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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA21995-S47, NDA22044-S48, NDA202270-S22
Drug Name:	Januvia ® (sitagliptin), Janumet ® (sitagliptin + metformin IR FDC), Janumet ®XR (sitagliptin + metformin XR FDC)
Indication(s):	An adjunct to diet and exercise to improve glycemic control in [redacted] (b) (4) with T2DM
Applicant:	Merck
Date(s):	Stamp date: 6/4/2020
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Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Wenda Tu, PhD
Concurring Reviewers:	Yun Wang, PhD, Team Lead
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Key Words:	Pediatric study, Glycemic Control, T2DM

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1 EXECUTIVE SUMMARY

The applicant, Merck & Co., Inc., has submitted this supplemental new drug application (sNDA) to support changes to *Section 8.4: Pediatric Use* in the labels for JANUVIA, JANUMET® and JANUMET® XR[1]. The proposed changes provided additional information on the drug's efficacy and safety for pediatric use. Specifically, the drug was found not effective among the pediatric population based on the results from three pediatric studies: P083, P170 and P289. The three studies intended to investigate the potential use of sitagliptin as treatment for type 2 diabetes mellitus (T2DM) in pediatric patients (10 to 17 years old), either as an initial oral anti-hyperglycemic agency (AHA) therapy (P083), or as add-on to metformin (P170) or to metformin XR (P289). Due to the similarity in study designs and study populations between Studies P170 and P289, data collected from these two studies are pooled together for statistical efficacy analysis.

1.1 Brief overview of Clinical Study

P083 is a multi-center, randomized, double-blind, parallel group, placebo-controlled that consists of a 20-week Phase A study plus a 34-week Phase B study. It compares the effect of Januvia (sitagliptin) 100mg vs placebo during the first 20 weeks, and Januvia vs metformin for the remaining 34 weeks on glycemic control among 170 pediatric patients (10 to 17 years old) with T2DM. The primary efficacy endpoint for the study is change in A1c from baseline at Week 20.

P170 is a multi-center, randomized, double-blind, parallel group, placebo-controlled that consists of a 20-week base study and a 34-week extension study. It compares the effect of Janumet ® (sitagliptin and metformin IR[2], FDC[3]) against metformin IR on glycemic control among 124 pediatric patients (10 to 17 years old) with T2DM. The primary efficacy endpoint for the study is change in A1c from baseline at Week 20.

P289 is a multi-center, randomized, double-blind, parallel group, placebo-controlled that consists of a 20-week Phase A study and a 34-week Phase B study. It compares the effect of Janumet ® XR (sitagliptin and metformin XR, FDC) against metformin IR on glycemic control among 96 pediatric patients (10 to 17 years old) with T2DM. The primary efficacy endpoint for the study is change in A1c from baseline at Week 20.

More details on the three studies can be found in Section 2.1.3.

1.2 Statistical Issues

No major statistical issues have been identified. Regarding the pooled study of P170 & 289, inconsistent conclusions were derived based on the two estimands: the treatment policy estimand and the treatment effect estimand. This issue has been investigated in the report.

[1] XR: Extended release
[2] IR: Instant release
[3] FDC: Fixed Dose Combination

1.3 Collective Evidence

Under the treatment-policy estimand, data collected from all randomized and treated patients regardless of initiation of rescue therapy were used in the ANCOVA model pre-specified in the study protocols. Missing data were handled based on the return-to-baseline principle and Rubin's Rule for multiple imputation.

Regarding the primary analysis result, for Study P083, the change in A1c at Week 20 from baseline in patients treated with sitagliptin (N = 95) was estimated to be 0.06% compared to 0.23% in patients treated with placebo (N = 95), resulting in a difference of -0.17% (95% C.I.: -0.62, 0.28). For the Pooled analysis of P170 & 289, the change in A1c at Week 20 from baseline in patients treated with a fixed-does combination of sitagliptin and metformin (N = 107) was -0.23% compared to 0.09% in patients treated with metformin (N = 113), resulting in a difference of -0.33% (95% C.I.: -0.70, 0.05). Neither study demonstrated superiority of sitagliptin regarding A1c reduction when compared to placebo, either as a mono-therapy or as an add-on to metformin.

Safety evaluation has shown that sitagliptin was generally well-tolerated through a 54-week length of treatment.

1.4 Conclusion and Recommendations

Since superiority of HbA1c reduction was not demonstrated by either Study P083 or by the pooled study of P170 & P289, the applicant did not plan to make any efficacy claim for sitagliptin use among pediatric patients (10 to 17 years old) with T2DM. The applicant only sought to add these three studies' information in Section 8.4: Pediatric Use. From a statistical perspective, the applicant's proposal is approvable.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. The current indication for sitagliptin (Januvia®) is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The approved doses for sitagliptin are 100 mg, 50 mg (for patients with moderate renal impairment), or 25 mg (for patients with severe renal impairment) once daily.

Besides, sitagliptin is also used to manufacture Janumet® (a combination of sitagliptin and metformin IR) and Janumet® XR (a combination of sitagliptin and metformin XR). Both products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin (IR or XR) is appropriate. The dosing for Janumet® and Janumet® XR should be individualized based on patients' current regimen, effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

2.1.2 Studies Reviewed

This submission consists of three studies: P083, P170 and P289. Table 1 provides an overview of the three studies.

Table 1. Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment (Sample Size)	Primary Efficacy Objective/Hypothesis	Primary Efficacy Endpoint/Analysis
P083	MC, R, DB, PG, PC trial (20-wk Phase A + 34-wk Phase B)	Sita 100mg (n = 95) Placebo/metformin (n = 95†)	**Objective:** Assess the effect of treatment with sitagliptin compared with that of placebo on A1c in pediatric patients (10 to 17 years old) with inadequate glycemic control **Hypothesis**: The addition of sitagliptin reduces A1c more than the addition of placebo after 20 weeks of treatment (with H_0: difference = sitagliptin - placebo = 0).	**Primary Endpoints**: Change in A1c from baseline at Week 20 **Analysis**: Treatment policy estimand based on FAS/RTB (analyzed by ANCOVA‡).
P170	MC, R, DB, PG, PC trial (20-wk base study + 34-wk extension study)	Sita/Met IR FDC (n = 62) Metformin IR (n = 62)	**Objective**: Assess the effect of the addition of sitagliptin relative to placebo on A1c in pediatric patients (10 to 17 years old) with inadequate glycemic control on metformin therapy. **Hypothesis**: The addition of sitagliptin reduces A1c more than the addition of placebo after 20 weeks of treatment (with H_0: difference = sitagliptin - placebo = 0).	**Primary Endpoints**: Change in A1c from baseline at Week 20 **Analysis**: Treatment policy estimand based on FAS/RTB (analyzed by ANCOVA#).
P289	MC, R, DB, PG, PC (20-wk Phase A + 34-wk Phase B)	Sita/Met XR FDC (n = 45) Metformin XR (n = 51)		

***** MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, FAS: full analysis set, RTB: return to baseline; Sita: sitagliptin, Met: metformin.
† The original design involves 4 arms: Sita, placebo/Met, Met and placebo/Sita. The latter two arms were dropped based on Amendment P083-05. In analysis of Phase A (wk-20) data, the two placebo groups are combined into a single placebo group.
‡ The ANCOVA model includes treatment, baseline A1c value, baseline BMI percentile, insulin use at screening (Y/N).
The ANCOVA model includes treatment, baseline A1c value, baseline BMI percentile, insulin use at screening (Y/N), study type (P170 and P289) and the baseline metformin dose (<1500mg, 1500mg or > 1500mg)

2.2 Data Sources

The Electronic Document Room (EDR) locations for the three NDA submissions are listed as follows:

- NDA21995-S47: \\CDSESUB1\evsprod\NDA021995\0505
- NDA22044-S48: \\CDSESUB1\evsprod\NDA022044\0254
- NDA202270-S22: \\CDSESUB1\evsprod\NDA202270\0147

All the datasets (both in ADAM format and STDM format) and the programming codes for the statistical analyses documented the NDA submission can be found under the subdirectory: m5/datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There was no issue on data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

P083 was a double-blind, randomized, parallel-group, placebo-controlled and multi-center, 2-phase trial (Figure 1). In Phase A, subjects who met progressively stricter hyperglycemic thresholds initiated rescue with metformin in a blinded manner (Rescue Step 1). Subjects randomized to placebo who did not initiate glycemic rescue therapy with metformin in Phase A, received metformin (in a blinded manner) in Phase B. Rescue in Phase B potentially involved 2 steps. Rescue Step 1 was blinded metformin for the sitagliptin group or blinded sitagliptin for the placebo/metformin group. Subjects who continued to meet glycemic rescue criteria after Rescue Step 1 initiated insulin or up-titrated existing insulin therapy (Rescue Step 2). Subjects with A1C ≥7.0% in Phase B could be treated to achieve a target A1C goal <7.0% using the glycemic rescue therapy options from Rescue Step 1 or 2.

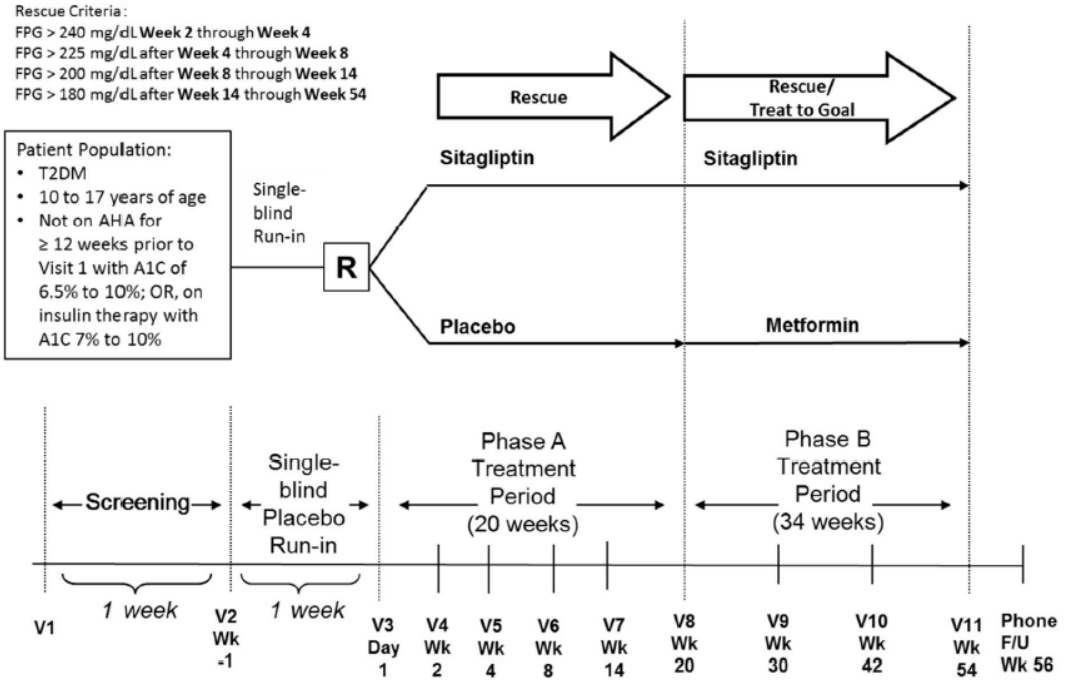
P170 was a double-blind, randomized, parallel-group, placebo-controlled and multi-center, 2-phase trial (Figure 2). At screening, subjects in Study P170 were on stable treatment for at least 12 weeks with metformin IR alone or in combination with insulin. Before randomization in the base study, subjects were switched from their dose of metformin IR to the appropriate corresponding dose of Sponsor-supplied metformin IR. Subjects were stratified according to their daily dose of metformin at Visit 1. Subjects eligible for randomization in the base study were assigned in a 1:1 ratio to blinded treatment with either Sita/Met IR FDC (Sita/Met IR FDC group) or placebo matching metformin IR (Metformin IR group). The extension study was added approximately 3 years after the base study began. Subjects who completed the base study before the extension study was available were not eligible to enter the extension study. After the extension study became available, eligible subjects who completed the base study entered the

extension study and continued the same double-blind study medication assigned at randomization in the base study.

In the base and extension studies, subjects who met predefined hyperglycemic thresholds were to initiate insulin or titrate the dose of their background insulin therapy (glycemic rescue). The type of insulin initiated as glycemic rescue therapy was at the investigator's discretion in the base study, but only insulin glargine was initiated as glycemic rescue therapy in the extension study.

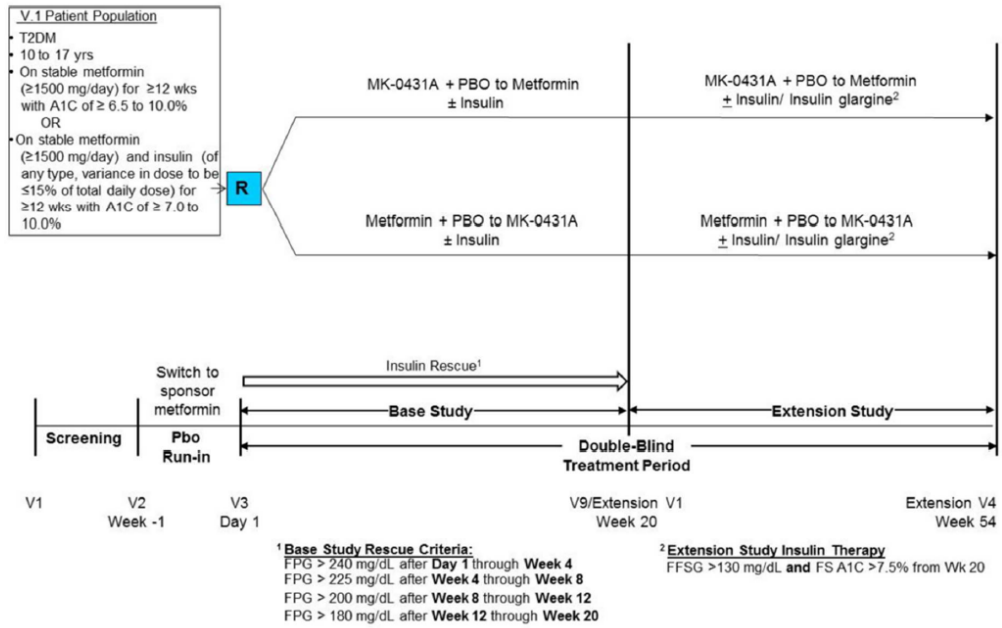
Study P289 was a double-blind, randomized, parallel-group, placebo-controlled and multi-center 2-phase, trial (Figure 3). At screening, subjects in Study P289 were on stable treatment for at least 12 weeks with metformin alone or in combination with insulin. Before randomization, subjects were switched from their dose of metformin (IR or XR) to the appropriate corresponding dose of Sponsor-supplied metformin XR. Subjects were stratified according to their daily dose of metformin (IR or XR) at Visit 1. Subjects eligible for randomization were assigned in a 1:1 ratio to blinded treatment with either the Sita/Met XR FDC and placebo-matching metformin XR (Sita/Met XR FDC group) or placebo-matching Sita/Met XR FDC and metformin XR (Metformin XR group). In Phases A and B, subjects who met predefined hyperglycemic thresholds were to initiate open-label insulin glargine or titrate the dose of their background insulin therapy (glycemic rescue).

Figure 1. P083 Trial Design



Source: Page 37 of the Clinical Report P083V01

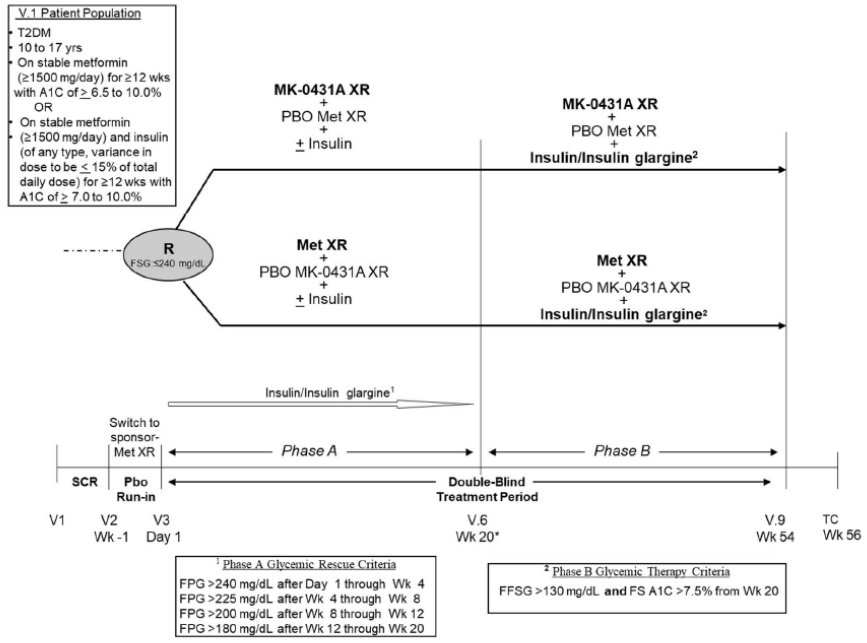
Figure 2. P170 Trial Design



A1C=hemoglobin A1C; FFSG=fasting fingerstick glucose; FPG=fasting plasma glucose; FS=fingerstick; Pbo/PBO=placebo; R=randomization; T2DM=type 2 diabetes mellitus; V=visit; Wk=week.

Source: Page 34 of the Clinical Report P170

Figure 3. P289 Trial Design



* V.6 was shown incorrectly as Wk 26 instead of Wk 20 in the figure in the protocol for P289-10.
A1C=hemoglobin A_{1c}; FFSG=fasting fingerstick glucose; FPG=fasting plasma glucose; FS=fingerstick; FSG=fingerstick glucose; Met=metformin; Pbo/PBO=placebo; R=randomization; SCR=screening; T2DM=type 2 diabetes mellitus; TC=telephone call; V=visit; Wk=week; wks=weeks; XR=extended-release.

Source: Page 31 of the Clinical Report P289

Sample size

For Study P083, a total of 190 patients were randomized and treated: 95 subjects in the sitagliptin arm and 95 subjects in the placebo arm. Power calculation was based on 90 subjects per arm. Assuming an effective sample size of 77 patients and a conditional standard deviation of 1.1%, this provides 80% power to detect a treatment difference of 0.5% in A1c reduction at Week 20 (with two-sided α=0.05).

For the pooled study of P170 & 289, a total of 220 patients were randomized and treated: 107 subjects in the sitagliptin & metformin arm and 113 subjects in the metformin arm. Power calculation was based on 90 patients (pooled patients from both P170 and P289) randomized to each treatment. Assuming an effective sample size of 80 patients per treatment at Week 20, and a conditional standard deviation of 1.1%, this provides 80% (90%) power to detect a treatment difference of 0.5% (0.6%) in A1c reduction at Week 20 (with two-sided α=0.05).

Primary endpoints for efficacy evaluation

Change in HbA1c from baseline at Week 20.

3.2.2 Statistical Methodologies

Estimand

The applicant proposed two estimands: the treatment policy (TP) estimand and the treatment effect (TE) estimand. For the two estimands, the target population is identical and is defined as pediatric patients (10 to 17 years old, inclusive) with T2DM who have inadequate glycemic control. The definitions for variable/endpoint, intercurrent event and population-level summary parameter for the two estimands are listed as follows:

- Endpoint:
  - TP: change from baseline in A1c at Week 20
  - TE: change from baseline in A1c at Week 20
- Intercurrent Event
  - TP: regardless of whether study medication or rescue medication was taken up to Week 20
  - TE: data obtained after discontinuation of treatment or after taking rescue medication are not relevant to this estimand

- Population-Level Summary:
  - TP: difference in endpoint means comparing the effect of being randomized to the drug vs the control
  - TE: difference in endpoint means comparing the effect of drug vs. the control

Accordingly, analyses corresponding to the TE estimand will exclude data after the last dose of study medication (plus a 5-day offset) as well as data after the initiation of rescue medication.

Analyses corresponding to the TP estimand will include all available data at the Week 20 timepoint, including data after the last dose of study medication in any patient who remains in the study after discontinuing study medication.

The applicant's primary analyses

For the TP estimand, the primary endpoint of A1C was analyzed using analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment, insulin use at screening (yes/no), baseline BMI percentile, and baseline A1C value as covariates. For the pooled study of P170 & 289, the study type (P170 and P289) and the baseline metformin dose (<1500mg, 1500mg or > 1500mg) were also included as covariates.

A retrieved-dropout (RD) approach for missing data imputation would be used if feasible. The RD analysis used patients who discontinued from study medication but had Week 20 A1C measurement as reference group to impute the missing Week 20 data for patients who were in the same arm and discontinued the study medication and had no Week 20 data. However, since there was no sufficient RD data, the Return-to-Baseline (RTB) approach for missing data imputation was used instead. The RTB analysis included all patients with a baseline A1c measurement. Missing A1c values at Week 20 was imputed from a normal distribution with the expected value set to the patient's baseline value plus a standard deviation using the root mean squared error from the ANCOVA model based on the trial completers. The imputation procedure was repeated 100 times and Rubin's rule was used to combine the result for statistical inference.

For the TE estimand, the constrained longitudinal data analysis (cLDA) was used to analyze the primary endpoint. The model included time (categorical), treatment, time by treatment, baseline BMI percentile, insulin use at screening (yes/no) as covariates. The analysis for the pooled study also included study (P170 and P289), time by study, metformin dose, and the interactions of time by metformin dose. Different from the traditional LDA, the cLDA assumed that a common baseline mean across treatment groups within each combination of baseline metformin dose/insulin use/ study (for pooled study analysis only) and a different mean for each treatment at each of the post-baseline time points. The Kenward-Roger adjustment was used with restricted maximum likelihood (REML) to make proper statistical inference. An unstructured covariance matrix was used to model the correlation among repeated measurements.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

For Study P083 (Table 2), 96 subjects were randomized to the sitagliptin group, 95 to the placebo group. 1 subject in the sitagliptin group was not treated. So, a total of 190 patients were used as the full analysis set (FAS) under the treatment policy estimand. In both Phases A and B, discontinuation from the treatment/study occurred in higher proportion of subjects in the sitagliptin group than in the placebo group. Data on the specific reasons for the discontinuation were not notably different between the two groups. The most commonly reported reason for treatment/study discontinuation in both groups was withdrawal by parent/guardian or by subject.

Table 2. Patient Disposition in P083 and Reasons for Treatment/Study Discontinuation

	Sitagliptin (%)	*Placebo (%)*	*Total (%)*
Randomized	96	95	191
Randomized & Treated Study drug (FAS)	**95**	**95**	**190**
Status for Study Medication in Phase A			
Started	95	95	190
Completed	84 (88.4)	87 (91.6)	171 (90.0)
Discontinued	11 (11.6)	8 (8.4)	19 (10.0)
• Adverse Event	2 (2.1)	0 (0.0)	1 (0.5)
• Non-compliance with study drug	2 (2.1)	2 (2.1)	4 (2.1)
Physician decision	1 (1.1)	0 (0.0)	1 (0.5)
• Subject did not wish to continue for reasons related to assigned study treatment	0 (0.0)	1 (1.1)	1 (0.5)
• Subject did not wish to continue for reasons unrelated to assigned study treatment	1 (1.1)	1 (1.1)	2 (1.1)
• Withdrawal by parent/guardian	4 (4.2)	2 (2.1)	6 (3.2)
• Withdrawal by subject	1 (1.1)	2 (2.1)	3 (1.6)
Status for Trial Segment Phase A			
Started	96	95	191
Completed	85 (88.5)	91 (95.8)	176 (92.1)
Discontinued	11 (11.5)	4 (4.2)	15 (7.9)
• Lost to Follow-Up	2 (2.1)	0 (0.0)	2 (1.0)
• Screen Failure	1 (1.0)	0 (0.0)	1 (0.5)
• Withdrawal by Parent/Guardian	5 (5.2)	2 (2.1)	7 (3.7)
• Withdrawal by Subject	3 (3.1)	2 (2.1)	5 (2.6)
Status for Study Medication in Phase B			
Started	84	87	171
Completed	60 (71.4)	67 (77.0)	127 (74.3)
Discontinued during Phase B	15 (17.9)	11 (12.6)	26 (15.2)
• Adverse Event	4 (4.8)	1 (1.1)	5 (2.9)
• Lost to follow-up	3 (3.6)	0 (0.0)	3 (1.8)
• Non-compliance	1 (1.2)	1 (1.1)	1 (0.6)
• Physician decision	0 (0.0)	1 (1.1)	1 (0.6)
• Pregnancy	0 (0.0)	1 (1.1)	1 (0.6)
• Subjects did not wish to continue for reasons related to assigned treatment	1 (1.2)	2 (2.3)	3 (1.8)
• Subjects did not wish to continue for reasons unrelated to assigned treatment	1 (1.2)	1 (1.1)	2 (1.2)
• Withdrawal by parent/guardian	1 (1.2)	1 (1.1)	2 (1.2)
• Withdrawal by subject	4 (4.8)	3 (3.4)	7 (4.1)
Status not recorded	9 (10.7)	9 (10.3)	18 (10.5)
Status for Trial Segment Phase B			
Started	85	91	176
Completed	64 (75.3)	73 (80.2)	137 (77.8)
Discontinued	11 (12.9)	7 (7.7)	18 (10.2)
• Lost to Follow-Up	4 (4.7)	2 (2.2)	6 (3.4)

• Withdrawal by Parent/Guardian	2 (2.4)	2 (2.2)	4 (2.3)
• Withdrawal by Subject	5 (5.9)	3 (3.3)	8 (4.5)
Status not recorded	10 (11.8)	11 (12.1)	21 (11.9)

Source: The CSR of P083.

Table 3. Patient Disposition in P170 and Reasons for Treatment/Study Discontinuation

	Sita/Met IR (%)	***Met IR (%)***	***Total (%)***
Randomized	63	62	125
Randomized & Treated	**62**	**62**	**124**
Status for Study Medication in Base Study			
Started	62	62	124
Completed Base Study	58 (93.5)	60 (96.8)	118 (95.2)
Discontinued during Base Study	4 (6.5)	2 (3.2)	6 (4.8)
• Adverse event	0 (0.0)	2 (3.2)	2 (1.6)
• Non-compliance	1 (1.6)	0 (0.0)	1 (0.8)
• Lost to follow-up	1 (1.6)	0 (0.0)	1 (0.8)
• Pregnancy	1 (1.6)	0 (0.0)	1 (0.8)
• Withdrawal by subject	1 (1.6)	0 (0.0)	1 (0.8)
Status for Trial Segment Base Study			
Started	63	62	125
Completed	59 (93.7)	62 (100.0)	121 (96.8)
Discontinued	4 (6.3)	0 (0.0)	4 (3.2)
• Lost to Follow-Up	1 (1.6)	0 (0.0)	1 (0.8)
• Technical Problems	1 (1.6)	0 (0.0)	1 (0.8)
• Withdrawal by Subject	2 (3.2)	0 (0.0)	2 (1.6)
Status for Study Medication in Extension Study			
Started Extension Study	27	29	56
Completed Extension Study (Week 21 – Week 52)	24 (88.9)	24 (82.8)	48 (85.7)
Discontinued during Extension Study	3 (11.1)	5 (17.2)	1 (1.8)
• Adverse Event	1 (3.7)	0 (0.0)	1 (1.8)
• Non-compliance	0 (0.0)	1 (3.4)	1 (1.8)
• Pregnancy	0 (0.0)	1 (3.4)	1 (1.8)
• Subject did not wish to continue for reasons related to the assigned treatment	0 (0.0)	1 (3.4)	1 (1.8)
• Subject did not wish to continue for reasons unrelated to the assigned treatment	0 (0.0)	1 (3.4)	1 (1.8)
• Withdrawal by parent/guardian	1 (3.7)	1 (3.4)	2 (3.6)
• Withdrawal by subject	1 (3.7)	0 (0.0)	1 (1.8)
Status for Trial Segment Extension Study			
Started	28	30	58
Completed	25 (89.3)	28 (93.3)	53 (91.4)
Discontinued	3 (10.7)	2 (6.7)	5 (8.6)
• Withdrawal by Parent/Guardian	1 (3.6)	1 (3.3)	2 (3.4)
• Withdrawal by Subject	2 (7.1)	1 (3.3)	3 (5.2)

Source: The CSR of P170

For Study P170 (Table 3), 63 subjects were randomized to the Sita/Met IR group, 62 to the Met IR group. 1 subject in the Sita/Met IR group was not treated. So, a total of 124 patients were used as the full analysis set under the treatment policy estimand. Data on the specific reasons for the discontinuation were not notably different between the two groups.

Table 4. Patient Disposition in P289 and Reasons for Treatment/Study Discontinuation

	Sita/Met XR (%)	***Met XR (%)***	***Total (%)***
Randomized	47	51	98
Randomized & Treated Study drug	**45**	**51**	**96**
Status for Study Medication in Base Study			
Started	45	51	96
Completed Base Study	41 (91.1)	43 (84.3)	84 (87.5)
Discontinued during Base Study	4 (8.9)	8 (15.7)	12 (12.5)
• Adverse Event	2 (4.4)	2 (3.9)	4 (4.2)
• Physician Decision	0 (0.0)	3 (5.9)	3 (3.1)
• Withdrawal by Parent/Guardian	1 (2.2)	3 (5.9)	4 (4.2)
• Withdrawal by Subject	1 (2.2)	0 (0.0)	1 (1.0)
Status for Trial Segment Base Study			
Started	47	51	98
Completed	42 (89.4)	47 (92.2)	89 (90.8)
Discontinued	5 (10.6)	4 (7.8)	9 (9.2)
• Lost to Follow-Up	1 (2.1)	1 (2.0)	2 (2.0)
• Screen Failure	2 (4.3)	0 (0.0)	2 (2.0)
• Withdrawal by Parent/Guardian	1 (2.1)	3 (5.9)	4 (4.1)
• Withdrawal by Subject	1 (2.1)	0 (0.0)	1 (1.0)
Status for Study Medication Extension Study			
Started Extension Study	41	43	84
Completed Extension Study	36 (87.8)	38 (88.4)	74 (88.1)
Discontinued during Extension Study	5 (12.2)	5 (11.6)	10 (11.9)
• Adverse Event	1 (2.4)	1 (2.3)	2 (2.4)
• Lost to follow-up	1 (2.4)	1 (2.3)	2 (2.4)
• Non-compliance	0 (0.0)	1 (0.0)	1 (1.2)
• Physician's decision	1 (2.4)	0 (0.0)	1 (1.2)
• Subject did not wish to continue for reasons related to the assigned treatment	1 (2.4)	0 (0.0)	1 (1.2)
• Withdrawal by parent/guardian	1 (2.4)	0 (0.0)	1 (1.2)
• Withdrawal by Subject	0 (0.0)	2 (4.7)	2 (2.4)
Status for Trial Segment Extension Study			
Started	42	47	89
Completed	39 (92.9)	43 (91.5)	82 (92.1)
Discontinued	3 (7.1)	4 (8.5)	7 (7.9)
• Lost to Follow-Up	1 (2.4)	2 (4.3)	3 (3.4)
• Withdrawal by Parent/Guardian	1 (2.4)	0 (0.0)	1 (1.1)
• Withdrawal by Subject	1 (2.4)	2 (4.3)	3 (3.4)

Source: The CSR of P289.

For Study P289 (Table 4), 47 subjects were randomized to the Sita/Met IR group, 51 to the Met IR group. 2 subjects in the Sita/Met IR group were not treated. So, a total of 96 patients were used as the full analysis set under the treatment policy estimand. Data on the specific reasons for the discontinuation were not notably different between the two groups.

Major baseline demographics and disease characteristics for P083, P170 and P289 are summarized in Tables 5, 6, 7, respectively. For each study, the baseline demographics and disease characteristics are generally comparable between the two trial arms. Also, for each study, the applicant has met the PMR written request's requirement on participant's age and gender; i.e., at least 30% of randomized patients must be 10-14 years old, and at least 30% of randomized patients must be female.

Table 5. Demographics and Baseline Characteristics for P083 (FAS)

		Sitagliptin N=95	***Placebo N=95***	***Total N=190***
Age				
	Mean (SD)	14.3 (2.0)	13.7 (1.9)	14 (2.0)
	Median (Min, Max)	15.0 (10, 17)	14.0 (10, 17)	14.0 (10, 17)
	≤ 14 years at EOT (%)	47 (49.5)	62 (65.3)	109 (57.4)
	>14 years at EOT (%)	48 (50.5)	33 (34.7)	81 (42.6)
Sex				
	Female (%)	41 (43.2)	34 (35.8)	75 (39.5)
	Male (%)	54 (56.8)	61 (64.2)	115 (60.5)
Ethnicity				
	Hispanic or Latino	36 (37.9)	35 (36.8)	71 (37.4)
	No Hispanic or Latino	53 (55.8)	57 (60.0)	110 (57.9)
	Unknown	6 (6.3)	3 (3.2)	9 (4.7)
Race				
	White	48 (50.5)	50 (52.6)	98 (51.6)
	Black	8 (8.4)	2 (2.1)	10 (5.3)
	Asian	13 (13.7)	16 (16.8)	29 (15.3)
	American Indian or Alaska Native	6 (6.3)	9 (9.5)	15 (7.9)
	Multiple	20 (21.1)	18 (18.9)	38 (20.0)
Insulin use at Visit 1				
	Yes (%)	11 (11.6)	11 (11.6)	22 (11.6)
	No (%)	84 (88.4)	84 (88.4)	168 (88.4)
Duration of diabetes (years)				
	Mean (SD)	0.6 (1.1)	0.8 (1.4)	0.7 (1.3)
	Median (Min, Max)	0.2 (0.1, 9.0)	0.3 (0, 7.5)	0.2 (0.0, 9.0)
HbA1c (%)				
	Mean (SD)	7.4 (1.0)	7.6 (1.1)	7.5 (1.0)
	Median (Min, Max)	7.2 (5.8, 10.0)	7.3 (6.2, 11.9)	7.2 (5.8, 11.9)
Body mass index (BMI) (kg/m^2)				
	Mean (SD)	33.3 (7.7)	31.2 (7.7)	32.3 (7.8)
	Median (Min, Max)	31.8 (21.4, 54.6)	29.8 (19.3, 57.0)	30.6 (19.3, 57.0)
BMI Percentile				
	Mean (SD)	97.9 (3.6)	96.3 (8.8)	97.1 (6.8)
	Median (Min, Max)	99.5 (77.0, 100)	99.2 (31.9, 100)	99.4 (31.9, 100)

Table 6. Demographics and Baseline Characteristics for P170 (FAS)

		Sita/Met IR N=62	*Met IR N=62*	*Total N=124*
Age				
	Mean (SD)	14.4 (2.2)	13.9 (1.8)	14.1 (2.0)
	Median (Min, Max)	15.0 (10, 17)	14 (10, 17)	14.0 (10, 17)
	≤ 14 years at EOT (%)	26 (41.9)	40 (64.5)	66 (53.2)
	>14 years at EOT (%)	36 (58.1)	22 (35.5)	58 (46.8)
Sex				
	Female (%)	21 (33.9)	22 (35.5)	43 (34.7)
	Male (%)	41 (66.1)	40 (64.5)	81 (65.3)
Ethnicity				
	Hispanic or Latino	23 (37.1)	23 (37.1)	46 (37.1)
	No Hispanic or Latino	35 (56.5)	36 (58.1)	71 (57.3)
	Unknown	4 (6.5)	3 (4.8)	7 (5.6)
Race				
	White	24 (38.7)	23 (37.1)	47 (37.9)
	Black	2 (3.2)	2 (3.2)	4 (3.2)
	Asian	21 (33.9)	22 (35.5)	43 (34.7)
	American Indian or Alaska Native	0 (0.0)	1 (1.6)	1 (0.8)
	Multiple	14 (22.6)	13 (21.0)	27 (21.8)
Insulin use at Visit 1				
	Yes (%)	8 (12.9)	8 (12.9)	16 (12.9)
	No (%)	54 (87.1)	54 (87.1)	108 (87.1)
Duration of diabetes (years)				
	Mean (SD)	2.1 (1.5)	2.1(1.7)	2.1 (1.6)
	Median (Min, Max)	1.7 (0.1, 6.8)	1.8 (0.3,8.0)	1.7 (0.1, 8.0)
HbA1c (%)				
	Mean (SD)	8.0 (1.2)	8.1 (1.1)	8.1 (1.1)
	Median (Min, Max)	7.8 (5.9, 11.9)	8.1 (6.1, 10.1)	7.9 (5.9, 11.9)
Body mass index (BMI) (kg/m^2)				
	Mean (SD)	31.2 (8.0)	31.1 (9.5)	31.1 (8.7)
	Median (Min, Max)	28.9 (18.5, 58.7)	27.4 (21.2, 63.5)	27.9 (18.5, 63.5)
BMI Percentile				
	Mean (SD)	95.5 (8.4)	94.8 (8.1)	95.2 (8.2)
	Median (Min, Max)	99.0 (53.6, 100)	98.6 (53.6, 100)	98.7 (53.6, 100)

Source: The CSR of P170.

Table 7. Demographics and Baseline Characteristics for P289 (FAS)

		Sita/Met XR N=45	*Met XR N=51*	*Total N=96*
Age				
	Mean (SD)	14.8 (1.9)	14.9 (1.6)	14.8 (1.7)
	Median (Min, Max)	15.0 (10, 17)	15.0 (10, 17)	15.0 (10, 17)
	≤ 14 years at EOT (%)	16 (35.6)	16 (31.4)	32 (33.3)
	>14 years at EOT (%)	29 (64.4)	35 (68.6)	64 (66.7)
Sex				
	Female (%)	13 (28.9)	19 (37.3)	32 (33.3)
	Male (%)	32 (71.1)	32 (62.7)	64 (66.7)
Ethnicity				
	Hispanic or Latino	11 (24.4)	20 (39.2)	31 (32.3)
	No Hispanic or Latino	29 (64.4)	28 (54.9)	57 (59.4)
	Unknown	5 (11.1)	3 (5.9)	8 (8.3)
Race				
	White	22 (48.9)	27 (52.9)	49 (51.0)
	Black	2 (4.4)	4 (7.8)	6 (6.3)
	Asian	15 (33.3)	6 (11.8)	21 (21.9)
	American Indian or Alaska Native	3 (6.7)	9 (17.6)	12 (12.5)
	Multiple	3 (6.7)	5 (9.8)	8 (8.3)
Insulin use at Visit 1				
	Yes (%)	9 (20.0)	8 (15.7)	17 (17.7)
	No (%)	36 (80.0)	43 (84.3)	79 (82.3)
Duration of diabetes (years)				
	Mean (SD)	2.2 (1.3)	2.3 (1.9)	2.3 (1.6)
	Median (Min, Max)	2.2 (0.3, 5.4)	2.0 (0.3, 8.6)	2.2 (0.3, 8.6)
HbA1c (%)				
	Mean (SD)	7.9 (0.9)	8.0 (1.1)	7.9 (1.0)
	Median (Min, Max)	7.9 (6.3, 10.1)	7.8 (6.0, 10.4)	7.8 (6.0, 10.4)
Body mass index (BMI) (kg/m^2)				
	Mean (SD)	31.3 (8.4)	29.9 (7.2)	30.6 (7.8)
	Median (Min, Max)	30.2 (19.3, 64.7)	28.0 (14.4, 48.3)	29.4 (14.4, 64.7)
BMI Percentile				
	Mean (SD)	94.9 (10.6)	91.6 (19.5)	93.1 (16.0)
	Median (Min, Max)	98.8 (40.1, 100)	98.3 (0.1, 100)*	98.6 (0.1, 100)

* A patient from Study P289 was found to have extremely low BMI (i.e., BMI = 14.4 with BMI percentile 0.1). We are not sure if this is the real case or a typo. Since the primary endpoint measurement for this patient seems correct, we did not send an IR to dig into this data issue.
Source: The CSR of P289.

3.2.4 Results

Primary Endpoint: Changes in HbA1c (%) from baseline at Week 20

The primary efficacy analysis results for Study P083 based on the TE estimand and the TP estimand are presented as follows.

Table 8. Primary Analysis Results for Changes in HbA1c (%) at Week 20 Using the Treatment Policy Estimand (P083)

Treatment	Baseline		Week 20		Change from Baseline		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% C.I.)
Sita/Met FDC	95	7.43 (1.02)	84	7.25 (1.68)	95	-0.15(1.56)	0.06 (-0.34, 0.47)
Metformin	95	7.58 (1.06)	87	7.65 (1.70)	95	0.03 (1.46)	0.23 (-0.19, 0.65)
Pairwise Comparison			Difference in LS Means (95% CI)				p-Value
Sita/Met FDC vs Metformin			-0.17 (-0.62, 0.28)				0.463

* For baseline and Week 20, N is the number of subjects with non-missing assessments at the specific timepoint. For change from baseline, N is the number of subjects in the population.

** Based on an ANCOVA model including terms for treatment, baseline BMI percentile, insulin use at screening (yes/no) and baseline A1c value.

Source: The CSR of P083.

Table 9. Primary Analysis Results for Changes in HbA1c (%) at Week 20 Using the Treatment Effect Estimand (P083)

Treatment	Baseline		Week 20		Change from Baseline		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% C.I.)
Sita/Met FDC	95	7.43 (1.02)	78	7.18 (1.66)	95	-0.13(1.58)	-0.01 (-0.35, 0.34)
Metformin	95	7.58 (1.06)	73	7.47 (1.63)	95	0.01 (1.45)	0.18 (-0.17, 0.53)
Pairwise Comparison			Difference in LS Means (95% CI)				p-Value
Sita/Met FDC vs Metformin			-0.19 (-0.68, 0.30)				0.448

* For baseline and Week 20, N is the number of subjects with non-missing assessment at specific timepoint. For Change from Baseline, N is the number of subjects in the population.

** Based on a cLDA model including terms for treatment, time, baseline BMI percentile, insulin use at screening(yes/no), interaction of time by treatment, with the constraint that the mean baseline is the same for all treatment groups.

Source: The CSR of P083.

As presented in Table 8, the treatment difference between the sitagliptin arm and the placebo arm is estimated to be -0.17 with the 95% C.I. (-0.62, 0.28) under the treatment policy estimand. As the C.I. contains zero, superiority of sitagliptin is not established from Study 083. The analysis using the treatment effect estimand also provides similar evidence, as displayed in Table 9.

Next, the primary efficacy analysis results for the Pooled Study of P170 & 289 are presented in Tables 10 and 11.

Table 10. Primary Analysis Results for Changes in HbA1c (%) at Week 20 Using the Treatment Policy Estimand (P170 & 289)

Treatment	Baseline		Week 20		Change from Baseline		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% C.I.)
Sita/Met FDC	107	7.96 (1.11)	95	7.34 (1.46)	107	-0.62(1.40)	-0.23 (-0.61, 0.14)
Metformin	113	8.06 (1.07)	108	7.83 (1.63)	113	-0.25 (1.56)	0.09 (-0.27, 0.46)
Pairwise Comparison			Difference in LS Means (95% CI)				p-Value
Sita/Met FDC vs Metformin			-0.33 (-0.70, 0.05)				0.087

* For baseline and Week 20, N is the number of subjects with non-missing assessments at the specific timepoint. For change from baseline, N is the number of subjects in the population.

** Based on an ANCOVA model including terms for treatment, baseline metformin dose (< 1500mg, 1500mg, >1500mg), study (P170, P289), baseline BMI percentile, insulin use at screening (yes/no) and baseline A1c value.
Source: The ISE of Pooled Study

Table 11. Primary Analysis Results for Changes in HbA1c (%) at Week 20 Using the Treatment Effect Estimand (P170 + 289)

Treatment	Baseline		Week 20		Change from Baseline		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% C.I.)
Sita/Met FDC	107	7.96 (1.11)	91	7.29 (1.45)	107	-0.60(1.40)	-0.23 (-0.94, -0.22)
Metformin	113	8.06 (1.07)	86	7.54 (1.45)	113	-0.42 (1.43)	-0.09 (-0.43, 0.26)
Pairwise Comparison			Difference in LS Means (95% CI)				p-Value
Sita/Met FDC vs Metformin			-0.49 (-0.90, -0.09)				0.018

* For baseline and Week 20, N is the number of subjects with non-missing assessment at specific timepoint. For Change from Baseline, N is the number of subjects in the population.

** Based on a cLDA model including terms for treatment, time, study (P170, P289), baseline BMI percentile, insulin use at screening (yes/no), interaction of time by baseline metformin dose, time by study and time by treatment with the constraint that the mean baseline is the same for all treatment groups.
Source: The ISE of the Pooled Study.

Based on the treatment policy estimand, the treatment difference between the Sita/Met FDC arm and the metformin arm is estimated to be -0.33 with 95% C.I. (-0.70, 0.05), indicating an insignificant treatment effect of Sita/Met FDC (See Table 10). On the other hand, the treatment difference is -0.49 with 95% C.I. (-0.90, -0.09) under the treatment effect estimand, suggesting a nominally significant treatment effect of Sita/Met FDC (See Table 11). The inconsistent outcomes derived from the two estimands deserve further investigation.

Separate Analyses on P170 and P289

To facilitate our understanding of the inconsistent results as described in the last section, a separate ANCOVA analysis was performed on Study P170 and Study P289 respectively, with details presented in Table 12. As shown in the table, while the study results for P170 successfully demonstrated that the investigational drug was nominally superior to metformin regarding glycemic control, the result of P289 suggested otherwise.

Table 12. ANCOVA Analyses on P170 and P289

	Study P170 (N = 124)	Study P289 (N = 96)
Change in A1C from Baseline at Week 20	LS Mean (95% CI)	LS Mean (95% CI)
Sita/Met	-0.44 (-0.97, 0.09)	0.02 (-0.52, 0.56)
Metformin	0.14 (-0.37, 0.65)	-0.009 (-0.54, 0.52)
Difference in LSmeans (95% CI)	-0.58 (-1.07, -0.10) P-value = 0.02	0.03 (-0.57, 0.62) P-value = 0.93

* The analysis is conducted based on the treatment policy estimand. Return-to-baseline and Rubin's Rule are used for missing data imputation.

For further investigation, summary statistics on the longitudinal data regarding change in A1c (%) on P170 and P289 are displayed in Table 13. Information on P083 is also included in the table for reference.

Table 13. Summary Statistics for A1c (%) Change from Baseline Over Time

	P170			P289			P083		
Treatment	N	Mean (SD)	Median	N	Mean (SD)	Median	N	Mean (SD)	Median
Time 1									
Drug	56	-0.93 (0.86)	-0.80	42	-0.60 (0.79)	-0.55	75	-0.39 (0.67)	-0.30
Control	59	-0.30 (1.03)	-0.30	50	-0.15(0.89)	-0.20	84	-0.19 (1.01)	-0.10
Time 2									
Drug	55	-0.96 (1.15)	-0.90	40	-0.40(1.24)	-0.55	83	-0.25 (1.09)	-0.30
Control	56	-0.40 (1.24)	-0.25	46	-0.24(1.53)	-0.10	76	-0.03 (1.26)	-0.10
Time 3									
Drug	52	-0.90 (1.34)	-0.80	39	**-0.19 (1.40)**	-0.60	78	-0.13 (1.58)	-0.10
Control	49	-0.33 (1.53)	-0.20	37	**-0.54 (1.30)**	-0.20	73	0.01 (1.45)	0.00

** N is the number of patients who stayed on their assigned treatment at a given time point.*
** Time 1, 2 and 3 are Weeks 6, 12 and 20 for Studies 170 and 289, and Weeks 8, 14 and 20 for Study P083.*
Source: The CSR's of P083, P170 and P289.

As Table 13 demonstrated, for a given trial at a particular time point, the drug arm always achieves better performance than the control arm regarding mean reduction in A1c (%), with only one exception from Study P289 at Week 20 (highlighted in bold), where the control arm averages a 0.54% reduction in A1c level, as opposed to only a 0.19% reduction in the treatment arm. To better understand this seemingly *reversed* mean effect of A1c reduction at Week 20, we took a further look of the A1c measurements collected from patients who had missing A1c records and/or resorted to rescue medication during the primary study. Table 14 displays the details.

Table 14. A1C (%) change from baseline in patients in P289 who had missing A1c records and/or resorted to rescue medication during the primary study.

		A1c (%) Change			*End of Study Status*
Treatment	Patient ID	Week 6	Week 12	Week 20	
		-0.3	-1.0	x	Primary study completed (missing visit at Week 20)
Sita/Met XR FDC		0.6	1.7	x	Study withdrawn by subject
		-0.4	(-0.5)	(-0.9)	Primary study completed
		x	x	x	Treatment discontinued due to AE
		x	x	x	Study withdrawn by parent/guardian
		-0.9	(-0.4)	x	Treatment discontinued due to AE
		-0.9	-1.2	x	Treatment discontinued due to AE
		0.0	0.2	(0.8)	Treatment discontinued due to AE
		1.1	0.8	(-1.4)	Treatment discontinued based on physician's decision
		-0.2	1.4	(1.2)	Primary study completed
		0.7	1.5	x	Study withdrawn by parent/guardian
		1.3	2.0	(2.6)	Primary study completed
Met XR		1.0	2.0	(2.6)	Primary study completed
		1.6	3.1	(3.3)	Primary study completed
		2.0	3.9	(1.6)	Primary study completed
		0.8	x	(-1.2)	Primary study completed
		0.8	x	(1.1)	Primary study completed
		0.0	x	x	Treatment discontinued based on physician's decision
		0.4	x	x	Study withdrawn by parent/guardian
		-0.4	x	(-0.5)	Treatment discontinued based on physician's decision

* Patients with IDs in bold represent those who resorted to rescue medication after they deviated from their assigned treatment.

** Data entries marked as x mean missing A1c records.

*** Data entries in parenthesis are collected as retrieved dropouts after patients deviated from their assigned treatment.

As shown in Table 14, within the control arm, 11 out of the 14 patients (79%) who deviated from their assigned treatment prior to Week 20 experienced a *rise in A1c level from baseline* at the last time point observed before their deviation. In contrast, only 1 of the 6 deviants (17%) in the treatment arm experienced an increased A1c level from baseline at the last time point observed prior to their deviation. Since by the time of Week 20, the control arm has been rid of most subjects who had poor glycemic control (i.e., an increased A1c level compared to the baseline),

this may explicate why the control arm outperforms the treatment arm at Week 20 regarding the mean A1c (%) change, as presented in Table 14. [4]

Additionally, the ID in bold in Table 14 were for the patients who resorted to rescue medication after they deviated from their assigned treatment. For many patients, rescue medication may help mitigate their hyperglycemic condition, as are the cases for (b) (6) , etc. Hence, when the statistical analysis is conducted under the treatment policy estimand (where all data regardless of intercurrent events are taken into consideration), the glycemic lowering effect of the rescue medication may partially contribute to the finding that the investigational drug fails to demonstrate a significant treatment effect compared to the control drug.

3.2.5 Conclusion

Based on the statistical analyses pre-specified in the study protocols, neither Study P083 nor the Pooled Study of P170 & 289 was able to provide sufficient evidence to demonstrate efficiency of the investigational product. Therefore, the applicant made no efficacy claim in the label. Of note, an unbalanced dropout pattern was observed in P289; i.e., most patients in the control arm who deviated prematurely from control treatment had poor treatment effect prior to their dropout. Since some of the dropouts benefited from the rescue medication, this may partially explain the inconsistent results derived from the treatment policy estimand and the treatment effect estimand of the pooled study.

3.3 Evaluation of Safety

For each individual trial (P083, P170 and P289), the safety and tolerability of sitagliptin through 54 weeks were assessed among the *All Subjects as Treated* (AsaT) population, which consists of all randomized patients who took at least 1 dose of study medication. All individual studies included summaries of specific adverse events (including nature, frequency and relationship to treatment), vital signs, laboratory parameters (including hematology and biochemistry), pubertal development based on Tanner staging, growth parameters based on height standard deviation score and incidence of hypoglycemia. Overall, Sitagliptin was found generally well-tolerated over 54 weeks in all three studies. Please refer to Section 12 in clinical study reports for detailed safety analysis results for each individual study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses guided by the treatment policy estimand framework (i.e., the ANCOVA model applied to the treatment policy FAS with missing data imputed based on the return-to-baseline principle) were performed for Study P083 and for the Pooled Study of P170 & 289, respectively. For each study, subgroups are defined by sex (Female vs Male), race (White vs Others), and age (≥ 14 vs < 14). The analysis results are presented as follows.

[4] Of note, this unbalanced dropout pattern was not observed in either P083 or P170.

Table 15. A1C(%) Change from Baseline at Week 20 for Different Subgroups ANCOVA Analysis on Treatment Policy FAS (P083)

Treatment	Baseline		Week 20		Change from baseline in A1c at Week 20		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)	Difference in LS Mean (95% CI)
Gender							
Male							
Sita/Met FDC	41	7.47 (1.04)	38	7.70 (2.10)	41	0.43 (-0.25, 1.11)	-0.04 (-0.86, 0.77)
Metformin	34	7.36 (0.78)	30	7.72 (1.60)	34	0.47 (-0.29, 1.24)	
Female							
Sita/Met FDC	54	7.40 (1.01)	46	6.88 (1.14)	54	-0.20 (-0.69, 0.30)	-0.36 (-0.87, 0.16)
Metformin	61	7.71 (1.18)	57	7.61 (1.76)	61	0.16 (-0.32, 0.64)	
Race							
White							
Sita/Met FDC	48	7.40 (1.09)	42	7.23 (1.52)	48	0.00 (-0.59, 0.59)	-0.12 (-0.71, 0.46)
Metformin	50	7.47 (1.10)	45	7.57 (1.63)	50	0.13 (-0.50, 0.76)	
Other							
Sita/Met FDC	47	7.46 (0.94)	42	7.28 (1.85)	47	0.12 (-0.47, 0.71)	-0.22 (-0.91, 0.47)
Metformin	45	7.71 (1.02)	42	7.74 (1.78)	45	0.34 (-0.24, 0.92)	
Age							
≤ 14 Years Old							
Sita/Met FDC	47	7.46 (1.02)	42	7.06 (1.48)	47	-0.21 (-0.69, 0.27)	-0.23 (-0.78, 0.31)
Metformin	62	7.64 (1.14)	57	7.49 (1.41)	62	0.02 (-0.46, 0.50)	
> 14 Years Old							
Sita/Met FDC	48	7.40 (1.02)	42	7.45 (1.86)	48	0.40 (-0.30, 1.10)	-0.30 (-1.04, 0.44)
Metformin	33	7.47 (0.91)	30	7.97 (2.14)	33	0.70 (-0.05, 1.44)	

Source Based on the reviewer's analysis and the the adeff dataset provided by the Applicant

Table 16. A1C(%) Change from Baseline at Week 20 for Different Subgroups ANCOVA Analysis on Treatment Policy FAS (P170 & 289)

Treatment	Baseline		Week 20		Change from baseline in A1c at Week 20		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)	Difference in LS Mean (95% CI)
Gender							
Male							
Sita/Met FDC	34	7.62 (1.24)	28	6.87 (1.19)	34	-0.26 (-1.11, 0.60)	-0.60 (-1.34, 0.14)
Metformin	41	8.01 (1.05)	38	7.76 (1.89)	41	0.34 (-0.55, 1.24)	
Female							
Sita/Met FDC	73	8.11 (1.01)	67	7.54 (1.53)	73	-0.18 (-0.60, 0.23)	-0.21 (-0.64, 0.23)
Metformin	72	8.08 (1.08)	70	7.87 (1.47)	72	0.02 (-0.37, 0.42)	
Race							
White							
Sita/Met FDC	46	7.84 (1.04)	37	7.36 (1.51)	46	-0.17 (-0.78, 0.45)	-0.04 (-0.65, 0.57)
Metformin	50	8.04 (1.08)	46	7.68 (1.72)	50	-0.12 (-0.69, 0.44)	
Other							
Sita/Met FDC	61	8.05 (1.16)	58	7.32 (1.45)	61	-0.32 (-0.81, 0.16)	-0.54 (-1.02, -0.06)
Metformin	63	8.07 (1.06)	62	7.94 (1.56)	63	0.21 (-0.27, 0.71)	
Age							
≤ 14 Years Old							
Sita/Met FDC	42	8.06 (1.13)	37	7.43 (1.34)	42	-0.28(-0.83, 0.27)	-0.39 (-0.98, 0.21)
Metformin	56	8.14 (1.03)	54	7.84 (1.61)	56	0.10 (-0.46, 0.67)	
> 14 Years Old							
Sita/Met FDC	65	7.89 (1.09)	58	7.28 (1.55)	65	-0.24 (-0.77, 0.29)	-0.21 (-0.72, 0.30)
Metformin	57	7.97 (1.10)	54	7.82 (1.65)	57	-0.03 (-0.53, 0.47)	

Source Based on the reviewer's analysis and the the adeff dataset provided by the Applicant

For both studies, the treatment arm was found to perform better than the control arm across all subgroups in terms of glycemic control. The treatment difference between the two arms, however, is generally not statistically significant. (The only exception appears in the *Other* race category from the Pooled Study of P179 & 289, which is most likely a type I error). The insignificant results derived from the subgroup analyses are consistent with the findings based on the entire population.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There is no major statistical issue for efficacy and safety evaluation in this submission.

5.2 Collective Evidence

Under the treatment-policy estimand, data collected from all randomized and treated patients regardless of initiation of rescue therapy were used in the ANCOVA model pre-specified in the study protocols. Missing data were handled based on the return-to-baseline principle and Rubin's Rule for multiple imputation.

Neither of the two efficacy analysis results for Study P083 and the Pooled Study of P170 & 289 was able to demonstrate superiority of sitagliptin regarding A1c reduction when compared to placebo, either as a mono-therapy or as a add-on therapy to metformin.

Safety evaluation has shown that sitagliptin was generally well-tolerated through a 54-week length of treatment.

5.3 Conclusions and Recommendations

The statistical findings in this submission failed to demonstrate superiority of sitagliptin compared to placebo regarding glycemic control in pediatric patients (10 to 17 years old) with T2DM.

5.4 Labeling Recommendations

The applicant proposed the following change to Section 8.4 Pediatric Use of the labels for Janumet® XR:

Similar proposed changes can also be found in the labels for Janumet® and Januvia®. These label changes reflect the findings from the pediatric trials P083, P170 and P289; hence the proposed changes are approvable.

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/

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11/10/2020 09:22:40 AM

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