.0;78.0)	(31.0;65.0)	(29.0;79.0)	(21.0;77.0)	(32.0;65.0)	(21.0;80.0)
Weight (kg)	Mean (SD)	87.0 (18.8)	88.2 (16.4)	91.2 (23.9)	89.0 (21.7)	87.4 (16.6)	90.2 (19.1)	85.4 (19.3)	86.0 (20.0)	87.6 (20.0)
	Median	85.0	86.0	87.0	86.0	84.0	89.6	83.0	81.9	85.0
	Range	(45.3;164)	(53.0;123)	(55.2;163)	(40.0;188)	(54.0;133)	(51.0;139)	(47.0;168)	(50.8;140)	(40.0;188)
BMI (kg/m^2)	Mean (SD)	31.3 (5.2)	32.0 (4.6)	33.0 (7.0)	32.4 (6.0)	31.3 (5.1)	32.3 (6.8)	31.4 (6.0)	31.8 (5.3)	31.8 (5.8)
	Median	30.6	31.0	31.1	31.7	30.1	30.7	30.5	30.6	30.9
	Range	(19.7;46.6)	(24.9;41.8)	(21.6;55.4)	(19.3;55.3)	(24.9;44.4)	(20.4;53.4)	(18.1;73.0)	(24.2;43.7)	(18.1;73.0)
eGFR ($mL/min/1.73m^2$)	Mean (SD)	88.8 (19.5)	95.7 (19.2)	87.0 (18.2)	90.6 (18.5)	90.1 (18.1)	85.9 (15.3)	91.4 (18.6)	94.1 (20.2)	90.2 (18.7)
	Median	86.0	92.0	85.0	90.0	88.0	86.0	89.0	100	89.0
	Range	(49.0;176)	(57.0;150)	(54.0;135)	(45.0;165)	(50.0;143)	(50.0;138)	(55.0;171)	(35.0;150)	(35.0;176)
HBA_{1c} (%)	Mean (SD)	7.80 (0.90)	8.03 (0.98)	7.64 (0.87)	7.84 (0.89)	7.43 (0.66)	7.55 (0.85)	7.83 (0.92)	7.75 (0.86)	7.78 (0.90)
	Median	7.6	8.0	7.5	7.7	7.4	7.4	7.8	7.5	7.6
	Range	(6.0;10.3)	(6.5;10.0)	(6.2;10.1)	(5.5;10.5)	(6.0;9.0)	(5.6;9.8)	(5.6;11.0)	(6.0;9.8)	(5.5;11.0)

Source: Attachment 3 of exposure-response analysis report

Table 11: Placebo effect observed in selected studies

Study (N)	HbA1c changes from baseline, LS mean (SE)* in the placebo group
DIA2001 (N = 61)	-0.22 (0.70)
DIA3006 (N = 181)	-0.17 (0.060)
DIA3004 (N = 87)	-0.03 (0.090)
DIA2003 (N = 92)	-0.01 (0.069)

*SE – standard error

Source: Table 3 of modeling analysis plan

Method

The exposure-response model integrated a turnover model for HbA1c with an E_{max} model relating the HbA_{1c}-lowering effect of canagliflozin to the canagliflozin plasma exposure at time *t* using the following set of structural equations

$$\frac{dH(t)}{dt} = Ef + k_{in} - k_{out}H(t) \quad (1)$$

$$Ef = k_{out}\left(Ef_c + Ef_p\right) \cdot \frac{H(0) - 5}{8 - 5} \quad (2)$$

$$Ef_c = E_{max} \cdot \frac{C(t)}{C(t) + EC_{50}} \quad (3)$$

$$Ef_p = \theta \quad (4)$$

where *H(t)* is the HbA1c at time *t*, *H*(0) is the estimated individual HbA1c at baseline, and *kin* and k_{out} are rate parameters related to hemoglobin (Hb) glycation and red blood cell turnover. The equations scales the combined HbA_{1c}-lowering effects of canagliflozin (Ef_c) and placebo treatment (Ef_p) to the individual HbA_{1c} at baseline relative to a reference baseline HbA_{1c} of 8.0% and a physiological minimum HbA_{1c} of 5.0%. Incorporation of baseline HbA1c into the equations was done since it is known that the baseline HbA1c affects the magnitude of glucose-lowering in response to antihyperglycemic agents and the observation that virtually no reductions in plasma glucose are observed in subjects with normal plasma glucose (HbA1c values of approximately 5.0%) who are treated with canagliflozin. Equation (3) describes the E_{max} model relating the HbA_{1c}-lowering effect of canagliflozin, Ef_c, to the canagliflozin plasma exposure at time *t*, *C*(*t*). Equation (4) describes the placebo effect Ef_p, which includes the HbA_{1c}-lowering effects of diet and exercise counseling. The parameter θ is the study-specific steady-state placebo effect. For details see sponsor's exposure-response analysis report.

Internal Validation

Model diagnostics included graphs of observed HbA1c values versus individual and population predicted HbA1c values, and the weighted residuals versus time and population-predicted HbA_{1c} values. Potential bias in the random effect corresponding to the efficacy parameters across different doses were assessed graphically. For details see sponsor's exposure-response analysis report.

External Validation

The exposure-response model was externally validated by using it to predict the post-treatment HbA_{1c} observations of BID dosing from DIA2003. Prediction of the external HbA1c observations was performed and diagnostic displays, including visual and numerical prediction checks (VPC and NPC, 1000 simulated external datasets because of smaller N), observed vs. individually predicted (DV vs IPRE) among others, were used to

assess the quality of the external predictions. For details see sponsor's exposure-response analysis report.

Results
The key results of the population PK-PD analysis are shown in section 2.1.2.

4.3 Simulation to bridge the efficacy of QD and BID regimens

Two slightly varying simulation methodologies were employed by the sponsor in discussion with the Agency and are described below. Overall the results were consistent and not dependent on the methodology employed indicating the robustness of the simulation results.

Methodology 1

The patient demographics and baseline HbA1c conditions utilized for QD-BID bridging simulations are shown in Table 5 (section 2.1.3). The demographics correspond to the canagliflozin treated subjects in DIA 2001. For each subject, his/her set of post-hoc PK random effects estimates and associated set of baseline covariates were utilized to obtain subject-specific predicted PK profiles under each of the 4 combinations of canagliflozin dosing regimen and total daily dose (TDD) (50 and 150 mg BID; 100 and 300 mg QD) based on the population PK model. Each of the subject-specific predicted PK profiles, together with the baseline covariates and post-hoc estimated PD random effects corresponding to the same subject, were used with the dynamic PK/PD model to produce a corresponding subject-specific HbA1c profile (one for each subject-dose regimen combination, for a total of 287 x 4 = 1,148 HbA1c profiles). Intra-subject variability was incorporated in the generated subject-specific HbA1c profiles (dynamic PK/PD model prediction stage) via simulated, independent intra subject errors following the associated log-normal distribution estimated. While the treatment duration period in DIA2001 was 12 weeks, the majority of Phase 3 studies in the canagliflozin program had a duration of 26 weeks, so the cross-over studies were simulated out to a duration of 26 weeks per period. Because the simulated intra-subject errors in HbA1c were generated using a pseudo random number algorithm, multiple trial simulations were done to ensure that the conclusions were not dependent on the specific pseudo-random numbers generated for a single trial simulation and to quantify the impact of intra-subject variability on the mean results and their precision for trials of this size. The trial simulation procedure was repeated 100 times (with only the intra-subject errors varying from trial to trial), using identical four-period crossover designs and 287 canagliflozin-treated patients having the same baseline demographic and baseline characteristics as subjects in Study DIA2001 with the same associated post-hoc estimates for the PK and PD random effects. The mean baseline HbA_{1c} values for the 100 simulated trials for each canagliflozin dosing regimen are presented in Table 12

Results: The mean HbA_{1c} changes from baseline profiles for the individual simulated trials (and their respective overall averages) are displayed, per treatment arm, in Figure 9. For each of the TDD groups (100 and 300 mg), the overall mean HbA_{1c} profiles are very

similar for BID and QD regimens, as illustrated in Figure 6 (section 2.1.3) which compares the overall mean HbA_{1c} change from baseline profiles for BID and QD regimens within each of the TDD groups. The variability in the simulated mean HbA_{1c} change from baseline profiles across the simulated trials is seen in Figure 9, with the trial-to-trial variability covering a range of approximately ±0.1% from the overall mean values, is due to the intra-subject variability in the simulations. Figure 10 shows the distribution of mean QD vs. BID difference in HbA_{1c}-lowering effect at the final visit (Week 26). The variation across simulated trials is again evident, being contained within the interval ±0.1%. Majority of the trials favor the BID regimen compared to the QD regimen. For further details see sponsor's response to information request submitted on July 3rd, 2014.

Methodology 2

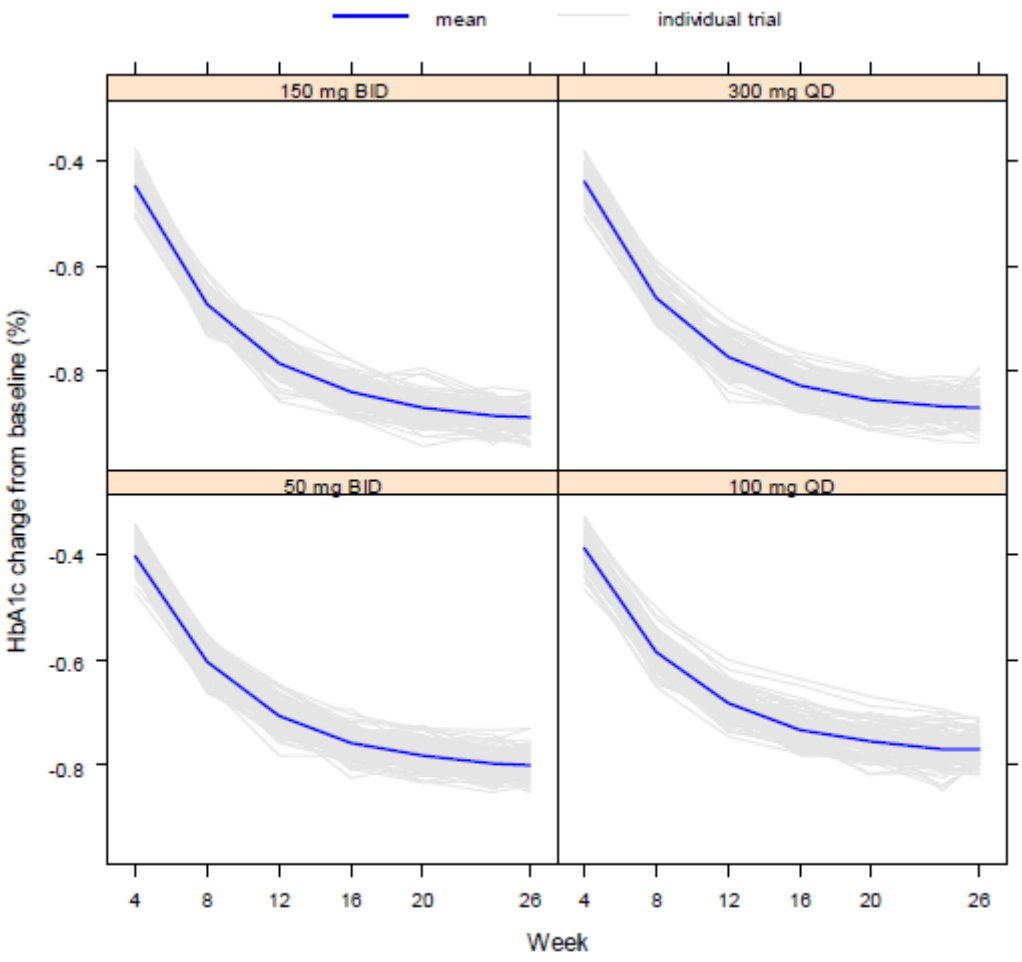
The results described above and in section 2.1.3 are consistent with the simulation results presented by the sponsor previously in the exposure-response analysis report that incorporated both inter- and intra-subject variability. In this strategy, the simulations utilized the patient demographics from all subjects (N=1046) in the treatment arms in studies 3006, 2003 and 2001 (Table 10). The subject-specific concentration profiles were obtained using the individual subject baseline covariate values (100 simulations per individual subject baseline covariate values, for each dose regimen) and by simulating random effects from their estimated distribution (inter-subject variation) without incorporating intra-subject variability. Because the exposure-response model is based on steady-state drug concentrations, 24-hour steady-state concentration profiles were simulated. The subject-specific HbA1c profiles were also produced based on the baseline covariate values, assuming the DIA3006 study effect for all subjects, and incorporating both inter- and intra-subject variability, with random effects and intra-subject errors simulated from the respective estimated distributions. The baseline HbA1c for each dosing regimen was 7.77. Based on these simulations, the differences between the BID and QD mean profiles were small (at most 0.023% for 100 mg TDD and 0.011% for 300 mg TDD, up to Week 26) and not considered clinically meaningful. For details see section 5.5 of sponsor's exposure response analysis report.

Table 12: Simulated mean baseline from 100 simulations

Canagliflozin Dose Regimen	Mean	Median	SEM
50 mg BID	7.710	7.712	0.019
150 mg BID	7.713	7.715	0.017
100 mg QD	7.705	7.704	0.021
300 mg QD	7.709	7.710	0.019

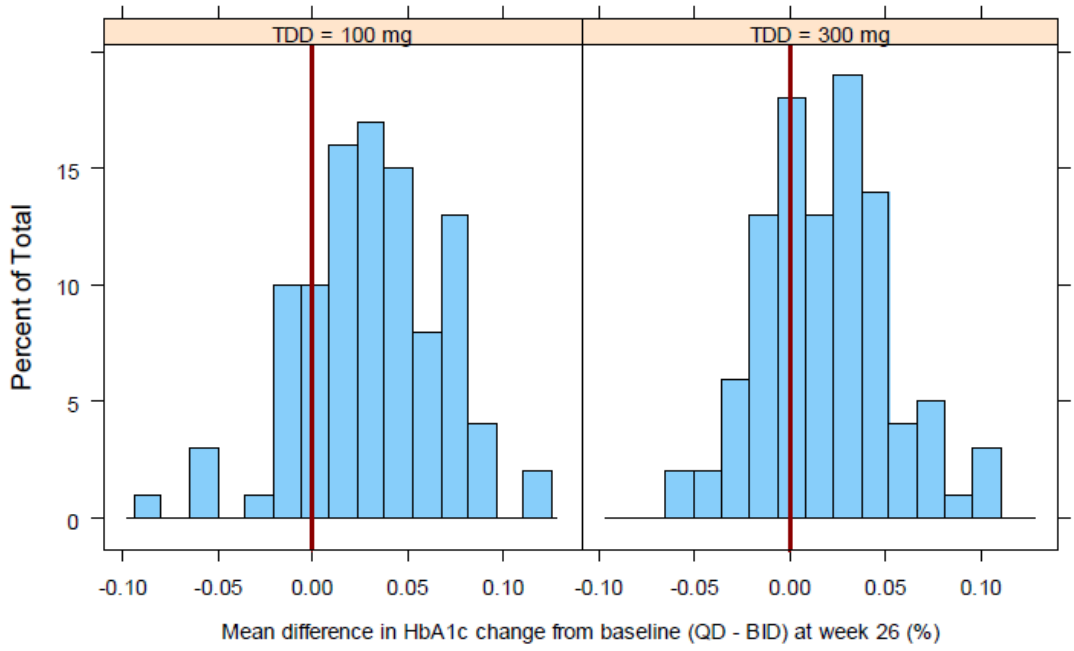
Key: BID=twice daily; QD=once daily; HbA_{1c}=glycated hemoglobin; SEM=standard error of the mean

Source: Table 2 of sponsor's response to information request submitted on July 3rd, 2014



Key: BID=twice daily; QD=once daily; HbA_{1c}=glycated hemoglobin
Note: The *individual trial* curves show the mean values for N=287 subjects in each simulated trial and the *mean* curves shows the mean response across the 100 simulated trials.

Figure 9: Mean HbA1c changes from baseline profiles for 100 simulated four-period crossover trials and respective overall means, per treatment arm. Source: Figure 1 of sponsor's response to information request submitted on July 3rd, 2014



Key: BID=twice daily; QD=once daily; HbA_{1c}=glycated hemoglobin; TDD=total daily dose
Note: Positive differences indicate greater efficacy with BID regimen. Negative differences indicate greater efficacy with QD regimen.

Figure 10: Distribution of mean difference in HbA1c change from baseline at week 26 between QD and BID dosing regimens per TDD, based on 100 simulations Source: Table 2 of sponsor's response to information request submitted on July 3rd, 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANSHU MARATHE
07/19/2014

RITESH JAIN
07/20/2014

LOKESH JAIN
07/20/2014

NITIN MEHROTRA
07/20/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-353 (0019); Re-submission	**Biopharmaceutics Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DMEP		
Applicant:	Janssen Pharmaceuticals Inc.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	--		
Generic Name:	Canagliflozin-Metformin HCl Fixed Dose Combination Tablets	**Date Assigned:**	Dec 14, 2012.
Indication:	Treatment of Type 2 diabetes	**Date of Review:**	Mar 10, 2014.
Formulation/strength	Immediate Release Tablet 50/500 mg, 150/500 mg, 50/1000 mg, 150/1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Feb 10, 2014	Feb 10, 2014		Jun 10, 2014

Resubmission:

On February 10, 2014, the Applicant Resubmitted NDA 204353 for Canagliflozin-Metformin HCl Fixed Dose Combination Tablets. This Resubmission provides the Applicant's responses for the Complete Response (CR) issued by FDA on December 11, 2013.

The Biopharmaceutics Review was completed during the first review cycle and the Application was recommended for approval (see Dr. Eradiri's DARRTS entry dated July 26, 2013). The current Resubmission does not contain any new Biopharmaceutics information for review.

Recommendation:

From the ONDQA-Biopharmaceutics viewpoint, the current resubmission of NDA 204353 for Canagliflozin-Metformin HCl Fixed Dose Combination Tablets is recommended for approval. Biopharmaceutics does not have any further review activities on this re-submission.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

OKPONANABOFA ERADIRI
03/10/2014

ANGELICA DORANTES
03/10/2014

NDA: 204353	Submission Date(s): 12/12/2012
Brand Name	TBD
Generic Name	Canagliflozin/Metformin FDC tablets
Reviewer	Ritesh Jain, Ph.D.
Clinical Pharmacology Team Leader	Lokesh Jain, Ph.D.
Pharmacometrics Reviewers	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Janssen Research and Development.
Submission Type; Code	Original NDA 505(b)(2); Standard
Formulation; Strength(s)	Immediate Release Fixed Dose Tablet; 50/500, 50/1000, 150/500, 150/1000 mg/mg of canagliflozin and metformin respectively
Proposed Indication	Dosing is individualized based on safety and efficacy; recommended for twice daily dosing with meals

List of Figures and Tables:

1 Executive Summary

Canagliflozin (NDA 204042) is a recently approved orally active reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is a transporter expressed at the luminal membrane of the S1 and S2 segments of the proximal renal tubules which is responsible for the majority of reabsorption of filtered glucose from the renal tubular lumen. Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin is currently marketed as immediate-release tablets of 100 mg and 300 mg dose strengths as once daily (QD) dosing regimen. In this NDA, sponsor is developing immediate release (IR) fixed dose combination (FDC) of canagliflozin/metformin oral tablets for twice daily administration (BID). The sponsor is proposing 4 different FDC tablet strengths of canagliflozin/metformin 50mg/500mg, 50mg/1000mg, 150mg/500mg, and 150mg/1000mg. This application is submitted as a 505(b)(2) pathway, as this NDA relies on the data submitted in the canagliflozin NDA 204042 (recently approved) and in the metformin NDA 20-357.

The FDC tablets of canagliflozin/metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are:

- Not adequately controlled on a regimen containing immediate release metformin or canagliflozin
- In patients who are already treated with both canagliflozin and immediate release metformin

The proposed recommended starting dose for canagliflozin/metformin FDC tablets is:

(b) (4)

- Patients already treated with canagliflozin and metformin individual components may be switched to canagliflozin/metformin FDC containing the same total daily doses of each component.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) and Division of Pharmacometrics have reviewed the clinical pharmacology data submitted under NDA 204353, dated 12/12/2012, and recommend not approving this product in this cycle because of the following reasons:

1) Sponsor failed to demonstrate that patients who are taking individual tablets of canagliflozin in once daily (QD) regimen along with metformin tablet in BID regimen will have similar efficacy when they switch to FDC of canagliflozin/metformin in BID dosing regimen.

Sponsor's Phase 2 trial testing the 50 mg and 150 mg BID dose groups did not include the corresponding QD regimens and thus could not establish that BID regimen resulted in similar response (change in HbA1c from baseline) as the QD regimen. Furthermore, in a cross-trial comparison, the placebo adjusted HbA1c change from baseline with canagliflozin BID dosing regimen was lower (-0.44% with 50 mg BID dose and -0.60 % with 150 mg BID dose) than the response observed by the QD regimens (-0.59 % with 100 mg QD dose and -0.67 with 300 mg QD dose) in earlier conducted Phase 3 trials. The sponsor attributed difference in baseline HbA1c between the trials as a possible reason for the observed discrepancies in the trial and used a bootstrap analysis to explain the same. The analysis was reviews by the Office of Biostatistics and was deemed to be inadequate (see Statistic review by Dr. Wei Liu). During the review cycle the sponsor was encouraged to bridge the QD to BID dosing regimen through exposure-response analysis. Following the late cycle meeting, sponsor submitted a brief PK/PD modeling plan on 10/14/2013 which had several deficiencies that were conveyed to the sponsor (see section 1.3). Sponsor resubmitted another plan that requires further discussions and subsequent modifications before an agreement can be reached. Thus, while in principle a model based PK/PD approach is feasible, the sponsor's modeling approach cannot be reviewed within this review cycle. (Please refer to section 2.2.6 for further details). Thus, due to lack of adequate data to bridge efficacy between patients on canagliflozin QD and metformin BID dosing regimens taken as separate tablets and wanted to switch to FDC of canagliflozin/metformin BID dosing regimen, we recommend not approving this application in the current review cycle.

The sponsor is advised to discuss their PK/PD plan in detail following the complete response action of this application. The Sponsor has agreed and is planning to have a face to face meeting with the Agency to discuss the path forward using the PK/PD approach.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The purpose of this application, (NDA 204353) by Janssen Research and Development, is to seek a marketing approval for the immediate release fixed dose combination (FDC) tablets of canagliflozin/metformin at four different dose strengths of canagliflozin/metformin 50mg/500mg, 50mg/1000mg, 150mg/500mg, 150mg/1000mg. The proposed recommended daily dose of canagliflozin/metformin FDC tablets is one tablet taken twice daily (BID).

Both canagliflozin and metformin are approved products. Canagliflozin (INVOKANA™) has been approved recently (2013) in the United States, under NDA

204042. Canagliflozin is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, both as monotherapy and as combination therapy with other anti-diabetic agents, including metformin. Canagliflozin is a SGLT-2 inhibitor and is currently marketed as immediate-release tablets of 100 mg and 300 mg dose strengths as QD dosing regimen. Metformin hydrochloride is an oral anti-hyperglycemic agent also used in the treatment of T2DM. Metformin belongs to the biguanide class of antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes.

The safety and efficacy of the concomitant use of canagliflozin and metformin is supported by Phase 3 trials that were submitted under canagliflozin program (NDA 204042). Under the canagliflozin program six Phase 3 studies evaluated once-daily (QD) administration of canagliflozin 100 mg or 300 mg in subjects with T2DM on a background of metformin (alone or in combination with other anti-diabetic agents). Some of the highlights of the Phase 3 clinical trials in canagliflozin program are listed below:

- Two Phase 3 studies (DIA3006 and DIA3009) in subjects on background of metformin alone with canagliflozin 100 mg and 300 mg QD dosing.
- Three Phase 3 studies (DIA3002, DIA3012, and DIA3015) where subjects on metformin in combination with another anti-hyperglycemic agents were given canagliflozin 100 mg and 300 mg QD dosing.
- In all the Phase 3 studies under canagliflozin program, canagliflozin was studied as once daily dosing of 100 mg or 300 mg tablets.

In this current NDA application, to support the BID dosing regimen of canagliflozin/metformin FDC formulation, the sponsor conducted a Phase 2 study (DIA 2003). Study DIA2003, was a 3-arm, 18-week study that demonstrated the safety and efficacy of the twice-daily dosing of 50 mg and 150 mg canagliflozin, relative to placebo, in subjects on a background of metformin.

Clinical Pharmacology program in this application is supported by following studies:

- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed canagliflozin/metformin FDC immediate release tablet to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively])

- A food effect study (DIA1037) evaluating the effect of food on the to-be-marketed canagliflozin/metformin FDC immediate release tablet.

- A Phase 1 PK/PD study (DIA1032), to demonstrate that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration

The FDC tablets of canagliflozin/metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are:

- In patients who are already treated with both canagliflozin and metformin
- Not adequately controlled on a regimen containing metformin or canagliflozin

Highlights of the studies which support the above two dosing indications are summarized below:

Studies that supports the use of FDC tablets in patients who are already treated with both canagliflozin and metformin

Communication History: During EOP2 meeting, sponsor asked if the Phase 1 PK/PD study in healthy subject comparing canagliflozin twice daily dosing with canagliflozin once-daily dosing (at the same total daily dose), will provide sufficient data for assessment to bridge the safety and efficacy information obtained using the once-daily canagliflozin dosing regimen employed in the Phase 3 program to the proposed twice-daily dosing with the canagliflozin/metformin immediate release FDC.

During the EOP2 meeting Agency clarified that the planned PK/PD study will not be sufficient because the PD marker that was used was not validated as a surrogate for efficacy. In the EOP2 meeting Agency recommended a head to head 16-20 week study to compare HbA1c change between QD vs BID dosing of canagliflozin.

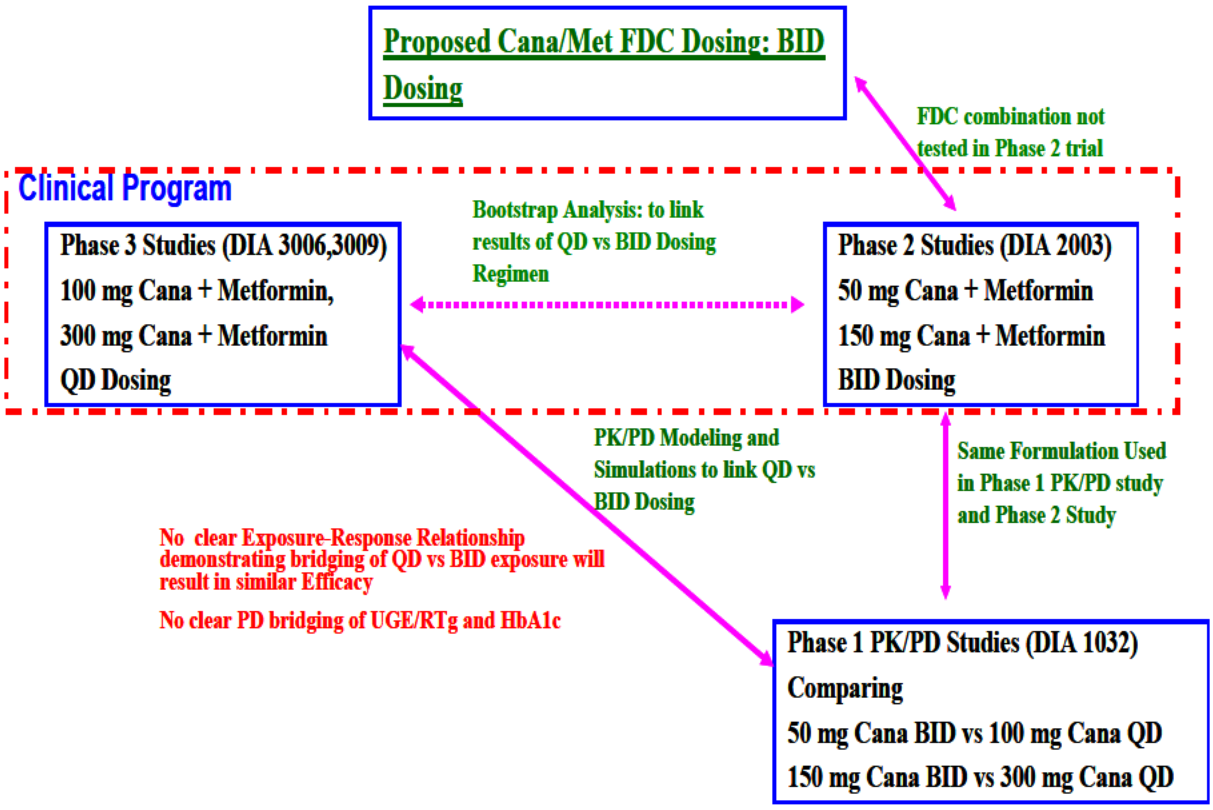
Current Clinical Program: Phase 3 trials conducted under canagliflozin NDA include studies that support the use of once daily canagliflozin along with metformin. Pivotal Phase 2 (DIA 2003) study submitted under this NDA only included twice daily arms of canagliflozin. Sponsor in their development program did not included a head to head comparison of patients who are on similar daily dose of canagliflozin and once daily dosing to that of patients with twice daily dosing regimen. This comparison is important to patients who are already on canagliflozin QD regimen and wanted to switch to the proposed FDC tablet which is a BID dosing regimen.

Sponsor's Phase 2 trial testing the 50 mg and 150 mg BID dose groups did not include the corresponding QD regimens and thus could not establish that BID regimen resulted in similar response (change in HbA1c from baseline) as the QD regimen. Furthermore, in a cross-trial comparison, the placebo adjusted HbA1c change from baseline with canagliflozin BID dosing regimen was lower (-0.44% with 50 mg BID dose and -0.60 % with 150 mg BID dose) than the response observed by the QD regimens (-0.59 % with 100 mg QD dose and -0.67 with 300 mg QD dose) in earlier conducted Phase 3 trials. Sponsor attributed these numerical differences in efficacy between the once-daily and twice-daily formulations of canagliflozin (in DIA3006 and DIA2003, respectively) are related to differences observed in baseline HbA1c between studies.

To bridge the QD dosing to BID dosing for canagliflozin sponsor used the following approach (Figure 1):

- Bootstrap approach

Figure 1: Figure Demonstrating the Studies that Sponsor Proposed to Bridge QD vs BID Dosing



Bootstrap Approach to Bridge QD vs BID Dosing:

To bridge the efficacy results of once daily dosing which was used in canagliflozin program to twice daily program which is proposed in this NDA, sponsor conducted a cross study comparison.

As indicated in Table 1, the placebo-subtracted change from baseline in HbA1c in Phase 2 study (DIA2003) at Week 18 was less than that observed in Phase 3 study (DIA3006) at Week 18. Sponsor attributed these numerical differences in efficacy between the once-daily and twice-daily formulations of canagliflozin (in DIA3006 and DIA2003, respectively) are related to differences observed in baseline HbA1c between studies.

To bridge these two trials and to determine whether the efficacy results in these two trials were different due to difference in baseline HbA1c values sponsor conducted a bootstrap simulation. The goal of this analysis was to assess the potential impact of baseline glycemic control on the primary efficacy analysis. Sponsor stated that the results of bootstrap simulation suggests that after adjustment for differences in the baseline HbA1c distribution, the results from DIA2003 are numerically similar to a comparable group of

subjects in DIA3006 at the same total daily dose of canagliflozin. Statistical team does not agree with the sponsor's bootstrap analysis because of 1) its post hoc in nature 2) did not include all prognostic factors that might result in difference in HbA1c to bridge QD and BID dosing regimens. Please refer to statistical review by Dr. Wei Liu for further details.

Table 1: Change from Baseline in HbA1c to Week 18 (LOCF)

	Placebo	Cana 100 mg Total Daily Dose	Cana 300 mg Total Daily Dose
Twice-Daily Dosing			
DIA2003			
N	92	90	91
Baseline, Mean (SD)	7.66(0.905)	7.63(0.844)	7.53(0.829)
Change from Baseline, LSM (SE)	-0.01(0.069)	-0.45(0.070)	-0.61(0.069)
Diff of LSM (SE) [b]		-0.44(0.098)	-0.60(0.098)
95% CI [a]		(-0.637;-0.251)	(-0.792;-0.407)
Once-Daily Dosing			
DIA3006 - Add-on to Metformin			
N	126	260	258
Baseline, Mean (SD)	7.94(0.927)	7.87(0.864)	7.85(0.895)
Change from Baseline, LSM (SE)	-0.22(0.066)	-0.82(0.046)	-0.90(0.046)
Diff of LSM (SE) [b]		-0.59(0.081)	-0.67(0.081)
95% CI [a]		(-0.751;-0.434)	(-0.833;-0.515)

[a] Pairwise comparison: CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline value as covariate.
[b] Placebo-subtracted change from baseline in LS Means.
Note: The table includes only the subjects who had both baseline and post-baseline HbA_{1c}.

Source: Sponsors report on comparison of hba1c. pg 8

PK/PD and modeling and simulations approach to bridge QD and BID Dosing regimen of Canagliflozin

Sponsor conducted a Phase 1 PK/PD study (DIA 1032) in healthy subjects to assess the steady-state PK and PD of canagliflozin administered QD or BID at the same total daily dose of 100 and 300 mg.

The mean systemic exposure (AUC24h) at steady state was similar following QD and BID dosing regimens at the same total daily dose of 100 or 300 mg; the 90% CIs of the geometric mean ratios were within the equivalence limits of 80% to 125% (Table 2). Following QD and BID dosing, mean urinary glucose excretion in 24 hours (UGE24h) and 24-hour mean renal threshold for glucose excretion (RT_G) were similar for total daily doses of 100 and 300 mg (Table 3).

Table 2: Pharmacokinetic Parameters of Canagliflozin Following qd and bid Administration of Canagliflozin at the Same Total Daily Dose of 100 and 300 mg in Healthy Subjects (Study DIA1032)

	Mean (SD) on Day 5			
	Daily Dose of 100 mg		Daily Dose of 300 mg	
Parameter	50 mg bid N=16	100 mg qd N=17	150 mg bid N=16	300 mg qd N=16
t_{max}, h [a]				
Morning	1.50 (1.00 - 3.00)	2.00 (1.00 - 4.00)	1.50 (1.00 - 4.00)	1.75 (1.00 - 3.07)
Evening	1.75 (1.00 - 4.00)	-	1.09 (1.02 - 4.08)	-
C_{max}, ng/mL				
Morning	568 (125)	943 (239)	1,864 (366)	3,213 (841)
Evening	504 (144)	-	1,764 (349)	-
AUC_{12h}, ng.h/mL	3,254 (589)	-	11807 (1,799)	-
AUC_{24h}, ng.h/mL	6,242 (1,252)	6,377 (1,285)	22,973 (3,568)	22,804 (4,650)
Geometric Means Ratio, % (90% CI) [b]	99.32 (94.71; 104.16)		97.08 (94.59; 99.62)	
$t_{1/2}$, h	15.3 (4.5)	14.3 (3.5)	14.1 (1.7)	14.8 (3.8)

N = maximum number of subjects with data.
[a] Median (range). [b] Test: bid; reference: qd.
Source: Mod5.3.4.1\DIA1032\Table 9, Table 10

Source: Sponsors report on summary of Clinical Pharmacology pg 59

Table 3: 24-Hour Mean RTG and UGE24h Following qd and bid Administration of Canagliflozin at the Same Total Daily Dose of 100 and 300 mg in Healthy Subjects (Study DIA1032)

	Mean (SD) on Day 5			
	100 mg Total Daily Dose		300 mg Total Daily Dose	
Parameter	100 mg qd N=17	50 mg bid N=17	300 mg qd N=16	150 mg bid N=17
24-Hour Mean RT_G, mg/dL	61.6 (9.03)	60.6 (8.69)	53.4 (7.89)	52.3 (9.54)
UGE_{24h}, g	47.7 (11.0)	51.3 (10.6)	56.7 (14.0)	57.9 (15.2)

N = maximum number of subjects with data.
Source: Mod5.3.4.1\DIA1032\Output DPD02, Output DPD01A

Source: Sponsor's report on summary of Clinical Pharmacology pg 59

The planned PK/PD study is not sufficient to bridge the QD and BID dosing of canagliflozin because the PD marker that was used was not validated as a surrogate for HbA1c efficacy response. Sponsor justifies the PK/PD bridging by referring to PK/PD modeling report that they submitted under Canagliflozin program (NDA 204042). Based on the available concentration range, the data submitted in NDA 204042 do not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. During the late cycle meeting, the sponsor was advised that while in principle, a PK/PD model based approach is feasible, sponsor's current PK/PD model developed has several limitations (as listed below) and is inadequate to bridge the QD and BID dosing regimen. The following highlight the limitation in sponsor's PK/PD model and the advice that was communicated to the sponsor:

- *"The current PK/PD model is based on the steady state average concentration (C_{avg}) as the PK metric. Although we encourage you to submit the additional analyses you proposed for the C_{avg} metric during the late-cycle meeting, we continue to believe that the modeling effort based on C_{avg} assumes that the QD and BID regimens will yield a similar PD response. In order to address this, we recommend that you develop a dynamic PK/PD model that utilizes the complete time profile of drug concentrations and links that with the time-profiles for HbA1c utilizing data from Phase 3 trials and Phase 2 trials including DIA2001. We also recommend that while updating your model, you include data from the Phase 3 efficacy and safety trial in patients with renal impairment to explore the effect of eGFR on HbA1c response. Inclusion of a wide range of eGFR will provide additional check on the robustness of the model by accounting for diminishing efficacy with declining renal function as expected based on canagliflozin's mechanism of action."*

- *"Based on the current model, the difference in HbA1c response between the 100 mg and 300 mg doses is under predicted. As mentioned in the PK/PD analysis report and further discussed during the late cycle meeting, the possibility exists that the 300 mg dose not only acts through SGLT-2 but also through SGLT-1. This effect is not quantified and accounted for in your current PK/PD model. In order to establish a robust exposure-response relationship, you need to address this deficiency. Your model should predict the HbA1c response at both dose levels and account for the contribution of SGLT-1 for the higher dose."*

- *"Your data from Phase 1 study (NAP1002) shows saturation in RT_G response beyond 100 mg dose. Since RT_G is a driver for HbA1c response in your current model, this may also have contributed to the under prediction of HbA1c response for the 300 mg dose. We recommend that you consider reducing the model to link canagliflozin PK to fasting plasma glucose (FPG) and FPG to HbA1c."*

- *"Standard model diagnostics as well as an external validation should be performed. For external validation, predict the HbA1c response for DIA2003 that utilized BID regimens."*

- *"This model can then be used to simulate the PK and PD profiles on QD and BID dose administration. The utility of the model to bridge the QD and BID regimens will be a review issue. In your modeling plan, elaborate on the metrics you plan to use to compare the simulated QD and BID profiles."*

- *"Results based on PD markers (UGE, RTg) are considered only supportive to bridge QD and BID regimens because of lack of an established correlation between UGE/RTg and HbA1c. Therefore, the primary emphasis will be on the comparison of HbA1c response."*

Following discussion at the late cycle meeting sponsor submitted a revised PK/PD modeling plan (See Appendix 4.1) that requires further discussions and subsequent modifications before an agreement can be reached. Thus, while in principle a model based PK/PD approach is feasible, the sponsor's modeling approach cannot be reviewed within this review cycle. (Please refer to section 2.2.6 for further details). . (Please refer to section 2.2.6 for further details).

Studies that supports the twice daily use of FDC tablets in patients who are on background metformin therapy alone:

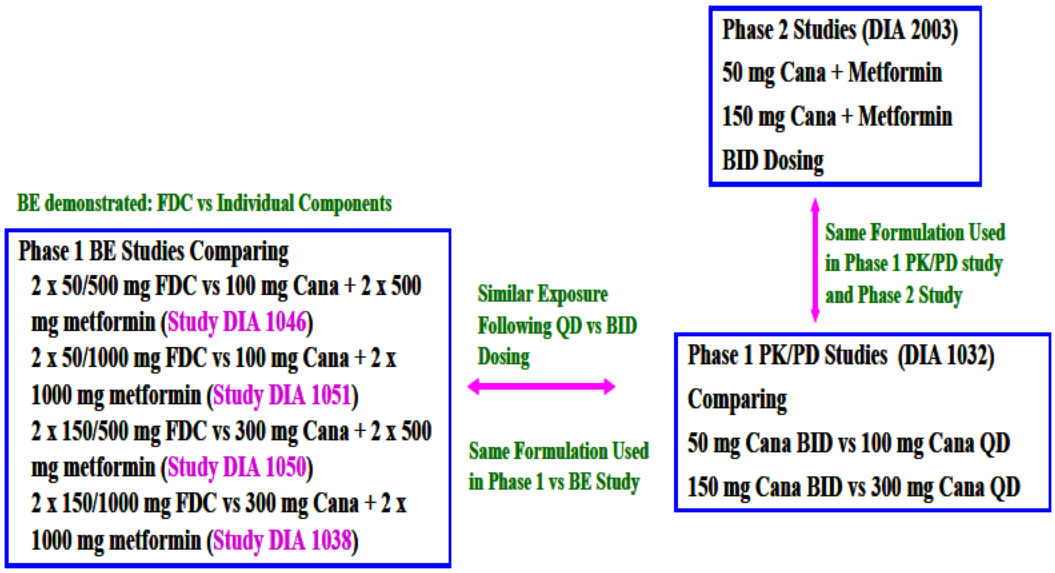
Sponsor conducted a Phase 2 study (DIA 2003) which examined the effect of twice daily dosing of canagliflozin (50 mg and 150 mg bid) in patients with stable background metformin therapy. In this study sponsor demonstrated that canagliflozin when dosed twice daily, at total daily doses of 100 mg (given as 50 mg BID) and 300 mg (given as 150 mg BID), provides statistically significant glycemic efficacy in add-on use with metformin monotherapy. Lease square mean changes from baseline was -0.60% and -0.44% following administration of 150 mg bid and 50 mg bid canagliflozin doses, respectively.

Studies that bridge the formulation used in Phase 2 study (DIA 2003) to the proposed to- be-marketed formulation:

In the Phase 2 study the individual tablets of canagliflozin and metformin were used (50 mg canagliflozin tablet for the 50 mg dose and one 100 mg tablet + one 50 mg tablet over-encapsulated for administration of a single capsule for the 150 mg dose). To link the individual tablets used in pivotal Phase 2 study to the proposed to-be marketed FDC tablets of canagliflozin and metformin sponsor conducted a Phase 1 PK/PD study and 4 pivotal bioequivalence studies (Figure 2).

To bridge the canagliflozin 100 mg and 300 mg once daily tablets to 50 mg and 150 mg twice daily tablets used in Phase 2 study sponsor conducted a Phase 1 PK/PD study (DIA 1032). Phase 1 PK/PD study results showed similar exposures between once daily and twice daily formulation of canagliflozin. In addition this Phase 1 study utilized 50 mg and 150 mg twice daily formulation of canagliflozin that is similar to the one used in the pivotal Phase 2 study.

Figure 2: Figure Demonstrating the Link Between Formulation used in Phase 2 study to the Proposed To-Be-Marketed Formulation



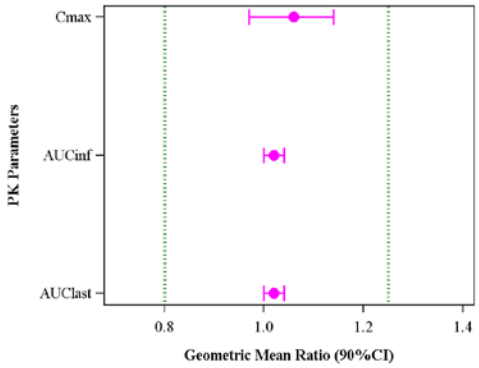
Thus, similar exposure between BID dosing formulations (50 mg and 150 mg) and QD dosing formulation of canagliflozin provides an indirect link to formulation used in Phase 2 study to the once daily tablet formulation of canagliflozin used in pivotal BE studies.

The pivotal BE studies compared the proposed to be marketed FDC tablets of different strengths to the individual once daily tablets of (100 mg and 300 mg) canagliflozin given with metformin. When dosed as the FDC product in the pivotal BE study, both canagliflozin and metformin met the standards for bioequivalence to the individual tablets given concurrently at all dose strengths. Figure 3 shows 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were entirely contained within 0.80 to 1.25 for both canagliflozin and metformin at highest (Study 1038) and lowest (DIA 1046) dose strengths.

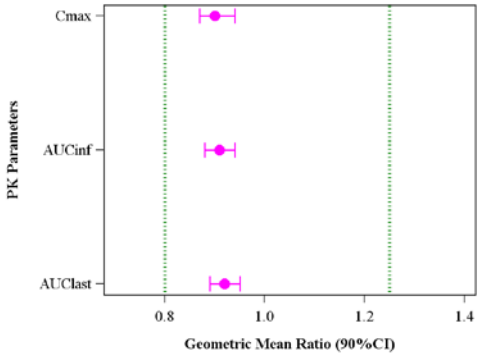
Figure 3: A) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 300 mg and Metformin 2*1000 mg and FDC Product (2 x 150/1000 mg FDC). B) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 100 mg and Metformin 2*500 mg and FDC Product (2 x 50/500 mg FDC).

A) **BE Study DIA 1038**

Canagliflozin

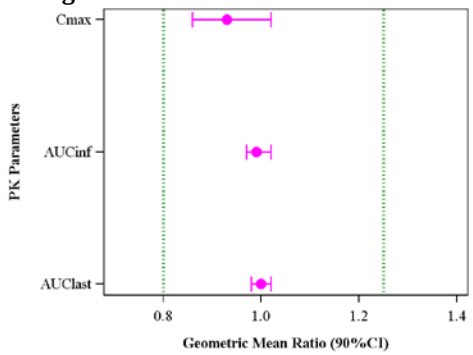


Metformin

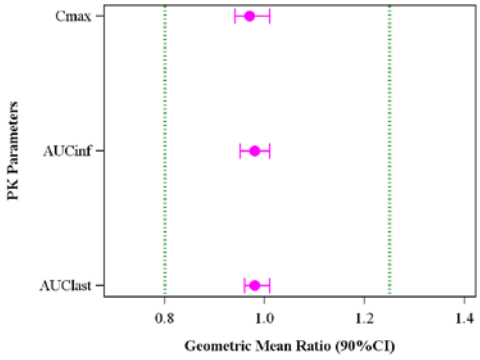


B) **BE Study DIA 1046**

Canagliflozin



Metformin



Food-Effect Study:

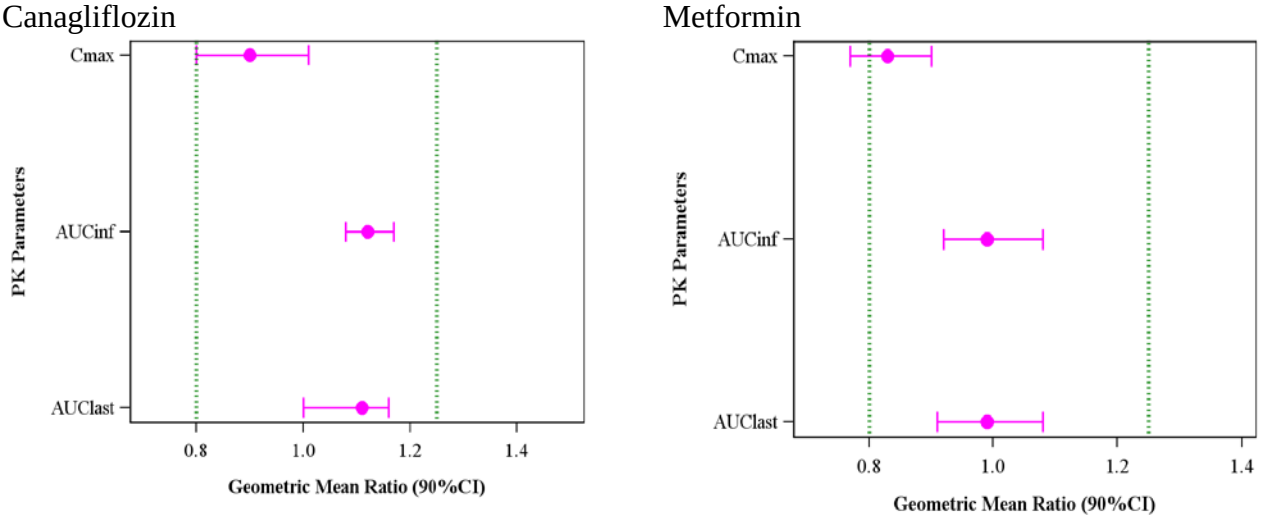
The effect of high fat meal on the single-dose pharmacokinetics of the proposed FDC tablet of CANA/MET IR at highest dose strength (150mg/1000mg) was examined in a randomized, open-label, single-dose, 2-period crossover study (DIA 1037) in 24 healthy adult subjects.

The Cmax, AUClast, and AUC∞ ratios of geometric means and associated 90% CIs for canagliflozin between fed and fasting conditions were contained within the bioequivalence limits of 80 to 125% indicating no effect of food on the pharmacokinetics of the canagliflozin (Figure 4). Regarding the metformin component of the canagliflozin/metformin FDC tablet, this study demonstrated a decrease in Cmax of about 16% and no change in AUClast or AUC∞. Median T_{max} increased by approximately 2

hours for canagliflozin and approx 1 hour for metformin FDC was administered under fed conditions compared with administration under fasted conditions.

Figure 4: Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Canagliflozin and Metformin Pharmacokinetic Parameters Following Administration of the canagliflozin/metformin IR FDC Tablet With and Without Food.

A) **BE Study DIA 1038**



Drug- Drug Interaction: No drug-drug interaction study between metformin and canagliflozin was conducted under this NDA. However, sponsor conducted drug-drug interactions study under canagliflozin NDA (NDA204042). No clinically meaningful drug-drug interaction was observed between metformin and canagliflozin. Please refer to Clinical Pharmacology review by Dr. Jayabharathi Vaidyanathan for further details

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

Both canagliflozin and metformin are approved products. Canagliflozin (INVOKANA™) has been approved recently (2013) in the United States, under NDA 204042. Canagliflozin is a SGLT-2 inhibitor and is currently marketed as immediate-release tablets of 100 mg and 300 mg dose strengths as QD dosing regimen.

Metformin hydrochloride is an oral anti-hyperglycemic agent also used in the treatment of T2DM. Metformin belongs to the biguanide class of antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes. Glucophage® (NDA 20357) is available as 500 mg, 850 mg and 1000 mg immediate release tablets for BID administration.

The canagliflozin/metformin HCl film-coated tablets are immediate release tablets containing a fixed dose combination (FDC) of canagliflozin and metformin hydrochloride. The sponsor is proposing 4 different FDC strengths of canagliflozin/metformin 50mg/500mg, 50mg/1000mg, 150mg/500mg, 150mg/1000mg. The proposed recommended daily dose of canagliflozin/metformin FDC tablets is one tablet taken twice daily. This NDA is submitted as a 505(b)(2) application, as this NDA relies on the data submitted in the canagliflozin NDA 204-042 (recently approved) and in the Glucophage® NDA 20-357.

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

The purpose of this application is to develop immediate release FDC tablets of canagliflozin and metformin. Canagliflozin as immediate-release tablets of 100 mg and 300 mg dose strengths as QD dosing regimen. Metformin (Glucophage® NDA 20357) is available as 500 mg, 850 mg and 1000 mg immediate release tablets for twice daily administration. The proposed recommended daily dose of canagliflozin/metformin FDC tablets is one tablet taken BID.

The safety and efficacy of the concomitant use of canagliflozin and metformin is supported by Phase 3 trials that were submitted under canagliflozin NDA (NDA 204042). Under the canagliflozin program six Phase 3 studies evaluated QD administration of canagliflozin 100 mg or 300 mg in subjects with T2DM on a background of metformin (alone or in combination with other anti-diabetic agents).

As summarized above all the phase 3 studies under canagliflozin program used canagliflozin 100 mg or 300 mg tablets as QD dosing regimen. To support the BID dosing regimen of canagliflozin/metformin FDC formulation, the sponsor during the EOP2 meeting clarified whether a Phase 1 PK/PD study in healthy subject comparing canagliflozin twice daily dosing with canagliflozin once-daily dosing (at the same total daily dose), will provide sufficient data for assessment to bridge the safety and efficacy information obtained using the once-daily canagliflozin dosing regimen employed in the

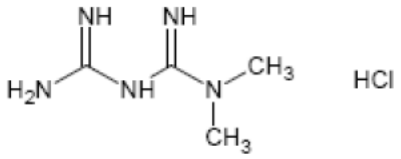
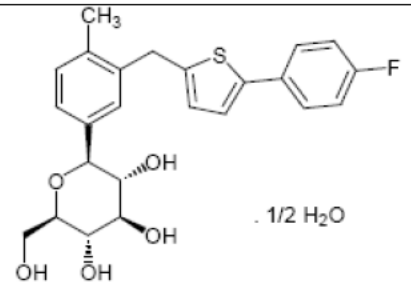
Phase 3 program to the proposed twice-daily dosing with the canagliflozin/metformin immediate release FDC.

During the EOP2 meeting Agency clarified that the planned PK/PD study will not be sufficient because the PD marker that was used was not validated as a surrogate for efficacy. In the EOP2 meeting Agency also recommended a head to head 16-20 week study to compare HbA1c change between QD vs BID dosing of canagliflozin.

Reviewers Comment: During the EOP2 meeting Agency clearly stated that the planned PK/PD study will not be sufficient because the PD marker is not validated as a surrogate for efficacy. Agency also warned the Sponsor that they will take a risk and they might need to conduct a clinical trial if they rely just on PK/PD for bridging QD vs BID dosing. In addition during EOP2 meeting DMEP also recommended that clinical study of 16-20 weeks comparing QD and BID dosing can be acceptable. However, during post meeting minutes, Agency agreed with the sponsor's current Phase 2 study design which is 3-arm study with 60-80 patients per arm, at least 16 weeks in duration, in patients with T2DM, with 2 doses of canagliflozin (50 mg and 150 mg BID) and placebo. Sponsor in all follow up communication with Agency used this as a reference to justify their development program.

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?

	Metformin HCL	**Canagliflozin**
Description	White or almost white crystals	White to off-white powder.
Chemical Name	*N*,*N*-dimethyl-,monochloride, Imidodicarbonimidic diamide	(1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate
Molecular Formula	$C_4H_{11}N_5 \cdot HCl$	$C_{24}H_{25}FO_5S \cdot 1/2\ H_2O$
Molecular Weight	165.62	453.53

Structural Formula		
Solubility	Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.	It is very soluble in inorganic solvents such as soluble in *N, N* dimethylformamide, tetrahydrofuran, methanol, acetone, propylene glycol. Drug substance in insoluble or practically insoluble in aqueous media such as water, 0.1 N HCl, phosphate buffer etc.

Formulation: In addition to the active Ingredients (canagliflozin and metformin) FDC tablets contains several inactive ingredients. : The composition of the formulations for canagliflozin/metformin fixed dose combination tablets are shown in the Tables 4-7 below:

Table 4: Composition of 50/500 mg Canagliflozin/Metformin IR Tablets per Unit Dose

Component	Quality Reference[a]	Role	% w/w	mg/tablet
Core tablet				
(b) (4)				
Canagliflozin	Company Specification	Active	(b) (4)	51.00[b]
(b) (4)				(b) (4)
Metformin hydrochloride	Company Specification	Active	(b) (4)	500.00
(b) (4)				(b) (4)
Film-coating				
(b) (4)	Company Specification Ph.Eur./USP	Film-coat		(b) (4) (b) (4)
		Total film coated tablet weight		802.13

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.
[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous) (b) (4)

Source: Sponsor report on Drug Product Description Pg.2 (2.3.P.1)

Table 5: Composition of 50/1000 mg Canagliflozin/Metformin IR Tablets per Unit Dose

Component	Quality Reference[a]	Role	% w/w	mg/ tablet
Core tablet				
(b) (4)				
Canagliflozin	Company Specification	Active	(b) (4)	51.00[b]
(b) (4)				
Metformin hydrochloride	Company Specification	Active	(b) (4)	1000.00
(b) (4)				
Film-coating				
(b) (4)		Film-coat (b) (4)	(b) (4)	
Total film coated tablet weight				1526.63

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.
[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous)
(b) (4)

Source: Sponsor report on Drug Product Description (2.3.P.1)

Table 6: Composition of 150/500 mg Canagliflozin/Metformin IR Tablets per Unit Dose

Component	Quality Reference[a]	Role	% w/w	mg/ tablet
Core tablet				
(b) (4)				
Canagliflozin	Company Specification	Active	(b) (4)	153.00[b]
(b) (4)				
Metformin hydrochloride	Company Specification	Active	(b) (4)	500.00
(b) (4)				
Film-coating				
(b) (4)		Film-coat (b) (4)	(b) (4)	
Total film coated tablet weight				962.55

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.
[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous)
(b) (4)

Source: Sponsor report on Drug Product Description (2.3.P.1)

Table 7: Composition of 150/1000 mg Canagliflozin/Metformin IR Tablets per Unit Dose

Component	Quality Reference[a]	Role	% w/w	mg/ tablet
Core tablet				
(b) (4) Canagliflozin	Company Specification	Active	(b) (4)	153.00[b]
(b) (4) Metformin hydrochloride	Company Specification	Active	(b) (4)	1000.00
(b) (4)				
Film-coating				
(b) (4)		Film-coat (b) (4)	(b) (4)	
		Total film coated tablet weight		1687.05

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.
[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous)

(b) (4)

Source: Sponsor report on Drug Product Description (2.3.P.1)

2.1.3 What is the therapeutic indication and dosing recommendations?

The FDC tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin. FDC tablet can also be used in patients who are already treated with both canagliflozin and metformin. FDC tablet is intended to be given twice daily with meals with gradual dose escalation to reduce the gastrointestinal side effects due to metformin

The dosing of FDC tablet should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 150 mg canagliflozin/1,000 mg metformin hydrochloride twice daily with meals

The proposed dosing recommendations are as follows:

- In patients currently on canagliflozin and not currently treated with metformin

(b) (4)

- (b) (4)
-

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

Yes. DSI inspection is requested for the pivotal BE study (Study # DIA 1038) and Phase 1 PK/PD study assessing the steady state PK/PD of once daily vs. twice daily dosing with canagliflozin (Study# DIA1032).

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 FDC tablets of canagliflozin/metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are:

- Not adequately controlled on a regimen containing metformin or canagliflozin
- In patients who are already treated with both canagliflozin and metformin

Highlights of the studies which supports the above two dosing indications are summarized in section 2.2.2, 2.2.3 and 2.2.4

Overall the safety and efficacy of the concomitant use of canagliflozin and metformin is supported by Phase 3 trials that were submitted under canagliflozin program (NDA 204042). Summary of these trials and the clinical pharmacology studies conducted to support this NDA are presented above under "Summary of Important Clinical Pharmacology Findings". Please refer to Clinical Pharmacology review by Dr. Jaya Vaidyanathan for further details on clinical program under canagliflozin NDA.

2.2.2 What study/studies supports the use of FDC tablets in patients who are on background metformin therapy alone?

Sponsor conducted a Phase 2 study (DIA 2003) which examined the effect of twice daily dosing of canagliflozin (50 mg and 150 mg bid) in patients with stable background metformin therapy.
This Phase 2 study was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, global multicenter study that was intended to evaluated the efficacy, safety, and tolerability of canagliflozin in subjects with type 2 diabetes mellitus (T2DM) who were inadequately controlled on metformin monotherapy. The primary objective of this Phase 2 study was to assess the effect of canagliflozin 150 mg administered twice daily on HbA1c relative to placebo following 18 weeks of treatment.

In this study sponsor demonstrated that canagliflozin when dosed twice daily, at total daily doses of 100 mg (given as 50 mg BID) and 300 mg (given as 150 mg BID), provides statistically significant glycemic efficacy in add-on use with metformin monotherapy. Lease square mean changes from baseline was -0.60% and -0.44% with the 150 mg BID and 50 mg BID canagliflozin doses, respectively (Table 8).

Table 8: Primary Endpoint Analysis: Change from Baseline in HbA1c to Week 18 – LOCF

	Placebo (N=93)	CANA 50 mg bid (N=93)	CANA 150 mg bid (N=93)
Blood hemoglobin A_{1c} (%)			
Value at Baseline			
N	92	90	91
Mean (SD)	7.66 (0.905)	7.63 (0.844)	7.53 (0.829)
Value at Week 18 LOCF			
N	92	90	91
Mean (SD)	7.62 (1.016)	7.16 (0.856)	6.94 (0.623)
Change from Baseline			
N	92	90	91
Mean (SD)	-0.04 (0.764)	-0.47 (0.684)	-0.58 (0.759)
LS Mean (SE)	-0.01 (0.069)	-0.45 (0.070)	-0.61 (0.069)
P-value(minus Placebo)[a]		<0.001	<0.001
Diff. of LS Means (SE)		-0.44 (0.098)	-0.60 (0.098)
95% CI[a]		(-0.637;-0.251)	(-0.792;-0.407)

[a] Pairwise comparison: p-values and CIs are based on the ANCOVA model with treatment, glycemic control (whether HbA_{1c} value ≥8.0%), and baseline HbA_{1c}.
Note: The table only includes subjects who had both baseline and post-baseline HbA_{1c}.
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Source: Sponsor report of Phase 2 Study DIA2003 pg 53

Reviewers Comment: The Sponsor did not conduct a clinical study in which the safety and efficacy of canagliflozin dosed twice daily was directly compared with that seen with once-daily dosing of canagliflozin in subjects with type 2 diabetes mellitus (T2DM), nor was a once-daily dosing arm included in the DIA2003 study. As discussed later in section 2.2.4, since sponsor did not include a once daily canagliflozin arm in study DIA 2003 it becomes difficult to bridge the use of this FDC tablets in patients who are on once daily canagliflozin and wants to switch to FDC tablets, especially in light of observed low efficacy for BID compared to QD dosing regimen based on cross study comparison.

2.2.3 How are the formulation used in Phase 2 study (DIA 2003) linked to the proposed to be marketed formulation?

The strategy used to bridge the individual tablets of canagliflozin and metformin with the proposed to-be marketed FDC tablets of canagliflozin and metformin is summarized above in Figure 2 under "Summary of Important Clinical Pharmacology Findings".

Reviewer's comment: In terms of pharmacokinetics, QD and BID dosing provides similar exposures (see above, Table 2). As expected the Cmax was lower following BID dosing (see above, Table 2). The twice daily formulation used in PK/PD study is similar to formulation used in the phase 2 study DIA 2003. The once daily formulation of canagliflozin is similar to the formulation used in pivotal BE study. As seen is Figure 2 sponsor only provides an indirect bridge between formulations used in Phase 2 study to the proposed to be marketed formulation.

2.2.4 What study/studies supports the use of FDC tablets in patients who currently on individual tablets of canagliflozin as QD dosing and metformin immediate release tablet as twice daily dosing?

As discussed in section 2.1.1, sponsor in their development program did not includ a head to head comparison of patients who are on similar daily dose of canagliflozin and once daily dosing to that of patients with twice daily dosing regimen. Phase 3 trials conducted under canagliflozin NDA include studies that support the use of once daily canagliflozin along with metformin. Pivotal Phase 2 submitted under this NDA only included twice daily arms of canagliflozin. Sponsor in their development program did not included a head to head comparison of patients who are on similar daily dose of canagliflozin given in once daily dosing and twice daily dosing regimen. This comparison is important to determine that patients who are already on canagliflozin QD regimen and switch to the proposed FDC tablet (which is a BID dosing regimen) retain the same efficacy. The sponsor proposed to use the bootstrap approach and PK/PD modeling and simulation approach to bridge the QD and BID dosing regimens which is discussed above under "Summary of Important Clinical Pharmacology Findings"

2.2.5 Are the active moieties in the plasma appropriately identified and measured?

Yes. Please refer to the section 2.6 for details of the bioanalytical method.

2.2.6 Exposure Response

2.2.6.1 What are the characteristics of the exposure-response relationships for efficacy and whether it can be used to bridge QD and BID dosing regimen of canagliflozin?

Sponsor justifies the PK/PD bridging of QD and BID dosing of canagliflozin by referring to PK/PD modeling report that they submitted under Canagliflozin program (NDA 204042). Based on the available concentration range, the data submitted in NDA 204042 do not show a robust relationship between plasma canagliflozin concentrations and HbA1c response for canagliflozin. During the late cycle meeting, the sponsor was advised that the PK/PD model developed based on the current data has several limitations (see section 1.3 summary of important clinical pharmacology above) and is inadequate to bridge the QD and BID dosing regimen.

Following discussion at the late cycle meeting sponsor submitted a revised PK/PD modeling plan (See Appendix 4.1). Sponsor's revised modeling plan still had several issues as listed below that were communicated to the sponsor. Sponsor following this communication again resubmitted a plan (Appendix 4.3) for which, at this point, the review team feels that while a PK/PD model based approach is feasible, it needs further discussion before reaching an agreement and thus can not be reviewed at this review cycle.

- *There is not sufficient pharmacokinetic (PK) data for the bridging analysis. The studies included in your model development are DIA 2001 and DIA 3006. Since PK data was not collected in DIA 3006, the PK profile will be predicted based on population PK analysis. The parameters in the final population PK model were fixed based on your initial analysis of Phase 1 data (Table 1 and Table 9 of population PK report). The IIV on the absorption parameters were high. Given the lack of PK data (available from approximately 33% of patients in Dataset 1), we do not believe that you will be able to adequately predict the PK profiles in DIA 3006.*

- *Dose regimen will be used as a covariate in the dynamic, integrated PK/PD model by allowing the model parameters associated with canagliflozin effect (i.e., Emax and EC50) to be different for QD and BID dosing regimens. We do not think this is a valid approach because Emax and EC50 are drug specific parameters and should not vary between the two dosing regimens.*

- *Additionally we believe that a covariate approach to test the difference between QD and BID regimen is not applicable in this case because data from BID regimen is limited to 300 mg BID dose group. Results from DIA 2001 (Table 8 of CSR) show that the change in HbA1c for the 300 mg BID group (-0.95) is similar to the 300 mg QD group (-0.92) even when the total daily dose is doubled. This suggests saturation of response at these two dose levels. Thus a covariate analysis in this case will not show any difference between the QD and BID regimen even if differences do exist.*

- *Your data from Phase 1 study (NAP1002) shows saturation in RTG response beyond 100 mg dose. Since RTG is a driver for HbA1c response in your current model, this would likely lead to saturation of HbA1c response at higher doses. Thus this model might not be able to predict the dose response of the 100 mg and 300 mg dose groups and it might show saturation at higher doses.*

- *The modeling plan does not define the criteria to evaluate the difference in efficacy between the QD and BID regimens. It appears that the difference between QD and BID profiles in a typical subject with their associated confidence bands will be assessed only graphically. Graphical comparison alone may not be sufficient and a quantitative criteria will need to be pre-defined for assessing the differences between dosing regimens.*

- *Although, in principle, the modeling approach is feasible but due to the limitations of the available data and the proposed analysis approach as outlined above, we do not believe the current proposal would be adequate to bridge the efficacy of QD and BID dosing.*

The sponsor is advised to discuss their PK/PD plan in detail following the complete response action of this application. The Sponsor has agreed and is planning to have a face to face meeting with the Agency to discuss the path forward using the PK/PD approach.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The intrinsic factors were not evaluated in this NDA. The intrinsic factors for the individual components canagliflozin and metformin were previously described in the corresponding clinical pharmacology reviews of these submissions.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1.1 Drug-Drug Interaction

No drug-drug interaction study between metformin and canagliflozin was conducted under this NDA. However, sponsor conducted drug-drug interactions study under canagliflozin NDA (NDA204042). No clinically meaningful drug-drug interaction was observed between metformin and canagliflozin. Please refer to Clinical Pharmacology review by Dr. Jayabharathi Vaidyanathan for further details

2.4.1.2 Food effect

The effect of high fat meal on the single-dose pharmacokinetics of the proposed FDC tablet of canagliflozin/metformin FDC at highest dose strength (150mg/1000mg) was examined in a randomized, open-label, single-dose, 2-period crossover study (DIA 1037) in 24 healthy adult subjects.

Summaries of the pharmacokinetic parameters of canagliflozin and metformin following administration in fed (high-fat meal) and fasted states are presented in Table 9 (also see above, Figure 4). C_{max}, AUC_{last}, and AUC_{∞} ratios of geometric means and associated 90% CIs for canagliflozin between fed and fasting conditions were contained within the bioequivalence limits of 80 to 125% indicating no effect of food on the pharmacokinetics of the canagliflozin (Figure 4). Regarding the metformin component of the CANA/MET

IR FDC tablet, this study demonstrated a decrease in Cmax of about 16% and no change in AUClast or AUC∞. Median T_{max} increased by approximately 2 hours for canagliflozin and approximately 1 hour for metformin FDC was administered under fed conditions compared with administration under fasted conditions.

Table 9: Summary of Pharmacokinetic Parameters of Canagliflozin and Metformin Following Administration in Fed (high-fat meal) and Fasted Condition

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	Canagliflozin/Metformin 150 mg/100 mg FDC tablets (Fed) (T)	Canagliflozin/Metformin 150 mg/100 mg FDC tablets (Fasted) (R)	
Canagliflozin			
C_{max} (ng/mL)	1325.7	1462.9	90.62 (80.72 – 101.73)
$AUC_{0\text{-last}}$ (ng.hr/mL)	12612.53	11307.01	111.55 (107.25 – 116.01)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	13117.46	11650.30	112.59 (108.03 – 117.35)
Median T_{max} (hr)	3.5	1.5	
Metformin			
C_{max} (ng/mL)	1373.58	1643.11	83.60 (77.21 – 90.51)
$AUC_{0\text{-last}}$ (ng.hr/mL)	10908.47	10950.95	99.61 (91.88 – 108.00)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	11222.95	11227.97	99.96 (92.34 – 108.19)
Median T_{max} (hr)	3.00	2.00	

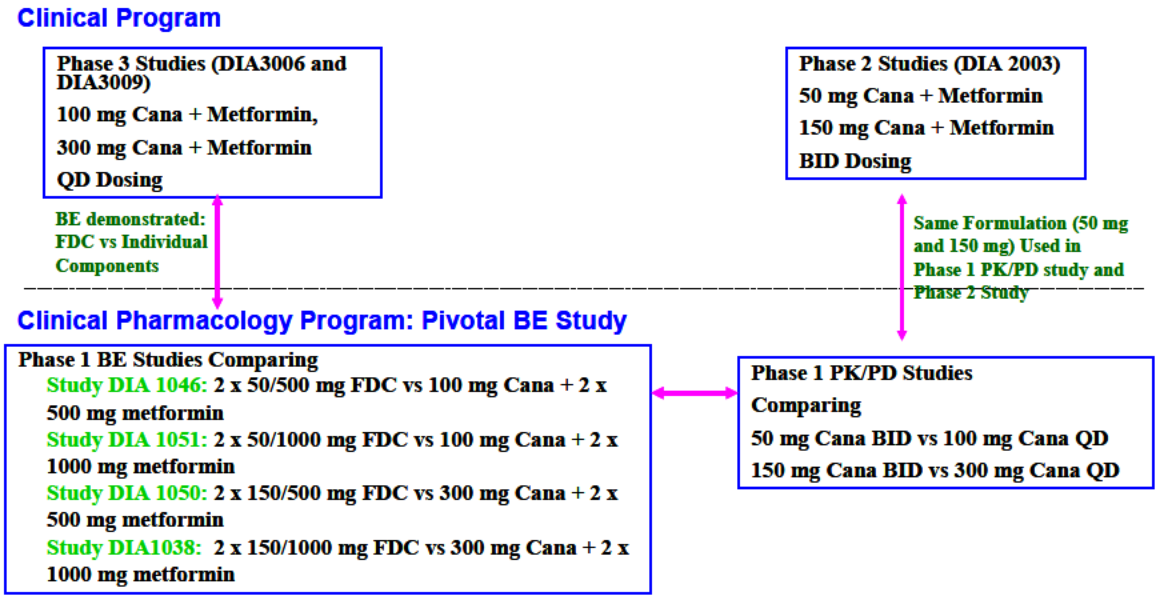
Reviewer's Comment: In the presence of food current Glucophage label reports a decrease of 40% in Cmax with no change in dosing recommendations. Thus, a slight decrease in Cmax of metformin in the presence of food following administration of FDC tablet is not clinically significant.

2.5 General Biopharmaceutics

2.5.1 Is the proposed to-be-marketed fixed dose formulation bioequivalent to the individual canagliflozin and metformin formulations?

Please refer to section 2.2.3 for further details on how the proposed to-be-marketed FDC tablets are linked to individual tablets that are used in pivotal Phase 2/Phase 3 trials. In the clinical Phase 3 program with QD dosing of canagliflozin sponsor used individual tablets of canagliflozin and metformin that were co-administered. Also, in the Phase 2 study the individual tablets of canagliflozin and metformin were used (50 mg canagliflozin tablet for the 50 mg dose and one 100 mg tablet + one 50 mg tablet over-encapsulated for administration of a single capsule for the 150 mg dose). To link the individual tablets used in pivotal Phase 2 and Phase 3 studies to the proposed to-be marketed FDC tablets of canagliflozin and metformin sponsor conducted a Phase 1 PK/PD study and 4 pivotal bioequivalence studies (Figure 5). Please refer to section 2.2.3 for further details on Phase 1 PK/PD study results, as this section will focus on four pivotal bioequivalence studies.

Figure 5: Figure demonstrating the formulations used in Phase 2 and Phase 3 studies and the studies conducted to bridge the formulation to the proposed to-be marketed formulation

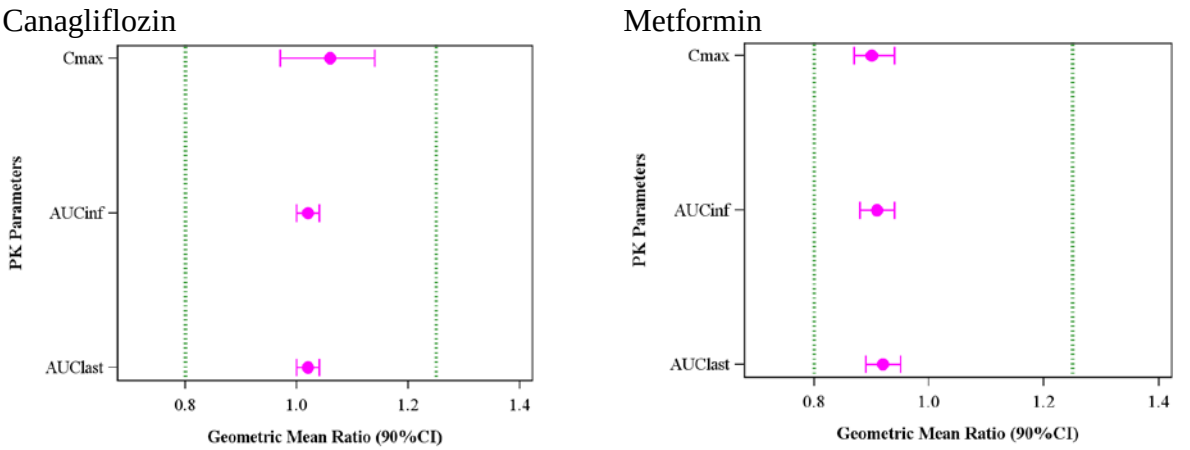


Sponsor conducted 4 Phase 1 BE studies that demonstrated the bioequivalence of the to-be-marketed canagliflozin/metformin FDC tablets to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively]). All the BE studies were randomized, 2-way cross over study where bioequivalence of FDC tablets was assessed following administration of FDC tablets and individual tablets in healthy fed subjects.

When dosed as the FDC product in the pivotal BE study, both canagliflozin and metformin met the standards for bioequivalence to the individual tablets given concurrently at all dose strengths. Figure 6 shows 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were entirely contained within 0.80 to 1.25 for both canagliflozin and metformin at highest (Study 1038) and lowest (DIA 1046) dose strengths. Figure 7 shows 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for middle two strengths. All four strengths of FDC tablets showed bioequivalence between individual tablets and FDC tablet.

Figure 6: A) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 300 mg and Metformin 2*1000 mg and FDC Product (2 x 150/1000 mg FDC). B) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 100 mg and Metformin 2*500 mg and FDC Product (2 x 50/500 mg FDC).

A) **BE Study DIA 1038**



B) **BE Study DIA 1046**

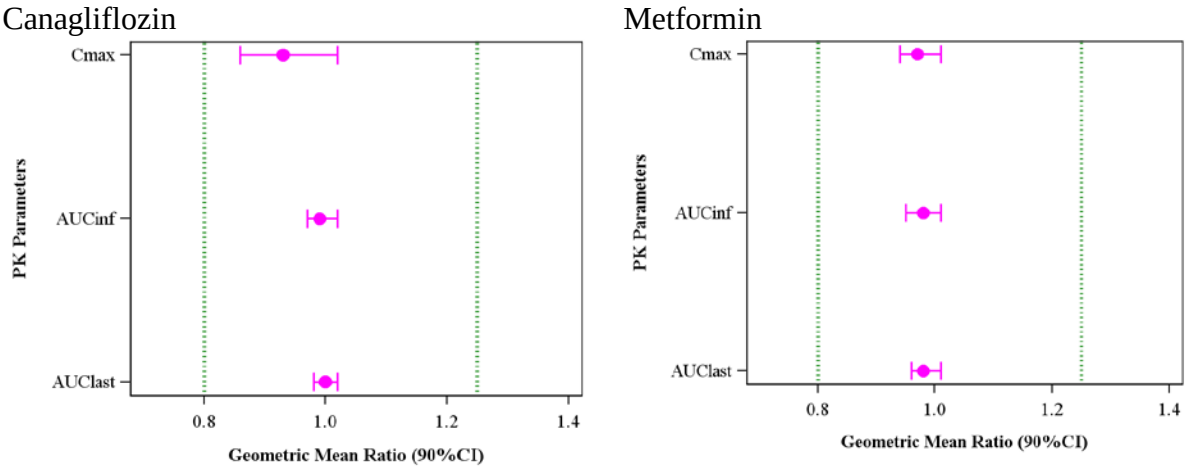
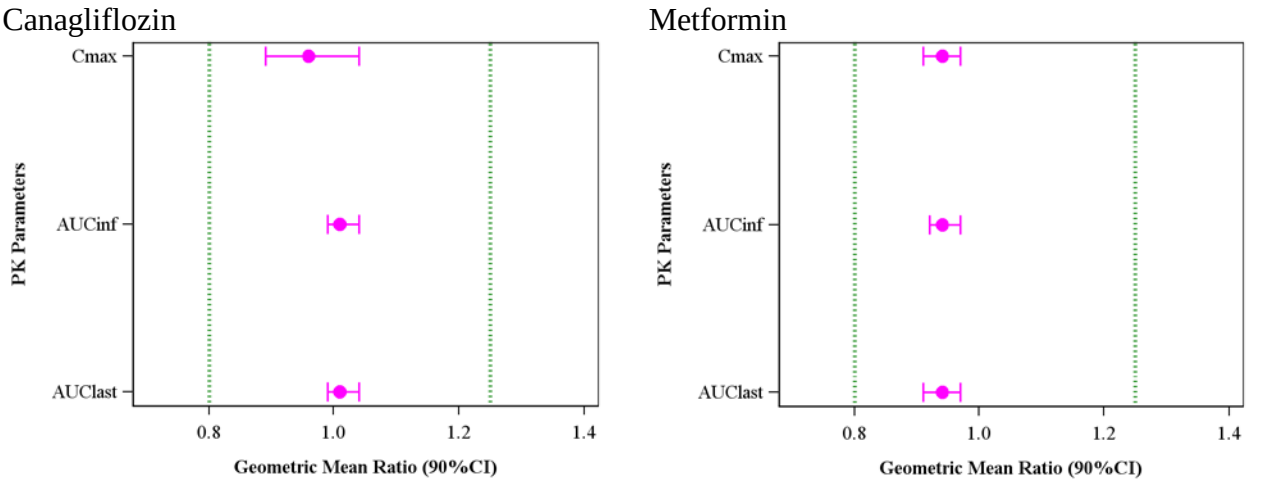
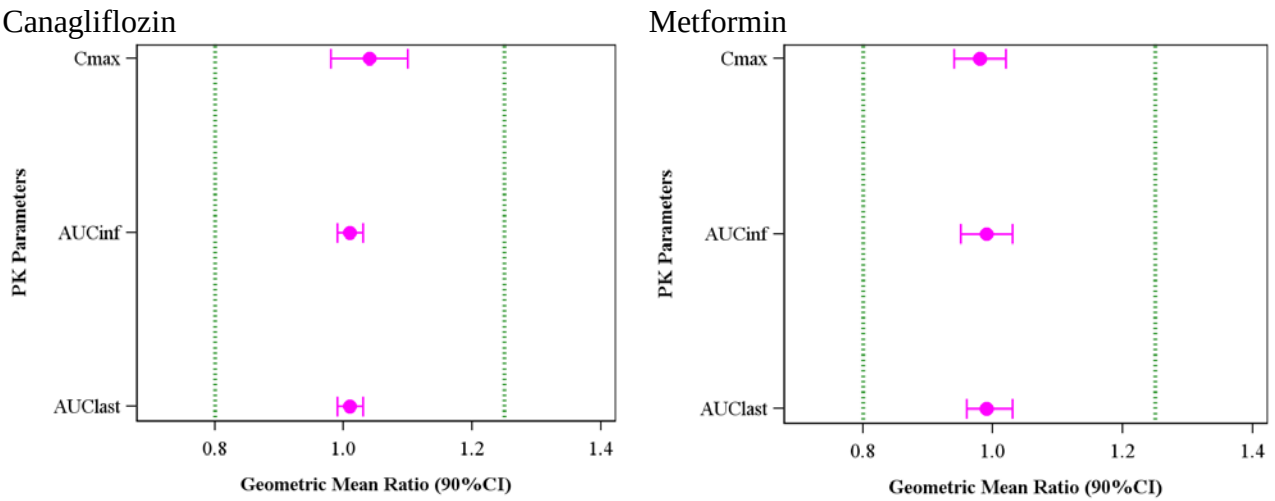


Figure 7: A) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 100 mg and Metformin 2*1000 mg and FDC Product (2 x 50/1000 mg FDC). B) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Canagliflozin and Metformin Following Co-administration of Canagliflozin 300 mg and Metformin 2*500 mg and FDC Product (2 x 150/500 mg FDC).

A) **BE Study DIA 1051**



B) **BE Study DIA 1050**



Reviewers Comment: The pivotal BE studies compared the proposed to be marketed FDC tablets of different strengths to the individual once daily tablets of (100 mg and 300 mg) canagliflozin given with metformin. To bridge the 100 mg and 300 mg once daily tablets to 50 mg and 150 mg twice daily tablets of canagliflozin sponsor conducted a Phase 1 PK/PD study (DIA 1032). Phase 1 PK/PD study results showed similar exposures between once daily and twice daily formulation of canagliflozin. In addition this Phase 1 study utilized 50 mg and 150 mg twice daily formulation of canagliflozin that is similar to the one used in the pivotal Phase 2 study. Thus similar exposure between BID dosing

formulations (50 mg and 150 mg) and QD dosing formulation of canagliflozin provides an indirect link of formulation used in Phase 2 study to the proposed to be marketed formulation.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma?

Concentrations of canagliflozin and metformin in plasma were measured using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS).

2.6.2 What bioanalytical methods are used to assess concentrations?

The assay for the quantification of total unchanged metformin (JNJ-1158196) in human plasma in clinical studies with the canagliflozin/metformin FDC tablets was based on LC-MS/MS and was validated for use at (b) (4) Report# BA1345), where all PK samples from studies with canagliflozin/metformin FDC tablets were analyzed.

To support the clinical studies with canagliflozin/metformin FDC tablets, an LC-MS/MS method was developed at (b) (4) for the quantification of metformin in human K2EDTA plasma samples (PBRL-RD-1092). This bioanalytical method was used to analyze metformin PK samples from studies that used the canagliflozin/metformin FDC tablets.

Canagliflozin plasma samples were extracted using (b) (4). Validated concentration ranges for canagliflozin was 5.0 mg/mL to 5000 ng/mL in plasma. Metformin plasma samples were extracted using (b) (4) technique. Validated concentration ranges for metformin are 5.0 to 2500 ng/mL. A brief summary of the different bioanalytical methods used is shown in the Tables 10 and 11 below. Accepted validation indicates that method met the FDA guidance “Bioanalytical Method Validation” recommendations, and was therefore acceptable.

Table 10: Assay Validation Results for Metformin

Method	LC-MS/MS Mod5.3.1.4\PBRL-RD-1092	
Study Location	Full Validation for Metformin	Partial Validation in the Presence of Canagliflozin
Laboratory	(b) (4)	(b) (4)
Analyte	metformin (JNJ-1158196)	metformin (JNJ-1158196)
Matrix	plasma	plasma
Validated conc range	5.00 to 2,500 ng/mL	5.00 to 2,500 ng/mL
Dilution integrity	10× and analysis up to 20,000 ng/mL	10× and analysis up to 20,000 ng/mL
Inter-run accuracy (% Bias)	−4.3 to −1.1	−1.7 to 4.6 [a]
Inter-run precision (%CV)	0.0 to 2.6	1.8 to 2.5 [a]
Intra-run accuracy (% Bias)	NA	NA
Intra-run precision (% CV)	2.3 to 3.9	NA
Intra-run accuracy ([x] × dilution) (% Bias)	−2.5 (10× dilution)	NA
Intra-run precision ([x] × dilution) (%CV)	4.5 (10× dilution)	NA
Selectivity	no relevant interferences	no relevant interferences
Stability in blood	0°C: 2 h; room temp: 2 h	0°C: 2 h; room temp: 2 h
Stability in plasma	f-t cycles: 4; ultrafreezer: 190 d; freezer: 190 d; room temp: 26 h	f-t cycles: 5; ultrafreezer: 190 d; freezer: 190 d; room temp: 70 h
Processed sample stability	191 h (at 10°C)	120 h (at 10°C)
Stability in stock solution	refrigerator: 10 d; room temp: 26 h	NA

conc = concentration, CV = coefficient of variation, f-t = freeze-thaw, NA = not available, temp = temperature.
Set temperatures for ultrafreezer: −70°C, freezer: −20°C.
[a] Calculated over the first 5 analytical runs with duplicate quality control samples.

Source: Sponsors report of Summary of Biopharmaceutic Studies and Associated Analytical Methods pg 84

Table 11: Assay Validation Results for Canagliflozin

Method Study Location	LC-MS/MS Mod5.3.1.4\BA1345 (Partial Validation in K_2EDTA) (b) (4)
Laboratory	
Analyte	canagliflozin (JNJ-28431754)
Matrix	plasma
Validated conc range	5.00 to 5,000 ng/mL
Dilution integrity	5×
Inter-run accuracy (% Bias)	96.9 to 101.9 [a]
Inter-run precision (%CV)	0.0 to 4.3
Intra-run accuracy (% Bias)	NA
Intra-run precision (%CV)	0.9 to 3.6
Intra-run accuracy ([x] × dilution) (% Bias)	95.0 [a] (5× dilution)
Intra-run precision ([x] × dilution) (%CV)	1.2 (5× dilution)
Selectivity	no relevant interferences [b]
Stability in blood	melting ice: 2 h [b]; room temp: 2h [b]
Stability in plasma	f-t cycles: 5 [b]; ultrafreezer: 142 d [b]; freezer: 142/135 d [c]; room temp: 73 h [b]
Processed sample stability	143 h [b]
Stability in stock solution	refrigerator: 20 d; room temp: 27 h

conc = concentration, CV = coefficient of variation, f-t = freeze-thaw, NA = not available, SAM = Standard A
Set temperatures for ultrafreezer: −70°C, freezer: −20°C, refrigerator: 4°C.
[a] % accuracy. [b] With and without the presence of metformin. [c] With/without the presence of metformin.

Source: Sponsors report of Summary of Biopharmaceutic Studies and Associated Analytical Methods pg 83

3 DETAILED LABELING RECOMMENDATION

None

Reviewer's Comment: No labeling reviews were done at this time.

4 APPENDIX

4.1 SPONSOR'S MODELING PLAN:

(b) (4)

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4.2 OCP FILING MEMO

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	204353	Brand Name	TBD
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Canagliflozin/Metformin Fixed Dose Combination Tablets
Medical Division	DMEP	Drug Class	
OCP Reviewer	Ritesh Jain, Ph.D.	Indication(s)	Treatment of Type-2 Diabetes (T2DM)
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	Immediate Release Fixed Dose Tablet; 50/500, 50/1000, 150/500, 150/1000 mg/mg of canagliflozin and metformin respectively
Pharmacometrics Reviewer		Dosing Regimen	Dosing is individualized based on safety and efficacy; recommended for twice daily dosing with meals
Date of Submission	12/12/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	11/07/2013	Sponsor	Janssen Research and Development.
Medical Division Due Date	11/07/2013	Priority Classification	S
PDUFA Due Date	12/12/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	X			
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:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

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Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		**Study: DIA1032**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**4**		
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**6**		

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 data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Comment is sent to the sponsor to clarify how they bridge the formulation used in the clinical study to the to-be marketed FDC formulation. Sponsor responded on 01/29/2013 providing their rationale, the adequacy of the bridge will be a review issue.
2	Has the applicant provided metabolism and				

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	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	
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	Sponsor is requesting a waiver for conducting pediatric studies in children

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	effectiveness, if the drug is indeed effective?				0 to <10 years of age and deferral in older children and adolescents ≥10 to <18 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.

You have indicated that the tablet formulations used in the study DIA2003 are linked to the to-be marketed canagliflozin/metformin immediate release fixed dose combination (CANA/MET IR FDC) tablets through the PK bioequivalence between twice-daily and once-daily administered tablets assessed in the study DIA1032. Adequacy of this bridging will be a review issue.

Ritesh Jain	02/04/2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	02/04/2013
Team Leader/Supervisor	Date

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

Filing Memo (Internal Memo)

1. **Background:**
   Canagliflozin is an orally active, reversible inhibitor of SGLT2 that is being developed as an oral antihyperglycemic agent by Janssen Research & Development. In this NDA sponsor is developing Immediate release fixed dose combination (FDC) of Canagliflozin/Metformin oral tablets. The sponsor is proposing 4 different FDC strengths of Canagliflozin/Metformin 50mg/500mg, 50mg/1000mg, 150mg/500mg, 150mg/1000mg.

The Clinical Development program for this NDA consists of following studies:

- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively])

- a food effect study (DIA1037) evaluating the to-be-marketed CANA/MET IR FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET IR FDC tablet

- A Phase 1 study (DIA1032), that demonstrated that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration

- A relative bioavailability study (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence studies

- A Phase 2 study (DIA2003) that examined twice-daily dosing of canagliflozin (50 mg and 150 mg bid)

2. Clinical Development Program:

6 Phase 3 studies conducted under Canagliflozin program (NDA 204042) evaluated once-daily administration of canagliflozin 100 mg or 300 mg in subjects with T2DM on a background of metformin (alone or in combination with other anti hyperglycemic agents). Some of the highlights of the Phase 3 clinical trials in canagliflozin program are listed below:

- Two Phase 3 studies (DIA3006 and DIA3009) in subjects on background of metformin alone with canagliflozin 100 mg and 300 mg QD dosing.
- Three Phase studies (DIA3002, DIA3012, and DIA3015) where subjects on metformin in combination with another anti-hyperglycemic agents were given canagliflozin 100 mg and 300 mg QD dosing.
- In all the Phase 3 studies canagliflozin and metformin were given as individual tablets of metformin and canagliflozin and not as FDC.
- Also, in all the Phase 3 studies canagliflozin was studied as once daily dosing of 100 mg or 300 mg tablets.

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

In this current NDA, to support the BID dosing regimen of Canagliflozin/metformin FDC formulation, the sponsor conducted a Phase 2 study (DIA 2003) where 50 mg canagliflozin BID and 150 mg canagliflozin BID dosing on background therapy of metformin was tested.

Study DIA2003, was a 3-arm, 18-week study that demonstrated the safety and efficacy of the twice-daily dosing of 50 mg and 150 mg canagliflozin, relative to placebo, in subjects on a background of metformin. The individual tablets used in this study were a 50 mg tablet for the 50 mg dose and one 100 mg tablet + one 50 mg tablet (over-encapsulated for administration of a single capsule) for the 150 mg dose.

Clinical Pharmacology Program:
Clinical Pharmacology program in this NDA is supported by following studies:

- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively])

- a food effect study (DIA1037) evaluating the to-be-marketed CANA/MET IR FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET IR FDC tablet

- A Phase 1 study (DIA1032), that demonstrated that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration

- A relative bioavailability study (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence studies

Bridge between the formulations used in Phase 2 study and to-be marketed formulation:

During the internal filing meeting, Phase 2 study (DIA2003) was considered to be pivotal to support the BID dosing in this NDA. In this Phase 2 study, the BID dosing of canagliflozin and metformin were given as individual tablets and not as FDC.

In Study DIA1032, Sponsor compared the steady-state PK and PD of canagliflozin administered at the same total daily dose either once-daily (300 mg or 100 mg) or twice-daily (150 mg [one 100 mg tablet + one 50 mg tablet] bid or 50 mg bid) in healthy subjects. This study demonstrated that systemic exposure (AUC_{24h}) of canagliflozin was bioequivalent between qd and bid dosing regimens at the same total daily dose of 300 mg or 100 mg. Also, the tablet formulations used in the DIA1032 and DIA2003 studies were similar.

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In addition sponsor conducted 4 Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively]).

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

4.3 Appendix 3: SPONSOR REVISE MODELING PLAN (SUBMITTED :11/07/2013)

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/s/

RITESH JAIN
11/15/2013

LOKESH JAIN
11/15/2013

ANSHU MARATHE
11/15/2013

NITIN MEHROTRA
11/15/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-353 (000)	**Biopharmaceutics Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DMEP		
Applicant:	Janssen Pharmaceuticals Inc.	**Acting Biopharmaceutics Team Leader:** John Z. Duan, Ph.D.	
Trade Name:	--		
Generic Name:	Canagliflozin-Metformin HCl Fixed Dose Combination Tablets	**Date Assigned:**	Dec 14, 2012.
Indication:	Treatment of Type 2 diabetes	**Date of Review:**	July 2, 2013
Formulation/strength	Immediate Release Tablet 50/500 mg, 150/500 mg, 50/1000 mg, 150/1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Dec 12, 2012	Dec 12, 2012		Dec 12, 2013
Type of Submission:	505(b)(2) NDA		
Type of Consult:	Dissolution methods and acceptance criteria		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission:

Canagliflozin/Metformin HCl IR is a fixed-dose combination (FDC) tablet dosage form intended to be used as an adjunct to diet and exercise in the management of type 2 diabetes mellitus (T2DM) patients who are not adequately controlled on a regimen containing metformin or canagliflozin. Metformin is a biguanide whereas canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor; the two different mechanisms of action are expected to produce beneficial additive effect in the treatment of T2DM. The four strengths of the FDC tablet intended for marketing are 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg (canagliflozin/metformin HCl).

Canagliflozin is practically insoluble in aqueous media as well as in buffered systems between pH 2-12.9. In contrast, metformin HCl is soluble in aqueous media over a pH range of 1.2 – 8.0. Separate dissolution methods were therefore developed for the two components in the FDC tablet. In addition, (b) (4) (b) (4)

Review:

The current NDA submission is cross-referencing NDA 204-042 for canagliflozin (single-entity) submitted in May 2012. The dissolution method for the canagliflozin component in this NDA, however, was modified from the single-entity product (NDA 204-042). This review centers on the acceptability of the dissolution methodology and the acceptance criteria for both active components in the FDC, canagliflozin and metformin HCl.

Reviewer's Comments:

1) Dissolution Method Development

The Applicant's justifications for choice of the dissolution methodology for each component are acceptable. Note that two different concentrations of Polysorbate 20 (0.025 % and 0.075 %) were selected for the two respective canagliflozin strengths in the FDC tablets and the surfactant concentrations less than those required for sink conditions were chosen. Although discriminating ability of the methods was demonstrated (b) (4), the dissolution methods were not sensitive to (b) (4) and extreme storage conditions ((b) (4)

2) Dissolution Methods

The following dissolution methods and dissolution acceptance criteria proposed by the Applicant have been reviewed and found acceptable:

API	USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
Canagliflozin, 50 mg	2	75 rpm	900 mL	37 ± 0.5 °C	0.025 % Polysorbate 20	Q= (b) (4)% at 30 min
Canagliflozin, 150 mg	2	75 rpm	900 mL	37 ± 0.5 °C	0.075 % Polysorbate 20	Q = (b) (4)% at 30 min
Metformin, 500 & 1000 mg	2	75 rpm	1000 mL	37 ± 0.5 °C	Phosphate buffer, pH 6.8	Q = (b) (4)% at 20 min

3) Labeling Consideration for FDC Tablet and single entity canagliflozin

During canagliflozin therapy, there may be a potential for urinary glucose levels in diabetic individuals to be abnormal while blood glucose levels remain within acceptable limits due to the drug's mechanism of action. Urinary glucose levels should therefore be evaluated only when blood glucose levels are also measured. In the unlikely event that urinary glucose levels are evaluated in isolation, that is, in the absence of blood glucose results, erroneous deductions about lack of control of systemic glucose may be made. Consideration for including this clinical scenario in the labeling may therefore be crucial. This issue was communicated to the Clinical and Clinical Pharmacology teams for assessment and possible inclusion in the labeling.

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 204-353 for Canagliflozin-Metformin HCl Film-Coated IR Tablets, 50/500, 150/500, 50/1000, 150/1000 mg. We found NDA 204-353 acceptable and an approval is recommended from the Biopharmaceutics perspective.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Z. Duan, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

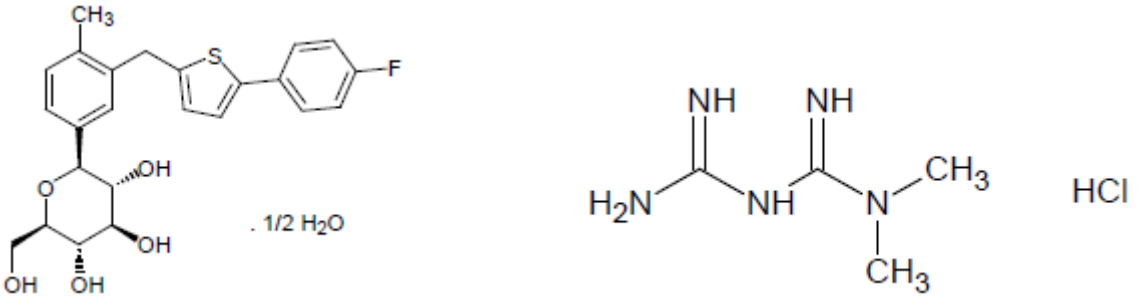
TABLE OF CONTENTS

1 INTRODUCTION

Canagliflozin/Metformin HCl Tablet is a fixed-dose combination (FDC) of both drugs that is intended to be used as an adjunct to diet and exercise in the management of T2DM. Canagliflozin, an inhibitor of sodium-glucose co-transporter-2 (SGLT2), is being developed as an antihyperglycemic agent for the treatment of subjects with T2DM. Pharmacologic inhibition of SGLT2 blocks renal tubular glucose reabsorption, thereby increasing urinary glucose excretion which, in turn, lowers plasma glucose in individuals with elevated blood glucose levels. Metformin, on the other hand, is a well-established antihyperglycemic agent that has been in use world-wide for several decades; it is a biguanide that decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. The Applicant is developing this FDC for patients whose blood glucose levels are not adequately controlled by either canagliflozin or metformin.

1.1 *Drug Substances*

The chemical structures of Cangliflozin and Metformin are displayed in Figure 1.



Canagliflozin Hemihydrate Metformin Hydrochloride

Figure 1: Chemical Structures of Canagliflozin and Metformin hydrochloride

Canagliflozin exists as a white to off-white crystalline powder that is practically insoluble in aqueous media throughout the entire physiologic pH range but soluble in most organic solvents. Solubility of canagliflozin improved in simulated intestinal fluids (FaSSIF, FeSSIF) compared to SIF and SGF; even in these media, the highest solubility observed in FeSSIF could only be defined as "slightly soluble'. Absolute bioavailability of canagliflozin was approximately 65%, indicative of poor to moderate permeability of the gastrointestinal tract. Caco-2 cell experiments showed that the drug molecule has intermediate permeability. The Applicant therefore stated that canagliflozin is a BCS Class 4 drug. Canagliflozin has five chiral centers.

Metformin is freely soluble in aqueous media throughout the physiologic pH range. Similar to canagliflozin, metformin is known to exhibit low intestinal permeability. It is therefore generally known to be a BCS Class 3 drug. The drug molecule does not have any asymmetric carbon atom.

1.2 *Drug Product*

The final dosage form is a film coated immediate-release tablet. (b) (4) The quantitative compositions of the CANA/MET 50/500 mg and 150/1000 mg tablet strengths are presented in Tables 1 and 2, respectively. The composition of the coating for each strength of the FDC Tablets is presented in Table 3.

Table 1. Quantitative composition of CANA/MET FDC 50/500 mg Tablets (G012)

Component	Quality Reference[a]	Role	% w/w	mg/tablet
Core tablet				
(b) (4)				
Canagliflozin	Company Specification	Active	(b) (4)	51.00 [b]
(b) (4)				
Metformin hydrochloride	Company Specification	Active	(b) (4)	500.00
(b) (4)				
Film-coating				
(b) (4)		Film-coat	(b) (4)	(b) (4)
		(b) (4)		
	Total film coated tablet weight			802.13

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous)

(b) (4)

Table 2. Quantitative composition of CANA/MET FDC 150/1000 mg Tablets (G018-01)

Component	Quality Reference[a]	Role	% w/w	mg/tablet
Core tablet				
(b) (4) Canagliflozin	Company Specification	Active	(b) (4)	153.00[b]
(b) (4) Metformin hydrochloride	Company Specification	Active	(b) (4)	1000.00
(b) (4)				
Film-coating				
(b) (4)		Film-coat (b) (4)	(b) (4)	
	Total film coated tablet weight			1687.05

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.

[b] Amount of canagliflozin equivalent to the labeled amount of canagliflozin (anhydrous)

(b) (4)

Table 3. Coating quantitative composition of CANA/MET IR FDC Tablets

Ingredient	Quality Reference	Amount per Unit (mg/Tablet)
		(b) (4)
Polyvinyl alcohol-partially hydrolyzed	Ph. Eur./USP	
Titanium dioxide	Ph. Eur./USP	
Macrogol (b) (4) PEG (b) (4)	Ph. Eur./NF	
Talc	Ph. Eur./USP	
Yellow iron oxide (b) (4)	EU Directive 2008/128/EC/NF	
Red iron oxide (b) (4)	EU Directive 2008/128/EC /NF	
Black iron oxide (b) (4)	EU Directive 2008/128/EC	

-- = Not present

2 PROPOSED DISSOLUTION METHODS

The Applicant proposes different dissolution methods for the two API components due to significant differences in solubility in aqueous media. In the case of canagliflozin, surfactant (polysorbate 20) concentrations of 0.025% and 0.075% in water are used for the 50 mg and 150 mg strengths, respectively. The proposed methods are summarized in Tables 4 and 5 below:

Table 4: Proposed dissolution method parameters for Canagliflozin in FDC Tablets.

API	USP Apparatus	Medium	Medium Volume	Temperature	Spindle Rotation Medium
Canagliflozin, 50 mg	II	0.025 % Polysorbate 20 (b) (4) (b) (4)	900 mL	37.0 ± 0.5°C	75 rpm
Canagliflozin, 150 mg	II	0.075 % Polysorbate 20 (b) (4) (b) (4)	900 mL	37.0 ± 0.5°C	75 rpm

Table 5: Proposed dissolution method parameters for Metformin in FDC Tablets.

API	USP Apparatus	Medium	Medium Volume	Temperature	Spindle Rotation
Metformin	II	Phosphate buffer, pH 6.8	1000 mL	37.0 ± 0.5°C	75 rpm

3 DEVELOPMENT OF DISSOLUTION METHODS

Initially, the Applicant made an attempt to use the already developed dissolution method for the single-entity product (NDA 204042) in the release testing of canagliflozin component of the FDC. A rapid dissolution rate ((b) (4)% dissolved in (b) (4) min) was observed and deemed to be non-discriminating for the FDC tablet. The USP monograph for metformin HCl tablets was followed in developing the dissolution method for metformin. Particular emphasis has therefore been placed on development of the dissolution method for canagliflozin.

3.1 *Canagliflozin*

(b) (4)

Reviewer's Comments on Dissolution Methods

All three dissolution methods are acceptable for the purposes of quality control release testing of the proposed CANA/MET IR FDC Tablets.

4 DISSOLUTION ACCEPTANCE CRITERIA

In a response to an IR letter, the Applicant stated that dissolution data from 12 registration batches (3 batches per strength), including 4 batches used in clinical studies, and 4 development batches were evaluated in setting the acceptance criterion for each component of the FDC tablet. The proposed dissolution acceptance criteria are:

Canagliflozin: Q = (b) (4) % at 30 min
Metformin: Q = (b) (4) % at 20 min

Excluding the development batches, the Reviewer-plotted individual vessel data for the 50 mg canagliflozin and 1000 mg metformin strengths are displayed in Figures 10 and 11, respectively. As expected, overall variability is higher (b) (4)

2 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

5 APPLICANT RESPONSES TO INFORMATION REQUESTS

Two sets of Information Requests (IR) were sent to the Applicant during the review cycle and are presented in the Appendix. The first set of comments centered on the dissolution development report while the second set sought clarifications on certain data transcriptions and evidence of robustness of dissolution and associated analytical methods. The Applicant's responses to the first set of comments have been incorporated into the review while the narratives of the responses to the second set are included in Appendix 7.2. Both sets of responses were acceptable from a biopharmaceutics perspective.

6 BIOPHARMACEUTICS REVIEW CONCLUSION

The ONDQA-Biopharmaceutics team has reviewed NDA 204-353 for Canagliflozin-Metformin HCl Film-Coated IR Tablets, 50/500, 150/500, 50/1000, 150/1000 mg. We found NDA 204-353 acceptable and an approval is recommended from the Biopharmaceutics perspective.

7 APPENDICES

7.1 *Filing Review Comments to Applicant; sent Feb 16, 2013*

1. Please provide a Dissolution Method Development Report including rationale for each of the three dissolution method conditions you have proposed in your NDA. Due to differences in dissolution media for the canagliflozin component of the FDC tablet compared to the proposed single-entity product in NDA #204-042, justification for development of the methods cannot be referenced to development parameters of the latter.

   Your dissolution development report should include the following:

   a. Solubility data already generated for the drug substances;

   b. Detailed description of the dissolution tests being proposed for the evaluation of your FDC product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution methods as the optimal tests for your product. Include data supporting the selection of the type and amount of surfactant. The testing conditions used for

each test should be clearly specified. We recommend use of at least twelve samples per testing variable;

c. Provide the complete dissolution profile data (*individual value, mean, n, SD, profiles*) for each entity.

d. Data to support the discriminating ability of the selected methods. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution methods should compare the dissolution profiles of the proposed product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition to (b) (4) reported in the NDA, present results of investigation of other critical manufacturing variables on the discriminating power of the dissolution methods.

2. Provide the rationale for selecting a rotation speed of 75 rpm for the dissolution testing of the canagliflozin component in the dissolution method development report. Provide dissolution data at 50 rpm.

3. Identify the FDC tablet lots/batches that were selected for setting the proposed dissolution acceptance criteria, including the lot numbers, the clinical studies in which they were used, and if they were registration batches on stability. Provide the complete dissolution data for the identified lots (*individual, mean, n, SD, profile*).

4. Provide the complete dissolution profile data (*i.e., 15, 20, 30, 45, and 60 minutes, n=12*) for the bio-batches (clinical & PK) and primary (registration) stability batches (*individual and mean value*s). If these are already provided in the CTD, please provide module and section numbers.

7.2 *Information Request to Applicant, sent June 6, 2013.*

1. In Module 2, section 2.7.1, Appendix 3.2 (page 81), you have tabulated the mean % dissolved (range) for both API components of the proposed FDC Tablets. Dissolution data for Lot # 1HG5153-X for both canagliflozin and metformin do not match the data for the same lot presented in module 3, section 3.2.P.5.6, Tables 17 and 18 (pages 29, 30). Check the data of the other lots and clarify which data sets are correct and which ones are wrong.

   Applicant's Response: The batch results presented in Module 2, section 2.7.1, Appendix 3.2 are correct. For the data presented in Module 3, section 3.2.P.5.6, Tables 17 and 18 (pages 29 and 30), batch numbers for batches 1HG5152-X and 1HG5153-X were erroneously switched. In addition, a typographical error was observed for batch 1HG5146-X in Table 17 (minimum value at the 5 minute time point for canagliflozin should read (b) (4) instead of (b) (4)). All data reported for the other tablet batches in Tables 17 and 18 are correct. A corrected section 3.2.P.5.6 is provided with this response.

2. In your response to FDA Communication dated Feb 16, 2013, you submitted individual vessel dissolution data for the FDC tablet batches that were used to establish the acceptance criteria for both API components (Tables 58 – 81). The mean data and particularly the ranges at each time point do not seem to match those in the original submission for most of the batches. Explain the differences in numerical values between these individual data sets and the Tables referred to in Comment 1 above. Clarify if some of the data sets are at T_0 or some other stability time point.

   Applicant's Response: The data provided in our response to FDA Communication dated Feb 16, 2013 and the data provided in the initial submission are different because they were generated on different representative samples of the same tablet lots.

   Data in Tables 58 to 81 in our response to FDA Communication dated Feb 16 2013 were generated at the proposed commercial manufacturing site (Janssen Ortho, LLC, Gurabo, Puerto Rico) at the time of release of the Cana/MET IR FDC tablets. Data were generated on 12 tablets of each strength of the 12 primary registration batches manufactured during July-Aug 2011.

   The data presented in Module 3 section 3.2.P.5.6 Tables 17 and 18 of the original NDA represent dissolution profile results generated at the start of the registration stability studies (Time Zero stability interval). These data were generated during Oct-Nov 2011 at the stability testing site (b) (4), on a different set of samples (6 tablets of each strength) of the same 12 registration batches tested in Gurabo. As the data were generated on a different set of samples of the same tablet lots, they are comparable but not identical.

3. In Dissolution Validation Reports DISS-37, DISS-41 and DISS-38 for 50 mg canagliflozin, 150 mg canagliflozin and metformin, respectively, section 2.5 summarizes the Robustness of dissolution and chromatographic assay parameters. You conclude that the dissolution and assay methods are robust based on the data generated by deliberately making small changes to the parameters. The data are neither presented nor referenced in a different section or subsection of the NDA. Provide the experimental data that support robustness of the methods.

Applicant's Response: The robustness conclusions in validation reports DISS-37, DISS-41 and DISS-38 are based on the experimental robustness data generated by deliberately making small changes to the assay and dissolution method parameters. These robustness experiments are described in robustness reports AD-IN-MRR-(b) (4)-28431754-ZAE-TAB-DISS-00179-V1, AD-IN-MRR(b) (4)-28431754-ZAE-TAB-DISS-00180-V1, and AD-IN-MRR-(b) (4)-1158196-AAC-TAB-DISS-00176-V1, respectively, included with this response.

In each validation report DISS-37, DISS-41 and DISS-38, the reference to the Robustness report is mentioned in the "Supporting documentation" section.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OKPONANABOFA ERADIRI
07/26/2013

JOHN Z DUAN
07/26/2013

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	**204353**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP II**	**Generic Name**	**Canagliflozin/Metformin Fixed Dose Combination Tablets**
Medical Division	**DMEP**	**Drug Class**	
OCP Reviewer	**Ritesh Jain, Ph.D.**	**Indication(s)**	**Treatment of Type-2 Diabetes (T2DM)**
OCP Team Leader	**Lokesh Jain, Ph.D.**	**Dosage Form**	**Immediate Release Fixed Dose Tablet; 50/500, 50/1000, 150/500, 150/1000 mg/mg of canagliflozin and metformin respectively**
Pharmacometrics Reviewer		**Dosing Regimen**	**Dosing is individualized based on safety and efficacy; recommended for twice daily dosing with meals**
Date of Submission	**12/12/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**11/07/2013**	**Sponsor**	**Janssen Research and Development.**
Medical Division Due Date	**11/07/2013**	**Priority Classification**	**S**
PDUFA Due Date	**12/12/2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**X**			
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:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

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

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		**Study: DIA1032**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**4**		
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**6**		

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 data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Comment is sent to the sponsor to clarify how they bridge the formulation used in the clinical study to the to-be marketed FDC formulation. Sponsor responded on 01/29/2013 providing their rationale, the adequacy of the bridge will be a review issue.
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	
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	Sponsor is requesting a waiver for conducting pediatric studies in children

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

	effectiveness, if the drug is indeed effective?				0 to <10 years of age and deferral in older children and adolescents ≥10 to <18 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.

You have indicated that the tablet formulations used in the study DIA2003 are linked to the to-be marketed canagliflozin/metformin immediate release fixed dose combination (CANA/MET IR FDC) tablets through the PK bioequivalence between twice-daily and once-daily administered tablets assessed in the study DIA1032. Adequacy of this bridging will be a review issue.

Ritesh Jain	02/04/2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	02/04/2013
Team Leader/Supervisor	Date

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

Filing Memo (Internal Memo)

1. **Background:**
   Canagliflozin is an orally active, reversible inhibitor of SGLT2 that is being developed as an oral antihyperglycemic agent by Janssen Research & Development. In this NDA sponsor is developing Immediate release fixed dose combination (FDC) of Canagliflozin/Metformin oral tablets. The sponsor is proposing 4 different FDC strengths of Canagliflozin/Metformin 50mg/500mg, 50mg/1000mg, 150mg/500mg, 150mg/1000mg.

The Clinical Development program for this NDA consists of following studies:

- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively])

- a food effect study (DIA1037) evaluating the to-be-marketed CANA/MET IR FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET IR FDC tablet

- A Phase 1 study (DIA1032), that demonstrated that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration

- A relative bioavailability study (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence studies

- A Phase 2 study (DIA2003) that examined twice-daily dosing of canagliflozin (50 mg and 150 mg bid)

2. Clinical Development Program:

6 Phase 3 studies conducted under Canagliflozin program (NDA 204042) evaluated once-daily administration of canagliflozin 100 mg or 300 mg in subjects with T2DM on a background of metformin (alone or in combination with other anti hyperglycemic agents). Some of the highlights of the Phase 3 clinical trials in canagliflozin program are listed below:

- Two Phase 3 studies (DIA3006 and DIA3009) in subjects on background of metformin alone with canagliflozin 100 mg and 300 mg QD dosing.
- Three Phase studies (DIA3002, DIA3012, and DIA3015) where subjects on metformin in combination with another anti-hyperglycemic agents were given canagliflozin 100 mg and 300 mg QD dosing.
- In all the Phase 3 studies canagliflozin and metformin were given as individual tablets of metformin and canagliflozin and not as FDC.
- Also, in all the Phase 3 studies canagliflozin was studied as once daily dosing of 100 mg or 300 mg tablets.

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

In this current NDA, to support the BID dosing regimen of Canagliflozin/metformin FDC formulation, the sponsor conducted a Phase 2 study (DIA 2003) where 50 mg canagliflozin BID and 150 mg canagliflozin BID dosing on background therapy of metformin was tested.

Study DIA2003, was a 3-arm, 18-week study that demonstrated the safety and efficacy of the twice-daily dosing of 50 mg and 150 mg canagliflozin, relative to placebo, in subjects on a background of metformin. The individual tablets used in this study were a 50 mg tablet for the 50 mg dose and one 100 mg tablet + one 50 mg tablet (over-encapsulated for administration of a single capsule) for the 150 mg dose.

Clinical Pharmacology Program:
Clinical Pharmacology program in this NDA is supported by following studies:

- Four Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively])

- a food effect study (DIA1037) evaluating the to-be-marketed CANA/MET IR FDC that showed that food did not affect canagliflozin bioavailability following single-dose administration of the 150/1,000 mg CANA/MET IR FDC tablet

- A Phase 1 study (DIA1032), that demonstrated that canagliflozin plasma pharmacokinetic and pharmacodynamic responses were similar at the same total daily dose (100 mg or 300 mg) regardless of once- or twice-daily administration

- A relative bioavailability study (DIA1036) that served as a pilot for the 4 Phase 1 bioequivalence studies

Bridge between the formulations used in Phase 2 study and to-be marketed formulation:

During the internal filing meeting, Phase 2 study (DIA2003) was considered to be pivotal to support the BID dosing in this NDA. In this Phase 2 study, the BID dosing of canagliflozin and metformin were given as individual tablets and not as FDC.

In Study DIA1032, Sponsor compared the steady-state PK and PD of canagliflozin administered at the same total daily dose either once-daily (300 mg or 100 mg) or twice-daily (150 mg [one 100 mg tablet + one 50 mg tablet] bid or 50 mg bid) in healthy subjects. This study demonstrated that systemic exposure (AUC_{24h}) of canagliflozin was bioequivalent between qd and bid dosing regimens at the same total daily dose of 300 mg or 100 mg. Also, the tablet formulations used in the DIA1032 and DIA2003 studies were similar.

In addition sponsor conducted 4 Phase 1 studies that demonstrated the bioequivalence of the to-be-marketed CANA/MET IR FDC to the individual components (for the tablet strengths of 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg [studies DIA1046, DIA1050, DIA1051, and DIA1038, respectively]).

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/s/

RITESH JAIN
02/07/2013

LOKESH JAIN
02/07/2013

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

NDA Number	204-353
Submission Date	12/12/2012
Product name, generic of active(s)	Canagliflozin/Metformin FDC Tablets
Dosage form and strength	IR Tablets; 50/500, 150/500, 50/1000, 150/1000 mg
Indication	Treatment of Type 2 diabetes
Applicant	Janssen Pharmaceuticals Inc.
Clinical Division	DMEP
Type of Submission	505(b)(2) New Drug Application
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

SUBMISSION

Canagliflozin/Metformin HCl Tablet is a fixed-dose combination (FDC) of both drugs that is intended to be used as an adjunct to diet and exercise in the management of Type 2 Diabetes Mellitus (T2DM). The Applicant is developing this FDC for patients whose blood glucose levels are not adequately controlled by either canagliflozin or metformin as well as for the convenience of those patients already taking both drug products.

The Applicant submitted NDA 204-042 for a canagliflozin single-entity product in May 2012 and is cross-referencing that filing. (b) (4) the dissolution media for the canagliflozin component in this NDA, was also modified from the single-entity product (NDA 204-042); assessment of the dissolution method and acceptance criteria will therefore be done independent of the method reported in NDA 204-042. In addition, the proposed dosing regimen of the FDC is twice-daily although the single-entity canagliflozin (NDA 204-042) is being evaluated for once-daily dosing.

PROPOSED DISSOLUTION METHODS

As previously stated, the Applicant altered the dissolution media for canagliflozin in the FDC tablet from that of the single-entity product. Due to lack of solubility of canagliflozin in aqueous media, the Applicant used two different concentrations of surfactant for dissolution testing of the two strengths of the drug in the FDC tablet. In addition, the Applicant developed a different method for metformin. Three dissolution methods are therefore proposed by the Applicant for dissolution testing of the FDC tablet formulation. The Table below (extracted from Module 2.7.1, section 1.2.3.2.1) displays details of the methods.

Table 6: Proposed Product Dissolution Methods and Specifications for CANA/MET IR FDC Tablets

(b) (4)

PROPOSED DISSOLUTION ACCEPTANCE CRITERIA

Canagliflozin: Q = (b) (4) % at 30 min
Metformin: Q = (b) (4) % at 20 min

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?	X		
2.	Does the application contain the dissolution method development report?		X	Recommendation will be made for this report to be requested in 74-day letter.
3.	Is there a validation package for the analytical method and dissolution methodology?	X		
4.	Does the application include a biowaiver request?		X	
5.	Is there information provided to support the biowaiver request?		N/A	
6.	Does the application include an IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?	X		Supportive study provided for canagliflozin and literature information cited for metformin.
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any in *vivo* BA or BE information in the submission?	X		These studies will be reviewed by OCP.
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	The NDA is fileable from a Biopharmaceutics perspective.
12.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		Please see comments below.

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

FILING COMMENTS TO BE SENT TO THE APPLICANT IN 74-DAY LETTER

1. Please provide a Dissolution Method Development Report including rationale for each of the three dissolution method conditions you have proposed in your NDA. Due to differences in dissolution media for the canagliflozin component of the FDC tablet compared to the proposed single-entity product in NDA #204-042, justification for development of the methods cannot be referenced to development parameters of the latter.

   Your dissolution development report should include the following:

   a. Solubility data already generated for the drug substances;

   b. Detailed description of the dissolution tests being proposed for the evaluation of your FDC product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution methods as the optimal tests for your product. Include data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. We recommend use of at least twelve samples per testing variable;

   c. Provide the complete dissolution profile data (*individual value, mean, n, SD, profiles*) for each entity.

   d. Data to support the discriminating ability of the selected methods. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution methods should compare the dissolution profiles of the proposed product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition to (b) (4) reported in the NDA, present results of investigation of other critical manufacturing variables on the discriminating power of the dissolution methods.

2. Provide the rationale for selecting a rotation speed of 75 rpm for the dissolution testing of the canagliflozin component in the dissolution method development report. Provide dissolution data at 50 rpm.

3. Identify the FDC tablet lots/batches that were selected for setting the proposed dissolution acceptance criteria, including the lot numbers, the clinical studies in which they were used, and if they were registration batches on stability. Provide the complete dissolution data for the identified lots (*individual, mean, n, SD, profile*).

4. Provide the complete dissolution profile data (*i.e., 15, 20, 30, 45, and 60 minutes, n=12*) for the bio-batches (clinical & PK) and primary (registration) stability batches (*individual and mean values*). If these are already provided in the CTD, please provide module and section numbers.

{See appended electronic signature page} 1/25/13
Okpo Eradiri, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D. Date
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OKPONANABOFA ERADIRI
01/29/2013

ANGELICA DORANTES
01/29/2013