CDTL Review
Division Summary Memo for Regulatory Action

Date	
From	Patrick Archdeacon, M.D.
NDA #	sNDA 021995/S-047 sNDA 022044/S-048 sNDA 202270/S-022
Applicant	Merck Sharp & Dohme Corp. (MSD)
Date of Submission Receipt	June 4, 2020
PDUFA Goal Date	December 4, 2020
Established (USAN) names	Sitagliptin, Sitagliptin/metformin HCl, Sitagliptin/metformin extended release
Trade names	Januvia, Janumet, Janumet XR
Dosage forms / Strength	NDA 021995: Oral tablet (25 mg, 50 mg, and 100 mg sitagliptin) NDA 022044: Oral tablet (50 mg/500 mg, 50 mg/1000 mg; [sitagliptin/metformin HCl]) NDA 202270: Oral tablet (100 mg/1000 mg, 50 mg/500 mg, 50 mg/1000 mg); [sitagliptin/metformin HCl extended-release])
Applicant Proposed Labeling Changes	To add information from three pediatric studies (P083, P170, and P289) to the Prescribing Information (PI) of three sitagliptin containing products (Januvia, Janumet, and Janumet XR)
Recommended Action	Approval; PMR 224-1, PMR 856-1, and PMR 1802-4 Fulfilled

1. Introduction

This document serves as the 'Summary Basis for Regulatory Action' memo for sNDAs seeking to add information to the Prescribing Information (PI) of three sitagliptin containing products (Januvia, Janumet, and Janumet XR) to support the addition of three pediatric studies (P083, P170, and P289) to the Prescribing Information (PI) of three sitagliptin containing products (Januvia, NDA 21995; Janumet, NDA 22044; Janumet XR, NDA 202270). On the basis of the data from the three phase 3 trials and also from a phase 1 trial (P296) previously submitted, the Pediatric Exclusivity Board determined at its October 20, 2020 meeting that the submission (in conjunction with the previous submission containing the results of P296) constitutes a fair response to the Written Request for NDAs 21995, 22044, and 202270, as amended on December 7, 2017; pediatric exclusivity was granted on this basis effective October 30, 2020. As detailed in the document, while the data from pediatric trial program failed to demonstrate evidence of effective in children with T2D (and therefore do not suffice to broaden the glycemic control indications to include children with T2D), the data from the three pediatric studies was determined to fulfill the three remaining Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs) for the three products: PMR 224-1, PMR 856-1, and PMR 1802-4. In addition, information describing the results of the pediatric program were added to Section 8.4 of the PIs for all three sitagliptin products.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety review (DMEP)	Kim Shimy	December 2, 2020
Statistical (DBII) review	Wenda Tu	November 10, 2020
Clinical Pharmacology review	Sang Chung	November 24, 2020
OPDP review	Samantha Bryant	November 5, 2020
Patient Labeling Review	Lonice Carter	November 18, 2020
DMEPA review	Ariane Conrad	August 7, 2020
PeRC minutes	Jacqueline Yancy	November 19, 2020
DMEP: Division of Metabolism and Endocrinology Products, **DBVII:** Division of Biometrics VII, **OPDP:** Office of Prescription Drug Promotion, **DMEPA:** Division of Medication Error Prevention and Analysis, **PeRC:** Pediatric Research Committee		

2. Background

The sNDA supplement addresses the use of sitagliptin in children with type 2 diabetes (T2D). Sitagliptin phosphate was approved in 2006 for the treatment of T2D in adults (NDA 21995; Januvia), sitagliptin phosphate combined with metformin hydrochloride immediate release (NDA 22044; Janumet) and sitagliptin phosphate combined with metformin hydrochloride extended release (NDA 202270; Janumet XR) were approved in 2007 and 2012, respectively,

for the same indication. T2D results as failing pancreatic β cells can no longer overcome increasing insulin resistance; it commonly presents in children and adults that are overweight and is more prevalent among certain racial and ethnic groups (with higher rates observed, for instance, in Hispanic, Native American, and African American populations). Though still primarily a disease of adulthood, the prevalence of pediatric T2D has been steadily increasing (new cases in the US have recently been estimated at 5,000 per year). However, while a large armamentarium of drugs has been approved to treat T2D in adults, few of these products have been rigorously studied in children with T2D. Currently, the only products approved for the treatment of T2D in pediatric patients are metformin (pediatric approval in 2000), liraglutide (pediatric approval in 2019), and insulin (though the majority of insulin products broadly indicated for "improve glycemic control in adults and children with diabetes mellitus" have not been formally evaluated in trials conducted in pediatric patients with T2D).

In general, T2D presents similarly in children as it does in adults. However, some data suggest that children may experience more rapid progression of the disease than do adults: compared to adults with T2D, in children with T2D, the insulin resistance exhibited by children is often greater, the deterioration of β cell function is often faster, and the development of diabetic complications (e.g., retinopathy, nephropathy, cardiomyopathy) is often sooner.

FDA has relied on authorities granted through both the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) to encourage investigation into the use of antihyperglycemic agents, including sitagliptin, in children with T2D. Concurrent with each the initial approvals of NDA 21995, NDA 22044, and NDA 202270, FDA issued PMRs (PMR 224-1; PMR 856-1; PMR 1802-1 and PMR 1802-2, respectively) requiring post-market pediatric studies. PMR 1802-1 was previously fulfilled in 2016 through the submission of the results of trial P296, a pediatric PK and swallowing ability study of Janumet XR. PMR-1802 was released and replaced (first with PMR 1802-3, then with PMR 1802-4). Trials P083, P170, and P289 were designed with FDA input to address the requirements of PMR 224-1, PMR 856-1, and PMR 1802-4. In addition, in 2007, the Applicant first submitted a proposed pediatric study request (PPSR) related to its sitagliptin products. The initial proposed pediatric study request ultimately led FDA to issue a Written Request for NDAs 21995, 22044, and 202270 in 2012 (the Written Request was subsequently amended, first in 2013 and again in 2017). Please see the Primary Clinical Review of this sNDA by Dr. Kim Shimy for additional details on the regulatory history underlying the PREA PMRs and also the Written Request.

On June 4, 2020, the Applicant submitted the sNDA to fulfill its remaining PREA PMRs and meet the requirements of the Written Request. Based on the results of the trials, the Applicant did not request broadening its indication for improved glycemic control in adults with T2D to the pediatric population with T2D (see Section 6 below for details regarding the results of the trials with respect to the antihyperglycemic effects observed). CDER's Pediatric Exclusivity Board concluded that the submission (when combined with the previous submission containing the results of Trial 296) met the requirements of the Written Request during its October 20, 2020 meeting; pediatric exclusivity was granted on this basis effective October 30, 2020.

3. CMC/Device

The submission does not contain new CMC data.

4. Nonclinical Pharmacology/Toxicology

The submission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Sang Chung from the Office of Clinical Pharmacology (OCP) wrote a memo to document the findings of two pediatric Phase 1 studies previously submitted and reviewed: P081 and P296.

P081 was a single-dose study that assessed the pharmacokinetics of sitagliptin in 35 patients with T2D aged 10 to 17 years. The PK study was conducted to help determine the dosing for the three Phase 3 pediatric trials (P083, P170, and P289). The results of P081 were reviewed by OCP prior to the initiation of the Phase 3 trials as part of the clinical pharmacology review of the PPSR; OCP concluded at that time that sitagliptin exposure in children with T2D as comparable to the sitagliptin exposure in adults with T2D. Based on the results of the P081, the dose of 100 mg sitagliptin once daily was selected for the three Phase 3 pediatric trials.

P296 was a pharmacokinetic and swallowability trial of Janumet XR tablets conducted in 12 patients with T2D aged 10 to 17 years. The results of P296 indicated no apparent issues with swallowability. Dr. Chung also concluded that there is no significant association between age and sitagliptin exposures or metformin exposures that would warrant a dose adjustment. As noted earlier, the results of P296 were previously determined to fulfill PMR 1802-1 in 2016 and to meet requirements of the Written Response in October 2020.

Dr. Chung also concluded that the results of P081 and P296 support the Applicant's proposal to remove language in section 12.3 of the Januvia, Janumet, and Janumet XR PIs stating that "Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed."

I concur with the findings and recommendations of Dr. Chung.

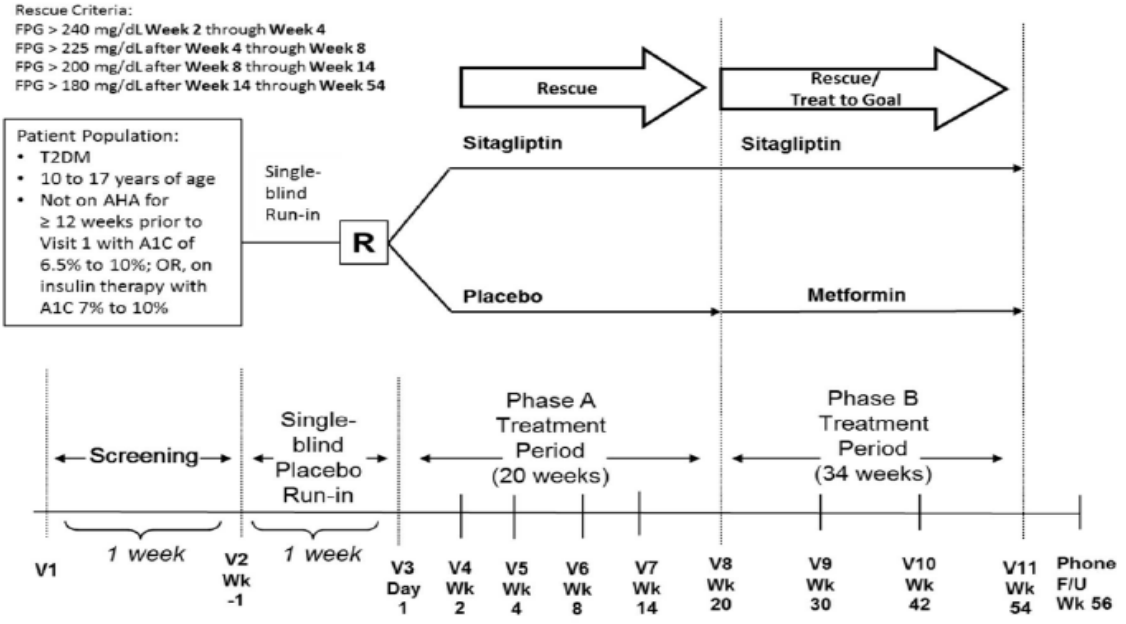
6. Clinical/Statistical- Efficacy

Dr. Wenda Tu from the Office of Biostatistics, Division of Biometrics II and Dr. Kim Shimy from the Division of Diabetes, Lipid Disorders, and Obesity reviewed the clinical data from the three Phase 3 pediatric trials (P083, P170, and P289) to assess efficacy. Overall, Drs. Tu and Shimy concluded that the data from the trials do not support a conclusion that sitagliptin is effective in children with T2D. Based on their analyses, they recommended language to

describe the results of the pediatric trials for addition to section 8.4 of the Januvia, Janumet, and Janumet XR PIs. I concur with their findings and recommendations.

In brief, the sitagliptin pediatric program comprises three studies of similar design. P083 is a multi-center, randomized, double-blind, parallel-group trial comparing sitagliptin 100 mg to placebo during the first 20 weeks of the trial (Phase A) and sitagliptin 100 mg to metformin for the remaining 34 weeks of the trial (Phase B). P170 is a multi-center, randomized, double-blind, parallel-group trial comparing sitagliptin and metformin IR to metformin IR for 54 weeks. P289 is a multi-center, randomized, double-blind, parallel-group trial comparing sitagliptin and metformin XR to metformin XR for 54 weeks. For all three trials, the primary efficacy endpoint is the change in HbA1c from baseline measured at Week 20. sitagliptin metformin XR to metformin XR for 54 weeks.

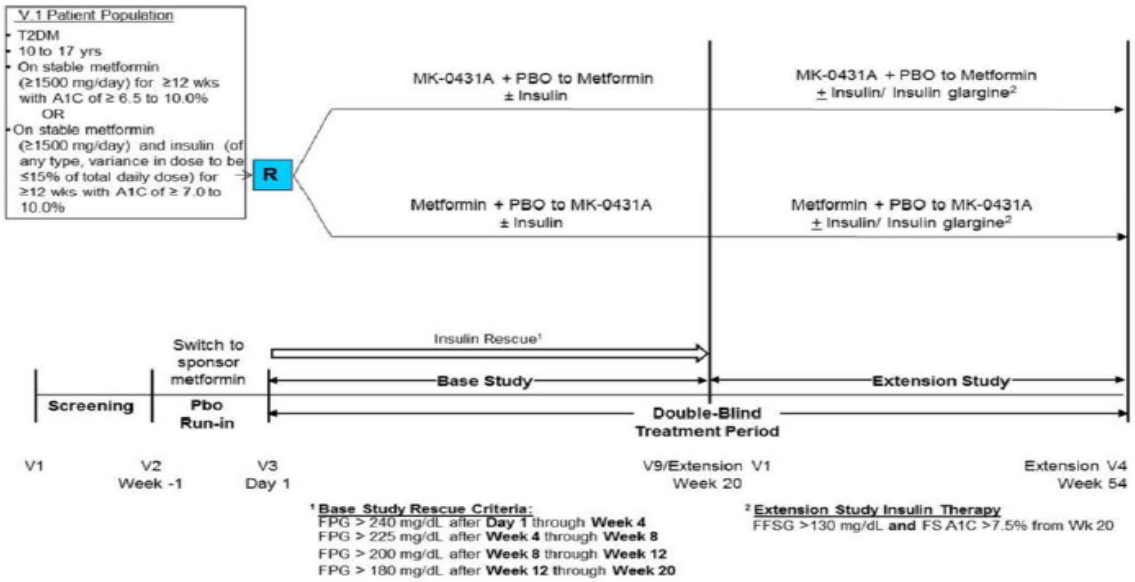
Figure 1: P083 Trial Design



A1c=hemoglobin A1c, FPG= fasting plasma glucose, FFSG= fasting fingerstick glucose, MK-0431A XR= Sita/Met XR FDC, R= randomization, V= visit, Wk= week, F/U= follow up

Source: FDA Primary Clinical Review

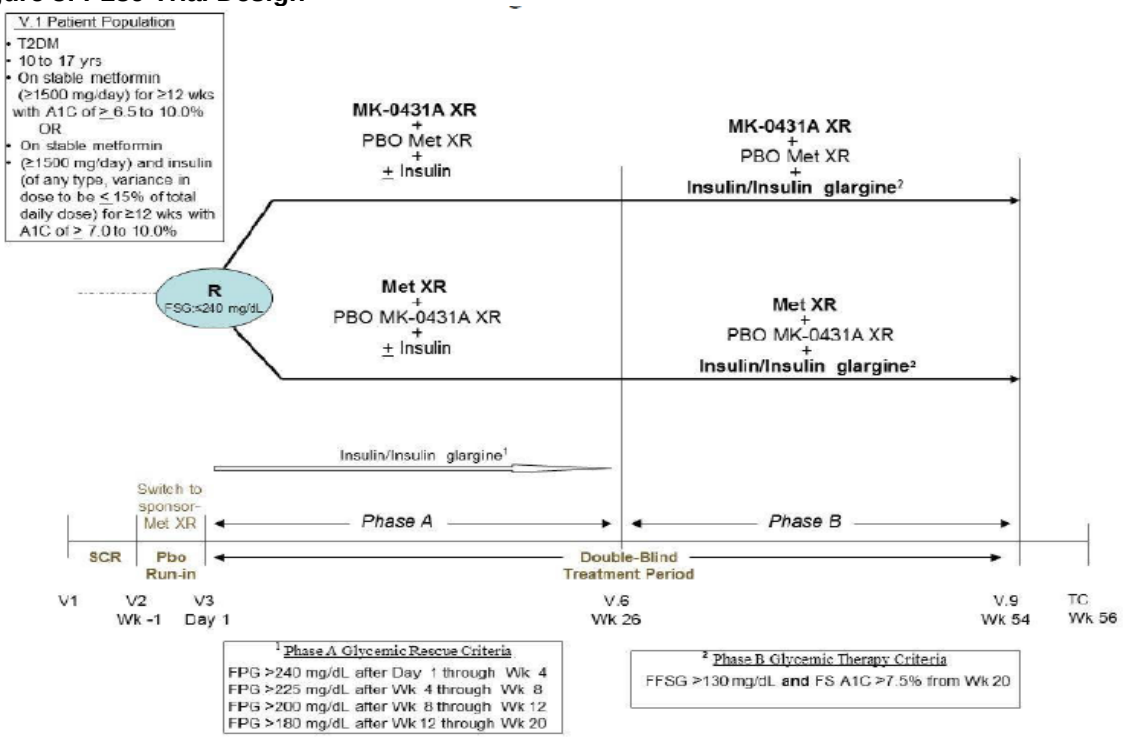
Figure 2: P170 Trial Design



A1c=hemoglobin A1c, PBO= placebo, FPG= fasting plasma glucose, FFSG= fasting fingerstick glucose, MK-0431A XR= Sita/Met XR FDC, R= randomization, SCR= screening, V= visit, Wk= week, wks= weeks, IR= immediate release

Source: FDA Primary Clinical Review

Figure 3: P289 Trial Design



A1c=hemoglobin A1c, PBO= placebo, FPG= fasting plasma glucose, FFSG= fasting fingerstick glucose, MK-0431A XR= Sita/Met XR FDC, R= randomization, SCR= screening, TC= telephone call, V= visit, Wk= week, wks= weeks, XR= extended release
Source: P289 protocol

Source: FDA Primary Clinical Review

Table 1: Demographics of Sitagliptin Phase 3 Pediatric Trials

	P083			P170			P289		
Parameters	Sitagliptin N=95	Placebo[1] N=95	Total N=190	Sita/Met IR FDC N=62	Met IR N=62	Total N=124	Sita/Met XR FDC N=45	Met XR N=51	Total N=96
Sex, n (%)									
Male	41 (43.2)	34 (35.8)	75 (39.5)	21 (33.9)	22 (35.5)	43 (34.7)	13 (28.9)	19 (37.3)	32 (33.3)
Female	54 (56.8)	61 (64.2)	115 (60.5)	41 (66.1)	40 (64.5)	81 (65.3)	32 (71.1)	32 (62.7)	64 (66.7)
Age (years)									
Mean (SD)	14.3 (2.0)	13.7 (1.9)	14 (2.0)	14.4 (2.2)	13.9 (1.8)	14.1 (2.0)	14.8 (1.9)	14.9 (1.6)	14.8 (1.7)
Min; Max	10; 17	10; 17	10; 17	10; 17	10; 17	10; 17	10; 17	10; 17	10; 17
10-14 years, n (%)	47 (49.5)	62 (65.3)	109 (57.4)	26 (41.9)	40 (64.5)	66 (53.2)	16 (35.6)	16 (31.4)	32 (33.3)
Race									
American Indian/Alaska Native	6 (6.3)	9 (9.5)	15 (7.9)	0 (0)	1 (1.6)	1 (0.8)	3 (6.7)	9 (17.6)	12 (12.5)
Asian	13 (13.7)	16 (16.8)	29 (15.3)	21 (33.9)	22 (35.5)	43 (34.7)	15 (33.3)	6 (11.8)	21 (21.9)
Black/African American	8 (8.4)	2 (2.1)	10 (5.3)	2 (3.2)	2 (3.2)	4 (3.2)	2 (4.4)	4 (7.8)	6 (6.3)
Multiple-Race[74]	20 (21.1)	18 (18.9)	38 (20.0)	14 (22.6)	13 (21.0)	27 (21.8)	3 (6.7)	5 (9.8)	7 (7.3)
Native Hawaiian/Other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (1.6)	1 (1.6)	2 (1.6)	0 (0)	0 (0)	0 (0)
White	48 (50.5)	50 (52.6)	98 (51.6)	24 (38.7)	23 (37.1)	47 (37.9)	22 (48.9)	27 (52.9)	49 (51.0)
Ethnicity									
Hispanic or Latino	36 (37.9)	35 (36.8)	71 (37.4)	23 (37.1)	23 (37.1)	46 (37.1)	11 (24.4)	20 (39.2)	31 (32.3)
Unknown	6 (6.3)	3 (3.2)	9 (4.7)	4 (6.5)	3 (4.8)	7 (5.6)	5 (11.1)	3 (5.9)	8 (8.3)

Source: Adapted from FDA Primary Clinical Review

Table 2: Baseline Characteristics of Sitagliptin Phase 3 Pediatric Trials

	P083			P170			P289		
Parameters	Sitagliptin N=95	Placebo[1] N=95	Total N=190	Sita/Met IR FDC N=62	Met IR N=62	Total N=124	Sita/Met XR FDC N=45	Met XR N=51	Total N=96
Body mass index percentile									
Mean (SD)	97.9 (3.6)	96.3 (8.8)	97.1 (6.8)	95.5 (8.4)	94.8 (8.1)	95.2 (8.2)	94.9 (10.6)	91.6 (19.5)	93.1 (16.0)
Min; Max	77; 100	32; 100	32; 100	54; 100	54; 100	54; 100	40; 100	0.1; 100	0.1; 100
≥85%, n (%)	94 (98.9)	91 (95.8)	185 (97.4)	55 (88.7)	54 (87.1)	109 (87.9)	42 (93.3)	45 (88.2)	87 (90.6)
HbA1c (%)									
Mean (SD)	7.4 (1.0)	7.6 (1.1)	7.5 (1.0)	8.0 (1.2)	8.1 (1.1)	8.1 (1.1)	7.9 (0.9)	8.0 (1.1)	7.9 (1.0)
Min; Max	5.8; 10.0	6.2; 11.9	5.8; 11.9	5.9; 11.9	6.1; 10.1	5.9; 11.9	6.3; 10.1	6.0; 10.4	6.0; 10.4
<8%, n (%)	70 (73.7)	60 (63.2)	130 (68.4)	34 (54.8)	30 (48.4)	64 (51.6)	26 (57.8)	29 (56.9)	55 (57.3)
Duration of T2D (years)									
Mean (SD)	0.6 (1.1)	0.8 (1.4)	0.7 (1.3)	2.1 (1.5)	2.1 (1.7)	2.1 (1.6)	2.2 (1.3)	2.3 (1.9)	2.3 (1.6)
Min; Max	0.1; 9.0	0.0; 7.5	0.0; 9.0	0.1; 6.8	0.3; 8.0	0.1; 8.0	0.3; 5.4	0.3; 8.6	0.3; 8.6
< 1 year, n (%)	78 (82.1)	79 (83.2)	157 (82.6)	19 (30.6)	21 (33.9)	40 (32.3)	10 (22.2)	15 (22.9)	25 (26.0)
Insulin Use, n (%)	11 (11.6)	11 (11.6)	22 (11.6)	8 (12.9)	8 (12.9)	16 (12.9)	9 (20.0)	8 (15.7)	17 (17.7)
Insulin dose (units/day)[2]									
Mean (SD)	47.5 (30.2)	36.7 (21.9)	42.1 (26.3)	56.5 (38.0)	36.3 (23.3)	46.4 (32.2)	41.8 (22.5)	30.1 (9.5)	36.3 (18.1)
Min; Max	10.0; 112.0	8.0; 72.0	8.0; 112.0	13; 125	10; 72	10; 125	20; 76	15; 43	15; 76
Metformin dose at baseline (n (%)									
<1500 mg/day				3 (4.8)	7 (11.3)	10 (8.1)	3 (6.7)	7 (13.7)	10 (10.4)
=1500 mg/day				11 (17.7)	8 (12.9)	19 (15.3)	12 (26.7)	11 (21.6)	23 (24.0)
>1500 mg/day				48 (77.4)	47 (75.8)	95 (76.6)	30 (66.7)	33 (64.7)	63 (65.6)

Sita/Met IR FDC, Fixed dose combination of sitagliptin and metformin immediate release; Met IR, metformin immediate release; Sita/Met XR FDC, Fixed dose combination of sitagliptin and metformin extended release; Met XR, metformin extended release; FPG, fasting plasma glucose; SD, standard deviation; T2D, type 2 diabetes; HbA1c, hemoglobin A1c; N or n, number.
[1] Includes 90 subjects from placebo/metformin arm and 5 subjects from placebo/sitagliptin arm
[2] Insulin users only

Source: Adapted from FDA Primary Clinical Review

Table 3: Disposition of Subjects through Week 20 in Sitagliptin Phase 3 Pediatric Trials

	P083 N (% of treated)			P170 N (% of treated)			P289 N (% of treated)			All trials
	Sitagliptin	Placebo[1]	Total	Sita/Met IR FDC	Met IR	Total	Sita/Met XR FDC	Met XR	Total	Total
Randomized	96[2]	95	191	62[2]	62	124	47	51	98	**413[2]**
Treated	95[3]	95	190	62	62	124	45	51	96	**410**
Discontinued study medication through week 20	11 (11.6)	8 (8.4)	18 (9.5)	4 (6.5)	2 (3.2)	6 (4.8)	4 (8.9)	8 (15.7)	12 (12.5)	
Discontinued study through week 20[4]	10 (10.5)	4 (4.2)	14 (7.4)	3 (4.8)	0 (0)	3 (2.4)	3 (6.7)	4 (7.8)	7 (7.3)	
Week 20 TP Estimand[5]	84 (87.5)	87 (91.5)	171 (90.0)	55 (88.7)	61 (98)	116 (93.5)	40 (88.9)	47 (92.2)	87 (90.6)	
Week 20 TE Estimand[5]	78 (81.2)	73 (76.8)	151 (79.5)	52 (83.9)	49 (79.0)	101 (81.5)	39 (86.7)	37 (72.5)	76 (79.2)	
Rescue therapy by week 20	5 (5.3)	12 (12.6)	17 (9.0)	2 (3.2)	12 (19.4)	14 (11.3)	2 (4.4)	7 (13.7)	9 (9.4)	

Abbreviations: TE, Treatment Effect; TP, Treatment policy; N, number; Sita/Met IR FDC, fixed dose combination of sitagliptin and metformin immediate release; Met IR, metformin immediate release; Sita/Met XR FDC, fixed dose combination of sitagliptin and metformin extended release; Met XR, metformin extended release
[1] P083 combined phase A data from placebo/metformin: N= 90 and placebo/sitagliptin: N = 5
[2] Subject who was randomized twice in P083 and P170 counted only once here.
[3] 1 subject excluded who did not get treatment
[4] includes discontinuations among treated subjects only[62].
[5] Number reflects subjects with both baseline and week 20 HbA1c measurements in the TP and TE estimands. Subjects in TP estimand were included regardless of treatment discontinuation or rescue therapy by week 20. Subjects in TE estimand did not discontinue therapy or receive rescue treatment by week 20.

Source: FDA Primary Clinical Review

Per the statistical analysis plan (SAP), the primary analysis was calculated using an intent-to-treat approach (i.e., the "treatment policy" estimand) in an ANCOVA model, with missing data handled based on the return-to-baseline principle and Rubin's Rule for multiple imputation. The SAP also specified that the primary efficacy analysis would be conducted for

P083 as a separate study and for P170 and P289 as a pooled analysis. For P081, the change in HbA1c at Week 20 from baseline in patients treated with sitagliptin was 0.06% compared to 0.23% in patients treated with placebo, resulting in a difference of -0.17% (95% CI: -0.62, 0.28). For the pooled analyses of P170 and P289, the change in HbA1c at Week 20 from baseline in patients treated with sitagliptin and metformin was -0.23% compared to 0.09% in patients treated with metformin alone, resulting in a difference of -0.33% (95% CI: -0.70, 0.05). As the primary analyses failed to demonstrate the superiority of sitagliptin over placebo, the conclusion of Drs. Tu and Shimy were that the sitagliptin pediatric program had not demonstrated the effectiveness of sitagliptin for improving glycemic control in children with T2D. I concur with this conclusion.

Table 4: Primary Efficacy Analysis Using ANCOVA analyses for Treatment Policy (ITT) Estimand

	P083		2-study pool (P170+P289)	
	Sitagliptin	Placebo	Sita/Met FDC	Metformin
Baseline				
N	95	96	107	113
HbA1c (%), mean (SD)	7.43 (1.02)	7.58 (1.06)	7.96 (1.11)	8.06 (1.07)
Week 20				
N[1]	84	87	95	108
HbA1c (%), mean (SD)	7.25 (1.68)	7.65 (1.70)	7.34 (1.46)	7.83 (1.63)
HbA1c Change from Baseline				
Mean (SD)	-0.15 (1.56)	0.03 (1.46)	-0.62 (1.40)	-0.25 (1.56)
LS Mean[2]	-0.06	0.23	-0.23	0.09
95% Confidence Interval	-0.34, 0.47	-0.19, 0.65	-0.61, 0.14	-0.27, 0.46
Difference in LS Means (Sitagliptin vs. placebo)	**-0.17**		**-0.33**	
95% Confidence Interval	**-0.62, 0.28**		**-0.70, 0.05**	
p-value	**0.463**		**0.087**	

[1]Subjects with both baseline and week 20 measurements
[2] Based on ANCOVA model adjusting for treatment, time, baseline BMI percentile, insulin use (yes/no) at screening, using RTB approach
Abbreviations: ANCOVA, Analysis of Covariance; LS, Least Squares; RTB, Return-to-baseline; SD, standard deviation; N= number; Sita/Met FDC, fixed dose combination of sitagliptin and metformin

Source: FDA Primary Clinical Review

Dr. Shimy noted in her review that the results of the three individual trials were somewhat discordant (including a nominally statistically different treatment difference in mean HbA1c change from baseline observed in P170, while the other two trials did not demonstrate a difference in the primary endpoint). Dr. Shimy also noted that the rate of rescue therapy in all three trials from weeks 0 to 20 was higher in the placebo arm than the sitagliptin arm (12.6% vs 5.3% in P083; 19.4% vs 3.2% in P170; 13.7% vs 4.4% in P289).

CDTL Comment: The totality of the data (including the greater rate of rescue therapy in the placebo arms compared to the sitagliptin arms) suggests that sitagliptin may have some pharmacodynamic effect in terms of glycemic lowering, but the clinical effect is not sufficiently large to have demonstrated statistical significance in the pre-specified primary analyses for trials of the size of P083, P170, and P289. Given that pediatric patients with T2D often progress rapidly in their disease, it is important that any antihyperglycemic agent granted a pediatric indication have an effect that will be

clinically significant. For that reason, I do not believe that sitagliptin products should receive a pediatric indication.

See the primary statistical review by Dr. Tu and the primary clinical review by Dr. Shimy for details regarding trial design, conduct, and statistical analyses.

7. Safety

Dr. Shimy also reviewed the clinical data from the three Phase 3 pediatric trials (P083, P170, and P289) to assess safety. The safety population comprised all randomized subjects who received at least one dose of study medication in the three trials (3-study pool; 410 patients total, with 202 patients exposed to sitagliptin and 210 patients exposed to a comparator product) followed for up to 54 weeks. Safety endpoints of interest were specified in the Written Request, based on the known safety profile of sitagliptin in adults.

There were two deaths in subjects that were randomized to sitagliptin, compared to no deaths in the subjects randomized to a comparator arm. However, both deaths occurred more than 4 months after the last exposure to sitagliptin. One of the deaths was due to complications of acute lymphoblastic leukemia (ALL), the other was due to acute heart failure (autopsy revealed right ventricular cardiomyopathy with fatty replacement and fibrosis of the right ventricle). After reviewing the events, Dr. Shimy concluded (and I concur) that sitagliptin was not likely to have been causally related.

In addition to the ALL event that resulted in a death, a second event of ALL was observed in another patient randomized to sitagliptin (i.e., in a safety population with only 208 patients exposed to sitagliptin, 2 patients experienced an event of ALL). While this finding is somewhat unusual, Dr. Shimy noted in her review that ALL is the most prevalent cancer among children and adolescents (constituting 20% of all cancers diagnosed in persons under the age of 20 years in the United States). Because of the relatively common occurrence of sitagliptin, the lack of any similar signal in sitagliptin animal carcinogenicity studies, the lack of any similar signal in the adult sitagliptin clinical data and post-marketing experience, the short duration of sitagliptin exposure, the improbably short latency of the onset of the ALL after sitagliptin exposure, Dr. Shimy concluded (and I concur) that these 2 events do not constitute an important new safety signal.

In general, serious adverse events were infrequent and balanced across the treatment arms in all three trials. See Table 5.

Table 5: Treatment-Emergent Serious Adverse Events in the Phase 3 Sitagliptin Pediatric Trials

		Treatment Arm			
		Sitagliptin N=202		Comparator N=208	
		N	% of Total	N	% of Total
Subjects with one or more SAE		15	7.42%	10	4.81%
Subjects with specific SAE					
Body System or Organ Class	**Dictionary-Derived Term**				
Gastrointestinal disorders	Abdominal pain upper[1]	0	0.00%	1	0.48%
	Diarrhea[1]	1	0.50%	0	0.00%
	Vomiting[1]	0	0.00%	1	0.48%
Immune system disorders	Type I hypersensitivity[97]	1	0.50%	0	0.00%
Infections and infestations	Abscess soft tissue	1	0.50%	0	0.00%
	Dengue fever	0	0.00%	1	0.48%
	Gastroenteritis	1	0.50%	0	0.00%
	Gastroenteritis viral	0	0.00%	1	0.48%
	H1N1 influenza	0	0.00%	1	0.48%
	Pneumonia	1	0.50%	0	0.00%
	Pyelonephritis	1	0.50%	0	0.00%
	Upper respiratory tract infection	1	0.50%	0	0.00%
Injury, poisoning and procedural complications	Concussion	0	0.00%	1	0.48%
Investigations	Blood glucose increased	1	0.50%	1	0.48%
Metabolism and nutrition disorders	Hyperglycemia	3	1.49%	1	0.48%
Musculoskeletal and connective tissue disorders	Synovial cyst	1	0.50%	0	0.00%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute lymphocytic Leukemia	1	0.50%	0	0.00%
Nervous system disorders	Epilepsy	0	0.00%	1	0.48%
Psychiatric disorders	Suicide attempt	0	0.00%	1	0.48%
	Affect lability	0	0.00%	1	0.48%
Reproductive system and breast disorders	Ovarian cyst ruptured	1	0.50%	0	0.00%
Respiratory, thoracic and mediastinal disorders	Asthma	1	0.50%	0	0.00%
Skin and subcutaneous tissue disorders	Erythema nodosum	0	0.00%	1	0.48%
Social circumstances	Sexual abuse	1	0.50%	0	0.00%

Source: FDA Primary Clinical Review

Dr. Shimy gave special attention to the safety issue of hypoglycemia. As described in her review, all events identified by the investigators and all observed glucose values ≤ 70 mg/dL were considered to define a hypoglycemic event. The events were also categorized as severe (defined as symptomatic hypoglycemia requiring third party assistance), symptomatic (defined as an event with clinical symptoms attributed to hypoglycemia, regardless of glucose level), asymptomatic (defined as an event without symptoms but with a measured plasma glucose ≤ 70 mg/dL), documented (defined as <54 mg/dL or ≤ 70 mg/dL). The analyses excluded data after the initiation of glycemic rescue therapies. Dr. Shimy concluded (and I concur) that patients receiving sitagliptin on a background of insulin therapy experienced an increased frequency of hypoglycemia, documented hypoglycemia (both <54 mg/dL or ≤ 70 mg/dL), symptomatic hypoglycemia, and asymptomatic hypoglycemia. When administered without concomitant insulin therapy, sitagliptin exposure was not associated with a statistically

significant increase in the frequency of hypoglycemia (thought numerically there were more events observed with sitagliptin than placebo). See Table 6

Table 6: Hypoglycemic Events in the Safety Population of the Phase 3 Sitagliptin Pediatric Trials

	Subjects not on background insulin			Subjects on background insulin		
	Sitagliptin N=130 n (%)	Comparator N=140 n (%)	Difference in % vs. Comparator (95% CI)[1]	Sitagliptin n (%)	Comparator n (%)	Difference in % vs. Comparator (95% CI)[1]
1 or more hypoglycemia episodes	42 (32.2)	30 (21.4)	**10.8 (0.2, 21.4)**	13 (52.0)	5 (21.7)	**29.8 (2.4, 52.6)**
BG < 54 mg/dL	13 (10.0)	9 (6.4)	3.5 (-3.2, 10.7)	11 (44.0)	2 (8.7)	**35.2 (10.8, 56.5)**
BG < 70 mg/dL	40 (30.8)	29 (20.7)	9.9 (-0.5, 20.3)	13 (52.0)	5 (2.7)	**29.8 (2.4, 52.6)**
Severe hypoglycemia	1 (0.8)	1 (0.7)	0.1	1 (4.0)	1 (4.3)	-0.5
Symptomatic	13 (10.0)	12 (8.6)	1.4 (-5.8, 8.6)	8 (32.0)	2 (8.7)	**23.1 (0.3, 45.2)**
Asymptomatic	35 (26.9)	24 (17.1)	9.7 (-0.2, 19.7)	11 (44.0)	3 (13.0)	**30.5 (4.5, 52.9)**
Hypoglycemia AE	18 (13.8)	16 (11.4)	2.3 (-5.8, 10.4)	9 (36.0)	3 (13.0)	22.9 (-1.6, 45.2)

n, number; %, percentage; BG, blood glucose; AE, adverse event; CI, confidence interval
Bolded CIs are those that exclude 0
Includes subjects who entered phase B (P083/P289) or extension (P170), excluding data after initiation of glycemic rescue therapy.
[1] based on Miettinen & Nurminen method stratified by study. 95% CI computer only for endpoints with at least 4 subjects with events in one or more treatment groups (except for symptomatic hypoglycemia).

Source: FDA Primary Clinical Review

Dr. Shimy noted in her review that the approved labeling for sitagliptin products already includes a Warning and Precaution for increased hypoglycemia when sitagliptin is used with insulin or insulin secretagogues, based on adult data. While the observations regarding hypoglycemia in the pediatric trials are consistent with those in the adult trials, she also cautioned that the definitions used for hypoglycemia (and therefore the data collected) in the adult sitagliptin trials differ somewhat from those used in the pediatric sitagliptin trial.

As per the Written Request, the sitagliptin pediatric program collected data on linear growth and pubertal development, bone markers and calcitonin, dentition, gastrointestinal adverse events, hypoglycemia, hypersensitivity reactions, infection, renal impairment, and pancreatitis. Overall, no significant differences were observed across treatment groups related to these safety endpoints, other than the expected association between sitagliptin and non-serious gastrointestinal adverse events, similar to that previously observed in adults. Please see Dr. Shimy's review for additional details.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring input from an advisory panel. Therefore, an advisory committee meeting was not convened for this sNDA.

9. Pediatrics

The sNDAs addressed three outstanding PREA PMRs associated with NDA 21995 (PMR 224-1), NDA 22044 (PMR 856-1), and NDA 202270 (PMR 1802-4). While the sNDAs did not support broadening the glycemic control indications for the NDAs to include children with T2D, the division determined that the three PMRs have been fulfilled. In addition, the data included in the sNDAs (in conjunction with data previously submitted) was determined by the Pediatric Exclusivity Board to constitute a fair response to the Written Request for NDAs 21995, 22044, and 202270, as amended on December 7, 2017; pediatric exclusivity was granted on this basis effective October 30, 2020.

10. Labeling

Based on the data submitted in the sNDAs, the PIs and the medication guides (MGs) for NDA 21995, NDA 22044, and NDA 202270 were revised.

Ariane Conrad from the Division of Medication Error Prevention and Analysis (DMEPA), Lonice Carter from the Patient Labeling Team in the Division of Medical Policy Programs (DMPP), and Samantha Bryant from the Office of Prescription Drug Promotion (OPDP) collaborated with DDLO to develop appropriate language for the PIs and MGs. Additional recommendations were provided by members of the Division of Pediatric and Maternal Health (DPMH).

The most substantial revision to the PIs of all three products is the addition of the following language to Section 8.4 of each product:

> **Pediatric Use**
>
> The safety and effectiveness of JANUMET XR have not been established in pediatric patients.
>
> Three 20-week double-blind, placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of sitagliptin in 410 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes, with or without insulin therapy (HbA1c 6.5-10% for patients not on insulin, HbA1c 7-10% for patients on insulin). At study entry, patients in study 1 were not treated with oral antihyperglycemic agents; patients in studies 2 and 3 were on maximally tolerated metformin therapy. The primary efficacy endpoint was the change from baseline in HbA1c after 20 weeks of therapy. The pre-specified primary efficacy analyses included data from study 1 and pooled data from studies 2 and 3, regardless of glycemic rescue or treatment discontinuation.
>
> In both efficacy analyses, the effect of treatment with sitagliptin was not significantly different from placebo. In study 1, the mean baseline HbA1c was 7.5%, and 12% of patients were on insulin therapy. At week 20, the change from baseline in HbA1c in patients treated with sitagliptin (N=95) was 0.06% compared to 0.23% in patients treated with placebo (N=95), a difference of -0.17% (95% CI: -0.62, 0.28). In studies 2 and 3, the mean baseline HbA1c was 8.0%, 15% of patients were on insulin and 72% were on metformin HCl doses of greater than 1,500 mg daily. At week 20, the change from baseline in HbA1c in patients treated with sitagliptin (N=107) was -0.23% compared to 0.09% in patients treated with placebo (N=113), a difference of -0.33% (95% CI: -0.70, 0.05).

While the data from the three pediatric trials was not adequate to support broadening the glycemic control indication in Section 1 to include children with T2D, DDLO determined (and

the consulting groups concurred) that the inclusion of some outcome data from the trials in Section 8.4 provided important value to prescribers and patients.

Other revisions to the PIs included 1) the deletion of the statement "Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed" from Section 12.3 of each of the PIs, as recommended by the clinical pharmacology review, 2) removal of diabetic ketoacidosis from limitations of use (to be consistent with current Division labeling practice), 3) removal of the statement in Warnings and Precautions that "there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction" (to be consistent with current Division labeling practice), 4) updates to the Warnings and Precautions for AKI and hypoglycemia (to be consistent with current Division labeling practice). In addition, the labeling for Janumet and Janumet XR were updated in sections 2, 4, 5, and 7 to reflect current metformin labeling.

The MGs for Januvia, Janumet, and Janumet XR were updated to reflect revisions to their respective PIs.

Finally, revisions to language in both the Janumet XR PI and MG that pertains to the issue of "ghost tablets" (incompletely digested tablets detectable in the feces) were discussed with the Applicant during this review cycle. Ultimately, no changes related to this issue were made to the labeling during this review cycle: the Division determined that the revisions should be deferred until clarity with the Applicant was reached regarding the underlying scientific and clinical issues.

> From the Janumet XR PI:
>
> <u>Incompletely Dissolved Tablets in Feces</u>
> Inform patients that incompletely dissolved JANUMET XR tablets may be eliminated in the feces. Tell patients that, if they repeatedly see tablets in feces, they should report this finding to their health care provider. Assess adequacy of glycemic control if a patient reports repeatedly observing tablets in feces.

From the Janumet XR MG:

- You may see something that looks like the JANUMET XR tablet in your stool (bowel movement). If you see tablets in your stool several times, talk to your doctor. Do not stop taking JANUMET XR without talking to your doctor.

The Applicant was advised to propose new language regarding this issue under a separate submission, to allow continued discussion on this topic without delaying action on the current NDA supplements.

11. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval, PMR 224-1, PMR 856-1, and PMR 1802-4 Fulfilled

See section 10 for description of revisions to labeling based on NDA 021995/S-047, NDA 022044/S-048, and NDA 202270/S-022

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

Additional note: Pediatric exclusivity previously granted, effective October 30, 2020, on the basis of data included in the sNDAs (in conjunction with previously submitted data).

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/

PATRICK ARCHDEACON
12/04/2020 11:50:37 AM