CLINICAL PHARMACOLOGY MEMO

NDA:	21995/S-047; 22044/S-048; 202270/S-022
Submission Date(s):	June 4, 2020
Brand Name:	Januvia®; Janumet®; Janumet XR®
Generic Name:	Sitaglipin; sitaglipin/metformin IR; sitagliptin/metformin XR
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Khurana Manoj, Ph.D.
OCP Division:	Division of Cardiometabolic and Endocrine Pharmacology
OND Division:	Division of Diabetes, Lipid Disorders, and Obesity
Sponsor:	Merck
Submission Type:	Prior Approval Supplement; Post Marketing Requirement • NDA 021995 PMR 224-1; \\CDSESUB1\evsprod\NDA021995\0505 • NDA 022044 PMR 856-1; \\CDSESUB1\evsprod\NDA022044\0254 • NDA 202270 PMR 1802-04; \\CDSESUB1\evsprod\NDA202270\0147
Formulation (Strength):	Oral tablets • NDA 021995; 25, 50 and 100 mg • NDA 022044; 50/500, 50/1000 mg • NDA 202270; 50/500, 50/1000, 100/1000 mg

Reference ID: 4707027

Summary of Clinical Pharmacology Findings

The sponsor submitted Prior Approval Supplement (PAS) for Januvia, Janumet and Janumet XR to change the labeling based on the pediatric clinical study results. The sponsor requested the Pediatric Exclusivity Determination provided that the study results in this submission satisfied the Written Request (WR) for Januvia, Janumet and Janumet XR (see the following table summary);

Table 1 Summary of clinical studies with WR and corresponding studies that the sponsor conducted and also submitted to support current supplements

Written Request Item		Study (Protocol)
Study 1 (Phase III)	You must submit the complete study report for study 083 conducted under IND 065495 (NDA 021995), a randomized, double-blind, placebo- controlled, safety and efficacy study of the effect of sitagliptin on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are not on treatment with an oral antihyperglycemic agent (AHA) or are on a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% for drug-naïve patients, and ≥7.0% and ≤10.0% for patients on insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- controlled Phase "A," and a, at least a 32-week, active-controlled Phase "B." The protocol must specify glycemic rescue and individual patient discontinuation criteria.	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control (Protocol 083, P083)
Study 2 (Phase III)	You must submit the complete study report for study 170 conducted under IND 070934 (NDA 022044), a randomized, double-blind, placebo- controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of insulin for > 12 weeks prior to screening and have inadequate glycemic control (HbA1c >6.5% and <10.0% for patients on metformin, and >7.0% and <10.0% for patients on metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- controlled "base study", and at least a 32-week, active-controlled "extension study". The protocol must specify glycemic rescue and individual patient discontinuation criteria.	A Multicenter, Double-blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A (A Fixed-Dose Combination Tablet of Sitagliptin and Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin) (Protocol 170, P170)
Study 3 (Phase I)	You must submit the complete study report for study 296 conducted under IND 101964 (NDA 202270), a Phase I PK study of JANUMET XR to assess the pharmacokinetics and ability for pediatric patients with type 2 diabetes to swallow MK 0431A XR tablets.	A Study to Assess the Pharmacokinetics and Ability for Pediatric Patients with Type 2 Diabetes to Swallow MK-0431A XR Tablets (Protocol 296, P296)
Study 4 (Phase III)	You must submit the complete study report for study 289, conducted under IND 101964 (NDA 202270), a randomized, double-blind, placebo controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed- dose	A Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety

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	combination tablet of sitagliptin and metformin extended release) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% for metformin-treated patients, and ≥7.0% and ≤10.0% for patients treated with metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- controlled Phase "A", and at least a 32-week, active-controlled Phase "B". The protocol must specify glycemic rescue and individual patient discontinuation criteria.	and Efficacy of MK-0431A XR (a Fixed-Dose Combination Tablet of Sitagliptin and Extended-Release Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin) (Protocol 289, P289).

It was concluded that the submission met the WR requirements in the CDER's Pediatric Exclusivity Board meeting held on 10/20/2020 (refer Pediatric Exclusivity Determination Checklist in DARRTS dated 10/30/2020). With regards to the pediatric efficacy and safety trials, see the review by Dr. Kim Shimy for details of Phase III studies (i.e., Study 1, 2 and 4, Table 1). There was no PK data collection from these studies and accordingly the acceptability of the efficacy and safety data is further deferred to reviews from statistical and clinical review disciplines.

The primary objective of Study P296 (i.e., Study 3, Table 1) was to assess the pharmacokinetics and ability for pediatric patients to swallow Janumet XR tablets as there was concern at swallowability of Janumet XR tablets due to larger dimension of Janumet XR tablets for pediatric subjects. Study design of P296 was an open-label, fixed-sequence, 2-period study in pediatric (age ranging from 10 to 17-year old) patients with Type 2 Diabetes Mellitus (T2DM) (n=12). Subjects received treatments as follows:

- Group 1; two final market image Janumet XR (50 mg/1000 mg) tablets on Day 1 and then two matching placebo tablets from Day 2 to 9
- Group 2; two matching placebo tablets from Day 1 to 9

PK of sitagliptin and metformin was characterized following Janumet XR on Day 1. PK parameters of sitagliptin and metformin were summarized in Table 2. Individual PK data indicate that there was no apparent issue with swallowability there were no missing PK parameters or significantly lower than average values. There was no significant association between age and exposure warranting a dose adjustment (Figure 1) and sitagliptin PK parameters following 100 mg (AUCinf=6020 nM*hr, Table 2) were consistent with those observed earlier in study P081 (i.e., AUCinf=5869 mM*hr). Swallowability was separately assessed using specific questionnaire at various time points and it was concluded that the medication was relatively easy to swallow. See the review by Dr. S.W. Johnny Lau dated 10/13/2015 in DARRTS for details of swallowability assessment.

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Table 2 Summary of PK parameters; sitagliptin and metformin (Source; Table 11-1, CSR of P296)

PK Parameters	Geometric Mean (CV%)	
	Sitagliptin	Metformin
$AUC_{0-\infty}$ [1]	6020 (24.8)	NA
AUC_{0-last} [1]	5940 (25.7)	NA
AUC_{0-24hr} [1]	5310 (22.4)	14200 (39.7)
C_{max} [2]	757 (40.1)	1490 (29.1)
T_{max} (hr) [3]	1.52 (0.97, 3.05)	5.00 (3.98, 7.22)
Apparent terminal $t_{1/2}$ (hr)	10.0 (27.3)	NA

1 Units of AUC are nM*hr for Sitagliptin and ng*hr/mL for Metformin respectively.
2 Units of Cmax are nM for Sitagliptin and ng/mL for Metformin respectively.
3 Median (Min, Max)
NA=Not Applicable; metformin PK assessment was limited to 24 hours as subjects resumed metformin 24 hours post dose of Janumet as indicated in the protocol

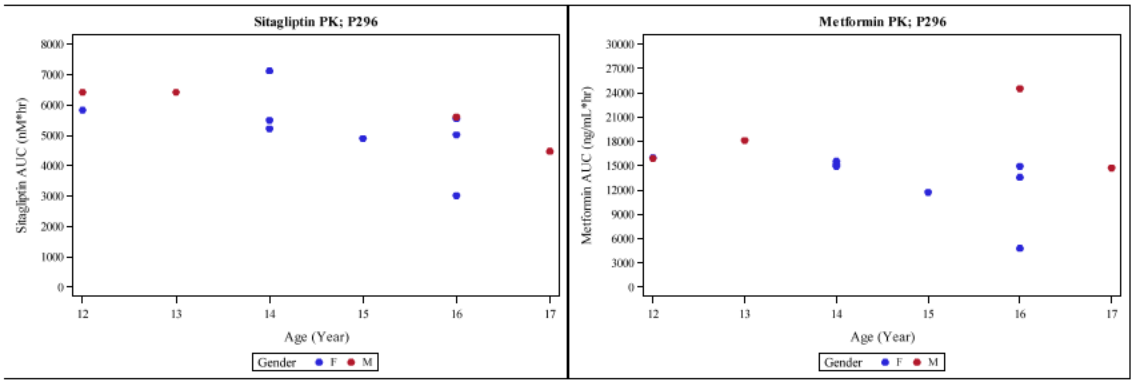

Figure 1 Relationship between sitagliptin or metformin (right) and age following two tablets of Janumet XR 50/1000mg in pediatric patients with T2DM (Study P296)

The standard LC/MS/MS method was used to measure sitagliptin and metformin plasma concentrations. The bioanalytical reports (section 16.1.11.2, CSR of P296 and 16.1.11.1, CSR of P081) indicate that the assay methods were appropriately validated in supporting the PK data from these studies.

The sponsor conducted a Phase I study (Study P081, NDA21995) to support sitagliptin dose for Phase III studies before the initiation of P083 (Study 1, Table 1). There was no apparent age-related exposure difference among pediatric subjects (Figure 2) as it was concluded that sitagliptin exposure in the proposed pediatric patients with T2DM was matching to that of adult patients with T2DM following the same doses (see the clinical pharmacology review for the PPSR dated on 11/27/2012). There were no additional findings from this submission related to results of Study P081.

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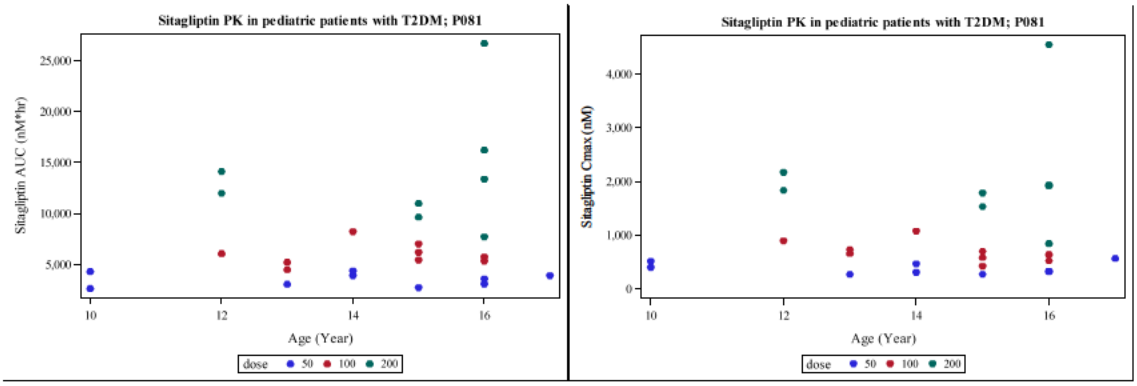

Figure 2 Relationship between sitagliptin AUC (left) or Cmax (right) and age following 50, 100 or 200 mg in pediatric patients with T2DM (Study P081)

Labeling Comments:

The sponsor proposed to delete the pediatric information in labeling section 12.3 of Januvia, (b) (4) as the pediatric indication is not approved and the PK study have been conducted. The sponsor's proposal is acceptable from the clinical pharmacology perspective.

(underlined text indicates addition and ~~strikethrough~~ text indicates deletion):

12.3 Pharmacokinetics

Pediatric Patients

~~Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.~~

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/s/

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11/24/2020 02:57:21 PM

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