CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216778Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 216778 (SDN7 or Seq.0007)
Link to EDR	\\CDSESUB1\evsprod\NDA216778\0007
Submission Date	09/22/2023
Submission Type	Standard review
Brand Name	Zituvimet XR
Generic Name	Sitagliptin and Metformin Hydrochloride Extended-Release Tablet
Dosage Form and Strength	Oral Extended-Release Tablet, Sitagliptin / Metformin Hydrochloride, 100 mg/1000 mg, 50/500 mg and 50 mg/1000 mg strengths
Route of Administration	Oral
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Zydus Worldwide DMCC
Associated IND	NA
OCP Review Team	Deepa A. Rao, PhD and Edwin Chow, PhD
OCP Final Signatory	Edwin Chow, PhD

Contents

1. Executive Summary

Per Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Zydus Worldwide DMCC (ZWD) submitted an original New Drug Application (NDA 216778/S-0007) to seek approval of its proposed formulations of sitagliptin and metformin hydrochloride extended-release tablets that has sitagliptin free base and metformin hydrochloride USP as the active ingredients. The proposed strengths are 50/500 mg, 50 mg/1000 mg, and 100 mg/1000mg.

ZWD references the Agency's earlier findings of safety and effectiveness in the listed drug (LD) product JANUMET® XR (sitagliptin and metformin hydrochloride) extended-release tablets (NDA #202270). The route of administration, dosage form, strengths and indication of ZWD's proposed drug product is same as that of the LD, i.e., JANUMET® XR. Metformin in both the ZWD's proposed drug product and the LD Janumet® XR product is present in the HCl salt form. However, unlike JANUMET® XR which uses the salt form of sitagliptin (sitagliptin phosphate monohydrate), the ZWD's proposed drug product has sitagliptin as a free base form.

The clinical development program consists of two pivotal, single dose, relative bioavailability (BA)/bioequivalence (BE) studies, a fasting relative BA/BE study (C1B01591) and a fed relative BA/BE study (C1B01592). ZWD submitted the pharmacokinetic (PK) study results from the two studies to support a PK/scientific bridge between the proposed drug product and the LD JANUMET® XR for sitagliptin and metformin hydrochloride extended-release tablets, 100 mg/1000 mg. ZWD submitted a biowaiver request for in vivo studies relying on the BE studies comparing the sitagliptin and metformin hydrochloride extended-release tablets, 100 mg/1000 mg to equal strength JANUMET® XR. The Sponsor's biowaiver communication also requests waiver for in-vivo bioequivalence studies for the lower strength sitagliptin and metformin hydrochloride extended-release tablets, 50/500 mg and 50 mg/1000 mg strengths. See biopharmaceutical review for final determination on biowaiver.

The PK study results of pivotal studies C1B01591 and C1B01592 demonstrated that the 90% confidence intervals (CI) and the geometric mean ratio (GMR) of proposed sitagliptin and metformin hydrochloride extended-release product to LD product are within the pre-specified limit of 80% to 125% for primary PK endpoints (peak concentration (C_{max}), Area Under the Curve from time zero to time t (AUC_t), and Area Under the Curve from time zero to infinity (AUC_i)) for both sitagliptin and metformin. The PK results support the conclusion that the proposed sitagliptin and metformin hydrochloride extended-release product and LD product are bioequivalent.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in NDA 216778/S-0007 and finds that the submitted PK results are acceptable to support approval from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None

2. Summary of Clinical Pharmacology Assessment

2.1 Findings of BE Studies

For the BE studies ZWD's proposed product containing sitagliptin and metformin hydrochloride extended-release tablets, 100 mg/1000 mg is compared to the LD JANUMET® XR sitagliptin and metformin hydrochloride 100 mg/1000 mg tablets. Assessments from these studies included ln transformed $C_{max,}$ AUC_t, and AUC_i for both sitagliptin and metformin. To establish bioequivalence, GMRs and their corresponding 90% confidence intervals (CI) between ZWD's proposed product and the LD are compared for both sitagliptin and metformin.

Study C1B01591 (pivotal fasting relative BE study)

Study C1B011591 is an open label, randomized, two-period, two-treatment, two-sequence, crossover, single oral dose relative bioavailability/bioequivalence study in 32 healthy subjects. Sitagliptin 90% CI intervals for GMRs for $C_{max,}$ AUC_t, and AUC_i compared to LD are 89.63% - 99.41%, 93.97% - 98.06%, and 94.00% - 97.98% respectively. Metformin 90% CI intervals for GMRs for $C_{max,}$ AUC_t, and AUC_i compared to LD are 101.32% - 112.00%, 96.33% - 107.56%, and 96.32% - 107.49% respectively. These results support that ZWD's proposed product is within the pre-specified BE acceptance criteria of 90 – 125% and thus bioequivalent to the LD.

Study C1B01592 (pivotal fed relative BE study)

Study C1B011592 is an open label, randomized, two-period, two-treatment, two-sequence, crossover, single dose oral bioavailability/bioequivalence study in 32 healthy subjects. Sitagliptin 90% CI intervals for GMRs for $C_{max,}$ AUC_t, and AUC_i compared to LD are 87.13% -94.24%, 91.29% - 96.87%, and 91.33% - 97.07% respectively. Metformin 90% CI intervals for GMRs for $C_{max,}$ AUC_t, and AUC_i compared to LD are 98.87% - 110.68%, 94.37% -113.10%, and 94.84% - 113.02% respectively. These results support that ZWD's proposed product is within the BE acceptance criteria of 90 – 125% and thus bioequivalent to the LD.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The LD, JANUMET® XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The Recommended dosing is:

- Take JANUMET® XR orally twice daily with meals. Patients taking two JANUMET® XR tablets should take the two tablets together once daily.
- Individualize the dosage of JANUMET® XR on the basis of the patient's current regimen, effectiveness, and tolerability.
- The maximum recommended daily dose is 100 mg of sitagliptin, and 2000 mg of metformin hydrochloride (HCl) extended release.
- The recommended starting dose in patients not currently treated with metformin is (b) (4) mg sitagliptin and (b) (4) mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.
- The starting dose in patients already treated with metformin should provide 100 mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin HCl immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of JANUMET® XR is two 50 mg sitagliptin and 1000 mg metformin HCl extended-release tablets taken together once daily.
- Maintain the same total daily dose of sitagliptin and metformin when changing between JANUMET (sitagliptin and metformin HCl immediate release) and JANUMET® XR.
- Do not split, crush or chew JANUMET XR tablets.

The proposed drug, Zituvimet XR, has proposed the same dosing regimen as JANUMET® XR.

2.2.2 Therapeutic Individualization

The proposed drug, Zituvimet XR, has proposed the same dosing regimen as JANUMET® XR.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

There are no significant content changes to the relevant clinical pharmacology sections in Zituvimet XR label compared to the JANUMET® XR label.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

On September 22, 2023, ZWD submitted an original 505(b)(2) New Drug Application under NDA216778 (SDN 7). The request is for approval to market its formulation of Sitagliptin and Metformin Hydrochloride Tablets, 100 mg/1000 mg extended-release tablets. Prior correspondence with the Agency in support of this 505 (b)(2) NDA application is shown below

Date	Communication from	Correspondence Details
Pre-NDA Meeting		
10/11/2021	Applicant	Request for Pre-NDA meeting (Type B) – Written Response Only (WRO) (eCTD Sequence # 0001)
10/21/2021	Agency	FDA granted Type B (Pre-NDA) Meeting Request as Written Responses Only.
11/2/2021	Applicant	Meeting Package for pre-NDA Meeting, Type B (WRO) submitted to Agency. (eCTD Sequence # 0002)
12/9/2021	Agency	Written Responses for Type B meeting received from the Agency.
2/2/2022	Applicant	Meeting Package for pre-NDA Meeting, Type C (WRO) - Follow up questions submitted to Agency. (eCTD Sequence # 0003)
2/22/2022	Agency	FDA granted Type C (Pre-NDA) Meeting Request as Written Responses Only.
4/14/2022	Agency	Written Responses for Type C meeting received from the Agency.
Pediatric Research Equity Act (PREA) Requirements		
4/25/2022	Applicant	Initial Pediatric Study Plan was submitted to Agency. (eCTD Sequence # 0004)
7/22/2022	Agency	Written Response for Initial Pediatric Study Plan received from the Agency.
7/27/2022	Applicant	Agreed Initial Pediatric Study Plan submitted to Agency. (eCTD Sequence # 0005)
8/26/2022	Agency	Agreed Initial Pediatric Study Plan – Agreement received from Agency.
Proprietary Name Review Request		
6/7/2023	Applicant	Request for Proprietary Names Review submitted to the Agency. (eCTD Sequence # 0006)
9/1/2023	Agency	Proprietary name granted

3.2 General Pharmacology and Pharmacokinetic Characteristics

Labeling of Zituvimet XR is the same as the LD, JANUMET® XR

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Two single-dose, pivotal bridging BE studies, under fasting and fed conditions, comparing ZWD's sitagliptin and metformin hydrochloride extended-release tablet to the LD JANUMET® XR were conducted to support this 505(b)(2) submission. The primary PK endpoints of sitagliptin and metformin between ZWD's proposed 100 mg/1000 mg drug product was compared to those of the LD, Merck's JANUMET® XR 100 mg/1000 mg tablet.

Study C1B01591 Pivotal Single Dose Fasting Study Results

This is an open label, randomized, two-period, two-treatment, two-sequence, crossover, single oral dose relative bioavailability/bioequivalence study. A total of 32 healthy adult subjects were planned and enrolled in the study with all 32 subjects completing period 1 and while 30 of the 32 subjects completed period 2. The Sponsor based their PK analysis on the 30 subjects that completed the study. Per the protocol, a 9-day washout period was instituted between the two periods. This is adequate since the elimination t1/2 of sitagliptin and metformin for LD extended-release tablet is ~ 12.4 hr and ~ 6.2 hr in plasma (17.6 hr from blood), respectively. Subjects received a single dose of the proposed drug or LD following a 10 hour overnight fast and with about 240 mL of 20% glucose solution in water at ambient temperature in each period. In each period, total 27 venous blood samples were collected at pre-dose (0.0 hour) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 16.0, 20.0, 24.0, 36.0 and 48.0 hours post dose after administration of each dose. The PK sampling timepoints are adequate to capture the full PK profiles of sitagliptin and metformin. The PK concentration measurements of sitagliptin and metformin in plasma PK samples were measured using validated LC-MS/MS method as described in the Appendix 4.1. Since 30 subjects completed both periods in the study, PK data from these subjects is used in PK and final statistical analysis for sitagliptin and metformin was done with 30 subjects excluding he dropouts. Subject (b) (6) administered test product) and (b) (6) (administered reference product) were withdrawn from the study at the end of period one due to vomiting. Applicant's results for the plasma concentration-time profiles and statistical analysis for sitagliptin (Figure 1, Table 1) and metformin hydrochloride (Figure 2, Table 2) are included below.

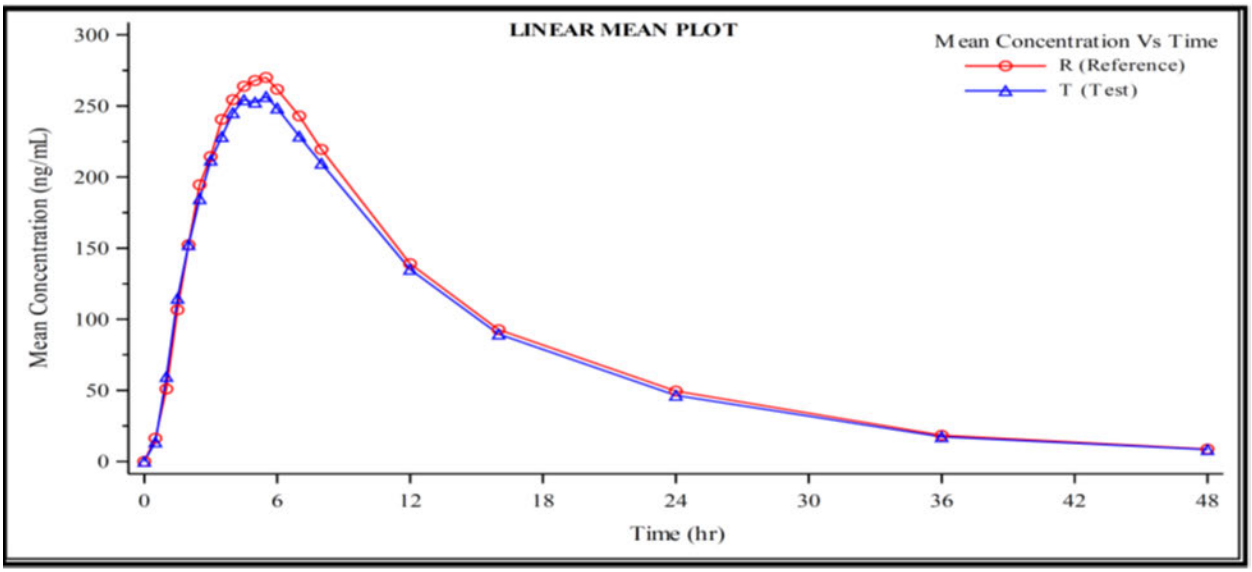

Figure 1: Linear Mean Concentration of sitagliptin in ZWD proposed drug product Zituvimet XR 100mg/1000 mg (test (T)) and Merck's Janumet® XR 100 mg/1000 mg (reference (R)) and. [Applicant Analysis; Clinical Study Report C1B01591 Figure 2.1]

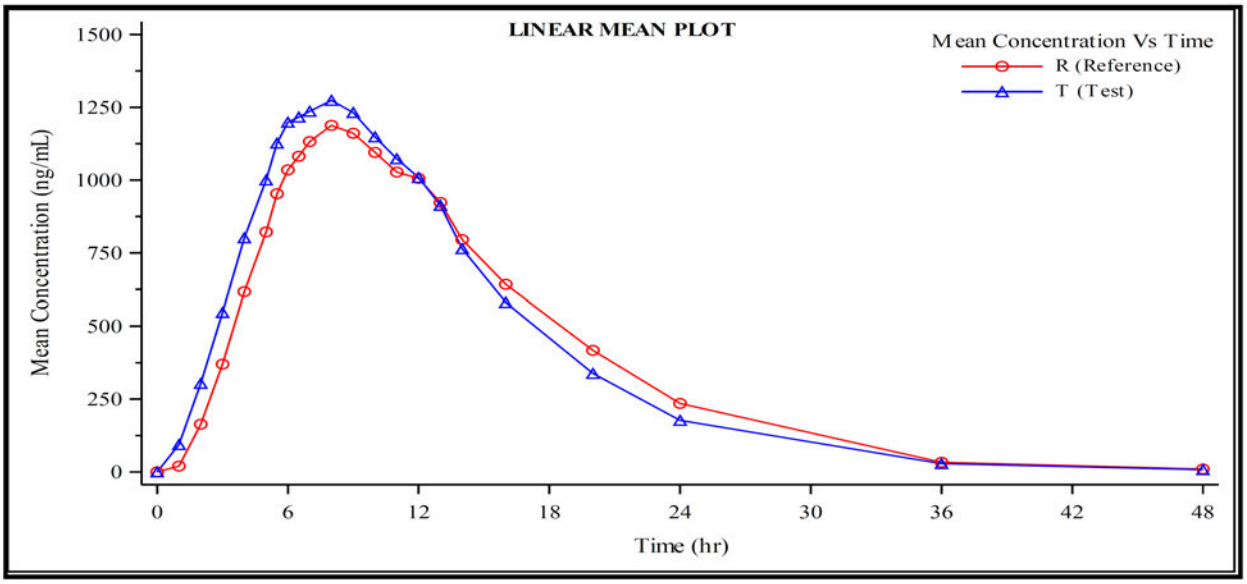

Figure 2: Linear Mean Concentration of metformin in ZWD proposed drug product Zituvimet XR 100mg/1000 mg (test (T)) and Merck's Janumet® XR 100 mg/1000 mg (reference (R)) and. [Applicant Analysis; Clinical Study Report C1B01591 Figure 2.2]

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	30	266.143	30	281.952	94.39
AUCt (ng/mL)*(hr)	30	3674.211	30	3827.564	95.99
AUCi (ng/mL)*(hr)	30	3780.272	30	3939.025	95.97
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/mL)	(89.63%; 99.41%)		80.00% - 125.00%		Bioequivalent
AUCt (ng/mL)*(hr)	(93.97%; 98.06%)		80.00% - 125.00%		
AUCi (ng/mL)*(hr)	(94.00%; 97.98%)		80.00% - 125.00%		

Table 1: Test (ZWD Proposed Drug Zituvimet XR) and Reference (Merck's Janumet® XR) Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Sitagliptin [Applicant Analysis; Clinical Study Report C1B01591 Table 2.2]

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	30	1315.592	30	1234.959	106.53
AUCt (ng/mL)*(hr)	30	17380.178	30	17074.165	101.79
AUCi (ng/mL)*(hr)	30	17516.460	30	17214.900	101.75
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/mL)	(101.32%; 112.00%)		80.00% - 125.00%		Bioequivalent
AUCt (ng/mL)*(hr)	(96.33%; 107.56%)		80.00% - 125.00%		
AUCi (ng/mL)*(hr)	(96.32%; 107.49%)		80.00% - 125.00%		

Table 2: Test (ZWD Proposed Drug Zituvimet XR) and Reference (Merck's Janumet® XR) Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Metformin [Applicant Analysis; Clinical Study Report C1B01591 Table 2.4]

Study C1B01592 Pivotal Single Dose Fed Study Results

This is an open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single oral dose relative bioavailability/bioequivalence study. A total of 32 healthy adult subjects were planned and enrolled. In Period 1, there are 32 PK evaluable subjects and 29 PK evaluable subjects in Period 2. Per the protocol, a 9-day washout period was instituted between the two periods. Subjects received a single dose of the proposed drug or LD following a 10-hour high fat, high calorie meal (~ 926 kcal) and 30 minutes after eating the standardized high-fat and high-calorie breakfast a with about 240 mL of 20% glucose solution in water. The

Applicant has met the caloric requirements (800 –1000 kcal) to conduct food-effect BA/BE study as outline in FDA Guidance. In each period, total 27 venous blood samples were collected at pre-dose (0.0 hour) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 16.0, 20.0, 24.0, 36.0 and 48.0 hours post dose after administration of each dose. The PK concentration measurements of sitagliptin and metformin in plasma PK samples were measured using validated LC-MS/MS method as described in the Appendix 4.1. PK and final statistical analysis for sitagliptin and metformin were performed on data collected from completed subjects in each period (period 1 – 32 subjects and period 2 – 28). Subjects (b) (6) and (b) (6) dropped out in Period 1 after receiving test and references products respectiv due to vomiting. Subject (b) (6) dropped out at the end of period 1 due to a positive urine alcohol test at the check-in day for Period 2. Subject (b) (6) dropped out in Period 2 after receiving the reference product due to vomiting. No further PK data was collected from these subjects and prior data was not included in the PK and statistical analysis. Applicant's results for the plasma concentration time profiles and statistical analysis are included below.

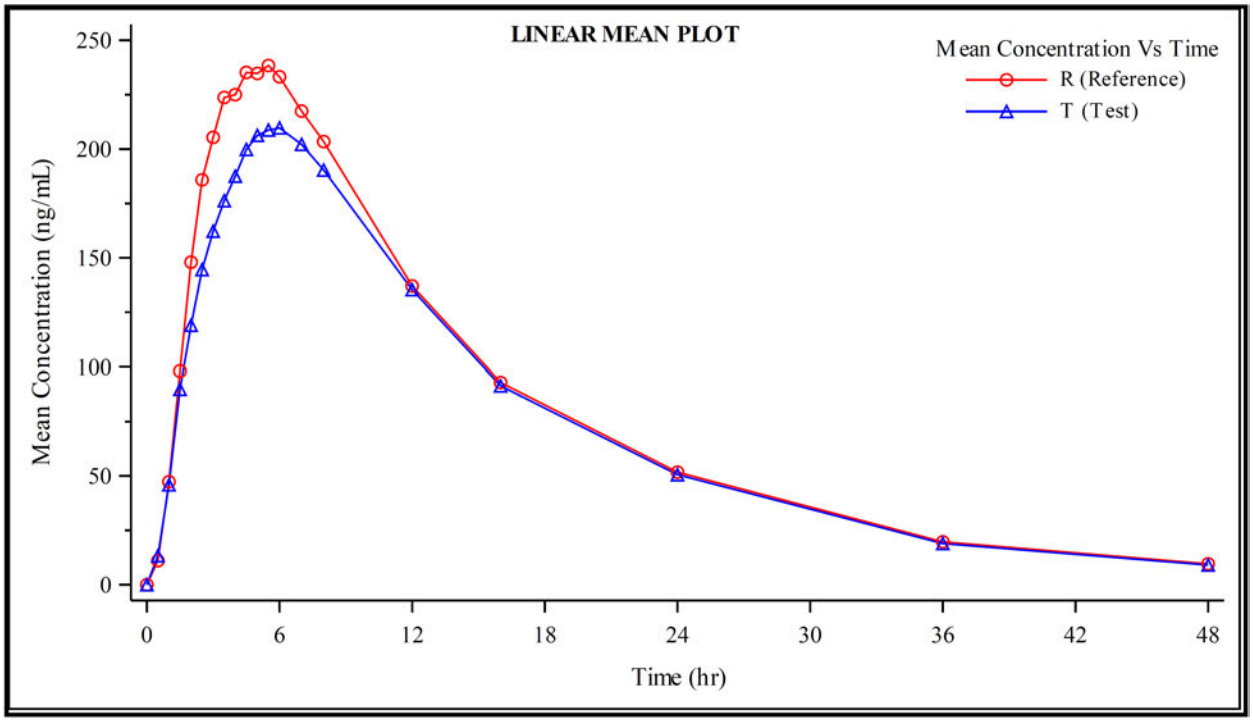

Figure 3: Linear Mean Concentration of sitagliptin in ZWD proposed drug product Zituvimet XR 100mg/1000 mg (test (T)) and Merck's Janumet® XR 100 mg/1000 mg (reference (R)) and. [Applicant Analysis; Clinical Study Report C1B01592 Figure 2.1]

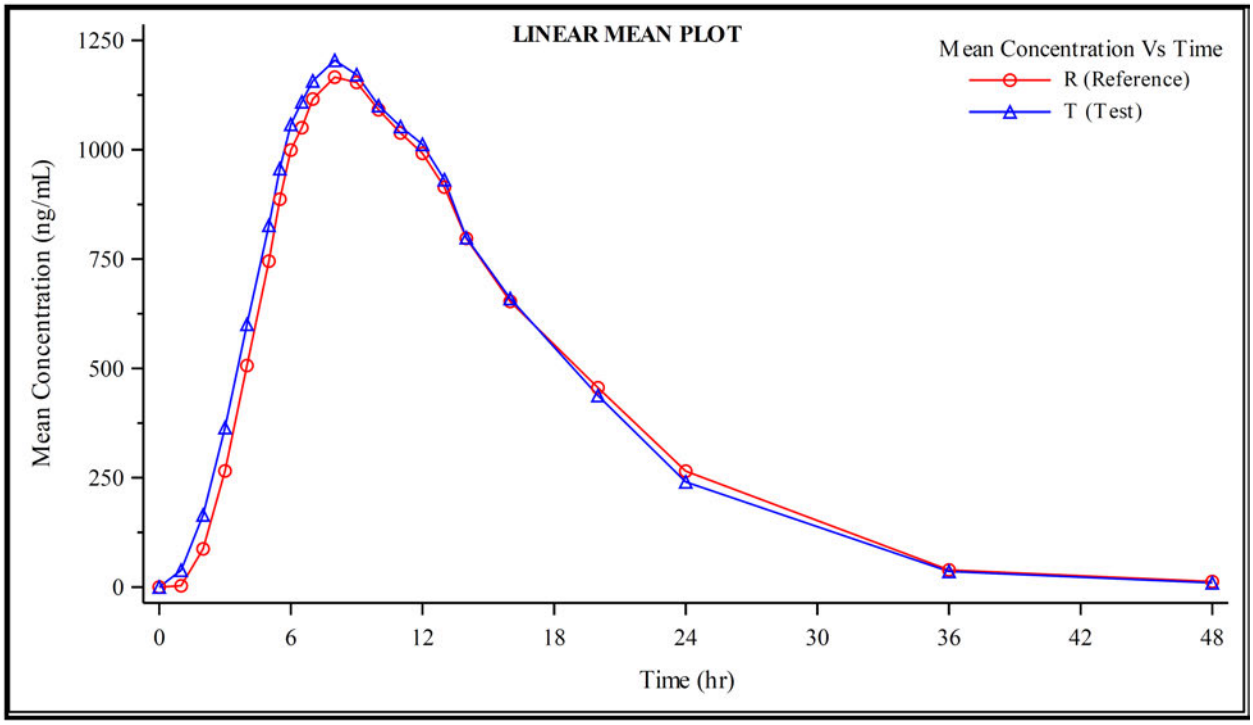

Figure 4: Linear Mean Concentration of metformin in ZWD proposed drug product Zituvimet XR 100mg/1000 mg (test (T)) and Merck's Janumet® XR 100 mg/1000 mg (reference (R)) and. [Applicant Analysis; Clinical Study Report C1B01592 Figure 2.2]

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	28	231.794	28	255.803	90.61
AUCt (ng/mL)*(hr)	28	3483.570	28	3704.259	94.04
AUCi (ng/mL)*(hr)	28	3609.778	28	3833.783	94.16
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/mL)	(87.13%; 94.24%)		80.00% - 125.00%		Bioequivalent
AUCt (ng/mL)*(hr)	(91.29%; 96.87%)		80.00% - 125.00%		
AUCi (ng/mL)*(hr)	(91.33%; 97.07%)		80.00% - 125.00%		

Table 3: Test (ZWD Proposed Drug Zituvimet XR) and Reference (Merck's Janumet® XR) Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Sitagliptin [Applicant Analysis; Clinical Study Report C1B01592 Table 2.2]

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	28	1299.246	28	1242.032	104.61
AUCt (ng/mL)*(hr)	28	17505.232	28	16943.577	103.31
AUCi (ng/mL)*(hr)	28	17711.651	28	17107.587	103.53
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/mL)	(98.87%; 110.68%)		80.00% - 125.00%		Bioequivalent
AUCt (ng/mL)*(hr)	(94.37%; 113.10%)		80.00% - 125.00%		
AUCi (ng/mL)*(hr)	(94.84%; 113.02%)		80.00% - 125.00%		

Table 4: Test (ZWD Proposed Drug Zituvimet XR) and Reference (Merck's Janumet® XR) Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Metformin [Applicant Analysis; Clinical Study Report C1B01592 Table 2.4]

Office of Study Integrity and Surveillance (OSIS) Inspection Assessment

OSIS has determined that inspections are not needed for both Cliantha, Vadodara and (b) (4) (b) (4) linical and analytical sites respectively. Office of Regulatory Affairs (ORA) conducted an inspection for the Cliantha, Vadodara (clinical site) in July 2022 for ANDA (b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site (b) (4) in (b) (4) for ANDAs (b) (4) and (b) (4) OSIS concluded that data from the reviewed studies were reliable from both the clinical and analytical sites. [Reference: DAARTS: NDA 216778: CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) 12/4/2023]

Reviewer Analysis:

- Study C1B01591 pivotal single dose fasting study results indicate that ZWD's Zituvimet XR 100 mg/1000 mg (Test; T) is BE to Merck's JANUMET® XR 100 mg/1000mg (Reference; R) under fasted conditions. This conclusion is supported because 90% CI of the GMRs for C_{max}, AUC_t and AUC_i of sitagliptin and metformin for the Test and Reference are within the BE acceptance criteria of 80 – 125% [Tables 1 & 2].
- Study C1B01592 pivotal single dose fed study results indicate that ZWD's Zituvimet XR 100 mg/1000 mg (Test; T) is BE to Merck's JANUMET® XR 100 mg/1000mg

(Reference; R) under fed conditions. This conclusion is supported because 90% CI of the GMRs for C_{max}, AUC_t and AUC_i of sitagliptin and metformin for the Test and Reference are within the BE acceptance criteria of 80 – 125% [Tables 3 & 4].

- OSIS inspection assessment confirms the reliability of the data from clinical and analytical sites used for the pivotal fasted (CIB01591) and fed studies (CIB01591).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen for Zituvimet XR is consistent with the LD, JANUMET® XR dosing regimen.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Zituvimet XR label section 12.3 incorporates the same language as the listed drug, JANUMET® XR label.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Zituvimet XR labeling is the same as the listed drug, JANUMET® XR labeling.

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Sitagliptin and metformin concentration in plasma PK samples was assessed using high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). The method validation summaries for sitagliptin and metformin for the pivotal fasting BE study (Study C1B01591) and pivotal fed BE study (C1B011592) are included below (Tables 5 – 8)

Reviewer Assessment based on FDA Bioanalytical Method Validation Guidance for Industry:

- Elements of the bioanalytical validation report that met acceptance criteria as outline in the FDA guidance include:
    - Calibration curve validation
    - Quality controls validation
    - Selectivity and Specificity
    - Carryover
    - Sensitivity
    - Accuracy and Precision
    - Other Validation Runs
    - Recovery
    - Stability
    - Dilution
    - Incurred Sample Reanalysis (ISR)
    - Repeat Analysis
- Overall, the bioanalytical method validation report is acceptable for the pivotal fasting BE study (C1B01591) and pivotal fed BE study (C1B011592)

4.1.1 Study C1B01591: LC-MS/MS method parameters for fasting study

Table 5: Summary of LC-MS/MS method parameters for sitagliptin (Study C1B01591)

Information Requested	
Bioanalytical method validation report location	Method Validation Report m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Sita/ Attachment 1 (i) of Sitagliptin/ Method Validation Report/ Page 01 to 243 Addendum-I m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Sita/ Attachment 1 (ii) of Sitagliptin/ Addendum-I to the Method Validation Report/ Page 01 to 13 Addendum-II m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Sita /Attachment 1 (iii) of Sitagliptin/ Addendum-II to the Method Validation Report/ Page 01 to 13 Addendum-III m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/ Sita / Attachment 1 (iv) of Sitagliptin/ Addendum-III to the Method Validation Report/ Page 01 to 218 Addendum-IV m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/ Sita / Attachment 1 (v) of Sitagliptin/ Addendum-IV to the Method Validation Report/ Page 01 to 215 Addendum-V m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt analyt-met/ Sita / Attachment 1 (vi) of Sitagliptin/ Addendum-V to the Method Validation Report/ Page 01 to 114
Analyte	Sitagliptin
Internal standard (IS)	Sitagliptin-D4
Method description	Liquid-liquid extraction with LC/MS/MS analysis
Limit of quantitation	2.000 ng/mL
Recovery of drug at each QC (%)	Avg.: 66.6 ± 3.4% HQC (750 ng/mL): 61.2% MQC-1 (375 ng/mL): 67.7% MQC-2 (150 ng/mL): 69.7% MQC-3 (75 ng/mL): 69.1% LQC (6 ng/mL): 65.5%

Average recovery of IS (%)	68.3 ± 3.1%
Standard curve concentrations (ng**/mL)**	2.000, 4.000, 10.00, 20.00, 40.00, 80.00, 200.0, 400.0, 800.0 and 1000
QC concentrations (ng/mL)	2.000 (LLOQ), 6.000 (LQC), 75.00 (MQC-3), 150.0 (MQC-2), 375.0 (MQC-1), 750.0 (HQC) and 1000 (ULOQ)
QC Intraday precision range (%)	0.3% to 6.6% (Intra-run)
QC Intraday accuracy range (%)	92.9% to 110% (Intra-run)
QC Interday precision range (%)	1.6% to 6.6% (Inter-run)
QC Interday accuracy range (%)	98.6% to 108% (Inter-run)
Bench-top stability (hrs)	30 hours at room temperature [For Sitagliptin] 27 hours at room temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Stock stability (days)	34 days for analyte and 33 days for internal standard at refrigerator temperature
Processed stability (hrs)	77 hours at room temperature and 97 hours at refrigerator temperature [For Sitagliptin] 77 hours at room temperature and 99 hours at refrigerator temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Freeze-thaw stability (cycles)	6 cycles [For Sitagliptin] 6 cycles [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Long-term storage stability (days)	95 days at -20°C temperature [For Sitagliptin] 96 days at -20°C temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Dilution integrity (%)	Up to 5000 ng/mL, Diluted 10 times
Selectivity	No significant interfering peak noted in blank plasma lots.

Table 6: Summary of LC-MS/MS method parameters for metformin (Study C1B01591)

Information Requested	
Bioanalytical method validation report location	Method Validation m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met/ Attachment 1 (i) Method validation report of Metformin/ Page 1 to 258 Addendum-I m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (ii)/ Addendum-I to the Method Validation Report of Metformin/ Page 1 to 83

	Addendum-II m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (iii)/ Addendum-II to the Method Validation Report of Metformin/ Page 1 to 35 Addendum-III m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (iv)/ Addendum-III to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-IV m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (v)/ Addendum-IV to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-V m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (vi)/ Addendum-V to the Method Validation Report of Metformin/ Page 1 to 47 Addendum-VI m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (vii)/ Addendum-VI to the Method Validation Report of Metformin/ Page 1 to 41 Addendum-VII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (viii)/ Addendum-VII to the Method Validation Report of Metformin/ Page 1 to 34 Addendum-VIII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (ix)/ Addendum-VIII to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-IX m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (x)/ Addendum-IX to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-X

	m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xi)/ Addendum-X to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-XI m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xii)/ Addendum-XI to the Method Validation Report of Metformin/ Page 1 to 93 Addendum-XII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xiii)/ Addendum-XII to the Method Validation Report of Metformin/ Page 1 to 14 Addendum-XIII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xiv)/ Addendum-XIII to the Method Validation Report of Metformin/ Page 1 to 43 Addendum-XIV m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met/Attachment 1 (xv)/ Addendum-XIV to the Method Validation Report of Metformin/ Page 1 to 17 Addendum-XV m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xvi)/ Addendum-XV to the Method Validation Report of Metformin/ Page 1 to 90 Addendum-XVI m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xvii)/ Addendum-XVI to the Method Validation Report of Metformin/ Page 1 to 10 Addendum-XVII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met/ Attachment 1 (xviii)/ Addendum-XVII to the Method Validation Report of Metformin/ Page 1 to 137 Addendum-XVIII m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/Met / Attachment 1 (xix)/ Addendum-XVIII to the Method Validation Report of Metformin/ Page 1 to 181

Analyte	Metformin
Internal standard (IS)	Metformin-D6
Method description	Solid phase extraction method with LC/MS/MS method
Limit of quantitation	10.00 ng/mL
Recovery of drug at each QC (%)	Avg.: 70.8% HQC: 74.5% MQC-1: 72.1% MQC-2: 69.9% MQC-2: 69.3% LQC: 68.4%
Average recovery of IS (%)	76.3%
Standard curve concentrations (ng/mL)	10.00, 20.00, 50.00, 100.0, 200.0, 500.0, 1000, 2000, 4000 and 5000
QC concentrations (ng/mL)	10.00 (LLOQ), 30.00 (LQC), 300.0 (MQC-3), 750.0 (MQC-2), 1500 (MQC-1), 3750 (HQC), and 5000 (ULOQ)
QC Intraday precision range (%)	0.5% to 4.6% [using API-3000 LC/MS/MS System] 0.7% to 5.5% [using API-4000 LC/MS/MS System]
QC Intraday accuracy range (%)	90.6% to 103% [using API-3000 LC/MS/MS System] 87.3% to 103% [using API-4000 LC/MS/MS System]
QC Interday precision range (%)	1.6% to 4.7% [using API-3000 LC/MS/MS System] 2.2% to 8.3% [using API-4000 LC/MS/MS System]
QC Interday accuracy range (%)	93.4% to 101% [using API-3000 LC/MS/MS System] 93.6% to 100% [using API-4000 LC/MS/MS System]
Bench-top stability (hrs)	30 hours at room temperature [For Metformin] 34 hours at room temperature [For Metformin fortified with Sitagliptin (1000 ng/mL)]
Stock stability (days)	17 days for analyte and internal standard at refrigerator temperature
Processed stability (hrs)	86 hours at room temperature and at refrigerator temperature
Freeze-thaw stability (cycles)	6 cycles [For Metformin and For Metformin fortified with Sitagliptin (1000 ng/mL)]
Long-term storage stability (days)	89 days at -20ºC Temperature [For Metformin] 99 days at -20ºC Temperature [For Metformin fortified with Sitagliptin (1000 ng/mL)])
Dilution integrity	25000 ng/mL, diluted 10 times 7500 ng/mL, diluted 2 times
Selectivity	No significant interfering peak noted in blank plasma lots

4.1.2 Study C1B01592: LC-MS/MS method parameters for fed study

Table 7: Summary of LC-MS/MS method parameters for sitagliptin (Study C1B01592)

Information Requested	
Bioanalytical method validation report location	Method Validation Report m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met/ sita-attachment-1-1-method-val-report of Sitagliptin/ Method Validation Report/ Page 01 to 243 Addendum-I m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / sita-attachment-1-2-addendum-1-method-val-report of Sitagliptin/ Addendum-I to the Method Validation Report/ Page 01 to 13 Addendum-II m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / sita-attachment-1-3-addendum-2-method-val-report of Sitagliptin/ Addendum-II to the Method Validation Report/ Page 01 to 13 Addendum-III m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / sita-attachment-1-4-addendum-3-method-val-report of Sitagliptin/ Addendum-III to the Method Validation Report/ Page 01 to 216 Addendum-IV m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / sita-attachment-1-5-addendum-4-method-val-report of Sitagliptin/ Addendum-IV to the Method Validation Report/ Page 01 to 213 Addendum-V m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / sita-attachment-1-6-add-5-method-val-report of Sitagliptin/ Addendum-V to the Method Validation Report/ Page 01 to 113
Analyte	Sitagliptin
Internal standard (IS)	Sitagliptin-D4
Method description	Liquid-liquid extraction with LC/MS/MS analysis
Limit of quantitation	2.000 ng/mL
Recovery of drug at each QC (%)	Avg.: 66.6 ± 3.4% HQC (750 ng/mL): 61.2% MQC-1 (375 ng/mL): 67.7% MQC-2 (150 ng/mL): 69.7% MQC-3 (75 ng/mL): 69.1% LQC (6 ng/mL): 65.5%

Average recovery of IS (%)	68.3 ± 3.1%
Standard curve concentrations (ng**/mL)**	2.000, 4.000, 10.00, 20.00, 40.00, 80.00, 200.0, 400.0, 800.0 and 1000
QC concentrations (ng/mL)	2.000 (LLOQ), 6.000 (LQC), 75.00 (MQC-3), 150.0 (MQC-2), 375.0 (MQC-1), 750.0 (HQC) and 1000 (ULOQ)
QC Intraday precision range (%)	0.3% to 6.6% (Intra-run)
QC Intraday accuracy range (%)	92.9% to 110% (Intra-run)
QC Interday precision range (%)	1.6% to 6.6% (Inter-run)
QC Interday accuracy range (%)	98.6% to 108% (Inter-run)
Bench-top stability (hrs)	30 hours at room temperature [For Sitagliptin] 27 hours at room temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Stock stability (days)	34 days for analyte and 33 days for internal standard at refrigerator temperature
Processed stability (hrs)	77 hours at room temperature and 97 hours at refrigerator temperature [For Sitagliptin] 77 hours at room temperature and 99 hours at refrigerator temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Freeze-thaw stability (cycles)	6 cycles [For Sitagliptin and For Sitagliptin fortified with Metformin (5000 ng/mL)]
Long-term storage stability (days)	95 days at -20°C temperature [For Sitagliptin] 96 days at -20°C temperature [For Sitagliptin fortified with Metformin (5000 ng/mL)]
Dilution integrity (%)	Up to 5000 ng/mL, Diluted 10 times
Selectivity	No significant interfering peak noted in blank plasma lots.

Table 8: Summary of LC-MS/MS method parameters for metformin (Study C1B01592)

Information Requested	
Bioanalytical method validation report location	Method Validation m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-1-method-val-report of Metformin/ Page 1 to256 Addendum-I m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-2-addendum-1-method-val-report / Addendum-I to the Method Validation Report of Metformin/ Page 1 to 83

	Addendum-II m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-3-addendum-2-method-val-report / Addendum-II to the Method Validation Report of Metformin/ Page 1 to 35 Addendum-III m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-4-addendum-3-method-val-report / Addendum-III to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-IV m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-5-addendum-4-method-val-report / Addendum-IV to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-V m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-6-addendum-5-method-val-report / Addendum-V to the Method Validation Report of Metformin/ Page 1 to 47 Addendum-VI m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-7-addendum-6-method-val-report / Addendum-VI to the Method Validation Report of Metformin/ Page 1 to 40 Addendum-VII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-8-addendum-7-method-val-report / Addendum-VII to the Method Validation Report of Metformin/ Page 1 to 34 Addendum-VIII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-9-addendum-8-method-val-report / Addendum-VIII to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-IX m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-10-addendum-9-method-val-report / Addendum-IX to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-X

	m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-11-addendum-10-method-val-report / Addendum-X to the Method Validation Report of Metformin/ Page 1 to 11 Addendum-XI m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-12-addendum-11-method-val-report / Addendum-XI to the Method Validation Report of Metformin/ Page 1 to 94 Addendum-XII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-13-addendum-12-method-val-report / Addendum-XII to the Method Validation Report of Metformin/ Page 1 to 14 Addendum-XIII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-14-addendum-13-method-val-report / Addendum-XIII to the Method Validation Report of Metformin/ Page 1 to 43 Addendum-XIV m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-15-addendum-14-method-val-report / Addendum-XIV to the Method Validation Report of Metformin/ Page 1 to 17 Addendum-XV m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-16-addendum-15-method-val-report / Addendum-XV to the Method Validation Report of Metformin/ Page 1 to 90 Addendum-XVI m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-17-addendum-16-method-val-report / Addendum-XVI to the Method Validation Report of Metformin/ Page 1 to 10 Addendum-XVII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-18-addendum-17-method-val-report / Addendum-XVII to the Method Validation Report of Metformin/ Page 1 to 138 Addendum-XVIII m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met / met-attachment-1-19-addendum-18-method-val-report / Addendum-XVIII to the Method Validation Report of Metformin/ Page 1 to 180

Analyte	Metformin
Internal standard (IS)	Metformin-D6
Method description	Solid phase extraction method with LC/MS/MS method
Limit of quantitation	10.00 ng/mL
Recovery of drug at each QC (%)	Avg.: 70.8% HQC: 74.5% MQC-1: 72.1% MQC-2: 69.9% MQC-2: 69.3% LQC: 68.4%
Average recovery of IS (%)	76.3%
Standard curve concentrations (ng/mL)	10.00, 20.00, 50.00, 100.0, 200.0, 500.0, 1000, 2000, 4000 and 5000 5000
QC concentrations (ng/mL)	10.00 (LLOQ), 30.00 (LQC), 300.0 (MQC-3), 750.0 (MQC-2), 1500 (MQC-1), 3750 (HCQ), and 5000 (ULQC)
QC Intraday precision range (%)	0.5% to 4.6% [using API-3000 LC/MS/MS System] 0.7% to 5.5% [using API-4000 LC/MS/MS System]
QC Intraday accuracy range (%)	90.6% to 103% [using API-3000 LC/MS/MS System] 87.3% to 103% [using API-4000 LC/MS/MS System]
QC Interday precision range (%)	1.6% to 4.7% [using API-3000 LC/MS/MS System] 2.2% to 8.3% [using API-4000 LC/MS/MS System]
QC Interday accuracy range (%)	93.4% to 101% [using API-3000 LC/MS/MS System] 93.6% to 100% [using API-4000 LC/MS/MS System]
Bench-top stability (hrs)	30 hours at room temperature [For Metformin] 34 hours at room temperature [For Metformin fortified with Sitagliptin (1000 ng/mL)]
Stock stability (days)	17 days for analyte and internal standard at refrigerator temperature
Processed stability (hrs)	86 hours at room temperature and at refrigerator temperature
Freeze-thaw stability (cycles)	6 cycles [For Metformin and For Metformin fortified with Sitagliptin (1000 ng/mL)]
Long-term storage stability (days)	89 days at -20ºC Temperature [For Metformin] 99 days at -20ºC Temperature [For Metformin fortified with Sitagliptin (1000 ng/mL)])
Dilution integrity	25000 ng/mL, diluted 10 times 7500 ng/mL, diluted 2 times
Selectivity	No significant interfering peak noted in blank plasma lots

4.2 Clinical PK and/or PD Assessments

The reviewer's assessment on PK parameter estimations and final statistical analysis for bioequivalence for the pivotal fed (study C1B01592) and fasting (study C1B01591) studies for ZWD's proposed product in comparison to the LD are included below.

4.2.1 Study C1B01591 Pivotal Single Dose Fasting Study Results

Reviewer's Analysis for Sitagliptin

~~Sitagliptin Analysis~~

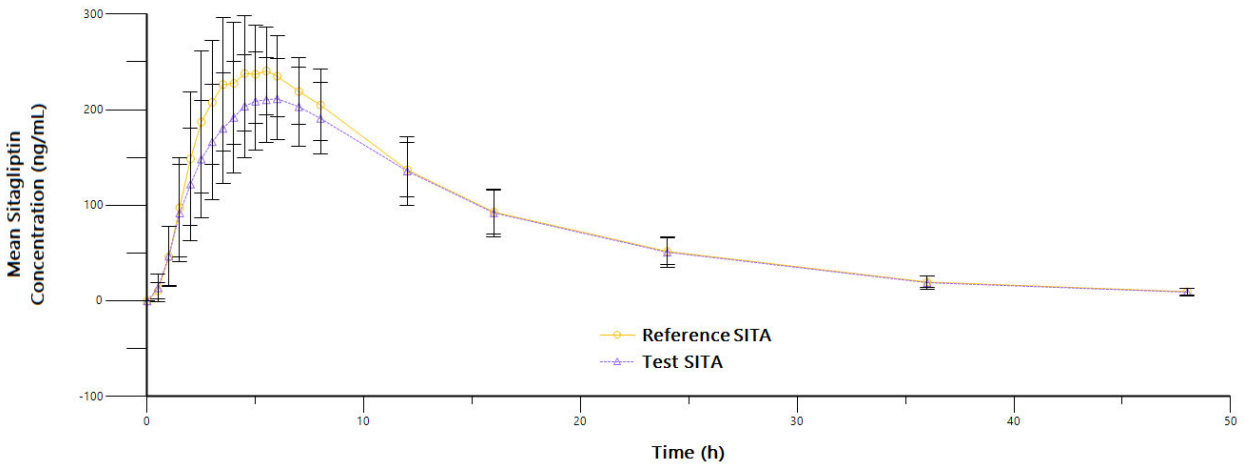

Figure 5: Sitagliptin concentration from ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fasting conditions [Source: FDA Analysis]

Parameters	Least Squares Geometric Means		Geometric Mean (Test/ Reference) Ratio (Expressed as %)	90% CI
	Test (n = 30)	Reference (n = 30)		
C_{max} (ng/mL)	232.34	254.86144	91.16	86.95 – 95.58
AUC_t (ng*h/mL)	3416.2	3634.7125	93.99	91.3 – 96.76
AUC_i (ng*h/mL)	3542.56	3765.259	94.09	91.32 – 96.94

Table 9: Bioequivalence calculation for sitagliptin in ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fasting conditions [Source: FDA Analysis]

Reviewer's Analysis for Metformin

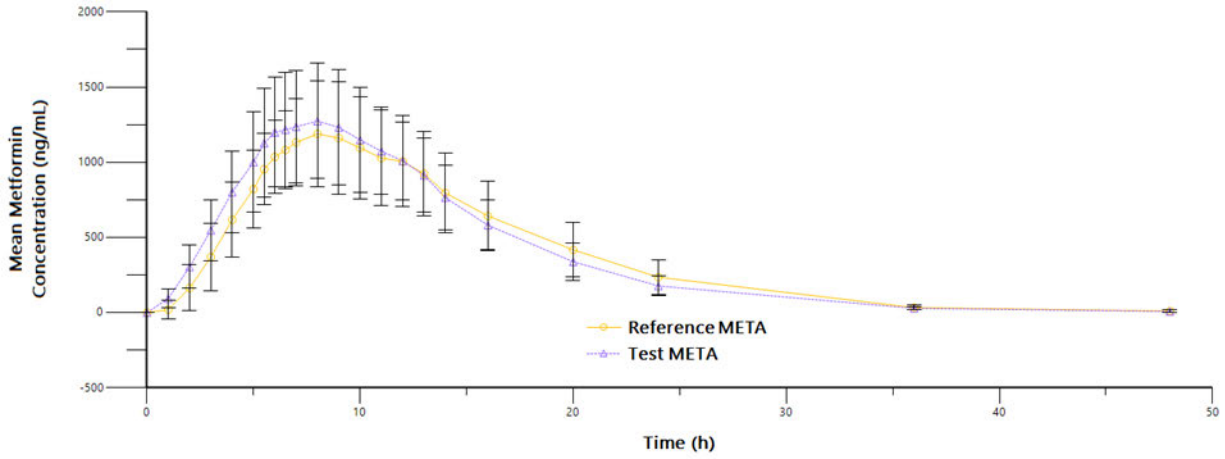

Figure 6: Metformin concentration from ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fasting conditions [Source: FDA Analysis]

Parameters	Least Squares Geometric Means		Geometric Mean (Test/ Reference) Ratio (Expressed as %)	90% CI
	Test (n = 30)	Reference (n = 30)		
C_{max} (ng/mL)	1315.59	1234.96	106.53	101.02 – 112.34
AUC_t (ng*h/mL)	17021.68	16625.79	102.38	97.06 – 107.99
AUC_i (ng*h/mL)	17157.9	16766.25	102.34	97.04 – 107.92

Table 10: Bioequivalence calculation for metformin in ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fasting conditions. [Source: FDA Analysis]

Reviewer Comments:

- Subjects (b) (6) and (b) (6) discontinued the study and 30 subjects were included in the PK and statistical analysis
- FDA's analyses confirmed Applicant's results.
- Applicant's results for pivotal fasting BE study C1B01591 are acceptable and support a scientific bridge to the LD JANUMET® XR tablet.

4.2.2 Study C1B01592 Pivotal Single Dose Fed Study Results

Reviewer's Analysis for Sitagliptin

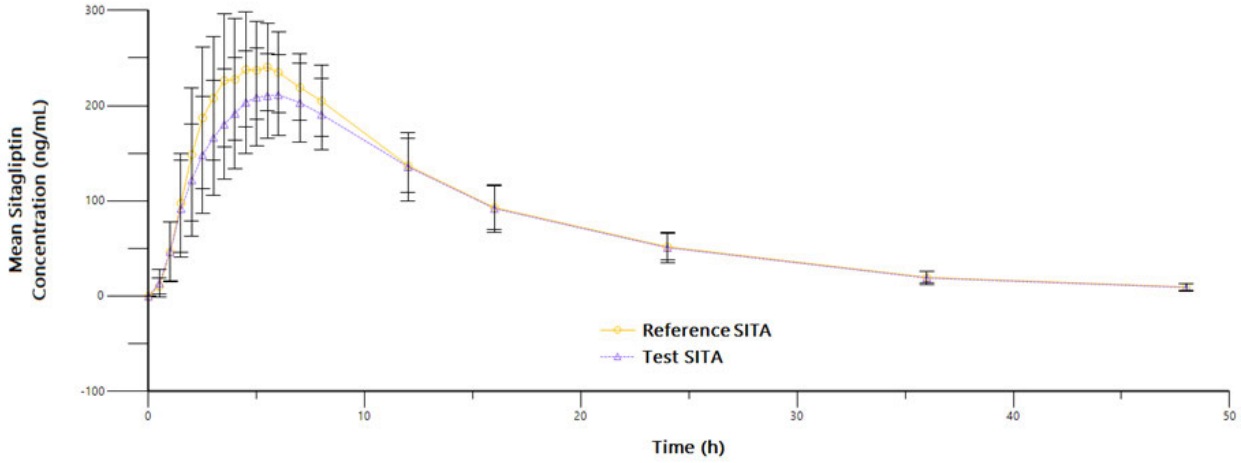

Figure 7: Sitagliptin concentration from ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fed conditions. [Source: FDA Analysis]

Parameters	Least Squares Geometric Means		Geometric Mean (Test/ Reference) Ratio (Expressed as %)	90% CI
	Test (n = 28)	Reference (n = 28)		
C_{max} (ng/mL)	232.34	254.86	91.16	86.95 – 95.58
AUC_t (ng*h/mL)	3416.2	3634.71	93.99	91.3 – 96.76
AUC_i (ng*h/mL)	3542.56	3765.26	94.09	91.32 – 96.94

Table 11: Bioequivalence calculation for sitagliptin in ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fed conditions. [Source: FDA Analysis]

Reviewer's Analysis for Metformin

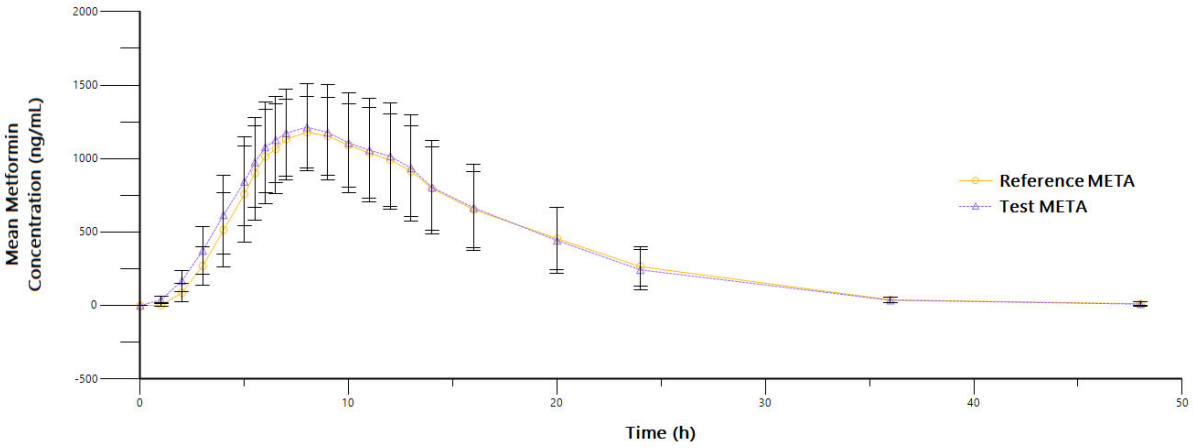

Figure 8: Metformin concentration from ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fed conditions. [Source: FDA Analysis]

Parameters	Least Squares Geometric Means		Geometric Mean (Test/ Reference) Ratio (Expressed as %)	90% CI
	Test (n = 28)	Reference (n = 28)		
C_{max} (ng/mL)	1302.37	1246.12	104.51	98.89 – 110.46
AUC_t (ng*h/mL)	17035.61	16596.3	102.65	93.47 – 112.73
AUC_i (ng*h/mL)	17239.97	16759.38	102.87	93.91 – 112.68

Table 12: Bioequivalence calculation for metformin in ZWD Zituvimet XR 100 mg/1000 mg tablets (Test) compared to Merck's JANUMET® XR 100 mg/1000 mg tablets (Reference) under fed conditions. [Source: FDA Analysis]

Reviewer Comments:

- Subjects (b) (6) and (b) (6) discontinued the study and 28 subjects were included in the PK and statistical analysis
- FDA's confirmed Applicant's results.

Applicant's results for pivotal fed BE study C1B01592 are acceptable and support a scientific bridge to the LD JANUMET® XR tablet.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEEPA A RAO
06/10/2024 09:51:40 AM

EDWIN C CHOW
06/10/2024 02:03:52 PM