CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 012995/S-047; NDA 022044/S-048; NDA 202270/S-022
Priority or Standard	Priority
Submit Date(s)	4 June 2020
Received Date(s)	4 June 2020
PDUFA Goal Date	4 December 2020
Division/Office	DDLO/OCHEN
Reviewer Name(s)	Kim Shimy, M.D.
Review Completion Date	4 December 2020
Established/Proper Name	Sitagliptin tablets, Sitagliptin and metformin tablets, sitagliptin and metformin extended release tablets
(Proposed) Trade Name	Januvia, Janumet, Janumet XR
Applicant	Merck Sharp & Dohme Corp.
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	100 mg daily
Applicant Proposed Indication(s)/Population(s)	Not Applicable
Recommendation on Regulatory Action	Approval; PMR 224-1, PMR 856-1, and PMR 1802-4 Fulfilled
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

Material Reviewed/Consulted	**Author**	**Date**
Statistical Review	Dr. Wenda Tu	10 November 2020
Clinical Pharmacology Memo	Dr. Sang Chung	24 November 2020
Clinical Pharmacology Memo, Trial P081	Dr. Sang Chung	27 November 2012
Clinical Pharmacology Review, Trial P296	Dr. S.W. Johnny Lau	23 October 2015

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Sitagliptin phosphate (proprietary name: Januvia, NDA 021995) is a highly selective dipeptidyl peptidase 4 (DPP-4) inhibitor that was initially approved in 2006 for the treatment of type 2 diabetes mellitus in adults. DPP-4 inhibitors improve glycemic control by preventing the enzymatic breakdown of the incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), leading to enhancement of incretin-stimulated insulin-release and glucagon suppression. Sitagliptin phosphate tablets are administered once daily and are available in strengths of (b) (4), 25 mg, 50 mg and 100 mg tablets. As sitagliptin is commonly administered as dual oral therapy with metformin to achieve glycemic control, fixed dose combination (FDC) tablets were subsequently developed. In 2007, an FDC tablet comprised of sitagliptin phosphate and metformin hydrochloride (proprietary name: Janumet, NDA 022044) was approved. This FDC is administered twice daily and is available as 50 mg / 500 mg, (b) (4) and 50 mg / 1000 mg FDC tablets. In 2012, an FDC tablet comprised of sitagliptin phosphate and extended release metformin hydrochloride (proprietary name: Janumet XR, NDA 202270) was approved. This product is administered as either one or two tablets once daily, and is available as 50 mg / 500 mg, 50 mg / 1000 mg and 100 mg / 1000 mg FDC tablets.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of sitagliptin in pediatric subjects with type 2 diabetes was not demonstrated in three randomized and placebo-controlled trials that evaluated sitagliptin as monotherapy (trial P083) and as add-on therapy to metformin (trials P170 and P289) over 20 weeks, followed by 34-week extensions. In the pre-specified primary analyses for the change from baseline in HbA1c at 20 weeks, there was a small numerical treatment difference (-0.2 to -0.3%) favoring sitagliptin over placebo that did not reach statistical significance. Although the rate of glycemic rescue therapy was numerically higher in the placebo arm through week 20, this imbalance disappeared from weeks 20 to 54. Sitagliptin was overall well-tolerated in pediatric patients with a similar safety profile to adults. Given the lack of statistical significance in the primary efficacy analysis and small nominal glycemic lowering compared to other approved therapies, I do not recommend granting a pediatric indication. My recommendation is consistent with the recommendations of other review disciplines.

Trials P083, P170 and P289 fulfill the Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) 224-1 (NDA 021995), PMR 856-1 (NDA 022044) and PMR 1802-4 (NDA 202270).

The Pediatric Exclusivity Board agreed that the phase III trials P083, P170, P289, and the phase I trial (P296) fulfilled the written request for NDA 021995, 022044 and 202270 issued on November 27th, 2012, and amended on May 7th, 2013 and December 7th, 2017 in accordance with the Best Pharmaceuticals for Children Act (BPCA). Pediatric exclusivity was granted for studies conducted with sitagliptin effective October 30th, 2020.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The prevalence of pediatric type 2 diabetes mellitus (T2D) has been increasing in the United States over the past 20 years[1]. Recent clinical trials in pediatric T2D suggest there may be two subgroups of patients, one that is more easily controlled on metformin monotherapy and one with rapid progression of disease[2]. Youth with T2D also have accelerated development of diabetes complications and comorbidities[2]. Treatment options for pediatric T2D are limited, and include metformin, liraglutide (pediatric approval in 2019) and insulin.

On June 4th, 2020, Merck (Merck Sharp and Dohme Corp.) submitted supplemental new drug applications for JANUVIA (NDA 021995), JANUMET (NDA 022044) and JANUMET XR (NDA 202270) pursuant to Section 505 (b) of the Food, Drug and Cosmetic Act. The submissions contained results of three pediatric phase III trials (P083, P170 and P289) conducted for the fulfillment of a written request as part of the Best Pharmaceuticals for Children Act and were accompanied by a request for pediatric exclusivity determination. Per the Pediatric Exclusivity Board, the completed phase III pediatric trials and a previously completed phase I pediatric PK study (P296) fulfill the November 27th, 2012 written request (amended on May 7th, 2013 and on December 7th, 2017). The submissions also address the Pediatric Research Equity Act (PREA) PMR # 224-1 (NDA 021995), PMR # 856-1 (NDA 022044) and PMR #1802-4 (NDA 202270). Based on results of the trials, Merck did not request a pediatric indication.

Three 20-week double-blind placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of sitagliptin. Trial P083 evaluated the effect of sitagliptin monotherapy while trials P170 and P289 evaluated sitagliptin as an add-on to maximally tolerated metformin therapy. All trials enrolled pediatric subjects 10 to 17 years (inclusive) with T2D and inadequate glycemic control with or without insulin therapy (hemoglobin A1c >6.5% and <10.0% for subjects not on insulin and hemoglobin A1c >7% and <10.0% for subjects on insulin). The primary efficacy endpoint was change from baseline in hemoglobin A1c (HbA1c) after 20 weeks of therapy. The prespecified primary efficacy analyses utilized an intention-to-treat population (including data obtained following glycemic rescue therapy or treatment discontinuation) for trial P083 individually and for trials P170 and P289 combined (2-study pool).

[1] Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care*. 2016;39(9):1635-1642. doi:10.2337/dc16-1066
[2] Zeitler P. Progress in understanding youth-onset type 2 diabetes in the United States: recent lessons from clinical trials. *World J Pediatr*. 2019;15(4):315-321. doi:10.1007/s12519-019-00247-1

Despite some evidence of a treatment effect of sitagliptin at earlier time points (i.e., by week 6 or 8), effectiveness of sitagliptin was not demonstrated in the primary efficacy analyses. In trial P083, the change from baseline in HbA1c at week 20 in subjects treated with sitagliptin was 0.06% compared to 0.23% in subjects treated with placebo (N=95), a difference of -0.17% (95% confidence interval (CI): -0.62, 0.28). In the 2-study pool, the change from baseline in HbA1c in subjects treated with sitagliptin (N=107) was -0.23% compared to 0.09% in subjects treated with placebo (N=113), a difference of -0.33% (95% CI: -0.70, 0.05). In secondary analyses that excluded data following rescue therapy or treatment discontinuation, nominal statistical significance was reached for 2-study pool (with slightly larger numerical treatment difference of -0.49% favoring sitagliptin) but not for trial P083. In all trials, the rate of glycemic rescue therapy was higher in the placebo arm through week 20 but this imbalance disappeared after week 20. In addition to a failure of the pre-specified primary analyses to meet statistical significance, the observed glycemic lowering of sitagliptin in the pediatric trials is notably lower than that seen in adult studies used to support efficacy of sitagliptin (in which a glycemic lowering of 0.6 to 0.8% in HbA1c was demonstrated). Overall, these results suggest that while there may some pharmacologic effect in children, the response to sitagliptin therapy is smaller in magnitude and is not durable in pediatric patients with T2D. This is most likely related to more rapid disease progression in the pediatric population that was studied.

Adverse reactions associated with sitagliptin treatment were generally similar to those reported in adult trials. Common adverse reactions included nasopharyngitis, upper respiratory tract infection and hypoglycemia. An increased risk of hypoglycemia episodes involving blood glucose < 54 mg/dL was found only when sitagliptin was used with concomitant insulin therapy. Adult studies also showed increased risk of hypoglycemia when sitagliptin was used with insulin therapy, however only symptomatic hypoglycemia episodes (with or without blood glucose measurements) were captured in the adult studies (limiting comparison with pediatric results). In the pediatric trials, episodes of severe hypoglycemia were rare and balanced between treatment arms. Most study participants were in the later stages of puberty and had nearly completed linear growth at baseline, limiting ability to interpret effects on height. Overall, sitagliptin therapy was well tolerated in the pediatric trials.

Despite the favorable safety profile and the trends suggesting a pharmacodynamic effect, I do not believe that there is reasonable benefit to support a pediatric indication, considering the smaller nominal effect on glycemic lowering observed compared to other approved therapies in pediatric T2D, which likely contributed to the absence of durability in treatment response, as well as the lack of statistical significance in the pre-specified primary analyses.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Analysis of Condition	• The prevalence of pediatric type 2 diabetes (T2D) has been increasing in the United States.
	  • T2D affects higher numbers of youth of racial and ethnic minorities.
	• Recent clinical trials in pediatric T2D suggests that while a subset of patients achieve glycemic control on metformin monotherapy, many patients experience rapid progression of beta-cell dysfunction and glycemic failure
	  ▪ There is limited knowledge regarding the factors that predicting disease course in pediatric T2D, however intrinsic differences in beta cell dysfunction may play a role.
	  ▪ Lower HbA1c on metformin monotherapy appears to correlate with durable control.
	• Youth with T2D have an accelerated development of diabetes complications and comorbidities.
		Type 2 diabetes in youth is increasing and disproportionately affects minority groups. Youth with T2D have a higher risk of complications and comorbidities.
		
		In contrast to adults, many youth with T2D experience rapid deterioration in beta cell function and inability to achieve glycemic control on metformin monotherapy. The factors predicting response to therapy and disease progression in pediatric T2D are not well described. Youths who achieve an HbA1c the pre-diabetic range on metformin monotherapy appear more likely to have stable disease.

Current Treatment Options	• Metformin, insulin and liraglutide are current therapeutic options for youth with type 2 diabetes. • Liraglutide (pediatric approval in 2019) appears to provide ~ 1% reduction in HbA1c compared to placebo	There are limited treatment options for pediatric patients with type 2 diabetes mellitus, including only one oral antihyperglycemic agent (metformin). Glycemic response to liraglutide in adults and youth with T2D appeared similar in clinical trials.
Benefit	• In pre-specified primary efficacy analyses including data obtained following rescue therapy or treatment discontinuation (reflecting an "intention-to-treat" population), sitagliptin did not demonstrate superiority over placebo after 20 weeks of therapy. In trial P083,	The effectiveness of sitagliptin to improve glycemic control in pediatric patients with T2D was not demonstrated in the primary "intention-to-treat" analyses. A small

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the change from baseline in HbA1c in subjects treated with sitagliptin was 0.06% compared to 0.23% in subjects treated with placebo (N=95), a difference of -0.17% (95% confidence interval: -0.62, 0.28). In the 2-study pool (combining data from trials P170 and P289), the change from baseline in HbA1c in subjects treated with sitagliptin (N=107) was -0.23% compared to 0.09% in subjects treated with placebo (N=113), a difference of -0.33% (95% confidence interval: -0.70, 0.05). • Results of secondary efficacy analyses that excluded data obtained following glycemic rescue therapy or treatment discontinuation (reflecting a "per-protocol" population) were discrepant. In trial P083, similar results were obtained to the pre-specified primary efficacy analysis. In the 2-study pool, a slightly larger treatment difference of -0.49% in HbA1c change was seen that reached nominal statistical significance, favoring sitagliptin over placebo. • Per-protocol analyses are not preferred for the demonstration of efficacy. Due to absence of statistical significance in the primary efficacy analysis, formal statistical testing for secondary analyses cannot be performed. • Subgroup analyses for the primary endpoint did not reveal any differences. • The rate of glycemic rescue therapy was higher in the placebo arm through week 20, however this imbalance disappeared from weeks 20 to 54. • An analysis of HbA1c change over time showed nominally statistically significant treatment differences favoring sitagliptin over placebo at	numerical treatment difference of 0.2 to 0.3% in HbA1c lowering was seen in the sitagliptin arm that did not reach statistical significance. Secondary "per-protocol" analyses yielded mixed results, with one analysis suggesting a more favorable benefit of sitagliptin over placebo that was not seen in the other analysis, however, the secondary analyses were inadequately powered for formal statistical testing. A pharmacologic effect of sitagliptin was supported by a higher rate of rescue therapy in the placebo arm through week 20, and by nominally statistically significant treatment differences evident at earlier time points (weeks 6 to 8 of therapy). However, treatment response did not appear durable given the absence of statistical significance at 20 weeks and because the initial imbalances in rescue therapy disappeared over time. Differences in treatment response between adult and pediatric trials may reflect more rapid disease progression in the pediatric trial population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	earlier time points (week 6 to 8), though the differences were not statistically significant at the 20-week timepoint specified for the primary analysis. • The magnitude of HbA1c lowering compared to placebo in adult trials of sitagliptin was 0.6 to 0.8%.	
Risk and Risk Management	• 2 deaths, both unrelated to study treatment, occurred more than 4 months after discontinuation of study medication in the sitagliptin arms. • The frequency of serious adverse events was low with no clinically relevant imbalances between treatment arms. • Common adverse reactions were similar to adult studies, including nasopharyngitis, upper respiratory tract infection and hypoglycemia. • An increased risk of hypoglycemia episodes involving blood glucose < 54 mg/dL was seen only when sitagliptin was used with concomitant insulin therapy. Severe hypoglycemia events were rare. • Adult studies also found an increased risk of hypoglycemia when sitagliptin was used along with insulin therapy, however only symptomatic hypoglycemia episodes were captured (with or without a blood glucose measurement). Therefore, it is unknown whether safety findings relating to hypoglycemia involving blood glucose < 54 mg/dL were different in adult and pediatric studies. • Most study subjects were in the later stages of puberty at baseline and many had nearly completed linear growth, limiting assessment of effects on height and puberty. • No new safety concerns were identified in the pediatric population.	Sitagliptin therapy appeared to be well tolerated in the pediatric population. Common adverse reactions were similar to those reported in adult studies. An increased risk of hypoglycemia associated with blood glucose < 54 mg/dL was seen only when sitagliptin was used along with background insulin therapy. Current labeling based on adult data includes a warning and precaution for increased risk of hypoglycemia when sitagliptin is used along with insulin or insulin secretagogues.

1.4. Patient Experience Data

This section is not relevant to the application.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2D) has been increasing over the past 20 years, with new cases in the US estimated at around 5,000 per year[1]. The prevalence of pediatric T2D appears to be higher in certain racial and ethnic groups (including Hispanic, American Indian and African American adolescents) and in adolescent girls (with a 60% higher prevalence rate than boys)[2]. Nearly 80 to 90% of youth with T2D have overweight and obesity. The onset of pediatric T2D often coincides with pubertal insulin resistance and it is rarely diagnosed in patients below 10 years of age.

The pathophysiology of pediatric T2D is similar to adults, involving non-autoimmune pancreatic β-cell failure occurring in the background of insulin resistance. However, pediatric T2D has several unique features compared to adult T2D. The degree of insulin resistance in pediatric T2D appears to be more profound than in adults, even at the same degree of adiposity[3],[4]. According to the TODAY study, nearly 50% of pediatric patients on metformin monotherapy failed glycemic control over a 4-year follow up with a median time to insulin of 11 months, far greater than the rates of glycemic failure reported in adults on metformin monotherapy[5]. Data from the TODAY study also suggests that some youth with T2D may experience more rapid deterioration of β-cell function as compared to adults[6], while others may exhibit more durable glycemic control on metformin monotherapy. This heterogeneity may indicate two subgroups of pediatric T2D, one that is easily controlled and another with more rapid progression of disease[7]. The predictors of treatment response in pediatric T2D are currently under study, however intrinsic differences in β-cell function may partly account for the heterogeneity in disease progression. TODAY study participants with durable glycemic control had lower HbA1c (<6.3% on metformin) and higher insulinogenic index at baseline[8]. In addition, participants with oral glucose tolerance test response curves characterized by "incessant increase" had greater 6-month decline in C-peptide index and higher rates of glycemic failure, supporting that reduced β-cell function near the time of diagnosis or after a short course of metformin may predict subsequent β-cell function and risk for treatment failure[7,9]. Youth with T2D also appear to have accelerated development of diabetes complications and co-morbidities, including high prevalence of hyperfiltration (predicting rapid GFR decline), diabetic retinopathy, and echocardiographic changes associated with major cardiovascular risk[7].

2.2. Analysis of Current Treatment Options

Compared to adults, there are limited treatment options for youths with T2D. Treatment options include metformin hydrochloride (pediatric approval in 2000), liraglutide (pediatric approval in 2019) and insulin. Metformin is the only oral antihyperglycemic agent approved for use in pediatric type 2 diabetes.

Metformin is a biguanide used to improve glucose tolerance in patients with T2D. Metformin has several physiologic effects including decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride products with an indication for use in pediatric type 2 diabetes (in children ages 10 years and older) include metformin hydrochloride immediate release tablets, immediate release oral solution and extended release oral suspension[3]. Pediatric dosing instructions for the immediate-release formulations include a starting dose of 500 mg twice daily with meals, and to increase dosage in increments of 500 mg weekly up to a maximum of 2000 mg per day given in divided doses twice daily. Pediatric dosing instructions for the extended-release oral suspension include a starting dose of 500 mg once daily with evening meal, and to increase dosage in increments of 500 mg weekly up to a maximum of 2000 mg once daily with the evening meal. Efficacy of metformin in children was supported by a double-blind placebo-controlled study in pediatric T2D patients aged 10 to 16 years that showed a significantly greater reduction in fasting plasma glucose (FPG) after 16 weeks of metformin compared to placebo (FPG change of -42.9 mg/dL in metformin group compared to + 21.4 mg/dL in placebo group, $P<0.0001$)[4]. The safety profile of metformin is similar in adults and children. Common adverse reactions include diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. Labeling for metformin also includes a boxed warning for lactic acidosis, as well as warnings and precautions regarding vitamin B12 deficiency and hypoglycemia with concomitant use with insulin and insulin secretagogues.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Similar to GLP-1, liraglutide increases cyclic AMP leading to insulin release in the presence of elevated glucose concentrations, delays gastric emptying and decreases glucagon secretion in a glucose-dependent manner. Liraglutide is available as an injection for subcutaneous use in pre-filled single patient-use pens delivering doses of 0.6 mg, 1.2 mg or 1.8 mg. Pediatric dosing instructions recommend initiating liraglutide at 0.6 mg daily for at least one week, to increase the dose to 1.2 mg daily if additional glycemic control is required, and to increase to 1.8 mg daily after at least 1 week of treatment with the 1.2 mg dose if additional glycemic control is still required. Efficacy of liraglutide in children was supported by a 26-week, double-blind, placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with T2D. All patients were randomized to liraglutide once daily or placebo in combination with metformin, with or without insulin treatment. At 26 weeks, treatment with liraglutide was superior in reducing HbA1c from baseline compared to placebo (estimated treatment difference in HbA1c reduction from baseline between liraglutide and placebo was -

[3] Metformin hydrochloride extended-release tablets are labeled only for adult use.
[4] While FPG may have been used in the past, HbA1c is currently the preferred surrogate endpoint to support an indication for the treatment of type 2 diabetes.

1.06% with 95% confidence interval of -1.65% to -0.46%). The safety profile of liraglutide in children and adults is similar, with the exception of hypoglycemia. In adults, serious hypoglycemia was seen when liraglutide was used with an insulin secretagogue or insulin, however in pediatric patients, the risk of hypoglycemia was higher with liraglutide treatment regardless of concomitant antidiabetic therapies. Labeled adverse reactions include nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation, and immunogenicity-related events (including urticaria). The liraglutide label also includes a boxed warning for thyroid C-cell tumors and contraindicated use in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Other warnings and precautions include pancreatitis, renal impairment, hypersensitivity and acute gallbladder disease.

The following subcutaneous insulin products have an indication "to improve glycemic control in adults and children[5] with diabetes mellitus" and therefore include pediatric patients with T2D:

- Humulin R (insulin human injection)
- Novolin R (insulin human injection)
- Humulin N (isophane insulin human injection)
- Novolin N (isophane insulin human injection)
- Novolin 70/30 (human insulin isophane suspension and human insulin injection)
- Humulin R U-500 (insulin human injection)
- Apidra (insulin glulisine [rDNA origin] injection)
- Fiasp (insulin aspart injection)
- Humalog (insulin lispro injection)
- Levemir (insulin detemir injection)
- Novolog (insulin aspart injection)
- Ryzodeg 70/30 (insulin degludec and insulin aspart injection)[6]
- Toujeo (insulin glargine injection)[7]
- Tresiba (insulin degludec injection)[8]

In the majority of insulin products, efficacy for the treatment of pediatric T2D was supported by studies of pediatric patients with type 1 diabetes and/or adult patients with diabetes mellitus. None of the insulin product labels listed above include any pediatric T2D efficacy trial data.

Among insulin products that do not include an indication for treatment of pediatric type 2

[5] Or "pediatric patients"
[6] Labeled indication for Ryzodeg includes pediatric patients 1 year and older with diabetes mellitus
[7] Labeled indication for Toujeo includes pediatric patients 6 years and older with diabetes mellitus
[8] Labeled indication for Tresiba includes pediatric patients 1 year and older with diabetes mellitus

diabetes[9], many are commonly used off-label in clinical practice for the treatment of pediatric T2D.

Overall, treatment options for pediatric T2D patients are limited, with only a single oral agent (metformin) and a GLP-1 agonist (liraglutide) apart from insulin products. Notably, many antihyperglycemic agents available to adults with T2D (including the commonly used drug classes of sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors and thiazolidinediones) are not approved for use in children with T2D. While some antihyperglycemic agents are used off-label, the safety and efficacy of these products have not been established in pediatric T2D.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sitagliptin phosphate (Januvia) was approved in 2006 for the treatment of type 2 diabetes mellitus in adults. FDC tablets of sitagliptin phosphate combined with metformin hydrochloride immediate release (Janumet) or extended release (Janumet XR) were subsequently approved in 2007 and 2012 (respectively). All three products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and are currently marketed in the U.S. Following initial approval, additional warnings and precautions were added to the product labels based on post-marketing safety reports and safety issues associated with the DPP-4 inhibitor drug class. These include acute pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), heart failure (observed with two other members of DPP-4 inhibitor class), acute renal failure sometimes requiring dialysis, increased risk of hypoglycemia when used with an insulin secretagogue or insulin therapy, serious allergic and hypersensitivity reactions, severe and disabling arthralgia (associated with DPP-4 inhibitors), bullous pemphigoid requiring hospitalization (associated with DPP-4 inhibitors), and absence of clinical studies establishing conclusive evidence of macrovascular risk reduction[10].

3.2. Summary of Presubmission/Submission Regulatory Activity

[9] Labels that exclude pediatric type 2 diabetes may indicate "treatment of adult and pediatric patients with type 1 diabetes and adults with type 2 diabetes" or may indicate approved treatment only in adults with diabetes.
[10] This warning was added due to the uncertainty around diabetes product cardiovascular safety prior to the 2008 diabetes cardiovascular guidance. Given current knowledge from cardiovascular outcome trials, this warning has been removed from other DPP-IV inhibitor labels.

Table 1 shows the regulatory history related to the sitagliptin pediatric development program[11].

Table 1: Regulatory History for Sitagliptin Pediatric Development Program

Date	Event/Description
BPCA-related regulatory activities	
2007-04-30	Proposed pediatric study request submitted for pediatric single dose PK study (P081) and phase III pediatric efficacy study (P083)
2008-05-20	P081 pediatric study protocol submitted
2012-09-06	P081 clinical study report (CSR) submitted
2012-11-27	FDA issues Written Request (WR) for NDAs 21995, 22044, 202270
2013-05-07	FDA issues revised WR (Amendment #1)
2017-12-07	FDA issues revised WR (Amendment #2)
PREA-related regulatory activities	
2006-10-16	Requirement for deferred pediatric post-marketing study with approval of Januvia (NDA 021995, PMR 224-1)[12]
2007-03-30	Requirement for deferred pediatric post-marketing study with approval of Janumet (NDA 022044, PMR 856-1)[12]
2009-05-13 to 2010-07-29	Submission of draft protocols for P170 (phase III pediatric efficacy studies, NDA 022044, PMR 856-1) and P083 (phase III pediatric efficacy study, NDA 021995, PMR 224-1) followed by FDA advice and protocol revisions

[11] Table does not include a complete list of every protocol amendment that was submitted/accepted. These are discussed in more detail in Section 6.
[12] Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive

2011-06-02	P083 and P170 protocols submitted
2012-02-02	Requirement for deferred pediatric post-marketing study with approval of Janumet XR (NDA 202270, PMR 1802-1, PMR 1802-2) [13]
2012-02-06	P296 protocol submitted (to satisfy PMR 1802-1), a pediatric PK study of Janumet XR with swallowing ability test
2012-03-12 to 2012-07-30	Submission of draft protocols for P289 (phase III pediatric efficacy study, NDA 202270, PMR 1802-2) followed by FDA advice and protocol revisions
2012-07-30	P289 protocol submitted
2012-09-12	FDA releases PMR 1802-2 and replaces with PMR 1802-03[14] (NDA 202270)
2013-04-29	FDA grants deferral extension request for study P083 (PMR 224-1) and P170 (PMR 856-1)
2013-10-07	FDA grants deferral extension request for study P296 (PMR 1802-1)
2014-03-03 to 2014-05-27	Type C meeting requested, and written advice provided by FDA regarding major protocol amendment to study P083 (amendment P083-05) [15], pooling strategy for studies P170 and P289, sample size reductions for P170 and P289, addition of 34-week extension to P170
2014-08-27	FDA confirms acceptance of protocol amendments 083-05, 170-02, 170-03, and 289-04

[13] PMR 1802-01: A pharmacokinetic study of JANUMET XR in pediatric patients 10 through 17 years of age (inclusive) with type 2 diabetes mellitus.
PMR 1802-02: A 54-week, randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of JANUMET XR vs. metformin in pediatric patients who are inadequately controlled on diet and exercise. You must also evaluate whether pediatric patients can safely swallow JANUMET XR over the course of the trial.
[14] PMR 1802-03: A 54-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of JANUMET XR versus metformin extended release in pediatric patients who are inadequately controlled on metformin immediate release. You must also evaluate whether pediatric patients can safely swallow JANUMET XR over the course of the trial.
[15] Protocol amendment P083-05 resulted in major changes to the study design of Study P083 including reduction of treatment arms from 4 treatment groups to 2 treatment groups, due to recruitment challenges. This amendment and its implementation are described in further detail in Section 6.1.1.

2014-10-03	FDA grants deferral extension request for P289 (PMR 1802-03)
2015-02-16	P296 CSR submitted
2015-06-22 to 2015-09-04	Type C meeting requested, and written advice provided by FDA regarding plan for integrated statistical analysis for studies P083, P170 and P289
2016-01-20	FDA confirms that NDA 202270 PMR 1802-01 has been fulfilled by submission of P296 CSR
2016-01-25	FDA grants deferral extension requests for study P083 (PMR 224-1), P170 (PMR 856-1), and P289 (PMR 1802-03)
2016-01-28	FDA releases PMR-1802-03 and replaces with PMR-04 (eliminating requirement to assess swallowability)
2017-01-19	Type C face to face meeting to discuss pediatric development program
2018-03-12	FDA agrees to 2 CSRs for P083 and 2 database locks to accommodate earlier submission of P083 in the European Union.
2019-05-02	FDA grants deferral extension for all pediatric phase III studies with new deadline of April 25th, 2021, matching the due date on the WR
2019-09-30	P083 CSR #1 submitted
2020-06-04	P083 CSR #2, P170 CSR and P289 CSR submitted (current submission)

Source: Reviewer generated based on Applicant provided regulatory history

3.3. Foreign Regulatory Actions and Marketing History

Since its initial approval in August 2006, sitagliptin has been registered and approved in more than 130 countries. Sitagliptin/metformin IR FDC has been registered and approved in more than 125 countries since March 2007, and sitagliptin/metformin XR FDC has been registered and approved in more than 30 countries since its first approval in February 2012.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In the current submission, the Applicant disclosed that unblinded data reports provided to the external data monitoring committee (DMC) for all phase III pediatric studies included incorrect treatment assignments that were based on "mock" allocation schedules (rather than actual randomized treatment) for DMC reviews conducted from 2014 through 2016 for trial P083, and from 2015 to 2016 for trials P170 and P289. Following an information request sent by the Agency on August 5th, 2020, the Applicant provided the Corrective Action Prevention Action (CAPA) and relevant DMC meeting memos[16]. According to the CAPA, the actual allocation schedules were loaded into the database for all 3 studies on March 28th, 2017 and the DMC re-analyzed data reports with the corrected tables. Root causes for the error were identified and corrective actions instituted[17]. There is no evidence that this error impacted the final dataset or final analyses for any of the pediatric phase III efficacy studies.

4.2. Product Quality

There is no new data regarding chemistry, manufacturing and controls (CMC), sterility, or biopharmaceutics in the submission.

4.3. Clinical Microbiology

There is no new data regarding microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There is no new data regarding non-clinical pharmacology or toxicology in the submission.

4.5. Clinical Pharmacology

The applicant previously submitted CSRs for two phase I pediatric PK trials, P081 (NDA 021995, eCTD sequence 0409) and P296 (NDA 202270, eCTD sequence 0084) which were reviewed by

[16] Only 5 of 9 DMC memos were provided. Following an additional information request sent by the Agency on September 2nd, 2020, the Applicant stated that the missing 4 DMC memos were never created due to an oversight and that no process audit was ever conducted to verify the effectiveness of the CAPA. This matter has been referred to the OSI enforcement group for follow up.

[17] Root causes included lack of communication (unblinded team was unaware that there were multiple allocation schedules), failure of those who were aware of multiple allocation schedules to load the correct allocation schedules into the database, and failure of the unblinding verification macro to identify the error. A review of other ongoing studies conducted by the Applicant did not reveal similar errors. Corrective measures included staff training, process changes, and modification of the unblinding verification macro.

the Office of Clinical Pharmacology (OCP). Below is a brief summary of the pertinent findings of each trial and conclusions from the clinical pharmacology reviews.

P081 [18]

P081, "A Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Sitagliptin in Adolescents," was a multicenter, randomized, double-blind, placebo-controlled, single-dose study involving 35 subjects aged 10 to 17 years with T2D. The purpose of this trial was to determine pediatric dosing for the phase III pediatric trials. 3 panels of subjects each were randomized in 3:1 ratio to receive single oral doses of sitagliptin (50 mg, 100 mg and 200 mg) or placebo. The Applicant concluded that the sitagliptin exposure in T2D adolescents was comparable to that of adults based on the geometric mean ratios (adolescent/adult) of 0.82 and 1.04 for dose adjusted $AUC_{0-\infty}$ and Cmax respectively (Table 2) and that the weighted average inhibition of plasma DPP-4 with sitagliptin was significantly different from placebo (Table 3). Based on results of this trial, the Applicant proposed 100 mg once daily for the pediatric efficacy and safety trial.

Table 2: Summary Statistics and Between-Population Comparisons for Sitagliptin Pharmacokinetics Parameters after Single-Dose Administration of Sitagliptin 50, 100 and 200 mg in Adolescent Subjects with T2DM

Pharmacokinetic Parameter	50 mg		100 mg		200 mg	
	N	GM (95% CI)‡	N	GM (95% CI)‡	N	GM (95% CI)‡
$AUC_{0-\infty}$ (nM·hr)	9	3438 (2881,4103)	9	5869 (4918,7003)	8	12965 (10749,15638)
C_{max} (nM)	9	366 (288,464)	9	666 (526,845)	8	1876 (1458,2413)
C_{24hr} (nM)	9	32 (25,41)	9	43 (34,55)	8	78 (60,101)
T_{max} (hr) ‖	9	3.0 (1.5,5.0)	9	3.0 (2.0,4.5)	8	2.5 (1.0,3.1)
Apparent $t_{1/2}$ (hr)§	9	12.1 (1.7)	9	11.2 (2.1)	8	11.7 (1.8)
Between-Populations Comparison#						
	N	GM (95% CI) ¶		GMR (90% CI) †		
$AUC_{0-\infty}$ (nM·hr)						
Adolescent	25	6424 (5740, 7190)		0.82 (0.66, 1.01)		
Adult §§	14	7851 (6360, 9691)				
C_{max} (nM)						
Adolescent	8	1876 (1435, 2453)		1.04 (0.75, 1.44)		
Adult	7	1803 (1354, 2401)				
C_{24hr} (nM)						

[18] Date of clinical pharmacology review: 11/27/2012, by Dr. Sang Chung. Note that this review was based only on the P081 CSR synopsis, as the full study report had not yet been provided. No new conclusions were identified in the clinical pharmacology memo for this application (submitted by Dr. Sang Chung on 11/24/2020).

Adolescent	8	78 (54, 112)	0.74 (0.48, 1.14)
Adult	7	106 (72, 156)	

‡ Back-transformed least-squares mean and confidence interval from ANOVA model performed on natural log transformed values
‖ Median (min, max) reported for T_{max}
§ Harmonic mean, jack-knife standard deviation reported for apparent $t_{1/2}$
¶ GM = Geometric Least-Squares Mean across dose strengths (for AUC $AUC_{0-\infty}$) or at 200 mg (for C_{max} and C_{24hr}). Back-transformed least-squares mean and confidence interval from linear mixed effect model (for AUC $AUC_{0-\infty}$) or ANOVA model (for C_{max} and C_{24hr}) performed on natural log-transformed values.
† GMR = Geometric least-squares mean ratio (Adolescent/Adult).
# Between population comparison was made for dose-adjusted (to 100 mg) sitagliptin AUC across all available doses in adolescent and adult subjects with T2DM, where comparison for sitagliptin C_{max} and C_{24hr} were made at 200 mg dose in adolescent and adult subjects.
§§ N=14 refers to 14 observations from 7 subjects

Source: Clinical pharmacology review, NDA 021995, dated 11/27/2012, by Dr. Sang Chung

Table 3: Summary Statistics of 24-Hour Weighted Average Inhibition and Percent Inhibition at 24 Hours Postdose of DPP-4 Activity after Single-Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Subjects with T2DM

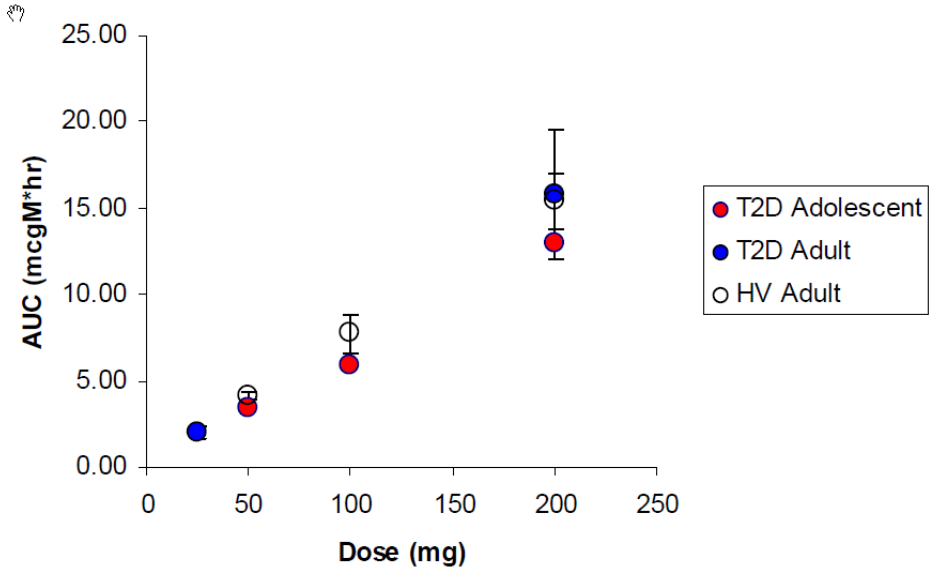
Treatment	N	LS Mean (95% CI)†	Difference (95% CI)††
24-Hour WAI of DPP-4 Activity			
Placebo Sitagliptin	8	6.76 (-6.21, 18.14)	
50 mg Sitagliptin	9	73.98 (70.59, 76.99)	67.23 (58.26, 76.59)
100 mg Sitagliptin	9	80.53 (77.98, 82.78)	73.77 (65.32, 82.65)
200 mg	8	87.96 (86.29, 89.43)	81.21 (73.09, 89.83)
Percent Inhibition of DPP-4 Activity at 24 Hours Postdose			
Placebo Sitagliptin	8	3.57 (-12.60, 17.43)	
50 mg Sitagliptin	9	53.98 (46.74, 60.24)	50.41 (37.57, 63.67)
100 mg Sitagliptin	9	62.78 (56.92, 67.84)	59.21 (47.21, 71.70)
200 mg	8	75.76 (71.70, 79.24)	72.19 (61.08, 83.94)

† LS Mean = Least-Square Mean; CI = Confidence Interval
††Difference = Difference of least-square means (Active - Placebo)

Source: Clinical pharmacology review, NDA 021995, dated 11/27/2012, by Dr. Sang Chung

OCP agreed with the Applicant's proposed dosing. The review by Dr. Chung notes that sitagliptin exposure in adolescents was 18% lower than that of adults (Figure 1), however this was felt not to be clinically relevant as the minimum effective dose in adults was identified as 50 mg, and sitagliptin exposure in adolescents following 100 mg was much greater than that of the minimum effective dose in adults. Dr. Chung's review also notes that DPP-4 inhibition data in adolescents (Table 3) and adults (Table 4) were comparable.

Figure 1: Geometric means of AUC by doses: T2D adolescent (n=9 per treatment), T2D adults (n=7 per dose) and HV (n=6 per dose), adult data are with between-subject standard deviation back-transform log scale



Source: Clinical pharmacology review, NDA 021995, dated 11/27/2012, by Dr. Sang Chung

Table 4: Weighted Average Inhibition of Plasma DPP-IV Activity Through 24 Hours Postdose Following Administration of Single Oral Doses of MK-0431 or Placebo in Subjects with Type 2 Diabetes (Percent Inhibition† From Baseline, Study 005)

Treatment Group	N	Mean	Between-Subject SD‡	Median	Minimum	Maximum	LS Mean§	95% CI for LS Mean
Placebo	56	1.9	4.7	1.6	-10.0	13.7	2.1	(-2.8, 6.7)
MK-0431 25 mg	56	68.1	5.7	67.5	55.4	82.7	68.1	(66.6, 69.6)
MK-0431 200 mg	56	91.4	2.2	91.3	83.6	96.4	91.4	(90.9, 91.8)

Source: Clinical pharmacology review, NDA 021995, dated 11/27/2012, by Dr. Sang Chung

P296[19]

P296, "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," was a multicenter, open-label, fixed-sequence, 2-period study involving 10 to 17-year-old male and female

[19] Date of clinical pharmacology review: 10/13/2015, by Dr. S.W. Johnny Lau. The purpose of the review was to determine whether study P296 fulfilled the PMR of NDA 202270 from a clinical pharmacology perspective. No new conclusions were identified in the clinical pharmacology memo for this application (submitted by Dr. Sang Chung on 11/24/2020).

subjects with T2D. Two groups (each with 12 subjects each, total N=24) received the following treatments:

- Treatment A (Group 1): 2 sitagliptin/metformin XR (50 mg/1000 mg) tablets with a low-to moderate fat meal (breakfast) on Day 1
- Treatment B: 2 matching placebo tablets on Days 2 – 4 once daily (Group 1) or Days 1 – 4 once daily (Group 2)
- Treatment C: Self-administration of 2 matching placebo tablets with the evening meal on Days 5 – 9 once daily (Groups 1 and 2)

All subjects answered a swallowing ability questionnaire on days 2, 4, 6, and 9. Serial blood samples were collected pre-dosing and 72 hours after dosing on Day 1 to measure sitagliptin and metformin concentrations. The objectives of the trial were to assess the safety and tolerability of the treatment administration, to determine swallowing ability and to determine PK parameters following consumption of low-to-moderate fat meal.

Results of the swallowing questionnaire showed that most (90% of subjects) found it easy to start swallowing the medication and more than half (50 to 60% of subjects) needed some extra help (water or moving heads back) to complete swallowing. The Applicant did not compare the pharmacokinetic results with any prior pediatric or adult data, however in his review Dr. Lau compared the results to a prior adult PK study (Study P164, NDA 202270). Dr. Lau concluded that, similar to the results of trial P081 (described above), the geometric mean sitagliptin $AUC_{0-\infty}$ in adolescents was lower than that of adults, however the Cmax and $t_{1/2}$ of adolescents were similar to those of adults (Table 5).

Table 5: Pharmacokinetic results of sitagliptin upon a single administration of 2 sitagliptin/metformin XR (50 mg/1000 mg) FDC tablets to adolescents and adults

	Sitagliptin Geometric Mean (CV%)		
Parameter	Adolescents (low-	Adults (fasted)	Adults (high fat meal)
$AUC_{0-\infty}$, nM•hr	6020 (24.8)	7581 (16)	7139 (19)
AUC_{0-last}, nM•hr	5940 (25.7)	7435 (16)	7036 (18)
AUC_{024hr}, nM•hr	5310 (22.4)	Not applicable	Not applicable
C_{max}, nM	757 (40.1)	883 (29)	736 (25)
T_{max} (hr) ¶	1.52 (0.97, 3.05)	2.5 (2.0, 5.0)	2.1 (1.0, 5.0)
Terminal $t_{½}$, hr§	10.0 (27.3)	12.6 (4.7)	12.1 (4.1)

¶ Median (Min, Max)
§Jack-knife Standard Deviation
Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log scale

Source: Clinical Pharmacology Review, NDA 202270, submitted 10/13/2015, by Dr. S.W. Johnny Lau.

With regards to metformin, the pharmacokinetic parameters in adolescents were also found to be similar to those of adults (Table 6).

Table 6: Pharmacokinetic results of metformin upon a single administration of 2 sitagliptin/metformin XR (50 mg/1000 mg) FDC tablets to adolescents and adults.

	Metformin Geometric Mean (CV%)		
Parameters	Adolescents (low-	Adults (fasted)	Adults (high fat meal)
$AUC_{0-\infty}$, ng•hr/mL	Not applicable	13975 (38)	22622 (18)
AUC_{0-last}, ng•hr/mL	Not applicable	13816 (33)	21710 (15)
AUC_{024hr}, ng•hr/mL	14200 (39.7)	Not applicable	Not applicable
C_{max}, ng/mL	1490 (29.1)	1802 (35)	1644 (17)
T_{max} (hr) ¶	5.00 (3.98, 7.22)	3.0 (2.0, 5.0)	5.0 (4.0, 7.0)
Terminal $t_{½}$, hr	Not applicable	12.3 (7.1)	9.3 (4.4)

¶ Median (Min, Max)
§Jack-knife Standard Deviation
Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log scale

Source: Clinical Pharmacology Review, NDA 202270, submitted 10/13/2015, by Dr. S.W. Johnny Lau.

Based on the pharmacokinetic results, Dr. Lau recommended using the same sitagliptin dose for subjects 10 to 17 years of age as the adult sitagliptin dose. Dr. Lau also recommended that 2000 mg metformin be used as the daily dose of the extended release portion of the sitagliptin/metformin XR (50 mg/1000 mg) FDC tablets in adolescents 10 to 17 years of age with T2D. Dr. Lau's review also notes that sitagliptin and metformin do not pharmacokinetically interact with each other.

Trial P296 was designed in order to fulfill PMR 1802-01 for NDA 202270 and was also included as part of the written request. On January 20th, 2016, the FDA confirmed that the PMR had been fulfilled. On October 30th, 2020, the Pediatric Exclusivity Board confirmed that trial P296 was conducted as specified in the written request.

4.6. Devices and Companion Diagnostic Issues

There are no devices included in this submission.

4.7. Consumer Study Reviews

This section is not applicable in this submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Three pediatric phase III clinical trials were reviewed (Table 7).

Table 7: Listing of Clinical Trials Relevant to this NDA/BLA

Trial	NCT #	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of subjects randomized	Study Population	Number of Centers and Countries[1]
		Controlled Studies to Support Efficacy and Safety						
P083[2]	0148-5614	Randomized, double-blind, safety and efficacy study of sitagliptin in pediatric T2D subjects, consisting of a screening period, one-week single-blind run-in period, 20-week placebo-controlled "Phase A" and 34-week active controlled "Phase B".	Phase A: Sitagliptin 100 mg daily or placebo Phase B: Sitagliptin 100 mg daily versus metformin 2000 mg daily	Primary efficacy endpoint: Change from baseline to week 20 HbA1c Safety endpoints assessed through week 54	54 weeks	191	Subjects with T2D, aged 10-17 years, not on background oral AHA therapy, with or without insulin	213 centers, 43 countries
P170[3]	0147-2367	Randomized, double-blind, placebo-controlled, safety and efficacy study of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin IR) in pediatric T2D subjects, consisting of a screening period, one-week single-blind run-in period, 20-week placebo-controlled "base" study and 34-week placebo-controlled "extension" study.	Base and Extension: Sitagliptin/Metformin IR twice daily versus metformin IR twice daily			124	Subjects with T2D, aged 10-17 years, on background therapy of metformin IR, with or without insulin	100 centers, 25 countries
P289	0176-0447	Randomized, double-blind, placebo-controlled, safety and efficacy study of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin IR) in pediatric T2D subjects consisting of a screening period, one-week single-blind run-in period, 20-week placebo-controlled "Phase A" and 34-week placebo-controlled "Phase B".	Phase A and Phase B: Sitagliptin/Metformin XR FDC once daily) versus metformin XR once daily			98	Subjects with T2D, aged 10-17 years, on background therapy of metformin XR, with or without insulin	139 centers, 31 countries

Abbreviations: HbA1c, hemoglobin A1c; T2D, type 2 diabetes, IR, immediate release; XR, extended release
[1]This includes the number of centers and countries involved in the clinical trial (including screening of subjects). Numbers of centers and countries from which randomized and treated subjects were drawn is discussed in section 6.1.2.
[2]The study P083 initially had 4 treatment groups but following amendment P083-05 the number of treatment groups was reduced to 2. See section 6.1.1 for further details.
[3]Extension study added 3 years after study start, so not all subjects in base study were eligible to participate. See section 6.1.1 for further details.

Source: Reviewer created

5.2. Review Strategy

Given that there was some heterogeneity in the results of individual trials, my review strategy for efficacy was primarily focused on conducting a detailed review and comparison of efficacy findings among the three phase III pediatric studies to better understand any potential differences that may have accounted for the discrepant results. To accomplish this, I reviewed the individual study protocols, protocol amendments, the written request, the statistical analysis plan, all individual study reports, as well as the clinical summaries of efficacy for the 2-study pool (combined data from P170 and P289) as well as the 3-study pool (combined data from P083, P170 and P289). I also performed additional reviews and analyses of the efficacy data using the submitted datasets, in conjunction with the primary statistical reviewer Dr. Wenda Tu. For the safety review, I focused primarily on reviewing combined safety data from the 3-study pool through week 54 (as detailed in the clinical summary of safety submitted under NDA 021995) as well as any safety data detailed in the individual trial reports. Further details on my approach to the safety review is described in section 8.1.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Pediatric Phase III clinical trials

6.1.1. Study Designs

Overview

The Applicant conducted three phase III clinical trials (P083, P170 and P289) to evaluate the safety and efficacy of sitagliptin in pediatric subjects with T2D. An overview of each of the three phase III trials are described below:

1. **P083**

Trial Title: "A Phase III, 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"

Trial Location: The trial was conducted across 213 centers and 43 countries.

Overview: The purpose of this trial was to evaluate the safety and efficacy of 54 weeks of sitagliptin therapy (100 mg daily) in pediatric subjects age 10 to 17 years with inadequately controlled T2D (with or without insulin therapy). Sitagliptin was compared to placebo from

weeks 0 to 20, and to metformin from weeks 20 to 54[20].

2. **P170**

Trial Title:

Base study: A Phase III, Multicenter, Double-blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy 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)

Extension study: A 34-week Follow-up to: A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy 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)

Trial Location: The trial was conducted in 100 centers across 25 countries.

Overview: The purpose of this trial was to compare the efficacy and safety of sitagliptin, administered as a fixed-dose combination with metformin immediate release (Sita/Met IR FDC) to metformin immediate release (Met IR) in pediatric subjects aged 10 to 17 years with T2D and inadequate glycemic control on metformin IR alone or in combination with insulin. The trial included a 20-week treatment period as part of the base study and a 34-week treatment period as part of the extension study. A separate but similarly designed trial (P289) compared the efficacy and safety of sitagliptin administered as a fixed-dose combination with metformin extended release (Sita/Met XR FDC) to metformin extended release (Met XR). Data from P170 and P289 were combined in the "2-study pool" to allow for pooled analysis of results.

3. P289

Trial Title: A Phase III Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety 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)

Trial Location: The trial was conducted in 139 centers in 31 countries

Overview: The purpose of this trial was to compare the efficacy and safety of sitagliptin, administered as a fixed-dose combination with metformin extended release (Sita/Met XR FDC)

[20] Subjects in the comparator arm ("placebo/metformin") received placebo from weeks 0 to 20 but were switched to metformin from weeks 20 to 54.

to metformin immediate release (Met XR) in pediatric subjects aged 10 to 17 years with T2D and inadequate glycemic control on metformin XR alone or in combination with insulin. The trial included a total 54-week treatment period, divided into a 20-week phase A and 34-week phase B. A separate but similarly designed trial (P170) compared the efficacy and safety of sitagliptin administered as a fixed-dose combination with metformin immediate release (Sita/Met IR FDC) to metformin immediate release (Met IR). Data from P170 and P289 were combined in the "2-study pool" to allow for pooled analysis of results.

Study Objectives:

The primary objectives of each of the three phase III studies are described in Table 8 **.** All study objectives were determined to have met the terms of the Written Request (WR)[21]. **Note that a primary efficacy objective was specified only for trial P083, the 2-study pool (combined data from P170 and P289) and the 3-study pool (combined data from all three trials), however, hypothesis testing for the 3-study pool was only permitted if P083 was successful.** Objectives for trials P170 and P289 alone were for safety and exploratory purposes.

Table 8: Study Objectives for Sitagliptin Phase III Pediatric Trials

Objectives	P083	2-study pool (P170+P289)	3-study pool (P083+P170+ P289)	P170	P289
Primary Objectives					
To assess the effect of treatment with sitagliptin compared with that of placebo on HbA1C at 20 weeks	X	X[1 or 2]	X		
To assess the safety and tolerability of sitagliptin	X	X[1 or 2]	X	X[1]	X[2]
Secondary/Exploratory Objectives					
To assess the effect of treatment with sitagliptin compared with that of placebo on					
HbA1c at 54 weeks	X	X[1 or 2]	X		
HbA1c at 20 weeks				X[1]	X[2]
FPG at 20 weeks and 54 weeks	X	X[1 or 2]	X		
FPG at 20 weeks				X[1]	X[2]
Proportion of subjects requiring glycemic rescue at 20 weeks and 54 weeks	X	X[1 or 2]			
Proportion of subjects at goal (HbA1c < 7.0%) at 20 weeks and 54 weeks	X	X[1 or 2]			
BMI at 20 and 54 weeks	X				
Fasting measures of beta cell function, 2-hour PMG, indices of insulin secretion derived from	X				

[21] Terms of WR reviewed at the pediatric exclusivity board meeting (10/28/2020)

C-peptide, insulin and glucose profiles with a standard meal challenge at 20 weeks and 54 weeks[22]					
To assess the effect of treatment with sitagliptin relative to placebo on:					
Growth velocity at 20 and 54 weeks	X	X[1 or 2]		X[1]	X[2]
Change from baseline in Tanner staging at 20 and 54 weeks	X	X[1 or 2]		X[1]	X[2]
Trial P083 only					
Skeletal maturation at 20 and 54 weeks	X				
% change from baseline on IGF-1 and IGF-BP3	X				
% change from baseline in markers of bone turnover and calcitonin at 20 and 54 weeks	X				
% change from baseline in CD26 expression at 20 and 54 weeks	X				
Change from baseline in measures of dentition at 20 and 54 weeks	X				
Trial P083 only: To assess the effect of treatment with placebo (weeks 0-20) followed by metformin (weeks 20-54) on:					
HbA1c at 54 weeks	X				
FPG at 54 weeks	X				
Proportion of subjects requiring glycemic rescue at 54 weeks	X				
BMI at 54 weeks	X				
Fasting measures of beta cell function, 2-hour PMG, indices of insulin secretion derived from C-peptide, insulin and glucose profiles with a standard meal challenge at 54 weeks[22]	X				

[1] Sitagliptin administered as Sita/Met IR FDC
[2] Sitagliptin administered as Sita/Met XR FDC
Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; PMG, post-meal glucose; IGF-1, Insulin-like growth factor 1; IGF-BP3, Insulin-like growth factor-binding protein 3; Sita/Met IR FDC, fixed-dose combination of sitagliptin and metformin immediate release; Sita/Met XR FDC, fixed dose combination of sitagliptin and metformin extended release

Source: Reviewer created

[22] Meal tolerance test (MTT) was only performed in subjects who agreed to undergo this procedure

Trial Designs

The trial designs for the three phase III pediatric studies are detailed below. Study designs were all consistent with the terms of the written request.

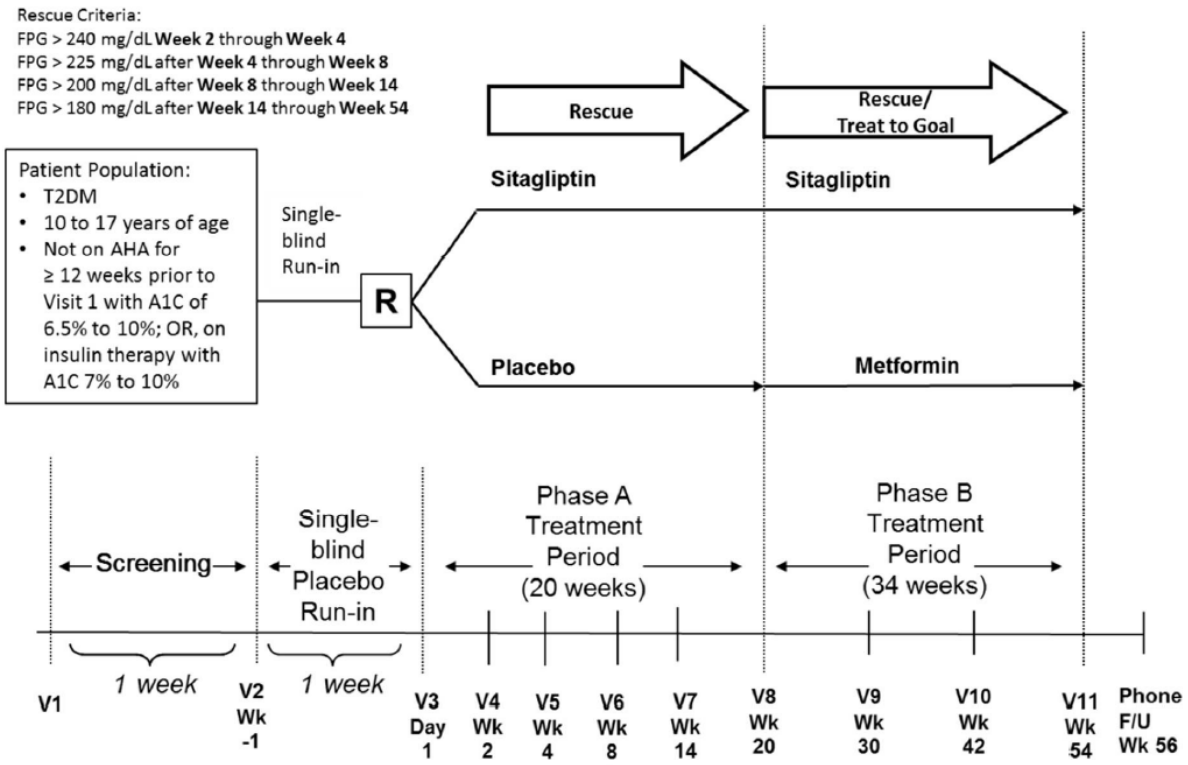
1. P083

Trial P083 was a multicenter, multinational, randomized, parallel-group, placebo-controlled trial comprised of a 1-week screening period, one-week single-blind run-in period and a 54-week double-blind treatment period (divided into a 20-week placebo-controlled "Phase A" and 34 week active-controlled "Phase B"[23]). Figure 2 shows the trial design.

Informed consent and assent, eligibility screening, vital signs, anthropometrics, and screening laboratory samples were obtained at visit 1 (screening)[24]. At visit 2 (start of placebo run-in), eligible subjects underwent diet and exercise counseling, training on self-monitoring of blood glucose (SMBG) and ketones, instruction on hypoglycemia monitoring and rescue criteria, baseline electrocardiogram, and initiated the placebo run-in. At Visit 3 (randomization), subjects underwent repeat eligibility screening, measurement of baseline endpoints[25], were randomized (1:1) to sitagliptin or placebo (stratified by insulin use at Visit 1: insulin user or non-insulin user) and received the first dose of double-blind treatment. During the double-blind treatment period, HbA1c was measured at weeks 8, 14, 20, 30, 42 and 54; FPG and other secondary efficacy endpoints were measured at weeks 20 and 54[26]. A telephone follow-up occurred 2 weeks after the end of the 54-week treatment period, or 14 days after study completion for those who discontinued study medication prior to study completion. Subjects who discontinued study medication prior to study completion were asked to return for key visits at week 20 and week 54[27].

[23] The original treatment duration was 16 weeks for Phase A and 38 weeks for Phase B. To allow for consistency with the other phase III pediatric trials (P170 and P289), following amendment P083-05 the duration of the treatment phases was adjusted to 20 weeks for Phase A and 34 weeks for Phase B.
[24] Investigators were allowed to test subjects with fingerstick HbA1c for screening purposes only, however only a central laboratory measured HbA1c was used to meet inclusion criteria for eligibility.
[25] Baseline endpoints included vital signs, tanner staging, height, weight, BMI percentile, waist circumference, bone age, quality of life questionnaire, baseline laboratory studies (see description of "Study Endpoints").
[26] See list of efficacy endpoints below under "Study Endpoints". Compliance, SMBG and AEs were monitored at all visits. Vital signs were measured at all in-person visits. Anthropometrics, ECG, and visual oral examination were monitored at weeks 20 and 54. See section 8.4.6 for description of laboratory measurements.
[27] If subjects were unwilling/unable to return, HbA1c and FPG were obtained from diabetes doctor records (if available)

Figure 2: 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: P083 Clinical Study Report

At the start of the trial, subjects were originally randomized into 4 treatment groups: Sitagliptin (sitagliptin in phase A and B), Metformin (metformin in phase A and B), Placebo/metformin (placebo in phase A and metformin in phase B) and Placebo/sitagliptin (placebo in phase A and sitagliptin in phase B). However, due to recruitment challenges**, following amendment P083-05 the treatment groups were reduced to 2 (sitagliptin and placebo/metformin,** as depicted above in Figure 2)**.** Randomization to the other 2 groups (i.e., metformin and placebo/sitagliptin) was discontinued, and those already randomized continued in the study according to their originally planned treatment assignment[28].

Reviewer comment: The elimination of two treatment arms mid-trial was a major change in study design. However, the 2 treatment groups that were discontinued (metformin and

[28] Data from subjects in the placebo/metformin (N=90) and placebo/sitagliptin (N=5) groups were combined into a single placebo group for the analysis from weeks 0 to 20. Data from those in the sitagliptin group (N=95) were compared to those in the placebo/metformin group (N=90) for analysis from weeks 0 to 54. Data from those in the metformin group (N=9) were excluded from the analyses.

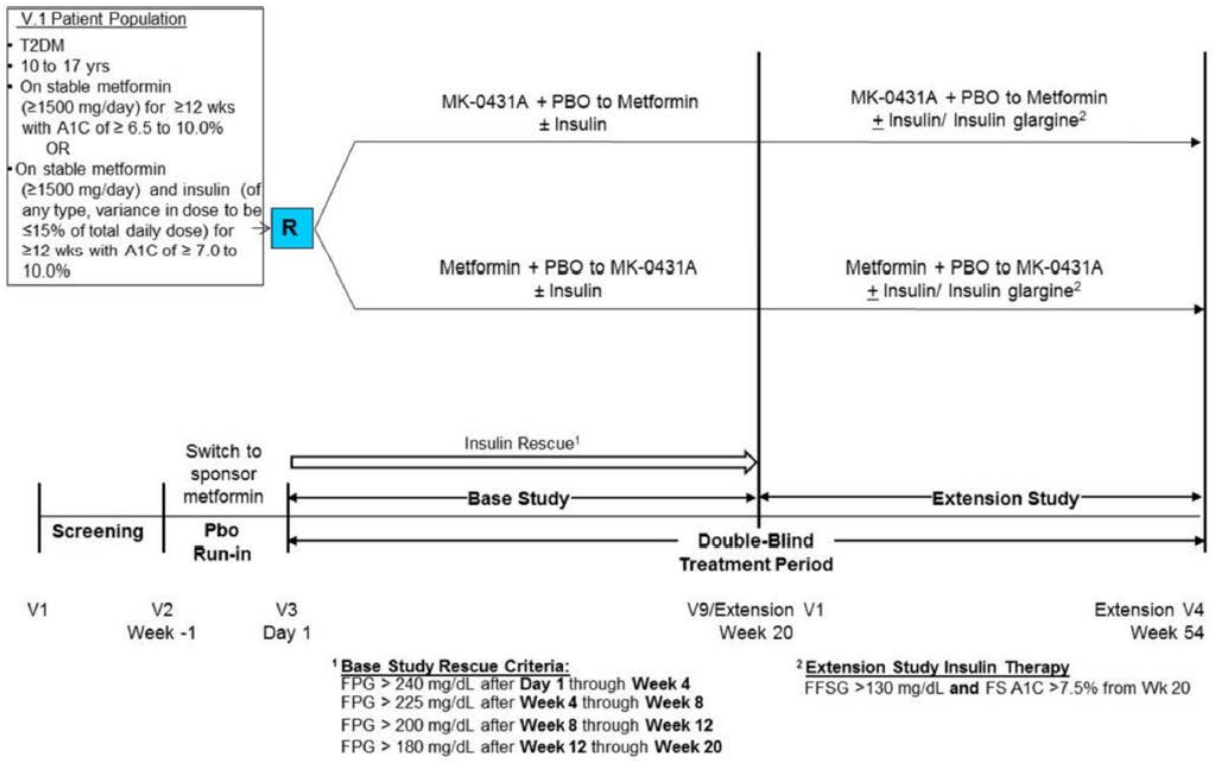
placebo/sitagliptin) would unlikely have contributed meaningful additional information to the safety and efficacy evaluation in the pediatric population. In the case of the metformin group, a comparison of metformin therapy to placebo is not directly relevant to the study objectives, and the remaining treatment groups (sitagliptin and placebo/metformin) allow for a comparison of sitagliptin to placebo and also provides some insight into how sitagliptin compares to metformin as an active control in Phase B. In the case of the placebo/sitagliptin group, the switch in study medication to sitagliptin in phase B would make this group an inappropriate control for the group that took sitagliptin in phase A and B. The amended analysis plan related to the study design change was reasonable (i.e., plan to use pooled phase A placebo data from subjects in the placebo/metformin group and those previously randomized to the placebo/sitagliptin group for any week 20 comparisons to the sitagliptin group, and to only consider data from the sitagliptin and placebo/metformin group for any week 54 analyses).

It is important to note that the P083 trial design differs from the other two trials (P170 and P289) in several aspects. The overall study design of trial P083 aimed to evaluate sitagliptin monotherapy, whereas the other two pediatric phase III trials evaluated sitagliptin as an add-on therapy to metformin. Trial P083 also differed with respect to the duration of the placebo-controlled period being limited to 20 weeks, followed by an "active-controlled" treatment period (comparing sitagliptin to metformin) for the last 34 weeks. The other two trials were placebo-controlled for entire 54-week treatment period (see detailed description of trial designs for P170 and P289 below). Given these differences, caution must be taken with pooled efficacy analyses of trial P083 combined with the other studies. Efficacy analyses from 3-study pool would likely only be relevant through week 20.

2. P170

Trial P170 was a multicenter, multinational, randomized, parallel-group, placebo-controlled trial consisting of a base study and extension study. The base study was comprised of a 1-week screening period, one-week single-blind run-in period, followed by a 20-week double-blind treatment period. Participants completing the base study were invited to participate in the extension study to allow for an additional 34-week double blind treatment period. Figure 3 shows the trial design.

Figure 3: 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: P170 protocol

The extension study was added 3 years after the start of the base study, therefore not all subjects who participated in the base study were eligible to participate[29].

Informed consent and assent, eligibility screening, vital signs, anthropometrics, and screening laboratory samples were obtained at visit 1 (screening)[24]. At visit 2 (start of placebo run-in), eligible subjects underwent diet and exercise counseling, training on self-monitoring of blood glucose (SMBG) and ketones, instruction on hypoglycemia monitoring and rescue criteria, baseline electrocardiogram, and initiated the placebo run-in. At Visit 3 (randomization), subjects underwent repeat eligibility screening, measurement of baseline endpoints[30], were randomized (1:1) to Sita/Met IR FDC or Met IR and received the first dose of double-blind treatment. Randomization was stratified by the subject's dose of metformin and insulin use at

[29] Extension study was added as part of amendment P170-03
[30] Vital signs, tanner staging, height, weight, BMI percentile, waist circumference, quality of life questionnaire, baseline laboratory studies (see description of "Study Endpoints" and section 8.4.6 for laboratory endpoints).

Visit 1 based on the following 6 strata:

(1) metformin dose of 1000, 1250, or 1275 mg, and insulin user
(2) metformin dose of 1500, 1700, or 1750 mg, and insulin user
(3) metformin dose of ≥2000 mg, and insulin user
(4) metformin dose of 1000, 1250, or 1275 mg, and non-insulin user
(5) metformin dose of 1500, 1700, or 1750 mg, and noninsulin user
(6) metformin dose of ≥2000 mg, and non-insulin user.

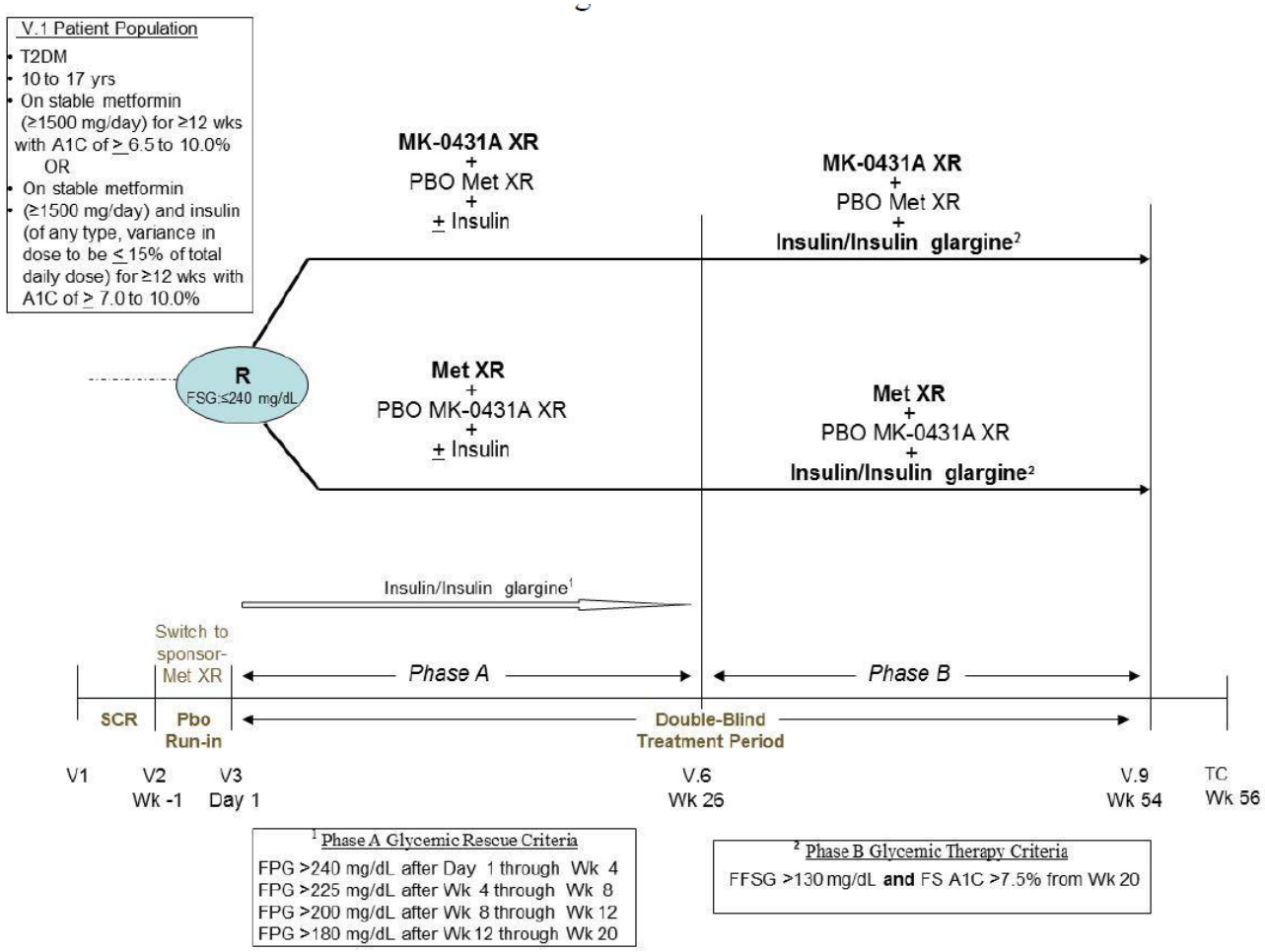
During the double-blind treatment period in the base study, HbA1c was measured at weeks 6 , 12 and 20. During the extension study, HbA1c was measured at weeks 28, 40 and 54. FPG and other secondary efficacy endpoints were measured at weeks 20 (in the base study) and 54 (in the extension study). A telephone follow-up occurred 2 weeks after the end of the treatment period (i.e., week 22 for those who only participated in the base study, week 56 for those who participated in the extension study or 14 days after study completion for those who discontinued study medication). Subjects who discontinued study medication prior to study completion were asked to return for key visits at week 20 and week 54[27].

Reviewer Comment:
Trial P170 was designed to evaluate the safety and efficacy of sitagliptin as an add-on therapy to metformin. This approach may be more relevant for the target population, as sitagliptin is most likely to be used as a second-line therapy in patients who have uncontrolled T2D on metformin.

3. P289

Trial P289 was a multicenter, multinational, randomized, parallel-group, placebo-controlled trial comprised of a 1-week screening period, 1-week single-blind run-in period, followed by a 54-week double-blind treatment period divided into phase A (weeks 0-20) and phase B (weeks 20-54). Figure 4 shows the trial design.

Figure 4: 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

Informed consent and assent, eligibility screening, vital signs, anthropometrics, and screening laboratory samples were obtained at visit 1 (screening)[24]. At visit 2 (start of placebo run-in), eligible subjects underwent diet and exercise counseling, training on self-monitoring of blood glucose (SMBG) and ketones, instruction on hypoglycemia monitoring and rescue criteria, baseline electrocardiogram, and initiated the placebo run-in. At Visit 3 (randomization), subjects underwent repeat eligibility screening, measurement of baseline endpoints[30], were randomized (1:1) to Sita/Met XR FDC or Met XR and received the first dose of double-blind treatment. Randomization was stratified by the subject's dose of metformin and insulin use at Visit 1 based on the following 6 strata:

(1) metformin dose <1500 mg and insulin user
(2) metformin dose of 1500 and insulin user
(3) metformin dose >1500 mg and insulin user
(4) metformin dose <1500 mg and non-insulin user
(5) metformin dose of 1500 mg and noninsulin user
(6) metformin dose of >1500 mg and non-insulin user.

During the double-blind treatment period (phase A and B), HbA1c was measured at weeks 6 , 12, 20, 28, 40 and 54. FPG and other secondary efficacy endpoints were measured at weeks 20 (phase A) and 54 (phase B). A telephone follow-up occurred 2 weeks after the end of the treatment period or 14 days after study completion for those who discontinued study medication. Subjects who discontinued study medication prior to study completion were asked to return for key visits at week 20 and week 54[27].

Reviewer Comment: Trial P289 was similarly designed to trial P170 to evaluate the safety and efficacy of sitagliptin as an add-on therapy to metformin and therefore pooled analysis of study results for P170 and P289 is appropriate. Of note, metformin XR is not currently approved for pediatric use. Data from adult studies suggest that the safety and efficacy of metformin IR is similar to metformin XR, and it is known that the safety and efficacy of metformin IR is similar in adults and children. Additionally, metformin XR is commonly used off-label for the treatment of pediatric T2D in clinical practice. Given that, it was reasonable to study sitagliptin as an add-on therapy to metformin XR in trial P289.

Key Inclusion/Exclusion Criteria:

The trial populations differed for trial P083 compared to trials P170 and P289. Trial P083 enrolled adolescents (aged 10 to 17 years) with inadequately controlled T2D, who were either not on oral anti-hyperglycemic therapy (AHA)[31] OR on a stable dose of insulin therapy[32] without any other AHA for at least 12 weeks prior to screening. In contrast, trials P170 and P289 enrolled adolescents (aged 10 to 17 years) with inadequately controlled T2D on ≥1500 mg/day of metformin[33] alone or in combination with a stable dose of any type of insulin therapy[34] for at least 12 weeks prior to screening. Subjects on any other AHA (apart from

[31] Subjects may have received oral AHA for no more than 10 days within the 12 weeks prior to screening.
[32] Variance in dose to be ≤15% of total daily dose.
[33] Subjects on stable doses of metformin ≥1000 to <1500 mg/day (alone or in combination with insulin) for ≥12 weeks were permitted to participate if there was documentation that they could not tolerate higher doses of metformin. Subjects on metformin doses < 1500 mg/day could have their metformin doses up titrated to ≥1500 mg/day and be eligible if the dose remains stable for ≥12 weeks.
[34] Variance in dose to be ≤15% of total daily dose. Subjects not on stable insulin doses at screening were eligible to participate after dose adjustment if the insulin dose remains stable for ≥12 weeks.

insulin) in addition to metformin were ineligible for trials P170 and P289.

Additional key inclusion/exclusion criteria are detailed below in Table 9. Note that due to recruitment challenges, all three studies underwent amendments to reduce the lower limit of HbA1c for inclusion from >7.0% to >6.5% and to allow for inclusion of subjects on background insulin (see description of protocol amendments for further details).

Given that trial P170 was divided into a base and extension study (added 3 years after trial start), additional key eligibility criteria for the P170 extension study included a requirement that the last dose of study medication from the base study was given < 14 days before entering the extension study, and that no other oral AHA had been initiated other than study medication or metformin.

Note that the WR specified that at least 30% of the randomized subjects must be 10 to 14 years of age and at least 30% of randomized subjects must be female (see "study results" below for details). For trial P083, the WR additionally specified that no subjects may have received more than 10 cumulative days of treatment with an oral AHA (i.e., metformin, SU, meglitinides, or alpha-glucosidase inhibitors) in the 12 weeks prior to Visit 1. Overall, the pediatric exclusivity board determined that these WR terms were met[35].

Table 9: Key Inclusion and Exclusion Criteria for Sitagliptin Phase III Pediatric Trials

Key inclusion Criteria	P083	P170	P289
Diagnosis of T2D based on ADA criteria along with clinical profile consistent with T2D	X	X	X
HbA1c 6.5 to 10% for those not on insulin, or 7.0% to 10% for those on insulin	X	X	X
BMI >85% or overweight/obese history at the time of T2D diagnosis	X	X	X
Fasting C-peptide >0.6 ng/mL	X	X[2]	X[2]
>80% compliance (site-performed tablet count) with placebo treatment during the single-blind run-in prior to randomization.	X	X	X
Key Exclusion Criteria			
History of other forms of diabetes or positive diabetes antibody screen[3]	X	X	X
Presence of symptomatic hyperglycemia[4] or moderate to large ketonemia detected at any point prior to randomization	X	X	X
Prior treatment with a DPP-4 inhibitor or GLP-1 receptor agonist[5]	X	X	X
Hypersensitivity or contraindication to metformin	X	X	X
Initiation of chronic treatment with medication known to cause weight gain or weight loss, requirement for greater than 2 weeks or repeated courses of	X	X	X

[35] Upon review of the medication dataset for P083, 18 subjects were on prior treatment with metformin. 1 of these subjects did not meet this criterion specified in the WR (i.e., oral AHA treatment of no more than 10 days in 12 weeks prior to Visit 1) due to receiving metformin for a total of 17 days, with the last dose of metformin given on the day of Visit 1. Given that this protocol deviation represented <1% (1/191) of all randomized subjects and since trial P083 enrolled more subjects than required in the WR (191 vs. 180), this term was overall felt to be met.

pharmacologic doses of corticosteroids[6]			
Surgical procedure within 4 weeks prior to screening or plan for major surgery during the study.	X	X	X
Exclusionary concomitant conditions			
Pregnancy[7]	X	X	X
Known cardiac disease other than hypertension	X	X	X
Blood pressure > 95 percentile despite appropriate antihypertensive therapy	X	X	X
Active liver disease (with the exception of non-alcoholic fatty liver disease)	X	X	X
Active nephropathy[8]	X	X	X
Chronic or progressive neurological or neuromuscular disorder	X	X	X
HIV	X	X	X
Clinically significant hematological disorder	X	X	X
Hyperthyroidism[9]	X	X	X
Abnormal growth or treatment with growth hormone	X	X	X
History of malignancy[10]	X	X	X
Idiopathic acute or chronic pancreatitis	X	X	X
Known history of illicit drug or alcohol abuse	X	X	X
Clinically significant ECG abnormality or prolonged QTc interval for age[11]	X	X	X
Exclusionary laboratory parameters			
ALT or AST > 2.5 x ULN	X	X	X
Abnormal TSH[12]	X	X	X
TG> 500 mg/dL[13]	X	X	X
Abnormally low hemoglobin	X	X	X
eGFR < 55 mL/min/1.73 m2	X		
eGFR <60 mL/min/1.73 m2 OR creatinine > 1.4 mg/dL in males and > 1.3 mg/dL in females		X	X

[1] FPG ≥126 mg/dL [7.0 mmol/L], or random plasma glucose ≥200 mg/dL [11.1 mmol/L], or two-hour oral glucose tolerance test [OGTT] plasma glucose ≥200 mg/dL [11.1 mmol/L], or A1C ≥6.5% [test performed using a method that is NGSP certified and standardized to the DCCT assay]
[2] for subjects with T2D < 2 years and for all subjects on background insulin
[3]anti-GAD or ICA-512
[4]On site fasting fingerstick glucose > 240 mg/dL detected at Visit 3 (Randomization)
[5]Subjects who participated in single dose studies at least 12 weeks prior to screening were eligible
[6]Inhaled, nasal and topical corticosteroids were permitted
[7]Pregnancy test performed at screening and at Visit 3 (Randomization)
[8]Subjects with diabetic nephropathy were eligible if they met all other eligibility criteria
[9] Subjects with treated hypothyroidism with normal TSH were eligible
[10]Subjects with non-recurrent and adequately treated non melanomatous skin carcinoma, carcinoma in situ of cervix, or other malignancies treated > 5 years prior to screening (with the exception of leukemia, lymphoma, malignant melanoma or renal cell carcinoma) were eligible, per discretion of investigator.
[11]Assessed at Visit 2
[12]Subjects with abnormal TSH could be rescreened following stable thyroid replacement for at least 6 weeks with no further dose changes pre-randomization
[13]Subjects with elevated TG could be rescreened following initiation of stable lipid lowering medication regimen for at least 4 weeks with no further dose changes pre-randomization
Abbreviations: T2D, type 2 diabetes; HbA1c, hemoglobin A1c; BMI, body mass index; HIV, human immunodeficiency virus; ECG, electrocardiogram, ULN, upper limit of normal; TG, triglycerides; eGFR, estimated

glomerular filtration rate

Source: Reviewer created

Reviewer Comment: Overall, the eligibility criteria for the pediatric phase III trials of sitagliptin were reasonable and generally consistent with other recent pediatric type 2 diabetes trials[10], with the exception of the fact that trial P083 enrolled subjects not on background oral AHA therapy (e.g., metformin). Given that the vast majority of adolescent patients with T2D are treated with metformin as a first line therapy, the P083 trial population may be less representative of the major target population for sitagliptin (i.e., T2D youth who are uncontrolled on metformin). However, sitagliptin therapy as an add-on to metformin therapy was explored in the other phase III trials (P170 and P289). Additionally, investigating sitagliptin monotherapy may be justified to provide alternative treatment options for T2D adolescents who are metformin-intolerant (or have a contraindication to metformin therapy).

Trials P170 and P289 enrolled pediatric T2D subjects who were uncontrolled on maximally tolerated doses of metformin, with a lower limit of HbA1c of 6.5% (for those not on insulin) and 7.0% (for those on insulin). Data from the TODAY study suggests that pediatric T2D patients with an HbA1c > 6.3% on metformin therapy were more likely to demonstrate treatment failure and deterioration beta cell function over time, compared to patients with HbA1c <6.3% who were more likely to have durable glycemic control[36]. Given the eligibility criteria, it is possible that the trial populations for P170 and P289 included a higher proportion of the subgroup of pediatric T2D patients who have rapid disease progression.

In contrast, due to differences in trial design, the population studied in the pediatric T2D trial for liraglutide (Ellipse)[10] may have included more subjects likely to have durable glycemic control. While similar HbA1c enrollment criteria were used in the Ellipse trial (HbA1c lower limit of 7% for those treated with diet and exercise and 6.5% for those on metformin and/or insulin), any enrolled subjects who were not on background metformin therapy were placed on maximally tolerated metformin after a run-in period prior to randomization, thereby allowing for greater inclusion of randomized subjects who could achieve a lower HbA1c on metformin (a subgroup more likely to have durable glycemic control).

See Table 19 for further details on baseline characteristics of the trial population for P170 and P289 in comparison to the Ellipse trial.

Glycemic Rescue Criteria:
In all three trials, the glycemic rescue criteria became progressively strict over the duration of the double-blind treatment period (Table 10), with more aggressive "treat-to-target" approaches being used from weeks 20 to 54. The glycemic rescue plan for studies P170 and

[36] Zeitler P, Hirst K, Copeland KC, et al. HbA1c After a Short Period of Monotherapy With Metformin Identifies Durable Glycemic Control Among Adolescents With Type 2 Diabetes. Diabetes Care. 2015;38(12):2285-2292

P289 were identical.

For all trials, compliance to blinded study medication was assessed prior to initiating any rescue medication. Prior to week 20, rescue therapy was initiated only if FPG was above the rescue threshold. Initial fasting fingerstick glucose (FFSG) values above the rescue threshold would trigger repeat FFSG, and FPG would be performed if there were 3 consecutive FFSG values above rescue threshold. Subjects who entered the study on background insulin continued the same dose (variance of ≤15% of total daily dose) and formulation of insulin throughout the study unless they met criteria for rescue (i.e., up titration of insulin), or unless down titration of dose was required due to hypoglycemia[37].

The insulin regimen and dosing to be used for rescue was at the discretion of the investigator, however prandial insulin could be added six weeks after initiating basal insulin if deemed appropriate. If initiation of insulin was considered unacceptable for subjects > 18 years, alternative oral AHAs could be used (with the exception of DPP-4 inhibitors, metformin, GLP-1 agonists) at the discretion of the investigator. If initiation of insulin was unacceptable for subjects < 18 years, they would be discontinued from study medication.

Table 10: Glycemic Rescue Plan for Sitagliptin Phase III Pediatric Trials

	P083	P170 and P289
Rescue Threshold through week 20		
FPG > 240 mg/dL	Week 2 through week 4	After day 1 through week 4
FPG >225 mg/dL	After week 2 through week 8	After week 4 through week 8
FPG >200 mg/dL	After week 8 through week 14	After week 8 through week 12
FPG > 180 mg/dL	After week 14	After week 12 through week 20
Rescue Agent through week 20	Rescue Step 1: Metformin Rescue Step 2: initiation or up titration of insulin	initiation or up titration of insulin
Glycemic Rescue criteria after week 20 to week 54	FPG > 180 mg/dL Treat-to-goal if HbA1c ≥7.0%[3]	FFSG >130 mg/dL AND FS HbA1c >7.5% [4]
Rescue Agent week 20 to week 54	Treat-to-goal Step 1[1]: Metformin (sitagliptin arm) or sitagliptin (placebo/metformin arm)[3] Treat-to-goal Step 2[2]: initiation or up titration of insulin	Initiation of insulin glargine or increase of background insulin therapy by at least 15% of total daily dose.

[1] for subjects who had not initiated rescue during weeks 0-20.
[2] if HbA1c remained ≥7% at least 6 weeks after rescue step 1 or treat-to-goal step 2.
[3] HbA1c values were unblinded for treat-to-goal.

[37] Subjects requiring transient (<14 days) initiation of insulin or increase in insulin dose >15% total daily dose at screening due to incurrent illness were not considered as having initiated rescue.

[4] At week 20, all subjects not rescued from weeks 0 to 20 underwent a check of FFSG and FS HbA1c. This process was repeated at all subsequent study visits for subjects who had not undergone rescue therapy. Additionally, for subjects who had not initiated insulin glargine or undergone increase of background insulin by at least 15%, if home FFSG measurements were > 130 mg/dL on 2 consecutive days, subjects would return to the clinic for an unscheduled visit at which time insulin glargine would be initiated or background insulin increased by at least 15% if FFSG was >130 mg/dL and the FS HbA1c was >7.5% at the clinic visit.
Abbreviations: FPG, fasting plasma glucose; FFSG, fasting fingerstick glucose; FS, fingerstick, HbA1c, hemoglobin A1c

Source: Reviewer created

Reviewer Comment: The limited guidance regarding the insulin regimen and dosing to be used for rescue therapy could have contributed to variability in glycemic outcomes after rescue. See section 6.1.2 and Figure 5 for further discussion of this issue.

Dose Selection/Study Treatments:
A dose of sitagliptin 100 mg daily was used in all phase III pediatric trials, based on evidence of similar pharmacokinetic profile of sitagliptin in adolescents and adults (discussed previously in Section 4.5), and because 100 mg daily is the currently labeled adult dose.

In all three trials, insulin used for background or rescue therapy was sourced locally and administered based on instructions from the investigator.

In trial P083, all subjects in the trial took 5 tablets per day (3 tablets prior to the morning meal and 2 tablets prior to the evening meal) from a single blister card for the duration of the study. Subjects in the sitagliptin arm received 1 tablet of sitagliptin daily and 2 tablets of metformin-placebo twice daily before meals in phase A and phase B. Subjects in the placebo/metformin arm received 1 tablet of sitagliptin-placebo daily and 2 tablets of metformin-placebo twice daily before meals in phase A, and 1 tablet of sitagliptin-placebo daily and 2 tablets of metformin twice daily before meals in phase B. For subjects initiating metformin therapy (either for glycemic rescue, as described above, or during phase B for those in the placebo/metformin arm) the metformin-placebo tablets were replaced by active metformin in a blinded fashion, starting at 500 mg/day and increased in 500 mg weekly increments to a total daily dose of 1000 mg BID by 3 weeks (if tolerated). Subjects unable to tolerate the higher dose of metformin would have the dose reduced at an unscheduled visit and would continue the maximal tolerated dose for the duration of the study.

In trials P170 and P289, subjects who entered the study on maximally tolerated doses of metformin were switched to sponsor-supplied metformin during the placebo run-in, and to study medications as indicated in Table 11 (P170) and Table 12 (P289). In trial P170, subjects took 2 tablets twice daily prior to morning and evening meals. In trial P289, subjects took 4 tablets once daily.

Table 11: Study Medications in Trial P170

Total Daily Dose of Metformin at **Visit 1**	Study medications initiated at **Visit 2** (placebo run-in)	Study medications initiated at **Visit 3** (Double-blind treatment period)	
		Sit/Met IR FDC arm	**Met IR arm**
1000, 1250, or 1275 mg	Met IR: 1000 mg daily (500 mg BID) + Placebo to Sita/Met IR FDC 50/500 mg (1 tablet BID)	Sita/Met IR FDC 100 mg/1000 mg daily (50/500 mg BID) + Placebo to Met IR 500 mg (1 tablet BID)	Met IR 1000 mg daily (500 mg BID) + Placebo to Sita/Met IR FDC 50/500 mg (1 tablet BID)
1500, 1700, or 1750 mg	Met IR: 1700 mg daily (850 mg BID) + Placebo to Sita/Met IR 50/850 mg (1 tablet BID)	Sita/Met IR FDC 100 mg/1700 mg daily (50/850 mg BID) + Placebo to Met IR 850 mg (1 tablet BID)	Met IR: 1700 mg daily (850 mg BID) + Placebo to Sita/Met IR 50/850 mg (1 tablet BID)
≥2000 mg	Met IR: 2000 mg daily (1000 mg BID) + Placebo to Sita/Met IR 50/1000 mg (1 tablet BID)	Sita/Met IR FDC 100 mg/2000 mg daily (50/1000 mg BID) + Placebo to Met IR 1000 mg (1 tablet BID)	Met IR: 2000 mg daily (1000 mg BID) + Placebo to Sita/Met IR 50/1000 mg (1 tablet BID)

Abbreviations: BID= twice daily, Met IR= metformin immediate release, Sita/Met IR FDC= fixed dose combination of sitagliptin and metformin immediate release.
Source: Reviewer created

Table 12: Study Medications in Trial P289

Total Daily Dose of Metformin at **Visit 1**	Study medications initiated at **Visit 2** (placebo run-in)	Study medications initiated at **Visit 3** (Double-blind treatment period)	
		Sit/Met XR FDC arm	**Met XR arm**

<1500 mg[38]	Met XR: 1000 mg daily *(2 tablets of 500 mg)* + Placebo to Sita/Met XR FDC 50/500 mg *(2 tablets daily)*	Sita/Met XR FDC 100/1000 mg daily *(2 tablets of 50/500 mg)* + Placebo to Met XR 500 mg *(2 tablets daily)*	Met XR: 1000 mg daily *(2 tablets of 500 mg)* + Placebo to Sita/Met XR FDC 50/500 mg *(2 tablets daily)*
1500 mg	Met XR: 1500 mg daily *(1 tablet of 500 mg and 1 tablet of 1000 mg)* + Placebo to Sita/Met XR FDC 50/500 mg *(1 tablet)* and placebo to Sita/Met XR 50/1000 mg *(1 tablet)* daily	Sita/Met XR FDC 100/1500 mg daily *(1 tablet of 50/500 mg and 1 tablet of 50/1000 mg)* + Placebo to Met XR 500 mg *(1 tablet)* and placebo to Met XR 1000 mg *(1 tablet) daily.*	Met XR: 1500 mg daily *(1 tablet of 500 mg and 1 tablet of 1000 mg)* + Placebo to Sita/Met XR FDC 50/500 mg *(1 tablet)* and placebo to Sita/Met XR 50/1000 mg *(1 tablet)* daily
>1500 mg	Met XR: 2000 mg daily *(2 tablets of 1000 mg)* + Placebo to Sita/Met XR FDC 50/1000 mg *(2 tablets daily)*	Sita/Met XR FDC 100 mg/2000 mg daily *(2 tablets of 50/1000 mg)* + Placebo to Met XR 1000 mg (*2 tablets daily*)	Met XR: 2000 mg daily *(2 tablets of 1000 mg)* + Placebo to Sita/Met XR FDC 50/1000 mg *(2 tablets daily)*

Abbreviations: Met XR= metformin extended release, Sita/Met XR FDC= fixed dose combination of sitagliptin and metformin extended release
Source: Reviewer created

Treatment Compliance*:*
According to the protocols, for all three trials compliance was "assessed by subject report which may be facilitated by tablet count"[39] at visit 3 (following the placebo run-in) and at all remaining visits during the double-blind treatment period. Compliance rate was defined as (Number of compliant days)/Number of days in the double blinded treatment period x 100%.

Reviewer Comment: It unclear to what extent tablet count was utilized in the assessment of compliance. Estimates of compliance based on patient report may have limited accuracy.

[38] Subjects were eligible on stable doses of > 1000 mg if there was documentation that they could not tolerate higher doses of metformin.
[39] Case report forms for medication compliance include a description of "number of units taken" but do not indicate whether this was obtained via patient report or tablet count.

Discontinuation Criteria:
Individual subject discontinuation criteria common to all three trials included withdrawal of informed consent or subject request for study discontinuation, subjects meeting glycemic rescue criteria for whom glycemic rescue medication was deemed clinically inappropriate, repeated episodes of hypoglycemia without reasonable explanation, elevation in AST/ALT >3 x ULN with or without elevation in total bilirubin >2x ULN and alkaline phosphatase <2x ULN, requirement for excluded medications, pregnancy, development of condition for which metformin or sitagliptin therapy is contraindicated, other medical condition or personal circumstance exposing subject to risk or preventing adherence to protocol.

Discontinuation criteria relating to renal function differed as follows:
P083: eGFR consistently <50 mL/min/1.73m2.
P170 and P289: serum creatinine concentrations consistently >1.5 mg/dL in males and >1.4 mg/dL in females OR eGFR consistently <60 mL/min/1.73m2.

Study Endpoints:

Efficacy Endpoints: The efficacy endpoints for the three trials are indicated in Table 13.

Table 13: Efficacy Endpoints for Sitagliptin Phase III Pediatric Trials

	P083	P170	P289
Primary Efficacy Endpoint			
Change from baseline in HbA1c at week 20	X	X (2-study pool)	
Secondary/Additional Efficacy Endpoints	X		
Change from baseline in HbA1c at week 54	X	X	X
Change from baseline in HbA1c at week 14	X		
Change from baseline in FPG at week 20 and week 54	X[1]	X	X
Proportion of subjects with HbA1c at goal (<7.0% and <6.5%) at week 20 and week 54	X	X	X
Proportion of subjects initiating glycemic rescue therapy at week 20 and week 54	X	X	X
Time to initiation of glycemic rescue therapy at week 20 and week 54	X	X (2-study pool)	
Percent change from baseline in lipid panel (triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), non-HDL, total cholesterol) at week 20 and week 54	X	X	X
Change from baseline in insulin, proinsulin, proinsulin/insulin ratio, HOMA-β, and HOMA-IR at weeks 20 and 54[2, 3]	X	X (2-study pool)	
Change from baseline in 2-hour PMG[3]	X		
Change from baseline in AUC endpoints (total AUC and excursion AUC) of glucose, insulin, C-peptide, insulin AUC/Glucose AUC at week 20 and week 54[3]	X		

Change from baseline in endpoints using the C-peptide minimal model at week 20 and week 4	X		
Change from baseline in endpoints derived from 9-point meal tolerance test (MTT) at week 20 and week 54[3]	X		

Any endpoints for individual trials P170 and P289 were also evaluated in the 2-study pool
[1] If FPG was missing at visits where meal tolerance test (MTT) data are collected, FPG was calculated as the average of the -10 min and 0 min measurements from the MTT
[2] Fasting insulin and proinsulin were not collected for subjects on background insulin therapy.
[3] only for subjects who agreed to meal tolerance test
Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; HOMA-β, homeostatic model assessment of β cell function; HOMA-IR, homeostatic model assessment of insulin resistance; PMG, post-meal glucose; AUC, area under the curve

Source: Reviewer Created

Safety Endpoints

A single external data monitoring committee (DMC) was used for all three pediatric phase III studies. Prespecified adverse events (AEs) of special interest included symptomatic hypoglycemia and selected gastrointestinal AEs (abdominal pain, diarrhea, nausea, vomiting). Other AEs of special interest reported in the CSRs included urinary tract infections, upper respiratory tract infections, renal-related AEs (defined by sponsor generated custom MedDRA query) and hypersensitivity AEs (defined based on narrow standardized MedDRA query for hypersensitivity). All episodes determined by the investigator to be hypoglycemia[40], and all glucose values $\leq$ 70 mg/dL were collected. Hypoglycemia episodes were categorized as severe (symptomatic hypoglycemia that required medical or non-medical assistance, whether or not such assistance was obtained), symptomatic (episode with clinical symptoms attributed to hypoglycemia, regardless of glucose level), asymptomatic (episode without symptoms but with measured plasma glucose $\leq$ 70 mg/dL), documented (< 54 mg/dL or $\leq$ 70 mg/dL[41]), and hypoglycemia AEs.

Additional safety endpoints common to all three studies included changes in growth velocity, tanner staging, BMI, BMI percentile[42], waist circumference, vital signs, laboratory safety studies (blood chemistry, hematology, urine microalbumin/creatinine ratio, and urinalysis) after 20 and 54 weeks.

Additional safety endpoints specific to trial P083 included changes in skeletal maturation (bone age), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGF-BP3), markers of bone turnover, calcitonin, CD26 expression and dentition[43] after 20 and 54 weeks.

[40] Episodes of hypoglycemia could be supported by but did not require confirmatory blood glucose levels.
[41] Subjects were counted according to lowest glucose value recorded.
[42] BMI percentile was based on CDC curves for subjects in the US, and based on WHO curves for non-US subjects
[43] A dental sub-study was added in amendment P083-12 to collect supplemental dental data (dental records from dental exam and dental photographs) for those who participated.

See Table 33 for further details on clinical safety measurements.

Statistical Analysis Plan:

Efficacy analyses: As discussed above, hypothesis testing was only performed for trial P083 and the 2-study pool (combining data from P170 and P289). Hypothesis testing was to be performed for the 3-study pool (combining data from all three studies) only if success was achieved for trial P083. For studies P170 and P289, summary statistics were provided for selected efficacy endpoints (HbA1c and FPG) by treatment group.

The primary efficacy population was the full analysis set (FAS), including all randomized subjects who took at least one dose of study medication and had a baseline measurement. Within the FAS, there were two efficacy estimands: the treatment policy (TP) and treatment effect (TE) estimands. The TP estimand included data after discontinuation of treatment or receiving rescue medication (reflecting an "intention-to-treat" population). The TE estimand excluded data after discontinuation of treatment or receiving rescue medication (reflecting a "per-protocol" population).

Consistent with the Agency's preference for an intention-to-treat approach, the TP estimand was used for testing of the primary hypothesis (comparing the efficacy of sitagliptin to that of placebo on change from baseline in HbA1C after 20 weeks of treatment) via an analysis of covariance (ANCOVA) model adjusted for treatment, insulin use at screening (yes/no), baseline BMI, baseline HbA1c value and baseline metformin dose (for studies P170 and P289 only). Missing data imputation for TP estimand used retrieved-dropout (RD) or return to baseline (RTB) approach if RD approach was not feasible. For trial P083 and the 3-study pool, sensitivity analyses for TP estimand were also performed using jump to reference and washout imputation.

Supportive efficacy analyses used the treatment effect (TE) estimand via constrained longitudinal data analysis model (cLDA)[44]. Kaplan-Meier analysis and summary statistics were used to describe the time to initiation of glycemic rescue therapy and the proportion of subjects initiating glycemic rescue therapy.

Safety analyses utilized all subjects as treated population and included descriptive statistics. P-values and 95% confidence intervals were included in analyses of AEs of symptomatic hypoglycemia and selected gastrointestinal adverse events. 95% confidence intervals were included in the analyses of AE summary measures, specific AEs, system organ classes (SOCs), pre-defined limit of change (PLDC), other hypoglycemia AEs and change from baseline in BMI,

[44] With the exception of triglycerides, which were analyzed by a non-parametric method, and proportion of subjects with A1c at goal at week 20 which used M&N method.

BMI percentile and waist circumference. Except for hypoglycemia, analyses for safety endpoints included data collected after initiation of glycemic rescue therapy. Analyses of hypoglycemia excluded data after initiation of glycemic rescue therapy and were performed separately for subjects with and without background insulin therapy.

Reviewer Comment: Study endpoints and the statistical analysis plan were consistent with the Written Request. Note that out of the three phase III pediatric trials, only trial P083 included endpoints for skeletal maturation and dentition. The use of the TP estimand for the primary hypothesis testing is appropriate, as it reflects an "intention to treat" population. Separate analyses of hypoglycemia in subjects with and without background therapy is warranted, given that an increased risk of hypoglycemia when adding sitagliptin to insulin or insulin secretagogue was noted in adult studies, and is included under labeled warnings and precautions.

Protocol Amendments:

Protocol amendments for trials P083, P170 and P289 are described separately below:

1. P083

In total, there were 16 protocol amendments submitted, of which 13 were implemented[45]. Of the 13 implemented amendments, 6 were global (Table 14) and 7 were country-specific[46]. As previously discussed, amendment P083-05 resulted in major changes in study design, including reduction from 4 to 2 treatment groups and adjustment of the lengths of phase A and B to be consistent with other planned phase III studies. Amendment P083-05 and P083-07 also included changes in eligibility criteria (broadening HbA1c criterion and allowing subjects on background insulin, respectively) to improve recruitment.

Table 14: Summary of Implemented Global Protocol Amendments in Trial P083

Amendment Number	Protocol Finalization	Key Changes
P083-00	02-MAY-2011	Original study protocol
P083-01	14-JAN-2013	Procedural and administrative changes.

[45] Amendments P083-11, P-083-14 and P084-15 were not implemented.
[46] Country specific amendments: P083-01 for Germany, P083-03 for Mexico, P083-03 for Brazil, P083-06 for Germany, P083-08 for Germany, P083-10 for Germany, P083-13 for Germany

P083-05	19-FEB-2014	• Lengthened the Phase A placebo-controlled portion from 16 weeks to 20 weeks, reduced Phase B active-controlled portion from 38 to 34 weeks. • Modified visit schedule to reduce the total number of visits from 13 to 11. • Removed the metformin group and the placebo/sitagliptin group from the study. Subjects already randomized to these groups would continue based on original treatment assignment. Data from subjects already randomized to metformin arm will be summarized separately. Phase A data from subjects already randomized to placebo/sitagliptin group will be combined with phase A data from subjects in the remaining placebo/metformin group. • Based on revised power calculations, the sample size for the entire study was reduced from 360 subjects to 170 subjects [2 treatment groups (sitagliptin or placebo) with 85 subjects/group]. • Changed inclusion criterion of A1C from ≥7% to ≥6.5%. • Modified the timeframe for prior treatment with insulin from 6 months to 12 weeks. • Eliminated exclusion criterion requiring more than 1 year of T2D diagnosis. • Last observation carried forward was replaced by multiple imputation method to account for missing week 20 data.
P083-07	01-DEC-2014	Modified eligibility criteria to include subjects on background insulin. Added instructions for managing subjects on background insulin therapy, insulin use (yes/no) as factor in primary analysis model, and separate hypoglycemia analyses for those with or without background insulin.
P083-09	27-AUG-2015	• Changed “adverse experience” to “adverse event.” • Complied with recommendations from the FDA to minimize missing data by clarifying post-study contact and follow up for subjects who discontinued prior to study completion. • Added analyses for HbA1c and FPG included data after initiation of rescue therapy and data collected after discontinuation of study medication.
P083-12	27-JAN-2017	Added the dental sub-study to allow for collection of supplementary data to augment visual oral examination data[43].

P083-16	12-JUN-2018	• Sample size increased to at least 190 subjects but no more than 220 subjects, including 10 to 11 subjects randomized to metformin arm prior to its removal from the study design. • Protocol updated to include 2 database locks, to accommodate submission based on regulatory agencies[47]. • Amended statistical methods to include treatment effect estimand and treatment policy estimand and their respective analyses. Added analyses using the Treatment Policy estimand including RD and RTB approaches for handling missing data. 2 sensitivity analyses were also added to comply with the Written Request.

Source: Reviewer modified table from P083 CSR

2. P170

In total, there were 16 protocol amendments submitted collectively for the base and extension study protocols, of which 12 were implemented[48]. Of the 12 implemented amendments, 11 were global (Table 15) and 1 was country-specific for the UK. Note that similar to trial P083, trial P170 also initially excluded subjects on background insulin therapy and included a lower limit of A1c of ≥7.0%. Both of these criteria were subsequently amended (i.e., to include those on background insulin and lower the limit of A1c to be ≥6.5%) to improve recruitment. Amendment P170-3 allowed for the creation of the 34-week extension study.

Table 15: Summary of Implemented Global Protocol Amendments for Trial P170

Amendment Number (Date Finalized)		Key Changes
Base Study	**Extension Study**	
P170-01 (31-AUG-2012)	NA	Incorporated procedural and administrative changes
P170-02 (08-APR-2014)	NA	• Updated analyses to reflect the pooled analysis of P170 and P289 data. • Reduced the sample size from 240 to 90 subjects and analysis was combined with P289 with adequate power for the primary analysis at Week 20. • The timeframe required for subjects to be off insulin therapy before Visit 1 was reduced from 6 months to 12 weeks. • A1C lower limit for inclusion changed from ≥7.0% to ≥6.5%. • Added growth velocity and Tanner staging

[47] Database lock 1 (DBL1) to be submitted in accordance with EU deadlines, including complete phase A data (through week 20) from all 190 randomized and treated subjects. Database lock 2 (DBL2) will occur following final data collection (through week 54). 2 clinical study reports to be submitted, the first based on DBL1, the second based on DBL2.

[48] Amendments P170-09, P170-10, P170-13 and P170-14 were not implemented

NA	P170-03 (08-APR-2014)	Created the 34-week extension study.
P170-04 (02-JAN-2015)	P170-05 (02-JAN-2015)	Modified eligibility criteria to include subjects on background insulin. Added instructions for managing subjects on background insulin therapy, insulin use (yes/no) as factor in primary analysis model, and separate hypoglycemia analyses for those with or without background insulin.
P170-07 (04-MAR-2015)	P170-08 (04-MAR-2015)	Changed "adverse experience" to "adverse event."
P170-11 (28-OCT-2015)	P170-12 (29-OCT-2015)	• Complied with recommendations from the FDA to minimize missing data by clarifying post-study contact and follow up for subjects who discontinued prior to study completion. • Updated sample size from approximately 90 subjects to approximately 130 subjects. • Added analyses for HbA1c and FPG included data after initiation of rescue therapy and data collected after discontinuation of study medication.
0431A-170-15 (03-APR-2018)	NA	• Increased sample size to at least 120 subjects but no more than 140 subjects. • Clarified statistical methods for analyses using the Treatment Effect estimand. Added analyses using the Treatment Policy estimand (applicable to base study only) including RD and RTB approaches for handling missing data.
NA	0431A-170-16 (03-APR 2018)	• Modified sample size to be consistent with changes to base study in amendment P170-05.

Source: Reviewer modified table from P170 CSR

3. P289

In total, there were 11 protocol amendments, of which 10 were implemented[49]. Of the implemented amendments, 5 were global (Table 16) and 5 were country-specific[50]. Note that similar to the other two trials (P083 and P170), P289 also initially excluded subjects on background insulin therapy and had an eligibility limit of A1c of ≥7.0%. These criteria were subsequently amended (i.e., to include those on background insulin and lower the limit of A1c to be ≥6.5%) to improve recruitment. All protocol amendments for P289 mirrored protocol amendments for P170, given the similar study designs and plan for pooled analysis of data.

Table 16: Summary of Implemented Global Protocol Amendments for Trial P289

Amendment Number	Protocol Finalization Date	Key Changes

[49] Amendment P289-09 was submitted but not implemented
[50] P289-01 and P289-02 for Brazil, P289-03 for South Africa, P289-06 and P289-11 for Saudi Arabia

P289-00	04-SEP-2012	Original study protocol
P289-04	09-APR-2014	• Updated analyses to reflect the pooled analysis of P170 and P289 data. • Reduced the sample size from 240 to 90 subjects and analysis was combined with P170 with adequate power for the primary analysis at Week 20. • The timeframe required for subjects to be off insulin therapy before Visit 1 was reduced from 6 months to 12 weeks. • A1C lower limit for inclusion changed from ≥7.0% to ≥6.5%. • Added Tanner staging
P289-05	12-JAN-2015	Modified eligibility criteria to include subjects on background insulin. Added instructions for managing subjects on background insulin therapy, insulin use (yes/no) as factor in primary analysis model, and separate hypoglycemia analyses for those with or without background insulin.
P289-07	31-AUG-2015	• Changed "adverse experience" to "adverse event." • Complied with recommendations from the FDA to minimize missing data by clarifying post-study contact and follow up for subjects who discontinued prior to study completion. • Added analyses for HbA1c and FPG included data after initiation of rescue therapy and data collected after discontinuation of study medication.
P289-10	03-APR-2018	• Increased sample size to at least 90 subjects but no more than 110 subjects • Clarified statistical methods for analyses using the Treatment Effect estimand. • Added analyses using the Treatment Policy estimand (applicable to base study only) including RD and RTB approaches for handling missing data.

Source: Reviewer modified from P289 CSR

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant affirms that the studies were conducted in accordance good clinical practice (GCP) standards and considerations for the ethical treatment of human participants.

Financial Disclosure

Overall, the Applicant adequately disclosed the financial interest of investigators. In trials P083 and P170, all investigators and sub-investigators[51] were certified regarding the absence of financial interests and/or arrangements. In trial P289, of the 240 investigators and sub-

[51] Total of investigators and sub-investigators: 293 for P083 and 176 for P170

investigators, 238 certified regarding the absence of financial interests and/or arrangements. 2 sub-investigators from different sites[52] did not return the requested certification form despite multiple due diligence attempts by the Applicant. A subsequent internal search conducted by the Applicant did not identify any financial interests or arrangements for these two sub-investigators. Only 1 of the sites included randomized subjects, representing 4% (4/98) of the trial population. Overall, the investigator financial disclosures do not raise significant concerns about the data integrity given that the trial was randomized and double-blinded and since the primary endpoint was an objective laboratory measurement (HbA1c).

Patient Disposition:

Overview:

In trial P083, a total of 685 subjects were screened and 200 were randomized[53] (96 to the sitagliptin group, 90 to placebo/metformin arm, 5 to placebo/sitagliptin arm , and 9 to the metformin arm).

Note: Due to the elimination of two treatment arms in trial P083, the following modifications to the statistical analysis plan were agreed upon as part of amendment P083-05: For analyses through week 20, phase A data from the placebo/metformin arm (N=90) and the placebo/sitagliptin group (N=5) were combined into a single placebo arm (N=95) and compared to phase A data from the Sitagliptin arm. For analyses through week 54 in trial P083, data from the placebo/metformin arm (N=90) was compared to data from the sitagliptin arm (N=95). Therefore, efficacy data from the 9 subjects in the metformin group and phase B data from the 5 subjects in the placebo/sitagliptin group in trial P083 are not are not discussed in this review.

In trial P170**,** a total of 205 subjects were screened, and 124 were randomized[54]. Of the 121 subjects who completed the base study, 58 entered the extension study[55].

[52] All other site investigators and sub-investigators from these two sites submitted the certification form.
[53] In trial P083, 1 subject was randomized twice, but included only once in the final count. This subject had consented under amendment P083-05 but was given a randomization number belonging to amendment P083-01 as amendment 083-05 had not yet been activated. The subject received study medication under the first randomization number for 6 days, was then discontinued from the study and randomized a second time 3 days later. Data associated with the second randomization number was included in the safety and efficacy analyses. No AEs were reported, and no efficacy or safety endpoints were collected under the first randomization number.
[54] In trial P170, 1 subject was given 2 screening numbers and 2 randomization numbers but included only once in final count.
[55] Most common (68%) reason for not entering P170 extension study was that it was unavailable when the subject completed the base study, since the extension study was added 3 years after the base study began.

Reviewer Comment: In trial P170, less than half of subjects who completed the base study entered the extension study. Due to lower number of subjects, it may be difficult to interpret any supportive efficacy analyses beyond week 20 based on data from trial P170 alone.

In trial P289, a total of 201 subjects were screened and 98 subjects were randomized.

In all three trials, all non-randomized subjects were screen failures. The most common reason for screen failure was ineligible A1c (most often due to HbA1c being below the lower eligibility threshold) [56].

Geographic Distribution:

In P083, randomized and treated subjects were drawn from 78 sites over 26 countries. Only 13.2 % (25/190) of subjects were from the United States. 30.0 % of subjects came from Latin America, 25.8 % came from Europe, and the remainder were from Asia/Pacific, Middle-East, Africa and Canada[57].

In P170, randomized and treated subjects were drawn from 48 sites over 18 countries. Only 10.5 % (13/124) of subjects were from the United States. 32.3% of subjects came from Asia/Pacific, 30.6 % of subjects came from Latin America, 17.7 % came from Europe, 8.1% came from the Middle East, and 1 subject was from Canada.

In P289, randomized and treated subjects were drawn from 44 sites over 18 countries. Only 16.7% (16/96) of subjects were from the United States. 22.9% of subjects each were from Latin America and from Europe, 14.6% of subjects each were from the Middle East and from Asia/Pacific, and 1 subject was from Australia.

Reviewer Comment: The rate of screen failure was 70% in trial P083, 39.5% in trial P170 and 51.2% in trial P289, predominantly due to ineligible HbA1c. The particularly high rate of screen failure in trial P083 may be related to the eligibility criteria, since subjects on background metformin (which is the first line therapy for most patients with pediatric T2D) were not enrolled. The relatively high rate of screen failure is similar to other pediatric type 2 diabetes trials[58], and may reflect the heterogeneity of the pediatric T2D population, since there is a subgroup of patients with better disease control who are likely ineligible for enrollment based on HbA1c below 6.5%. In all three trials, a minority of randomized subjects

[56] In a response to an information request issued on 10/26/2020, the Applicant confirmed that in subjects who were not randomized due to not meeting HbA1c criteria, it was more likely due to HbA1c being below the threshold (72.8% in trial P083, 64.3% in trial P170, and 50.0% in trial P289).
[57] 12.1% from Asia/Pacific, 14.2% from Middle East, 4.2% from Africa, and 1 subject from Canada.
[58] Rate of screen failure 56% in Ellipse trial, Liraglutide pediatric efficacy supplement clinical review, Dr. Tania Condarco, 6/17/2019, NDA 22341

were enrolled from the US, however as discussed in section 7.1.3, efficacy results did not appear to vary based on geographic location.

Subject Disposition, Weeks 0 to 20:

Table 17 summarizes the disposition of subjects participating in weeks 0 to 20 for all three trials. In total, 413 subjects[59] were randomized and 410 subjects were treated across all three trials.

During weeks 0 to 20, discontinuations were numerically greater in the sitagliptin arm versus the comparator in trials P083 and P170, however the reverse occurred in trial P289. The most common reason for study discontinuation in all trials was withdrawal by subject or parent/guardian[60]. No subjects discontinued the trial due to adverse events. Several subjects discontinued study medication due to adverse events, however, this occurred across treatment groups in the three trials with no obvious imbalance [61]. Adverse events leading to treatment discontinuation are discussed in section 8.4.3.

Numerically, the rate of rescue therapy from weeks 0 to 20 was higher in the comparator arm across all three trials (12.6 vs 5.3% in trial P083, 19.4 vs 3.2% in trial P170 and 13.7 vs 4.4% in trial P289).

In all three trials, the percentage of missing week 20 HbA1cs was around 10% for the TP estimand and around 21% for the TE estimand. The percentage of missing data in the TP estimand was higher in the sitagliptin arm, likely due to the greater rates of study discontinuation as discussed above. However, the percentage of missing data in the TE estimand tended to be higher in the comparator arm, likely reflecting exclusion of more HbA1c data following glycemic rescue. Overall, the percentage of missing data in the pre-specified primary efficacy estimand (TP estimand) was acceptable.

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[59] Subject who was randomized twice in P083 and P170 was counted only once here.

[60] In P083, reasons for study discontinuation in weeks 0-20 included withdrawal by subject and/or parent/guardian (Sitagliptin = 8, placebo = 4), loss to follow up (sitagliptin = 1), screen failure due to suspension of study site by IRB (sitagliptin = 1). In P170 reasons for study discontinuation in weeks 0-20 included withdrawal by subject (Sita/Met IR FDC = 2), loss to follow up (Sita/Met IR FDC=1), technical problems (Sita/Met IR FDC=1). In P289, reasons for study discontinuation in weeks 0-20 included loss to follow up (Sita/Met XR FDC=1, Met XR =1), withdrawal by parent/guardian or subject (Sita/Met XR FDC = 2 and Met XR = 3)

[61] In P083, reasons for discontinuation of study medication (weeks 0-20) included adverse event (2 subjects in sitagliptin arm only), non-compliance with study drug (2 subjects in each arm), physician decision (1 subject in sitagliptin arm) and other reasons (1 subject in sitagliptin arm and 2 in placebo arm). In P170, 2 subjects discontinued study medication during weeks 0-20 in Met IR arm due to an adverse event; in the Sita/Met IR arm reasons included lost to follow up (1), non-compliance with study drug (1), pregnancy (1) and withdrawal by subject (1). In P289, reasons for discontinuation of study medication during weeks 0-20 included adverse event (2 subjects in each arm), withdrawal by parent/guardian or subject (2 subjects in Sita/met XR arm and 3 subjects in Met XR arm), and physician decision (3 subjects in Met XR arm).

Table 17: Disposition of Subjects Participating in Weeks 0 to 20, Sitagliptin Phase III 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: Reviewer created, based on ADSL datasets and CSRs for P083, P170 and P289

[62] In P289, two subjects were discontinued from the study after randomization prior to treatment due to discovery of screen failure (reason for screen failure was invalid informed consent form in 1 subject, reason not provided for the other subject). These subjects were not counted in Table 17.

Subject disposition, weeks 20 to 54:

The disposition of subjects participating in weeks 20 to 54 of the three trials is described in Table 18.

During weeks 20 to 54, study discontinuations were higher in the sitagliptin arm versus the comparator arm in trials P083 and P170, but the reverse occurred in trial P289. Discontinuations of study medication were higher in the sitagliptin arm versus the comparator arm in P083 and P289, but the reverse occurred in trial P170. Again, the most common reason for study discontinuation during weeks 20 to 54 was withdrawal by subject or parent/guardian[63]. No subjects discontinued the trial due to adverse events. Several subjects discontinued study medication due to adverse events, though there was no evidence of imbalance between treatment arms[64]. Adverse events leading to treatment discontinuation are discussed in section 8.4.3.

In trial P083, the relatively lower rate of rescue therapy in the placebo/metformin arm compared to the sitagliptin arm (30.2 vs 40%) likely reflects the addition of metformin during phase B of the trial. In trials P170 and P289, the proportion of subjects participating in weeks 20 to 54 who required glycemic rescue therapy at *any* point in the trial (i.e., from weeks 0 to 54) was higher in the metformin arms compared to the Sita/Met FDC arms. However, the imbalance between treatment arms was **not** seen when considering rescue therapy that was initiated from weeks 20 to 54, a matter discussed later on in this review (see discussion of secondary endpoints in section 7.1.2).

As expected, missing HbA1c data at 54 weeks was greater than that at 20 weeks, but this was particularly pronounced for the TE estimand where the percentage of subjects with missing week 54 HbA1c exceeded 50% in one or both treatment arms. This is likely due to exclusion of more data following treatment discontinuation or rescue therapy.

[63] Reasons for study discontinuation (weeks 20-54) in P083 included withdrawal by parent/guardian (Sitagliptin = 7, placebo/metformin =5), loss to follow up (sitagliptin = 4, placebo/metformin =3). In P170, all study discontinuations during weeks 20-54 were due to withdrawal by parent/guardian or subject. In P289, reasons for study discontinuation in phase B included lost to follow up (Sita/Met XR=2, Met XR =1), and withdrawal by subject, parent/guardian (2 subjects in each arm).

[64] Reasons for discontinuation study medication (weeks 20-54) in P083 included adverse event (sitagliptin =4, placebo/metformin=1), loss to follow up (sitagliptin=3), non-compliance with protocol or study drug (1 in each arm), physician decision (placebo/metformin=1) and pregnancy (placebo/metformin=1). In P170, reasons for discontinuation of study medication (weeks 20-54) included adverse event (both arms), withdrawal by parent/guardian or subject (both arms), non-compliance with study drug (Met IR arm) and pregnancy (Met IR arm). In P289, reasons for discontinuation of study medication in phase B included hypoglycemia (Sita/Met XR=1), lost to follow up (1 in each arm), adverse event (Met XR=1), physician decision (Sita/Met XR=1), withdrawal by parent/guardian or subject (Sita/Met XR=1=2, Met XR=2), non-compliance with study drug (Met XR=1).

Table 18: Disposition of subjects participating in weeks 20 to 54, Sitagliptin Phase III pediatric trials

	P083 N (% of treated)			P170 N (% of treated)			P289 N (% of treated)		
	Sitagliptin	Placebo/ Metformin	Total	Sita/Met IR FDC	Met IR	Total	Sita/Met XR FDC	Met XR	Total
Started weeks 20-54	85	86	171	28	30	58	42	47	89
Treated weeks 20-54	85	86	171	27	29	56	41	43	84
Discontinued study medication weeks 20-54	15 (17.6)	11 (12.8)	26 (15.7)	3 (11.1)	5 (17.2)	8 (14.3)	5 (12.2)	5 (11.6)	10 (11.9)
Discontinued study weeks 20-54[1]	11 (12.9)	8 (9.3)	19 (11.1)	3 (11.1)	2 (6.9)	5 (8.9)	3 (7.3)	4 (9.3)	7 (8.3)
Week 54 TP Estimand[2]	74 (77.9)	76 (84.4)	150 (81.1)	24 (88.9)	27 (93.1)	51 (91.1)	36 (87.8)	39 (90.7)	75 (89.3)
Week 54 TE Estimand[2]	41 (43.1)	48 (53.3)	89 (48.1)	18 (66.7)	13 (44.8)	31 (55.4)	19 (46.3)	20 (46.5)	39 (46.4)
Rescue therapy from weeks 0 to 54	34 (40)	26 (30.2)	60 (35.1)	5 (18.5)	12 (41.4)	17 (30.4)	14 (34.1)	18 (41.8)	32 (38.1)

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] includes discontinuations among treated subjects only

[2] Number reflects those subjects with both baseline and week 54 HbA1c measurements in the TP and TE estimands. Subjects in TP estimand were included regardless of treatment discontinuation or rescue therapy by week 54. Subjects in TE estimand did not discontinue therapy or receive rescue treatment by week 54.

Source: reviewer created, based on CSRs for P083, P170 and P289 as well as review of ADSL datasets.

Reviewer Comment: While discontinuations tended to be higher in the sitagliptin versus the comparator arms, this was not a consistent finding across the three trials, and the rates of discontinuations overall were acceptable. There were no cases of study discontinuations due to adverse events, and relatively few cases of discontinuations of study medication due to adverse events with no obvious imbalance between treatment arms. The percentage of missing data for the pre-specified primary efficacy analysis (TP estimand at week 20) was acceptable. Due to very high percentage of missing data (>50% in at least one or both treatment arms) particular caution should be taken with any supportive 54-week efficacy analyses using the TE estimand.

It is notable that the rate of glycemic rescue therapy was consistently higher in the comparator arms across all three trials through week 20, however this imbalance did not persist from weeks 20 to 54 (see discussion of secondary endpoints in section 7.1.2). Rates of rescue therapy beyond week 20 in trial P083 cannot be compared to the other trials, since subjects in the placebo arm were switched to metformin.

The rate of discontinuations, proportion of subjects requiring glycemic rescue and percentage of missing data were generally consistent with those reported in the pediatric phase III trial of Liraglutide (Ellipse) [65].

Protocol Violations/Deviations:

1. P083:

Important protocol deviations were identified in 41.1% (39/95) and in 46.3% (44/95) of randomized and treated subjects in the sitagliptin and placebo arms[66], respectively. Among important protocol deviations, the most common deviations were related to trial procedures (29.5% in sitagliptin and 35.8% in placebo), specifically failure to conduct major/significant protocol specified efficacy and/or safety evaluations (10 subjects in sitagliptin arm, 14 subjects in the placebo arm). Additionally, there were 6 subjects in the sitagliptin arm and 1 subject in the placebo/sitagliptin arm who met rescue criteria but did not receive rescue medication. However, in all subjects experiencing a protocol deviation in rescue therapy, the deviation occurred at or beyond week 20. 4 out of the 6 subjects in the sitagliptin arm did eventually

[65] In Ellipse trial, the proportion of discontinuations was 15% in Liraglutide and 23% in placebo arms. Percentage of subjects requiring glycemic rescue by week 26 were 5% in Liraglutide arm and 19% in the placebo arm. Percentage of subjects requiring glycemic rescue by week 52 (end of trial) were 14% in the liraglutide arm and 31% in the placebo arm. Percentage of missing week 26 HbA1c values was 10.6% in the liraglutide arm, 14.5% in the placebo arm and 12.6% overall. NDA 22341, pediatric efficacy supplement clinical review, Dr. Tania Condarco, 6/17/2019

[66] Placebo arm (N=95) includes treated subjects in the placebo/metformin (N=90) and placebo/sitagliptin (N=5) arms prior to amendment P083-05. Important protocol deviations were identified in 36.7% (33/90) of subjects in the placebo/metformin arm.

receive rescue therapy by week 54[67]. Trial procedure deviations also included missing HbA1c results, lack of compliance with fasting fingerstick glucose measurements, and inappropriate unmasking of HbA1c or FPG (other than for rescue evaluation) at the local lab. Other protocol deviations included issues with the informed consent form, delays in safety reporting or repeat measurement in ALT/AST >3x ULN, and issues with study intervention (participants who received incorrect study treatment and/or were administered improperly stored study treatment)[68].

Reviewer Comment: In trial P03, there was an imbalance in protocol deviations relating to failure of administering appropriate rescue medication to subjects who met rescue criteria, impacting 6 subjects in the sitagliptin arm versus 1 subject in the placebo/sitagliptin arm. However, all of these deviations occurred between weeks 20 to 54, and all but 2 of the subjects in the sitagliptin arm eventually did receive rescue therapy by week 54. Therefore, this imbalance is not expected to materially impact the proportion of subjects receiving rescue therapy by week 20 or by week 54. Review of the other protocol deviations did not reveal any differences in treatment arms that would potentially invalidate the trial results.

2. P170

Important protocol deviations occurred in 40.3% (25/62) of subjects in the Sita/Met IR FDC arm, and in 38.8% (24/62) of subjects in the Met IR arm. The most common protocol deviations included issues with the informed consent form (12 subjects in Sita/Met IR FDC arm and 13 subjects in the Met IR arm) and trial procedures (11 subjects in the Sita/Met IR FDC arm and 16 subjects in the Met IR arm). Procedural protocol deviations included missing HbA1c measurements, incorrect rescue therapy, and participant who met rescue criteria but was not given rescue medication (impacting 3 subjects in Met IR arm only, however, 2 out of these 3 subjects eventually received rescue medication by week 54). Other less common protocol deviations included delays in safety reporting, failure to comply with discontinuation criteria, and failure to meet inclusion criteria. No differences in treatment arms were identified that would potentially impact the study results.

3. P289

Important protocol deviations occurred in 53.2% (25/47) of subjects in the Sita/Met XR FDC arm, and in 62.7% (32/51) subjects in the Met XR arm. The most common protocol deviation

[67] Based on review of the ADSL and ADEFF datasets and with confirmation from the Applicant following an information request submitted on 10/28/2020, subjects in sitagliptin arm who did not receive appropriate rescue therapy had met rescue criteria at week 28 (2 subjects), week 44 (1 subject), week 20 (2 subjects), or week 30 (1 subject). Of these subjects in the sitagliptin arm, all but 2 eventually received rescue therapy and were therefore included in estimates of glycemic rescue by week 54. The 1 subject in the placebo/sitagliptin arm who did not receive appropriate rescue therapy had met step-2 rescue criteria at week 36 (i.e., in phase B), therefore, this data would not be included in any analyses beyond week 20).

[68] Affected 3 subjects in sitagliptin arm and 2 subjects in the placebo arm.

was related to trial procedures, specifically failure to conduct major/significant protocol-specified efficacy and/or safety evaluations (11 subjects in the Sita/Met XR arm and 7 subjects in the Met XR arm). Other procedural deviations included inappropriate unmasking of HbA1c (other than for rescue evaluation), failure to review hypoglycemia assessment tools, missing HbA1c measurements, non-compliance with fasting fingerstick glucose measurements, incorrect rescue of participant, participant who met rescue criteria but was not given rescue medication (impacting 1 subject in the Sita/Met XR arm and 3 subjects in the Met XR arm, however, all but 1 subject in the Met XR arm had received rescue therapy by week 54). Another common protocol deviation was related to issues with informed consent form, which impacted 31.4% (16/51) subjects in the Met XR arm compared to 14.9% (7/47) subjects in the Sita/Met XR arm. This imbalance in informed consent form deviations accounts for the overall imbalance in important protocol deviations between the two treatment arms. Subjects with invalid informed consent were excluded from the analysis. 5 participants in the Sita/Met XR arm and 7 participants in the Met XR arm received incorrect study treatment or improperly stored study treatment[69]. Other protocol deviations occurring with minor frequency included failure to enforce discontinuation criteria and delay in safety reporting.

Reviewer Comment: In trial P289, protocol deviations occurred in 9.5% more subjects in the Met XR arm compared to the Sita/Met XR arm, primarily due to an increased incidence of protocol deviations relating to the informed consent form in the Met XR arm. Subjects with invalid informed consent form were excluded from the analysis, therefore this imbalance is unlikely to impact the safety and efficacy results.

In both trials P170 and P289, there were several protocol deviations relating to failure to administer rescue medication to participants meeting rescue criteria, occurring at greater frequency in the metformin arm compared to the Sita/Met FDC arm. However, nearly all of these participants did eventually receive rescue therapy by week 54 (and therefore would have been included in analyses of subjects receiving rescue therapy through week 54). Given that the Met XR arm had higher proportion of subjects receiving therapy compared to the Sita/Met XR FDC arm through week 20, this minor imbalance in protocol deviations would not materially change the results.

Demographic and Baseline Characteristics

The demographic and baseline characteristics for all treated subjects in trials P083, P170 and P289 are summarized in Table 20. Demographic and baseline characteristics for the 2-study pool and 3-study pool are summarized in Table 21.

[69] 2 additional subjects who received expired study medication in each treatment group were identified after the database lock and were therefore not included in the protocol deviation tables in the CSR.

In all three individual trials and in the 2-study and 3-study pools, the majority (>60%) of the trial population was female, consistent with gender distribution of pediatric T2D. Trial P289 had slightly older subjects (average age of 14.8 years) compared to the others (average age of 14.0 years in trial P083, 14.1 years in trial P170, 14.4 years in the 2-study pool, 14.2 years in the 3-study pool), however, it is uncertain that these minor age differences would impact the results. The average BMI percentile was > 93% in all three individual trials, consistent with high prevalence of overweight and obesity in pediatric T2D. Mean baseline HbA1c was lowest in trial P083 (7.5%, compared to 8.1% in trial P170, 7.9% in trial P289, 8.0% in the 2-study pool) with over 60% of subjects having an HbA1c of <8% in both treatment arms. Trial P083 also had the shortest average duration of T2D (0.7 years) compared to the other two individual trials (2.1 years in trial P170 and 2.3 years in trial P289). The lower mean HbA1c and shorter duration of T2D in trial P083 likely reflects the eligibility criteria, since patients who are not treated with oral antihyperglycemic agents are more likely to be recently diagnosed and in better glycemic control. In all three trials, a minority of subjects were on background insulin therapy (11.6% in trial P083, 12.9% in trial P170, 17.7% in trial P289, 15% in the 2-study pool and 13.4% in the 3-study pool). As previously discussed, background insulin therapy was to be maintained within 15% of the total daily dose during the treatment period, therefore, any changes in background insulin therapy during the trial were likely minor and impacted a minority of the trial participants. In trials P170 and P289, the majority of subjects (>60%) received a baseline metformin dose of > 1500 mg/day, reflecting enrollment of patients who were uncontrolled on maximally-tolerated metformin therapy.

In trial P289, there was a slight imbalance between treatment arms in a few categories, including percentage of subjects on background insulin therapy (20% in Sita/Met XR arm and 15.7% in the Met XR), percentage of female subjects (71.1% in Sita/Met XR arm and 62.7% in Met XR arm) and percentage of Asian subjects (33.3% in Sita/Met XR arm and 11.8% in Met XR arm). However, no such imbalance was noted between treatment arms in the 2-study pool, which was used for the primary efficacy analysis for trials P289 and P170. There was also a slight imbalance between treatment arms in P083 and P170, with the comparator arms having slightly younger subjects (lower mean age and higher percentage in the 10 to 14-year age group). I do not believe these minor imbalances would impact the results.

In terms of racial and ethnic distribution, trial P170 had fewer subjects of White race (38% compared to 51% for trials P083 and P289), and more subjects of Asian race (35% compared to 15% and 22% for trials P083 and P289, respectively), likely related to comparatively higher recruitment of subjects from the Asia/Pacific region in P170. All three individual trials as well as the 2-study and 3-study pools had around a third of subjects of Hispanic/Latino ancestry. It is important to note that the overall percentages of Black/African American and American Indian/Alaska Native race in all three trials were higher when considering their representation in the multiple-race category. Overall, representation of subjects of minority race and ethnicity groups was acceptable.

Demographic and baseline characteristics for subjects who entered the phase B (for trials P083 and P289) and the extension study (for trial P170) were generally similar to subjects participating in phase A (for trials P083 and P289) and the base study (for trial P170), with the exception of slightly higher mean baseline HbA1c in phase B subjects for trial P083 (7.8 % in sitagliptin arm, 8.0% in placebo/metformin arm and 8.1% overall). The higher mean HbA1c for participants in phase B of trial P083 could reflect a population at greater risk of progression of underlying disease compared to participants in phase A.

In all three trials, the most common medical condition other than T2D was obesity (37.2% in P083, 25.8% in P170 and 33.7% in P289). Other common medical conditions included dyslipidemia in trial P170 (16.8%), and acanthosis nigricans and asthma (13.3% and 12.2% respectively) in trial P289. In all three trials, subjects in the sitagliptin arm had a higher frequency of baseline gastrointestinal or hepatobiliary disorders, with other conditions occurring in higher frequency in the comparator arms[70]. Given that study treatment was randomized, these differences in baseline medical conditions are likely due to chance.

In trial P083, the most common prior medications were insulin glargine and metformin (reported in 18 subjects[35]). In trials P170 and P289, 100% of subjects were on prior treatment with metformin. The other most common prior medications were lipid modifying agents in P170 (12.1%) and agents acting on the renin-angiotensin system in P289 (10.2%).

Reviewer Comment: All three trials had predominantly female subjects with a minority of subjects on background insulin. There were some minor differences in demographic and baseline characteristics between the individual trials (e.g., comparatively shorter duration of T2D and lower baseline HbA1c in trial P083, and comparatively older subjects with slightly higher frequency of baseline insulin use in trial P289). Due to higher recruitment of subjects from the Asia/Pacific region in P170, the 2-study pool also had had nearly double the percentage of Asian subjects compared to P083 (29.1 vs. 15.3%), however the representation in other racial and ethnic categories were similar. Overall, I do not believe that these differences in trial population materially impacted the results. In general, demographic and baseline characteristics were reasonably balanced between treatment arms.

In all three trials, there appeared to be a higher frequency of baseline gastrointestinal or hepatobiliary disorders in the sitagliptin arms versus the comparator arms, however, no related safety signals were noted in the safety review (see section 8). All three trials met the

[70] In P083, subjects in the placebo arm had higher frequency of immune system disorders, respiratory disorders (asthma, sleep apnea, tonsillar hypertrophy) and psychiatric disorders (predominantly ADHD). In P170, subjects in the Met IR group had more nervous system, respiratory disorders, surgical or medical procedures and psychiatric disorders. In P289, subjects Met XR group had more psychiatric disorders, reproductive system disorders and acanthosis nigricans.

terms specified in the WR (>30% of randomized subjects were between 10-14 years old, >30% of randomized subjects were female, and total number of subjects randomized at least 350).

Compared to ethnic and racial minorities in the US population of youths with T2D reported in the SEARCH for Diabetes in Youth Study (2009)[71], all trials had an increased representation of subjects of Hispanic/Latino ethnicity, and of Asian, American Indian and multiple racial categories. The prevalence of T2D is known to be increasing more rapidly in some racial/ethnic backgrounds (e.g., Hispanic), therefore I believe the trial population appropriately represented minority racial and ethnic categories.

In the TODAY study[72], subjects who had a "pre-diabetic" HbA1c on metformin monotherapy were more likely to demonstrate durable glycemic control. Given that, I conducted an additional analysis to compare the mean baseline HbA1c and percentage of subjects with baseline HbA1c < 6.5% in the 2-study pool versus the liraglutide pediatric trial (Ellipse) (Table 19). **Baseline HbA1c for both trial populations (obtained on maximally tolerated metformin) were similar, however the liraglutide pediatric trial population included a higher percentage of subjects with HbA1c <6.5% (i.e., subjects who may be more likely to achieve durable glycemic control).** This finding is most likely related to differences in trial design. The study design for Ellipse involved an 11 to 12-week run-in period to achieve maximal tolerated metformin therapy for enrolled subjects who were not on metformin or on a metformin dose of < 2000 mg/day. Therefore, although both trial populations utilized similar HbA1c enrollment criteria, the Ellipse trial design allowed for inclusion of more subjects who could achieve an HbA1c below the lower limit of eligibility following the run-in period[73].

Table 19: Baseline HbA1c in Sitagliptin 2-Study Pool compared to Liraglutide Pediatric Trial

	Sitagliptin pediatric 2-study pool (P170 + P289)	Liraglutide pediatric trial (Ellipse)
Mean baseline HbA1c (%)[1]	8.0	7.8
Subjects with baseline HbA1c < 6.5% (%)		
Treatment arm	6%	14%
Comparator arm	3%	24%

[71] Distribution of race/ethnic categories of youth (aged <20 years) in SEARCH 2009 incidence populations: Hispanic = 18.6%; non-Hispanic 2.9%, White = 61%, Black =8.3%, American Indian (1.9%), Asian/Pacific Islander = 7.4%. [Dabelea D, Mayer-Davis EJ, Saydah S, et al. SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311:1778–1786]
[72] Zeitler P, Hirst K, Copeland KC, et al. HbA1c After a Short Period of Monotherapy With Metformin Identifies Durable Glycemic Control Among Adolescents With Type 2 Diabetes. Diabetes Care. 2015;38(12):2285-2292
[73] There was also an imbalance between the treatment arms in Ellipse (with higher percentage of subjects with baseline HbA1c < 6.5% in the comparator arm). While this theoretically could have reduced the effect size due to more durable control in the comparator arm, efficacy of liraglutide was still demonstrated based on a placebo-adjusted treatment difference of -1.06%.

[1] In both trial populations, baseline HbA1c was measured on maximally tolerated metformin, with or without basal insulin

Source: Reviewer generated based on ADSL dataset for 2-study pool, and Clinical Review of NDA 22341 pediatric efficacy supplement by Dr. Tania Condarco (6/17/2019)

Reviewer Comment: Compared to the liraglutide pediatric trial, the sitagliptin 2-study pool (trials P170 and P289 combined) had a lower percentage of subjects with baseline HbA1c < 6.5% on maximally tolerated metformin, possibly representing a population at higher risk for rapid T2D progression.

Table 20: Table of Demographic and Baseline Characteristics (All Subjects Treated) in Trials P083, P170 and P289

	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)
Height (cm)									
Mean (SD)	162.6 (11.9)	161.4 (11.4)	162.0 (11.7)	160.0 (10.1)	159.3 (10.7)	159.6 (10.4)	162.7 (7.5)	163.4 (8.1)	163.0 (7.8)
Min; Max	131; 195	136; 193	131; 195	140; 185	135; 184	135; 185	145; 180	143; 181	143;181

[74] P083: American Indian or Alaska Native AND Black or African American (Sitagliptin = 1, Placebo = 1), American Indian or Alaska Native AND Black or African American AND White (Placebo =1), American Indian or Alaska Native AND White (Sitagliptin = 11, Placebo = 11), Black or African American AND White (Sitagliptin =8, Placebo= 5). P170: American Indian/Alaska Native AND White (Sita/Met IR FDC = 6, Met IR =5), Black/ African American AND Asian (Sita/Met IR FDC= 1), Black/African American AND White (Sita/Met IR FDC = 6, Met IR=6), White AND Asian (Sita/Met IR FDC = 1, Met IR= 2). P289: American Indian/Alaska Native AND White (Sita/Met XR = 2, Met XR = 5), Black/African American AND Asian (Sita/Met XR=1)

Weight (kg)									
Mean (SD)	89.1 (25.3)	81.9 (24.8)	85.5 (25.2)	81.1 (26.8)	79.5 (27.2)	80.3 (26.9)	83.0 (23.6)	80.2 (21.9)	81.5 (22.6)
Min; Max	45.0; 174.4	37.7; 151.7	37.7; 174.4	37.4; 172.8	45.4; 162.2	37.4; 172.8	47.5; 160.6	33.6; 133.1	33.6; 160.6
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: Reviewer created, based on CSRs for P083, P170 and P289

Table 21: Demographic and Baseline Characteristics (All Subjects Treated) in 2-Study Pool and 3-Study Pool

	2-study pool (P170 + P289)			**3-study pool (P083 + P170 + P289)**		
Parameters	Sita/Met FDC N= 107	Metformin N=113	Total N=220	Sitagliptin N=202	Comparator N=208	Total N=410
Sex, n (%)						
Male	34 (31.8)	41 (36.3)	75 (34.1)	75 (37.1)	75 (36.1)	150 (36.6)
Female	73 (68.2)	71 (63.7)	145 (65.9)	127 (62.9)	133 (63.9)	260 (63.4)
Age (years)						
Mean (SD)	14.5 (2.1)	14.4 (1.8)	14.4 (1.9)	14.4 (2.0)	14.1 (1.9)	14.2 (2.0)
Min; Max	10; 17	10; 17	10; 17	10; 17	10; 17	10; 17
10-14 years, n (%)	42 (39.3)	56 (49.6)	98 (44.5)	89 (44.1)	118 (56.7)	207 (49.5)
Race						
American Indian/Alaska Native	3 (2.8)	10 (8.8)	13 (5.9)	9 (4.5)	19 (9.1)	28 (6.8)
Asian	36 (33.6)	28 (24.8)	64 (29.1)	49 (24.3)	44 (21.2)	93 (22.7)
Black/African American	4 (3.7)	6 (5.3)	10 (4.5)	12 (5.9)	8 (3.8)	20 (4.9)
Multiple-Race[75]	17 (15.9)	18 (15.9)	35 (15.9)	37 (18.3)	36 (17.3)	73 (17.8)
Native Hawaiian/Other Pacific Islander	1 (0.9)	1 (0.9)	2 (0.9)	1 (0.5)	1 (0.5)	2 (0.5)
White	46 (43.0)	50 (44.2)	96 (43.6)	94 (46.5)	100 (48.1)	194 (47.3)
Ethnicity						
Hispanic or Latino	34 (31.8)	43 (31.8)	77 (35)	70 (34.7)	78 (37.5)	148 (36.1)
Unknown	9 (8.4)	6 (5.3)	15 (6.8)	15 (7.4)	9 (4.3)	24 (5.9)
BMI percentile ≥85%	97 (90.7)	99 (87.6)	196 (89.1)	191 (94.6)	190 (91.3)	381 (92.9)
HbA1c (%)						
Mean (SD)	8.0 (1.1)	8.1 (1.1)	8.0 (1.1)	7.7 (1.1)	7.8 (1.1)	7.8 (1.1)
Min; Max	5.9; 11.9	6.0; 10.4	5.9; 11.9	5.8; 11.9	6.0; 11.9	5.8; 11.9
<8%, n (%)	60 (56.1)	59 (52.2)	119 (54.1)	130 (64.4)	119 (57.2)	249 (60.7)
Duration of T2D (years)						

[75] 2-study pool: American Indian/Alaska Native AND White (Sita/Met FDC=7.5%, Metformin = 8.8%), Black/African American AND Asian (Sita/Met FDC= 1.9%, Metformin=0%), Black/African American AND White (Sita/Met FDC=5.6%, Metformin= 5.3%), White AND Asian (Sita/Met FDC= 0.9%, Metformin 1.8%). 3-study pool: American Indian/Alaska Native AND Black/African American (Sitagliptin = 0.5%, Comparator = 0.5%), American Indian/Alaska Native AND Black/African American AND White (Comparator=0.5%), American Indian/Alaska Native AND White (Sitagliptin 9.4%, Comparator 10.1%), Black/African American AND Asian (Sitagliptin = 1%), Black/African American AND White (Sitagliptin =6.9%, Comparator=5.3%), White AND Asian (Sitagliptin 0.5%, Comparator 1%).

Mean (SD)	2.1 (1.4)	2.2 (1.8)	2.2 (1.6)	1.4 (1.5)	1.6 (1.8)	1.5 (1.6)
Min; Max	0.1; 6.8	0.3; 8.6	0.1; 8.6	0.1; 9.0	0.0; 8.6	0.0; 9.0
< 1 year, n (%)	29 (27.1)	36 (31.9)	65 (29.5)	107 (53.0)	115 (55.3)	222 (54.1)
Metformin dose at baseline, n (%)						
<1500 mg/day	6 (5.6)	14 (12.4)	20 (9.1)			
=1500 mg/day	23 (21.5)	19 (6.8)	42 (19.1)			
>1500 mg/day	78 (72.9)	80 (70.8)	158 (71.8)			
Insulin Use, n (%)	17 (15.9)	16 (14.2)	33 (15.0)	28 (13.9)	27 (13.0)	55 (13.4)
Insulin dose (units/day) in those using insulin						
Mean (SD)	48.7 (20.7)	33.2 (17.4)	41.2 (26.0)	48.2 (29.9)	34.6 (19.1)	41.5 (25.9)
Min; Max	13; 125	10; 72	10; 125	10; 125	8; 72	8; 125

Sita/Met FDC= Fixed dose combination of sitagliptin and metformin; FPG= fasting plasma glucose, SD= standard deviation, T2D= type 2 diabetes, HbA1c= hemoglobin A1c, N or n= number

Source: Reviewer generated, from summary of clinical efficacy for 2-study pool and 3-study pool

Treatment Compliance, Concomitant Medications, and Rescue Medication Use:

In all three trials, treatment compliance was similar in both treatment arms. From weeks 0 to 20, mean treatment compliance exceeded 92% with >90% of the population having >80% treatment compliance. Treatment compliance from weeks 0 to 54 was similar.

In trial P083, 81.7% of subjects reported taking concomitant medications. The most frequently reported concomitant medications were acetaminophen (21.5%) and insulin glargine (20.4%). Concomitant use of metformin (outside of rescue therapy) was reported in 17 subjects in the sitagliptin arm and 28 subjects in the placebo arm, however all of these subjects initiated metformin on or after the last dose of study medication.

In trial P170, 78.2% of subjects reported taking concomitant medications during the base study. The most frequently reported concomitant medications were drugs used in diabetes (29%, mostly insulin used as background, rescue or post-treatment therapy), antibacterial for systemic use (25.8%) and analgesics (25.8%). Similar findings were noted in the extension study.

In trial P289, 71.4% of subjects reported taking concomitant medications during the phase A. The most frequently reported concomitant medications were drugs used in diabetes (28.6%, mostly insulin used as background, rescue or post-treatment therapy), antibacterial for systemic use (17.3%) and agents acting on the renin-angiotensin system (14.3%). Similar findings were noted in phase B.

In all three trials, no imbalances in concomitant medication use were identified that would invalidate the trial results.

Rescue medication use is discussed later on in this review, including glycemic outcomes in rescued subjects (Figure 5), demographic and baseline characteristics of rescued subjects (Table 30), and proportion of subjects requiring glycemic rescue by week 20 and week 54 (see page **Error! Bookmark not defined.**).

Efficacy Results – Primary Endpoint:

The primary efficacy endpoint was the change in HbA1c from baseline at week 20. The primary efficacy analysis was performed with the treatment policy (TP) estimand (all randomized subjects who took at least 1 dose of study medication, with all post-baseline data included regardless of glycemic rescue or treatment discontinuation) for trial P083 individually and for the 2-study pool. Results of the primary efficacy analysis are displayed in Table 22. A return-to-baseline (RTB) approach was used because the prespecified minimum required number of retrieved dropout (RD) subjects for performing an RD approach was not met. The RTB analysis included all subjects with a baseline HbA1c measurement, with imputation of missing week 20

HbA1c values[76]. **In both pre-specified primary efficacy analyses, the effect of treatment with sitagliptin was not significantly different from that of the comparator at week 20.**

In trial P083, subjects in the sitagliptin arm had a reduction in least squares mean HbA1c of 0.06%, while subjects in the placebo arm had an increase in least squares mean HbA1c of 0.23%, representing a treatment difference of -0.17% (95% confidence interval -0.61, 0.28) for sitagliptin versus placebo[77].

In the 2-study pool, subjects in the Sita/Met FDC arm had a reduction in least squares mean HbA1c of 0.23%, while subjects in the placebo arm had an increase in least squares mean HbA1c of 0.09%, representing a treatment difference of -0.33% (95% confidence interval: -0.70, 0.05)[78].

Table 22: Primary Efficacy Analysis: Change from Baseline in HbA1c at Week 20 for Trial P083 and 2-Study Pool using ANCOVA analyses for Treatment Policy 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

[76] According to Dr. Tu's statistical review, missing HbA1c values were imputed from a normal distribution with the expected value set to the subject's baseline value plus a standard deviation using the root mean squared error from the ANOVA model based on trial completers. The imputation procedure was repeated 100 times and Rubin's rule was used to combine the results for statistical inference.
[77] The actual standard deviation in the sitagliptin arm (1.5) was higher than the estimated standard deviation used in the power calculations (1.1). However, the actual sample size was also higher than originally estimated. Based on communication with the statistical reviewer, the actual power was 80%, therefore there is no evidence that non-significant treatment effect was related to inadequate power.
[78] The actual standard deviation in the Sita/Met FDC arm (1.4) was higher than the estimated standard deviation used in the power calculations (1.1). However, based on communication with the statistical reviewer, the actual power was 90% therefore there is no evidence that non-significant treatment effect was related to inadequate power.

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: Reviewer generated, based on CSR for P083 and summary of clinical efficacy for 2-study pool.

As previously discussed, the preferred primary efficacy analysis utilized the TP estimand, which reflected an "intention-to-treat" population. In contrast, the TE estimand excluded post-baseline data obtained following treatment discontinuation or rescue therapy, which reflected a "per-protocol" population. Although analyses using the TE estimand are not preferred (due to the potential for bias relating to exclusion of data following randomization), given lack of efficacy in the TP estimand it may be informative to compare any differences in results obtained using the TE estimand.

Results using the TE estimand are displayed in Table 23 below. In trial P083, even when excluding post-baseline data obtained following glycemic rescue or treatment discontinuation, the effect of treatment with sitagliptin was not significantly different from that of the placebo at week 20. The estimated treatment difference in least squares mean HbA1c was -0.19 % (95% confidence interval: -0.68, 0.3, p-value 0.448). However, in the 2-study pool, nominal statistical significance was reached in the TE estimand, with an estimated treatment difference in least squares mean HbA1c of -0.49% (95% confidence interval -0.90, -0.09, p-value 0.018).

Table 23: Change from Baseline in HbA1c at Week 20 for Trial P083 and 2-Study Pool using cLDA analyses for Treatment Effect Estimand

	P083		**2-study pool**	
	Sitagliptin	Placebo	Sita/Met FDC	Metformin
Baseline				
N	95	95	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]	78	73	91	86
HbA1c (%), mean (SD)	7.18 (1.66)	7.47 (1.63)	7.29 (1.45)	7.54 (1.45)
HbA1c Change from Baseline				
Mean (SD)	-0.13 (1.58)	0.01 (1.45)	-0.6 (1.40)	-0.42 (1.43)

LS Mean[2]	-0.01	0.18	-0.58	-0.09
95% Confidence Interval	-0.35, 0.34	-0.17, 0.53	-0.94, -0.22	-0.43, 0.26
Difference in LS Means (Sitagliptin vs. placebo)	**-0.19**		**-0.49**	
95% Confidence Interval	**-0.68, 0.30**		**-0.90, -0.09**	
p-value	**0.448**		**0.018**	

[1]Subjects with both baseline and week 20 measurements. Week 20 HbA1c data obtained following glycemic rescue or treatment discontinuation was excluded from this analysis.
[2] Based on cLDA model adjusting for treatment, time, baseline BMI percentile, insulin use (yes/no) at screening.
Abbreviations: cLDA, constrained longitudinal data analysis; LS, Least Squares; SD, standard deviation; N, number; Sita/Met FDC, fixed dose combination of sitagliptin and metformin

Source: Reviewer generated, based on CSR for P083 and summary of clinical efficacy for 2-study pool.

Reviewer Comment: In both primary efficacy analyses (for trial P083 and the 2-study pool) using the TP estimand ("intention-to-treat" population), there was a small numerical difference (~-0.2 to 0.3%) in HbA1c change favoring sitagliptin over placebo that did not reach statistical significance. It is worth noting that in studies used to support efficacy of sitagliptin in adults, the treatment difference in HbA1c compared to placebo ranged from -0.6 to -0.8%[79]. Therefore, numerically, the treatment effect of sitagliptin appears reduced in pediatric patients compared to adults.

Results from the TE estimand (per-protocol population) were examined for supportive purposes. It is important to note that analyses using a "per-protocol" population are not preferred for the demonstration of effectiveness, due to the potential for bias introduced by exclusion of data following randomization. Additionally, given the absence of statistical significance in the primary outcome using the TP estimand, formal statistical testing in the TE estimand is not permitted. It is notable that despite excluding data following treatment discontinuation or rescue therapy, there was no difference in the results for trial P083 using the TE estimand compared to the TP estimand (both showing a non-significant -0.2% HbA1c change favoring sitagliptin over placebo). Interestingly, in the TE estimand analysis of the 2-study pool, a larger numerical treatment difference of - 0.49% was found favoring Sita/Met FDC over metformin and reaching nominal statistical significance. The reasons for the differences between the TP and TE estimand analyses in the 2-study pool are further explored below.

Primary Efficacy Endpoint Results in Individual Studies of P170 and P289
Due to differences in efficacy results with TE estimand versus the TP estimand in the 2-study pool, a more detailed examination of the primary efficacy outcome results for the individual studies P170 and P289 is warranted.

[79] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021995s045lbl.pdf

In the statistical review, Dr. Tu conducted a separate ANCOVA analysis for trial P170 and P289 using the TP estimand, as displayed in Table 24. In trial P170, a treatment difference of -0.58% favoring sitagliptin was demonstrated (reaching nominal statistical significance). However, no treatment difference was seen in trial P289.

Table 24: Change from Baseline in HbA1c (%) at Week 20 for Trials P170 and P289 using ANCOVA analyses for Treatment Policy Estimand

	Trial P170 (N = 124)	Trial P289 (N = 96)
Change in HbA1C from Baseline at Week 20	LS Mean (95% CI)	LS Mean (95% CI)
Sita/Met FDC	-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 LS means (95% CI)	**-0.58 (-1.07, -0.10)** P-value = 0.02	**0.03 (-0.57, 0.62)** P-value = 0.93

ANCOVA analysis was conducted based on the treatment policy estimand. Return-to-baseline and Rubin's Rule were used for missing data imputation.

Abbreviations: HbA1c, hemoglobin A1c; Sita/Met FDC, fixed dose combination of sitagliptin and metformin; LS, least squares; CI, confidence interval; ANCOVA, analysis of covariance

Source: Adapted from Table 12 of Dr. Tu's Statistical Review

To better understand the discrepancy between results of trial P170 and P289, it with worthwhile to examine the summary statistics for change from baseline in HbA1c at week 20 (Table 25). Notably, the standard deviations and ranges are quite broad in both trials and estimands, reflecting variability in results. Mean and median HbA1c changes are similar in magnitude for trial P170. However, in trial P289, mean and median HbA1c changes are discrepant. Most notably, in the TE estimand there is less reduction in mean HbA1c at week 20 but greater reduction in median HbA1c at week 20 in the Sita/Met XR arm (see bolded and italicized values in the table below).

Table 25: Change from Baseline in HbA1c (%) at Week 20 for Trials P170 and P289 using Summary Statistics for Treatment Policy and Treatment Effect Estimands

	P170		**P289**	
	Sita/Met IR FDC	Met IR	Sita/Met XR FDC	Met XR

TP Estimand[1]				
N	55	61	40	47
HbA1c at Baseline (%)				
Mean (SD)	8.05 (1.24)	8.14 (1.08)	7.83 (0.91)	8.01 (1.05)
HbA1c at Week 20 (%)				
Mean (SD)	7.14 (1.25)	7.86 (1.67)	7.62 (1.69)	7.80 (1.59)
HbA1c Change from Baseline (%)				
Mean (SD)	**-0.91 (1.34)**	**-0.29 (1.62)**	***-0.21 (1.38)***	***-0.21 (1.50)***
Median	-0.80	-0.20	***-0.60***	***-0.10***
Range	-5.10; 2.50	-4.80; 3.80	-2.60; 3.50	-3.90; 3.30
TE Estimand[2]				
N	52	49	39	37
HbA1c at Baseline (%)				
Mean (SD)	7.96 (1.13)	8.03 (1.09)	7.77 (0.84)	7.86 (1.00)
HbA1c at Week 20 (%)				
Mean (SD)	7.07 (1.20)	7.70 (1.57)	7.58 (1.70)	7.32 (1.26)
HbA1c Change from Baseline (%)				
Mean (SD)	**-0.90 (1.34)**	**-0.33 (1.53)**	***-0.19 (1.40)***	***-0.54 (1.30)***
Median	-0.80	-0.20	***-0.60***	***-0.20***
Range	-5.10; 2.50	-4.80; 3.10	-2.60; 3.50	-3.90; 1.40

[1] Including all post-baseline data following glycemic rescue or treatment discontinuation
[2] Excluding post-baseline data following glycemic rescue or treatment discontinuation
SD, standard deviation; N, number of subjects with both baseline and week 20 measurements; 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.

Source: Reviewer generated from CSRs

The discrepancy in mean and median HbA1c at 20 weeks in trial P289, which was most pronounced in the TE estimand, prompted a further analysis by Dr. Wenda Tu (statistical reviewer), described on page 22 of her statistical review (and also shown in Figure 12 in Appendix 13.2). Based on a distribution of the change from baseline in HbA1c included in the treatment effect estimand analysis, outliers with large increase in HbA1c were present in the Sita/Met XR arm, and outliers with a large decrease in HbA1c were present in the Met XR arm. Upon further investigation, many subjects who underwent rescue therapy in the metformin XR arm had a rise in week 20 HbA1c (Figure 5, trial P289); however these values were excluded for the TE estimand analysis which led to a more favorable mean change in HbA1c for the metformin XR arm.

Reviewer Comment: The individual results of trials P170 and P289 are discrepant. In trial P170, a numerical treatment difference in mean HbA1c change of ~ -0.6% favoring sitagliptin was demonstrated, however no numerical treatment difference was seen in trial P289.

While there were some minor differences in baseline and demographic characteristics

between trials P170 and P289 (e.g., slightly older mean age and slightly increased percentage of insulin users in trial P289), these would not be expected to impact the primary efficacy endpoint. There were no obvious differences in study conduct or treatment compliance in either of the trials to account for the differing efficacy results. Given the relatively small numbers in the individual trials (around 50 to 60 subjects in each arm), it is possible that the variable individual results were due to chance alone.

A discrepancy between the mean and median HbA1c results in trial P289 prompted further investigation. It appears that exclusion of unfavorable HbA1c data from rescued subjects (mostly in the metformin XR arm) led to a more favorable mean change in HbA1c in the metformin XR arm. Given that rescue therapy would typically be expected to lead to improvement in glycemic control, exclusion of more data following rescue therapy in the placebo arm would usually favor the treatment (drug) arm. Given that the reverse occurred in trial P289, further exploration of HbA1c results in rescued subjects was conducted for the other two trials (discussed below).

Primary Efficacy Endpoint in Rescued Subjects
To better understand the impact of inclusion or exclusion of HbA1c data following rescue therapy, change from baseline to week 20 HbA1c among rescued subjects was plotted graphically for trials P083 and P170 (Figure 5).

As previously mentioned, the majority of rescued subjects through week 20 in all three trials were in the comparator arm, with less frequency of rescue therapy in the sitagliptin arms. As was just noted, most rescued subjects in P289 had an increase from baseline in HbA1c at week 20. In trials P083 and P170, around half of rescued subjects had an increase from baseline in HbA1c at week 20, and half had a decrease from baseline in HbA1c at week 20. Overall, subjects who received rescue therapy did not necessarily have improved glycemic control compared to baseline at week 20. Therefore, the relatively increased inclusion of "rescued" week 20 HbA1c data in the comparator arms compared to the sitagliptin arms is unlikely to have reduced the treatment effect size in the TP estimand.

Reviewer Comment: Considering data from all three trials, rescued subjects overall did not necessarily demonstrate improved glycemic control compared to baseline by week 20. In study P289, most rescued subjects had worsened glycemic control compared to baseline; in trials P083 and P170, half of the rescued subjects had glycemic improvement while the other half had worsened glycemic control compared to baseline. I suspect that this variability may be related to absence of consistency regarding the insulin regimen and dosing to be used for rescue therapy (as it was left up to the investigator, rather than specified in the protocol). In addition, the rapid progression of underlying disease in some pediatric subjects may have required more aggressive rescue therapy to regain glycemic control than was instituted in the clinical trial setting.

Overall, the imbalance between rescued subjects (specifically higher rates in comparator arm vs. sitagliptin arm in all three trials) seems unlikely to have reduced the week 20 effect size in analyses that included data following glycemic rescue (i.e., in the TP estimand or intention-to-treat population).

Distribution of Change from Baseline in HbA1c at 20 weeks

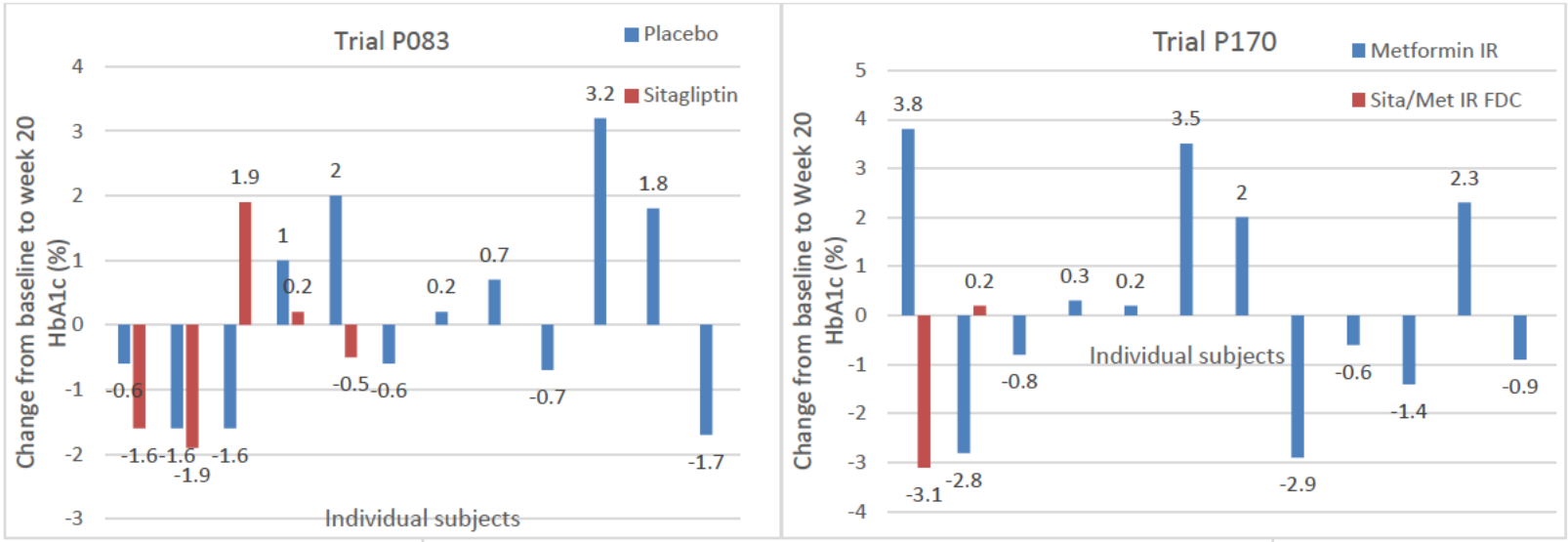
As previously discussed, there appears to be 2 major subgroups of patients with pediatric T2D: a group that displays more durable glycemic control and another group with rapid disease progression. Given that, I questioned whether there may be differential results in subgroups of the trial population. The distribution of change in HbA1c from baseline to week 20 in the treatment policy estimand are displayed for all three trials in Figure 6. While there were some outliers[80], there does not appear to be evidence of a bimodal distribution to suggest subgroups with differential response.

Reviewer Comment: In the TP estimand analysis, there was no evidence of a bimodal distribution in the primary efficacy endpoint. This finding, along with the negative subgroup analyses (discussed on page 87), argues against a differential treatment response in subgroups of pediatric T2D patients.

[80] A review of 2 outliers in P083 was conducted.

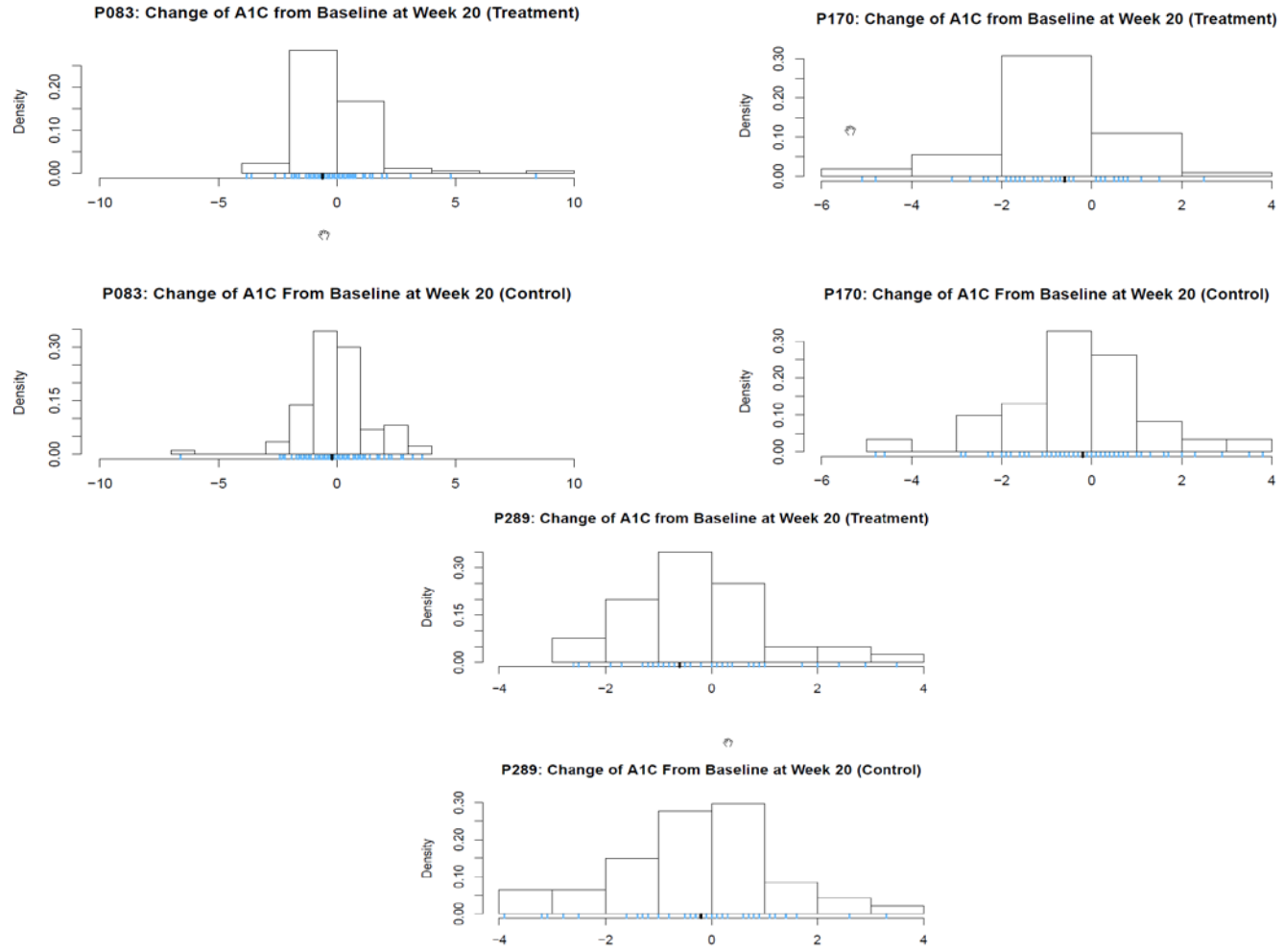
- 1 subject in the sitagliptin arm had an increase in HbA1c from baseline to week 20 of 8.4%. Baseline HA1c was 6.8%, rising to 7.5% by week 14 and to 15.2% by week 20. Following rescue therapy, HbA1c eventually declined to 9.6% by week 52.
- 1 subject in the placebo arm had a decrease in HbA1c from baseline to week 20 of 6.8%. HbA1c obtained at screening (visit 1) was 7.2%, but rose to 11.9% following the placebo-run in. FPG at the time was 96 mg/dL, which seems discrepant with HbA1c value. HbA1c subsequently declined to 5.6% at week 8 and remained generally below 6% for the duration of the trial. For this reason, I suspect that the baseline HbA1c measured following the placebo run-in may have been erroneous.

Figure 5: Change from Baseline in HbA1c at Week 20 among Rescued Subjects in Trials P083, P170 and P289



Source: Reviewer created from ADEFF dataset

Figure 6: Distribution of Change from baseline in HbA1c at Week 20 in Trials P083, P170 and P289 using Treatment Policy Estimand



Source: Generated by Dr. Wenda Tu, statistical reviewer

Subgroup Analyses for Primary Efficacy Endpoint:

Dr. Tu conducted subgroup analyses of baseline and demographic characteristics for the primary efficacy outcome using the TP estimand (Table 26 for trial P083 and Table 27 for the 2-study pool). In general, the results of the subgroup analyses were consistent with results for the entire population. In most analyses, there was a small treatment difference favoring sitagliptin over comparator, however, statistical significance was not reached (based on 95% confidence intervals including 0). The only case where statistical significance was reached was in the subgroup of "Other" race in the 2-study pool, however this finding is most likely due to chance.

Table 26: Change from Baseline in HbA1c (%) at Week 20 for Different Subgroups, using ANCOVA Analysis for Treatment Policy Estimand, Trial P083

Treatment	Baseline		Week 20		Change from baseline in HbA1c at Week 20		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)	Difference in LS Mean (95% CI)
Gender							
Male							
Sitagliptin	41	7.47 (1.04)	38	7.70 (2.10)	41	0.43 (-0.25, 1.11)	-0.04 (-0.86, 0.77)
Placebo	34	7.36 (0.78)	30	7.72 (1.60)	34	0.47 (-0.29, 1.24)	
Female							
Sitagliptin	54	7.40 (1.01)	46	6.88 (1.14)	54	-0.20 (-0.69, 0.30)	-0.36 (-0.87, 0.16)
Placebo	61	7.71 (1.18)	57	7.61 (1.76)	61	0.16 (-0.32, 0.64)	
Race							
White							
Sitagliptin	48	7.40 (1.09)	42	7.23 (1.52)	48	0.00 (-0.59, 0.59)	-0.12 (-0.71, 0.46)
Placebo	50	7.47 (1.10)	45	7.57 (1.63)	50	0.13 (-0.50, 0.76)	
Other							
Sitagliptin	47	7.46 (0.94)	42	7.28 (1.85)	47	0.12 (-0.47, 0.71)	-0.22 (-0.91, 0.47)
Placebo	45	7.71 (1.02)	42	7.74 (1.78)	45	0.34 (-0.24, 0.92)	
Age							
≤ 14 Years Old							
Sitagliptin	47	7.46 (1.02)	42	7.06 (1.48)	47	-0.21 (-0.69, 0.27)	-0.23 (-0.78, 0.31)
Placebo	62	7.64 (1.14)	57	7.49 (1.41)	62	0.02 (-0.46, 0.50)	
> 14 Years Old							
Sitagliptin	48	7.40 (1.02)	42	7.45 (1.86)	48	0.40 (-0.30, 1.10)	-0.30 (-1.04, 0.44)
Placebo	33	7.47 (0.91)	30	7.97 (2.14)	33	0.70 (-0.05, 1.44)	

Abbreviations: HbA1c, hemoglobin A1c, LS, least squares; CI, confidence interval; ANCOVA, analysis of covariance; N, number; SD, standard deviation

Source: Adapted from Table 15 from Dr. Tu's Statistical Review

Table 27: Change from Baseline in HbA1c (%) at Week 20 for Different Subgroups, using ANCOVA Analysis for Treatment Policy Estimand, 2-study pool (P170+P289)

Treatment	Baseline		Week 20		Change from baseline in HbA1c 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)	

Abbreviations: HbA1c, hemoglobin A1c, LS, least squares; CI, confidence interval; ANCOVA, analysis of covariance; Sita/Met FDC, fixed dose combination of sitagliptin and metformin; N, number; SD, standard

Source: Adapted from Table 16 from Dr. Tu's Statistical Review

Subgroup analyses conducted by the Applicant for trial P083 (Figure 9), the 2-study pool (Figure 10) and the 3-study pool (Figure 11) using the TE estimand also showed similar findings. Demographic and baseline characteristics investigated in the Applicant's subgroup analyses included baseline HbA1c level (above or below median), gender (male or female), race (white or non-white), ethnicity (Hispanic/Latino or not Hispanic/Latino), age (<14 and > 14 years), BMI percentile (below median and above median), duration of T2D (< 1 year and ≥ 1 year), and baseline insulin use (yes/no).

Reviewer Comment: In subgroup analyses, no differences in efficacy results were seen based on age, gender, race, ethnicity, baseline BMI percentile, background insulin use, baseline HbA1c or duration of diabetes.

Data Quality and Integrity:

There were no potential issues concerning the submitted data quality or integrity identified

during the review of the efficacy results.

Efficacy Results – Secondary and other relevant endpoints:

Secondary endpoints and additional analyses are discussed in section 7.1.2, as they are described across trials.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The pre-specified primary efficacy analyses (i.e., results of trial P083 and the 2-study pool) and results from the individual trials of P170 and P289 were already discussed in section 6.1.2. Pooled results for all three trials (3-study pool) are discussed below.

Primary Efficacy Endpoint in the 3-study pool

Results for the primary efficacy endpoint for the 3-study pool are indicated in Table 28**Error! Reference source not found.**. Due to lack of statistical significance in the primary efficacy analysis of study P083, hypothesis testing was not permitted in the 3-study pool.

Table 28: Change from Baseline in HbA1c at Week 20 for 3-study pool (P083+ P170+P289) using Treatment Effect and Treatment Policy Estimands.

	3-study pool (P083+P170+P289)			
	TP estimand[1]		**TE estimand**[2]	
	Sitagliptin	Comparator	Sitagliptin	Comparator
Baseline				
N	202	208	202	208
HbA1c (%), mean (SD)	7.71 (1.10)	7.84 (1.09)	7.71 (1.10)	7.84 (1.09)
Week 20				
N[3]	179	195	169	159
HbA1c (%), mean (SD)	7.30 (1.57)	7.75 (1.66)	7.24 (1.55)	7.51 (1.53)
HbA1c Change from Baseline				
Mean (SD)	-0.40 (1.49)	-0.13 (1.52)	-0.38 (1.50)	-0.22 (1.45)
LS Mean	-0.07	0.19	-0.36	-0.02

95% Confidence Interval	-0.33, 0.19	-0.06, 0.45	-0.59, -0.13	-0.20, 0.25
Difference in LS Means (Sitagliptin vs. comparator)	**-0.26**		**-0.38**	
95% Confidence Interval	**-0.55, 0.02**		**-0.69, -0.07**	
p-value	**0.070**		**0.017**	

[1] Analysis based on ANCOVA model adjusting for treatment, study (P083, P170, P289), baseline BMI percentile, insulin use (yes/no) at screening, baseline HbA1c value
[2] Analysis based on cLDA model adjusting for treatment, time, study (P083, P170, P289), baseline BMI percentile, insulin use (yes/no) at screening.
[3]Subjects with both baseline and week 20 measurements.
cLDA, constrained longitudinal data analysis; ANCOVA, Analysis of Covariance, LS, Least Squares; SD, standard deviation; N, number;
TP Estimand; Treatment policy estimand (including data obtained following glycemic rescue or treatment discontinuation); TE Estimand; Treatment effect estimand, (excluding data obtained following glycemic rescue or treatment discontinuation)

Source: Reviewer generated based on clinical summary of efficacy for 3-study pool

The written request specified that two sensitivity analyses must be conducted for the 3-study pool by varying the assumptions on missing data to investigate the impact of missing data on the primary analysis results. The Applicant conducted two separate sensitivity analyses using the treatment policy estimand to address missing data imputation, including an analysis with jump to reference and another with washout imputation. In the sensitivity analysis using jump to reference, a difference in least squares mean change from baseline HbA1c of -0.26 (95% confidence interval -0.50, -0.01, p-value 0.041) was found for sitagliptin versus comparator. In the sensitivity analysis using washout imputation, a difference in least squares mean change from baseline HbA1c of -0.30 (95% confidence interval -0.59, -0.01, p-value 0.044) was found for sitagliptin versus comparator.

Reviewer Comment: The treatment policy estimand analysis for the 3-study pool revealed a non-significant treatment difference of -0.26% change from baseline in least squares mean HbA1c at week 20 favoring sitagliptin over the comparator. In sensitivity analyses addressing missing data imputation in the treatment policy estimand, this treatment difference reached nominal statistical significance. In the treatment effect estimand analysis for the 3-study pool, a treatment difference of -0.38% change from baseline in HbA1c at week 20 was seen favoring sitagliptin over comparator, again reaching nominal significance.

Due to failure of superiority of sitagliptin in trial P083, formal hypothesis testing was not permitted for the 3-study pool, and any statistical inferences from analyses of the 3-study pool may be erroneous due to multiple comparisons. Additionally, due to differences between trial P083 (which evaluated sitagliptin monotherapy) and trials P170 and P289 (which evaluated sitagliptin as add-on therapy to metformin), caution must be taken when interpreting pooled efficacy results from all three studies.

7.1.2. Secondary and other Endpoints

General Approach to Secondary Endpoints

Given that efficacy of sitagliptin was **not** demonstrated in the primary efficacy analyses of the phase III pediatric program, my review of secondary endpoints was focused on those endpoints that would be most useful to explain any differences in the pharmacologic effect of sitagliptin in the pediatric population compared to adults, comparing differences across trials.

Important secondary efficacy endpoints for trial P083, 2-study pool and 3-study pool are displayed in **Error! Reference source not found.**.

Table 29: Selected Secondary Efficacy Endpoints for Trial P083, 2-Study Pool and 3-Study Pool using Treatment Effect Estimand

Secondary efficacy endpoint	P083	2-study pool	3-study pool
Mean change from baseline in FPG (mg/dL) at week 20			
Sitagliptin	10	3.0	6.2
Comparator	9.5	9.7	9.6
Treatment Difference, LS Means (95% CI)[1]	1.5 (-14.4, 17.5)	-10.8 (-25.9, 4.3)	
Proportion of subjects with HbA1c < 7.0% at week 20			
Sitagliptin, n (%)	47 (49.5)	46 (43.0)	93 (46.0)
Comparator, n (%)	35 (36.8)	35 (31.0)	70 (33.7)
Treatment Difference, % (95% CI)[2]	6.7 (-8.1, 21.2)	**16.0 (2.9, 28.9)**	
Proportion of subjects with HbA1c < 6.5% at week 20			
Sitagliptin, n (%)	29 (30.5)	31 (29.0)	60 (29.7)
Comparator, n (%)	22 (23.2)	23 (20.4)	45 (21.6)
Treatment Difference, % (95% CI)[2]	3.6 (-11.6, 18.3)	12.2 (0.0, 24.8)	
Proportion of subjects initiating glycemic rescue therapy, weeks 0 to 20, n (%)			
Sitagliptin	5 (5.3)	4 (3.7)	9 (4.5)
Comparator	12 (12.6)	19 (16.8)	31 (14.9)
Kaplan-Meier Difference, % (95% CI)	-7.5 (-15.7, 0.8)	**-13.2 (-21.1, -5.3)**	
Proportion of subjects initiating glycemic rescue therapy, weeks 20 to 54, n (%)[3]			
Sitagliptin		15 (22.7)	
Comparator		17 (26.6)	

Treatment effect estimand excluded data following initiation of rescue therapy and discontinuation of study medication. **Bolded results indicate when 95% CI excludes 0.**

[1] based on cLDA model using 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.

[2] Calculated via the M&N method stratified by baseline BMI percentile (≥ or < median), insulin use at screening

(yes/no), and baseline A1C (≥ or < median), following imputation of missing Week 20 data using standard multiple imputation techniques based on the cLDA model used for the primary analysis.
[3] % calculated based on total number of subjects participating in weeks 20-54 who had not been rescued through week 20 (N=66 for sitagliptin 2-study pool, N=64 for comparator 2-study pool)
Abbreviations: cLDA, constrained longitudinal data analysis; M&N, Miettinen and Nurminen; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; CI, confidence interval

Source: Reviewer generated based on CSRs for trial P083 and summary of clinical efficacy for 2-study pool and 3-study pool

Small increases in FPG from baseline to week 20 were seen in both treatment arms across the trials. While a numerically higher proportion of subjects achieved glycemic goals of HbA1c < 7% and <6.5% at week 20 in the sitagliptin versus the comparator arms, the treatment difference was nominally statistically significant only for the proportion of subjects achieving HbA1c < 7% in the 2-study pool. Further, by week 54, there was no difference in proportion of subjects meeting glycemic goals in the 2-study pool[81]. As previously mentioned, the proportion of subjects initiating glycemic rescue therapy was numerically higher in the comparator arm across all three individual trials (achieving statistical significance in the 2-study pool). However, from weeks 20 to 54, the proportion of subjects initiating glycemic rescue therapy was similar between treatment groups in the 2-study pool. As subjects in the placebo arm were switched to metformin therapy from weeks 20 to 54 in trial P083, the proportion of subjects requiring rescue therapy from weeks 20 to 54 in trial P083 cannot be meaningfully compared to results for weeks 0 to 20, or to results from the 2- study pool. No clinically meaningful differences were noted in other efficacy endpoints[82].

Kaplan Meier plots showing time to initiation of glycemic rescue therapy in trial P083 and the 20-study pool from weeks 0 to 20 and from weeks 0 to 54 are displayed in Figures 13-16 in the Appendix (see section 13.2). Overall, the trends in rescue therapy are consistent with the trends in HbA1c data by study week, suggesting an initial pharmacologic effect of sitagliptin that diminishes over time, coinciding with increased rescue therapy. There also appears to be a more pronounced increase in glycemic rescue therapy from weeks 20 to 54 in both treatment arms. This finding may support progression of underlying disease in the trial population over time, however may also reflect more stringent glycemic rescue criteria during weeks 20 to 54.

Reviewer Comment:

[81] Individual results for trial P170 and P289 regarding the proportion of subjects achieving glycemic goals was similar at week 20, but different at week 54. In trial P170, the proportion of subjects achieving HbA1c < 7% and <6.5% was higher in the Sita/Met IR arm compared to the Met IR arm at both weeks 20 and 54. In trial P289, the proportion of subjects achieving HbA1c <7% and <6.5% was higher in the Sita/Met XR arm compared to Met XR arm at week 20, but the reverse pattern was seen at week 54.
[82] In trial P083, no notable differences were observed between sitagliptin and placebo groups in change from baseline in fasting insulin, proinsulin/insulin ratio, HOMA-IR, or HOMA-β. Interpretation of secondary endpoints from the meal tolerance test was limited due to small numbers of participants.

Across all three trials, FPG increased from baseline to week 20 (though to variable degrees in each treatment arm, depending on the individual study). The overall increase in FPG from baseline to week 20 despite treatment with sitagliptin is consistent with the absence of glycemic efficacy at week 20.

As previously discussed, the proportion of subjects receiving rescue therapy was higher in the comparator arm from weeks 0 to 20 in all three studies. However, the proportion of subjects initiating rescue therapy from weeks 20 to 54 was similar between treatment arms in the 2-study pool. The disappearance of the initial imbalance in rescue therapy after week 20 is consistent with diminishing treatment effect of sitagliptin over time. Comparison of rates of rescue therapy between treatment arms from weeks 20 to 54 in trial P083 is limited due to subjects in the placebo group having been switched to metformin.

To further evaluate any evidence for underlying disease progression in the trial population, I calculated the proportion of subjects in the 2-study pool with "glycemic failure" defined as having both baseline and week 20 HbA1c >8%. 27.4% of subjects in the metformin arm, and 22.6% of subjects in the Sita/Met XR arm had both baseline and week 20 HbA1c > 8%. In both treatment arms, the proportion of subjects meeting glycemic failure appears grossly higher than that reported in treatment arms of the TODAY study by 5 months of follow up[83]. The median baseline HbA1c in the TODAY study was also lower than that of the sitagliptin 2-study pool (5.9 vs. 7.9%).

Reviewer Comment: The trial population in the sitagliptin 2-study pool appears to have relatively higher rates of "glycemic failure" (defined as baseline and week 20 HbA1c of >8%) at 5 months as compared to the trial population studied in the TODAY study. As previously discussed, by virtue of the HbA1c enrollment criteria (lower inclusion limit of ≥6.5%) aimed to enroll subjects uncontrolled on metformin, the sitagliptin program may have excluded more subjects likely to have durable glycemic control.

7.1.3. Subpopulations

Important subgroup analyses for the primary efficacy endpoint were previously discussed in section 6.1.2. In this section, I have provided additional information regarding the subpopulation of rescued subjects, as well as a description of efficacy as it relates to geographic region.

Rescued Subjects

[83] Note that in the TODAY study, glycemic failure was defined as HbA1c >8% for 6 months in subjects who were randomized to metformin alone, metformin and rosiglitazone or metformin and lifestyle changes. [TODAY Study Group, Zeitler P, Hirst K, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366(24):2247-2256. doi:10.1056/NEJMoa1109333]

Rescued subjects were generally similar to the overall population in the 3-study pool in terms of age, sex and duration of T2D (Table 30). Distributions of racial and ethnic categories are difficult to interpret due to small numbers, however there appears to be a higher representation of Hispanic/Latino subjects in those that were rescued compared to the overall population (50 vs. 36.1 %). Rescued subjects also tended to have higher baseline HbA1c compared to all subjects in the 3- study pool (8.8 vs. 7.8%), a finding that was most pronounced for rescued subjects the sitagliptin arm where the baseline HbA1c was 9.5%.

Table 30: Characteristics of Subjects receiving Rescue Therapy from Weeks 0 to 20 in the Sitagliptin Phase III Pediatric Trials

Parameters	Rescued subjects in Pooled Sitagliptin arm N=8	Rescued subjects in Pooled Comparator arm N=30	All rescued subjects N=38	All subjects in 3-study pool N=410
Female, n (%)	5 (62.5)	20 (66.7)	25 (65.8)	260 (63.4)
Mean Age (years)	14.8	14.0	14.1	14.2
Age group 10-14 years, n (%)	4 (50.0)	11 (36.7)	23 (60.5)	207 (50.5)
Race				
White	4 (50.0)	16 (53.3)	20 (52.6)	194 (47.3)
Asian	0 (0)	6 (20.0)	6 (15.8)	93 (22.7)
American Indian/Alaska Native	1 (12.5)	0 (0)	1 (2.6)	28 (6.8)
Black/African American	0 (0)	1 (3.3)	1 (2.6)	20 (4.9)
Black/African American and White	1 (12.5)	4 (13.3)	5 (13.2)	25 (6.1)
American Indian/Alaska Native and White	2 (25.0)	3 (10.0)	5 (13.2)	40 (9.8)
Ethnicity				
Hispanic or Latino	4 (50.0)	15 (50.0)	19 (50.0)	148 (36.1)
Mean HbA1c (%) at baseline	9.5	8.6	8.8	7.8
Duration of T2D (years)	1.6	1.7	1.7	1.6
Background Insulin Use, n (%)	0 (0)	6 (20.0)	6 (15.8)	55 (13.4)

Abbreviations: T2D= type 2 diabetes, HbA1c= hemoglobin A1c, N or n= number
"Pooled Sitagliptin arm" refers to those in the sitagliptin arm (P083), Sita/Met IR FDC arm (P170) and Sita/Met XR arm (P289)
"Pooled Comparator arm" refers to those in the placebo arm (P083), Met IR arm (P170) and Met XR arm (P289).

Source: Reviewer generated based on ADSL dataset for 3-study pool

The primary efficacy endpoint in rescued subjects was previously discussed in section 6.1.2,

(Figure 5). In general, rescued subjects did not necessarily demonstrate improvement from baseline HbA1c by week 20.

Geographic Region

As previously mentioned, a minority (13.2% or 54/410 treated subjects) of the trial population were enrolled from the US. Demographic characteristics for subjects randomized from the US were similar to the overall demographics of the 3-study pool (Table 21) apart from lower percentage of subjects in the 10 to 14 year age group (38.9%) and higher percentage of subjects of white race (68.5%), and of Hispanic/Latino ethnicity (57.4%)

I conducted an analysis of the primary endpoint results (change from baseline in HbA1c at week 20) based on geographic region (United States, Latin America, Europe, Middle East, Asia/Pacific, Africa, Canada and Australia) in each individual trial (data not shown). Overall, the small numbers of subjects from each geographic region limit any conclusions. However, there was no discernable pattern among geographic results across all studies, with significant variation in the treatment difference (sitagliptin versus comparator) when separated out by region and by trial.

7.1.4. Dose and Dose-Response

The dose and exposure response relationship were previously discussed in section 4.5. Data from two phase I pediatric PK studies suggested similar sitagliptin exposure and DPP-IV inhibition in adults and children, therefore it was determined that a single dose of sitagliptin (100 mg daily, equivalent to recommended dosing in adults) would be investigated in all three phase III pediatric trials. As discussed above, the pediatric trials failed to demonstrate efficacy of sitagliptin based on the pre-specified primary efficacy analysis. However, I do not believe that the lack of efficacy was related to inappropriate dose selection. Data from the phase III pediatric trials overall support an initial pharmacologic effect of sitagliptin (based on reduction in HbA1c at earlier time points) that diminished over time (see discussion in section 7.1.5 below). Therefore, absence of efficacy at 20 weeks was most likely related to more rapid disease progression in the pediatric trial population compared to adults.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Change in HbA1c from baseline by study week
As mentioned previously, change from baseline in HbA1c at week 14 (trial P083 only) and at week 54 were included in pre-specified secondary endpoints. Therefore, I was interested to know whether there were differences in glycemic effect at time points apart from week 20.

Table 31, Figure 7 and Figure 8 **Error! Reference source not found.**display the change in HbA1c by study week for trial P083 and the 2-study pool using the treatment effect estimand. **Error! Reference source not found.**In the 2-study pool, a significant treatment difference favoring

sitagliptin was seen at week 6, 12 and 20. By week 54, HbA1c rose in both treatment arms, though to a lesser degree with sitagliptin. In trial P083, a significant treatment difference favoring sitagliptin was seen at week 8 only. Though non-significant beyond week 8, the magnitude of the treatment difference also declined over time. By week 54, HbA1c increased compared to baseline in the sitagliptin arm. The relative decline in HbA1c in the placebo/metformin arm from weeks 20 to 54 (compared to weeks 0 to 20) likely reflects the addition of metformin starting at week 20.

Reviewer Comment: As previously discussed, phase B of trial P083 was designed as an "active control" period, comparing treatment of sitagliptin to metformin. At week 54, the change from baseline in HbA1c was -0.11% in the placebo/metformin arm compared to an increase of 0.45% in the sitagliptin arm. It is important to note that the results presented are from the treatment effect estimand and therefore a large percentage (>45%) of HbA1c data obtained following treatment discontinuation and rescue therapy was excluded. Using the treatment policy estimand (including HbA1c data after treatment discontinuation and rescue therapy), unadjusted mean change in HbA1c at week 54 was -0.08% in the placebo/metformin arm compared to 0.25% in the sitagliptin arm (Table 39). Overall, the results may suggest superior efficacy of metformin compared to sitagliptin though definitive conclusions are limited due to missing week 54 data.

Table 31: Change from Baseline in HbA1c by Study Week in Trial P083 and 2-Study Pool using cLDA analysis for Treatment Effect Estimand

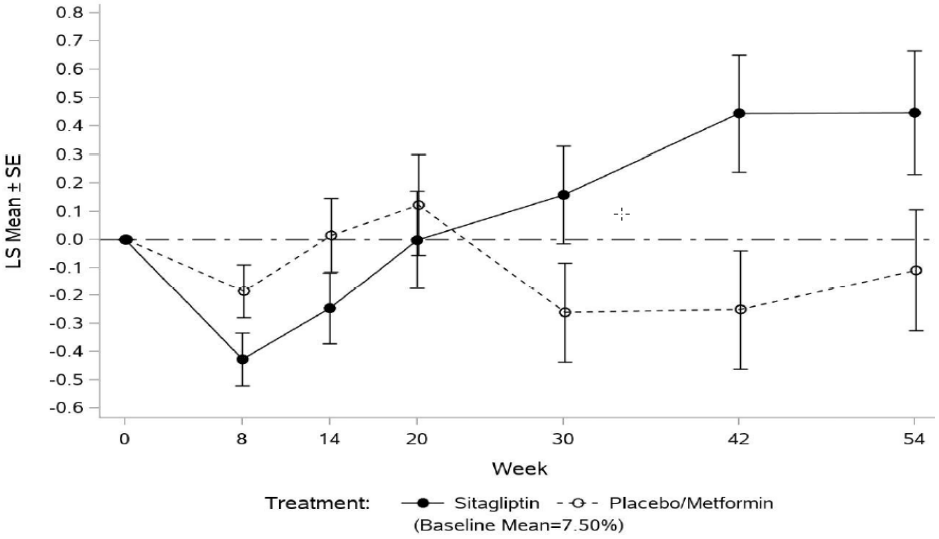
Trial	Arm	Change from Baseline HbA1c: LS Mean (95% CI)[1]			
		Week 6 or 8	Week 12 or 14	Week 20	Week 54
P083	Sitagliptin	-0.43 (-0.61, -0.24)	-0.25 (-0.49, 0.00)	-0.01 (-0.35, 0.34)	0.45 (0.01, 0.88)
	Placebo/Metformin	-0.16 (-0.34, 0.03)	0.05 (-0.20, 0.30)	0.18 (-0.17, 0.53)	-0.11 (-0.54, 0.32)
	Difference	-0.27 (-0.53, -0.01)*	-0.30 (-0.65, 0.06)	-0.19 (-0.68, 0.30)	
2-study pool (P170 + P289)	Sita/Met FDC	-0.84 (-1.06, -0.62)	-0.79 (-1.10, -0.48)	-0.58 (-0.94, -0.22)	0.35 (-0.48, 1.19)
	Metformin	-0.27 (-0.47, -0.07)	-0.28 (-0.57, 0.01)	-0.09 (-0.43, 0.26)	0.73 (0.48, 2)
	Difference	-0.57 (-0.81, -0.33)*	-0.51 (-0.86, -0.17)*	-0.49 (-0.90, -0.09)*	

HbA1c, hemoglobin A1c; LS, least squares; CI, confidence interval; cLDA, constrained longitudinal data analysis; Sita/Met FDC, fixed dose combination of sitagliptin and metformin
Treatment Effect estimand excludes data following rescue therapy or treatment discontinuation
[1] Based on cLDA model adjusting for treatment, time, baseline BMI percentile, insulin use (yes/no) at screening.
Trial P083: assessed HbA1c at week 8, 12, 20 and 54

Trial P170 and P289: assessed HbA1c at week 6, 12, 20 and 54. *p-value <0.05

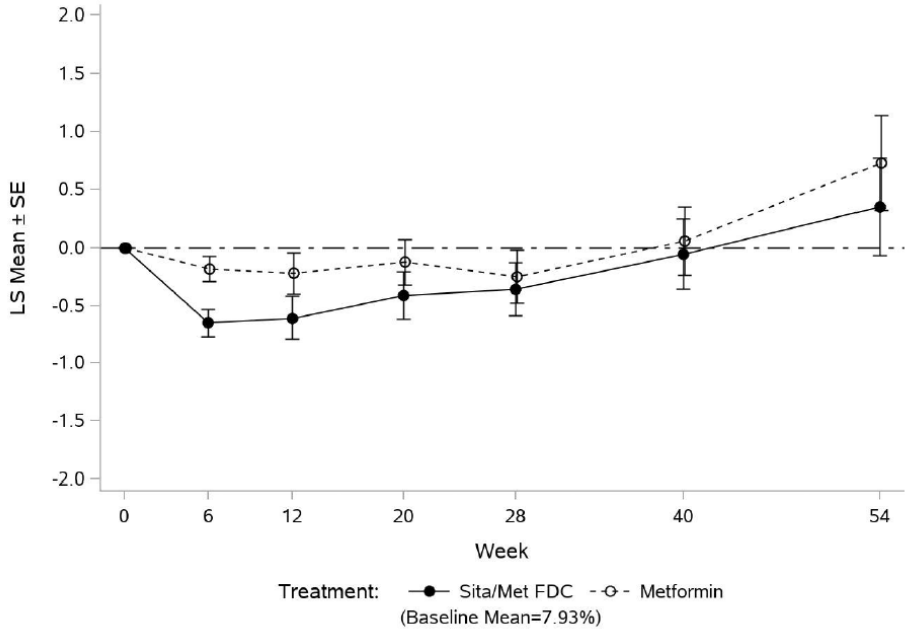
Source: reviewer generated based on CSR for P083 and summary of clinical efficacy for 2-study pool

Figure 7: Change from Baseline in HbA1c (%) from Weeks 0 to 54 in Trial P083 using cLDA analysis for Treatment Effect Estimand



Source: P083 CSR. cLDA= constrained longitudinal data analysis.

Figure 8: : Change from Baseline in HbA1c (%) from Weeks 0 to 54 in the 2-Study Pool (P170+P289) using cLDA analysis for Treatment Effect Estimand



Source: Summary of clinical efficacy for 2-study pool. cLDA= constrained longitudinal data analysis, Sita/Met FDC= fixed-dose combination of sitagliptin and metformin.

A weak initial pharmacologic effect of sitagliptin is also supported by data from the treatment policy estimand, displayed in Table 39 in Appendix 13.2. In all individual studies, and in the 2-study pool and in the 3- study pool, the mean change from baseline in HbA1c was numerically higher in the sitagliptin arm versus the comparator at weeks 6 or 8. The numerical treatment difference at week 6 or 8 ranged from -0.26 to -0.54%. However, in nearly all cases (except for trial P170), the numerical treatment difference declines over time. As previously mentioned, the numerical treatment difference here is lower than that seen in adult studies (-0.6 to -0.8%).

Reviewer Comment: In all trials, there appears to be a weak treatment effect of sitagliptin versus the comparator early on (weeks 6 to 8) but that effect diminishes by week 20 (as reflected by lack of statistical significance in the primary efficacy analysis). By week 54, HbA1c had increased above baseline in both the sitagliptin and placebo arms in the 2-study pool. Due to large percentage of missing data at week 54, differences in HbA1c change between treatment arms cannot be meaningfully compared. Overall, the results suggest a lack of durability of effect.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Trial P083 investigated the effect of sitagliptin monotherapy[84], while trials P170 and P289 evaluated sitagliptin as an add-on therapy to metformin. In both cases, efficacy was not demonstrated in the pre-specified primary efficacy analyses. Given that there were small numerical treatment differences favoring sitagliptin over placebo at 20 weeks that did not reach statistical significance, and since there was evidence of greater pharmacologic effect prior to week 20, I considered whether there may be some benefit to pediatric T2D patients outside of the trial population. Current understanding of pediatric T2D suggests that there may be two subgroups of patients, those who are able to achieve durable glycemic control on metformin monotherapy (also known as “responders”) and those who develop rapid disease progression (also known as “non-responders”)[85]. It appears that the sitagliptin pediatric trial population may have included more subjects at higher risk for rapid disease progression compared to other pediatric trials, therefore, it is possible this could have impacted the determination of efficacy.

An unanswered question is whether the efficacy outcome may have been different if the trials had studied the subgroup of “responder” patients with more durable glycemic control.

[84] Sitagliptin monotherapy was investigated in the majority of trial patients, however a minority were also treated with insulin. Subgroup analyses however did not demonstrate differential outcomes in insulin users or non-users.
[85] Zeitler P. Progress in understanding youth-onset type 2 diabetes in the United States: recent lessons from clinical trials. World J Pediatr. 2019;15(4):315-321. doi:10.1007/s12519-019-00247-1

However, given that these patients exhibit an excellent response to metformin monotherapy (typically achieving HbA1c well below glycemic treatment goals) there would not be an indication to seek additional treatment unless the patient was unable to tolerate metformin. It is unknown whether patients in the "responder" subgroup who are intolerant of metformin could benefit from sitagliptin therapy. The results of trial P083 do not support the use of sitagliptin monotherapy, although it is unclear what percentage of that population may have been in the "responder" subgroup (as the predictive factors for pediatric T2D disease progression have been most defined for patients who are on treatment with metformin, which was not applicable to the trial P083 population).

7.2.2. Other Relevant Benefits

Currently, metformin is the only approved oral antihyperglycemic agent for pediatric T2D. Other therapeutic options (liraglutide and insulin) involve subcutaneous injection, which can be a less convenient route of administration in pediatric patients. While having another oral therapeutic option may be more convenient, given the risk for rapid disease progression in the pediatric T2D population, other factors including magnitude of glycemic effect as well as durability of response are likely more important in the benefit-risk consideration.

7.3. Integrated Assessment of Effectiveness

The effectiveness of sitagliptin to improve glycemic control in pediatric patients with T2D was evaluated over three randomized and placebo-controlled trials. Trial P083 evaluated the effect of sitagliptin monotherapy versus placebo, while trials P170 and P289 evaluated sitagliptin as an add-on to maximally tolerated metformin therapy versus placebo. A minority of subjects in all three trials also received background insulin therapy. By definition, the trial population had uncontrolled T2D at study entry, with HbA1c $\geq$ 6.5% for those not on insulin or $\geq$7.0% for those on insulin, and therefore may have represented a population at higher risk for rapid disease progression[86]. The primary efficacy endpoint for all three trials was change from baseline in HbA1c at 20 weeks. The pre-specified primary efficacy analyses utilized an "intention-to-treat" population (including data obtained following glycemic rescue or treatment discontinuation) for trial P083 individually and for trials P170 and P289 combined (2-study pool).

Superiority of sitagliptin over placebo was not demonstrated in the pre-specified primary efficacy analyses. At week 20, primary analyses showed a small numerical treatment difference favoring sitagliptin over placebo that did not reach statistical significance. In trial P083, the change from baseline in HbA1c in subjects treated with sitagliptin was 0.06% compared to

[86] Zeitler P. Progress in understanding youth-onset type 2 diabetes in the United States: recent lessons from clinical trials. *World J Pediatr*. 2019;15(4):315-321. doi:10.1007/s12519-019-00247-1

0.23% in subjects treated with placebo (N=95), a treatment difference of -0.17% (95% CI: -0.62, 0.28). In the 2-study pool, the change from baseline in HbA1c in subjects treated with sitagliptin (N=107) was -0.23% compared to 0.09% in subjects treated with placebo (N=113), a treatment difference of -0.33% (95% CI: -0.70, 0.05).

In secondary analyses of the primary endpoint using a "per-protocol" population (excluding data obtained following rescue therapy or treatment discontinuation), a slightly larger numerical treatment difference of -0.49% favoring sitagliptin over placebo was seen in the 2-study pool that reached nominal statistical significance. However, for trial P083, the results of the "per-protocol" population analysis were no different than that of the "intention-to-treat" population. Summary results of trials P170 and P289 individually were discrepant. In trial P170, sitagliptin therapy was associated with a more favorable reduction in HbA1c at week 20, however no treatment difference was seen trial P289. No relevant differences in demographic or baseline characteristics were identified between the trials that could account for differential results. Rate of compliance with study treatment based on patient report exceeded 90% in all three trials. Results of subgroup analyses for the primary endpoint also did not reveal any differences.

A pharmacologic effect of sitagliptin was supported by several findings. The rate of rescue therapy through week 20 was higher in the placebo arm in all three trials. Secondary analyses at week 6 or 8 showed nominally statistically significant treatment differences between -0.2 to -0.5% favoring sitagliptin over placebo in trial P083 and the 2-study pool. A similar pattern was seen for trials P170 and P289 individually, both showing greater reduction in mean HbA1c in sitagliptin arm compared to placebo at time points prior to week 20. However, in all cases, numerical treatment differences declined over time, suggesting a lack of durability of response to sitagliptin therapy. By week 54, HbA1c had increased above baseline in both the sitagliptin and placebo arm in the 2-study pool, though a meaningful comparison between treatment arms could not be performed due to missing data. The initial imbalance in rescue therapy also disappeared, with similar proportions of subjects initiating rescue therapy from weeks 20 to 54 in both treatment arms in the 2-study pool.

In adult studies used to support efficacy, the treatment difference in HbA1c with sitagliptin compared to placebo ranged from -0.6% to -0.8% at 18 to 24 weeks. The difference in treatment response demonstrated in the adult and pediatric trials may be due to more rapid disease progression in pediatric T2D. While the trial population was generally similar to the population studied in pediatric trials of liraglutide, differences in study design may have accounted for enrollment of comparatively more patients at higher risk for rapid disease progression in the sitagliptin program. It is unknown whether a different treatment response would be demonstrated in the subgroup of pediatric patients with less rapid disease progression, however these patients are typically well-controlled on metformin monotherapy and therefore are unlikely to seek additional treatment.

Overall, I do not feel that the efficacy standard was met to support a pediatric indication for sitagliptin. Prespecified primary efficacy analyses of three randomized and controlled trials failed to demonstrate the superiority of sitagliptin over placebo. Although some nominal glycemic lowering was apparent, the magnitude of effect was small compared to available approved therapies[87], and there was a lack of durability in treatment response.

8. Review of Safety

8.1. Safety Review Approach

The safety population included all randomized subjects who received at least 1 dose of study medication in each of the three trials. As discussed in section 6.1.1, two treatment arms were eliminated from trial P083 as a result of amendment P083-05, however subjects previously randomized to these treatment arms completed the study based on the original assignment. Safety data for the 9 subjects in the eliminated metformin arm of trial P083 were not included for the purposes of this review. For the 5 subjects in the eliminated placebo/sitagliptin arm in trial P083, safety data was only considered from weeks 0 to 20, because the medication taken during weeks 20 to 54 (i.e., sitagliptin) would be an inappropriate control for the group randomized to receive sitagliptin for both phases of trial P083.

Safety endpoints of interest for the pediatric population were specified in the written request, based on known safety issues associated with sitagliptin (or other DPP-IV inhibitors) in adults. Safety endpoints and safety analyses were previously described in section 6.1.1.

The review of safety focuses on the entire 54-week trial period, including data from weeks 0 to 20 and data from weeks 0 to 54. For most safety endpoints, I primarily focused on the combined data reported in the 3-study pool, however I also reviewed any pertinent differences in safety findings among individual studies. Some safety outcomes were only assessed in trial P083 (e.g., bone age, dentition) and these are reported separately.

8.2. Review of the Safety Database

[87] The placebo-adjusted treatment effect for HbA1c change in pediatric trials of liraglutide was -1.06%. There is limited data on HbA1c lowering effect of metformin in pediatrics (labeled efficacy data includes only changes in fasting plasma glucose); results from one randomized controlled trial (*Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care. 2002;25(1):89-94*) suggest a treatment effect on HbA1c of -0.7% in the population studied.

8.2.1. Overall Exposure

The total size of the safety population was 410 subjects. Exposure to study treatment for subjects who participated in weeks 0 to 20 and weeks 0 to 54 are described in Table 32. The proportion of subjects participating in the trial declined over time. Additionally, some subjects in trial P170 were not eligible for participation in the extension study (weeks 20-54) due to its addition 3 years after the trial began.

Among subjects who participated during weeks 0 to 20, 202 subjects received sitagliptin and 208 subjects received the comparator. Among subjects who participated during weeks 0 to 54, 155 subjects received sitagliptin and 163 subjects received the comparator. Further details on the disposition of subjects treated in the individual studies are described in Table 17 (weeks 0 to 20) and in Table 18 (weeks 20 to 54).

Table 32: Exposure to Study Treatment, 3-study pool (P083 + P170 + P289)

	Sitagliptin	Comparator
Week 0 to 20		
Total subjects	202	208
Number of subjects with exposure:		
< 4 weeks	5	5
≥4 and < 8 weeks	6	2
≥8 and < 14 weeks	10	7
≥14 and < 20 weeks	89	97
≥20 weeks	92	97
Mean Duration (days)	127.8	131.5
Duration Range (days)	1; 161	2; 182
Week 0 to 54		
Total subjects	155	163
Number of subjects with exposure:		
< 4 weeks	1	1
≥4 and < 8 weeks	0	0
≥8 and < 14 weeks	2	5
≥14 and < 20 weeks	6	3
≥20 and < 30 weeks	9	14
≥30 and < 42 weeks	4	20

≥42 weeks	133	120
Mean Duration (days)	340.1	320.9
Duration Range (days)	10; 444	23; 418

8.2.2. Relevant characteristics of the safety population:

Demographic and baseline characteristics of the trial population have been previously discussed in section 6.1.2(summarized in Table 20 for the individual studies, and in Table 21 for the 3-study pool).

8.2.3. Adequacy of the safety database:

The trial size and safety endpoints were consistent with terms specified in the written request. Overall the safety database was considered adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

I did not identify any important data quality issues that impacted the safety review. I performed an assessment of random samples of subject level data of adverse events. No issues were identified. The submission was overall well organized.

8.3.2. Categorization of Adverse Events

All AEs were coded using MedDRA version 22.1.

An adverse event was defined as any untoward medical occurrence in a subject administered a product that does not necessarily have a causal relationship to treatment. Any worsening of a pre-existing condition temporally associated with the use of the product was also considered an AE. Expected changes resulting from normal growth and development were not considered AEs.

The safety population included all treated subjects. The Applicant did not specifically define "treatment-emergent" AEs in the protocol but did indicate that AEs were to be reported from the time of randomization (day 1 of treatment) until 14 days after discontinuation of treatment. The treatment-emergent flag in the datasets is consistent with this definition (i.e., AEs that occurred from time of randomization until 14 days post-treatment). In the ADAE datasets, AEs were categorized by severity (mild, moderate or severe), drug relatedness (yes/no), and whether they led to treatment discontinuation.

For my safety review, I considered all AEs in the ADAE dataset for the 3-study pool with a treatment-emergent flag. As discussed earlier, due to the protocol amendment resulting in the elimination of 2 treatment arms in trial P083, all AE data from subjects in the metformin arm and any phase B AE data from subjects in the placebo/sitagliptin arm in trial P083 were not included in this safety review or in the CSRs.

In the CSRs, the Applicant reported safety data separately for all subjects that participated in weeks 0 to 20 (i.e., phase A for P083 and P289 or the base study for P170) and for subjects that entered into the week 20 to 54 trial periods (i.e., phase B for P083 and P289 or the extension study for P170). However, any safety analyses that I conducted considered all safety data from weeks 0 to 54 among all treated subjects. These methodological differences may account for slight differences in the safety results reported in the CSR and in this review.

A serious adverse event was defined (consistent with ICH guidelines) as any AE that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly or birth defect, or any other important medical event. In addition, the Applicant considered any cancer events or events associated with an overdose to be considered serious. Categorization of hypoglycemia episodes are discussed further in section 8.4.4.

I performed a review of the investigators verbatim terms and correlation to preferred terms and did not identify any issues.

The written request specified that "all adverse events must be monitored until symptom resolution or until the condition stabilizes". Upon review of the submitted ADAE dataset for the 3-study pool[88], out of 1560 treatment-emergent AEs, the outcome of 15 AEs (representing ~ 1% of the total) was characterized as "unknown" while the outcomes for the remainder of the AEs were characterized as "not recovered/not resolved", "recovered/resolved", "recovered/resolved with sequelae". During the pediatric exclusivity board review, it was noted that while technically the sponsor did not meet the exact term of the written request, the term in this case was incomplete as it did not include all possible outcomes of an adverse event. Overall, it was determined that the Applicant fairly met the term of the written request given that an outcome was reported in 99% of treatment-emergent AEs.

Reviewer Comment: Overall, the definitions used to categorize adverse events were adequate and met the terms specified in the written request.

[88] Excluding AE data from subjects in the metformin arm and AE data from week 20-54 for subjects in the placebo/sitagliptin arm in trial P083

8.3.3. Routine Clinical Tests

Clinical tests performed for safety monitoring are described below in Table 33.

All laboratory tests were performed by the central laboratory with the exception of dipstick urinalysis, pregnancy test, CD26 assay. Laboratory tests obtained at screening[89], week 0, week 20 and week 54 visits were obtained in the fasting state.

Chemistry laboratory results were not masked but were flagged by the central laboratory if they met protocol-specified exclusion or discontinuation criteria (described in section 6.1.1). Any ALT or AST evaluations > 3 times upper limit of normal (ULN) were flagged by the central laboratory after randomization and subjects were retested.

Table 33: Clinical Tests for Safety monitoring, Sitagliptin Phase III Pediatric Trials

	Study visits where monitoring occurred	
Clinical test	**P170 and P289**	**P083**
Fasting Lipid analyses total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, non-HDL cholesterol	screening, week 0, week 20, week 54, R/D	
Hematology hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin concentration and mean corpuscular volume, white blood cell count and differential, platelet count, absolute neutrophil count	screening, week 0, week 12, week 20, week 28, week 54, R/D	screening, week 0, week 4, week 20, week 54, R/D
Serum chemistry sodium, potassium, chloride, bicarbonate, calcium, phosphorus, albumin, alkaline phosphatase (ALP), uric acid, serum protein, ALT, AST, creatine phosphokinase (CPK), total bilirubin, blood urea nitrogen, creatinine	screening, week 0, week 12, week 20, week 28, week 54, R/D	screening, week 0, week 4, week 20, week 30, week 42, week 54, R/D
Dipstick urinalysis[4]	screening, week 0, week 12[1], week 20, week 54, R/D	
Urine microalbumin/creatinine ratio[5]	week 0, week 12[1], week 20, week 54, R/D	
Urine pregnancy test[1]	at all in person study visits	
ECG	placebo run-in, week 20, week 54, R/D	
IGF-1 and IGF BP-3		week 0, week 20, week 54, R/D
CD26 assay CD26, CD3, CD8		week 0, week 20, week 54, R/D
Biochemical markers of bone turnover Urine N-terminal cross-linking telopeptide of bone		week 0, week 20, week 54, R/D

[89] If subject was not fasting at screening visit, fasting labs would be performed at the subsequent visit during the placebo-run in.

collagen (NTX) and creatinine, serum bone-specific alkaline phosphatase[3], calcitonin		
Bone age		week 0, week 20, week 54, R/D

R/D= rescue/discontinuation visit.
Week 0 measurements were performed at randomization (prior to treatment)
[1] week 12 urine testing only included in trial P170
[2] for females only
[3] ostase assay
[4] If urine dipstick was positive for blood, white blood cells, or protein, complete analysis was sent to central laboratory
[5] Urine microalbumin/creatinine ratio was not collected if subject was menstruating, had vigorously exercised within 24 hrs, or had fever or active infection within 48 hrs of the visit.

Source: Reviewer created, based on trial protocols

Visual oral examinations were also performed in trial P083 at the week 0 visit (prior to randomization), at week 20, week 54 and at rescue or discontinuation visits.
In all three trials, Tanner staging was monitored at randomization, week 20, week 54 and at rescue or discontinuation visits. Vital signs were monitored at all in person visits. Height, weight and waist circumference were monitored at screening, randomization, week 20, week 54 and at rescue or discontinuation visits.

Laboratory testing drawn for efficacy analyses included hemoglobin A1c, fasting plasma glucose, fasting insulin and pro-insulin in all three trials. Meal tolerance testing was also performed but only for some subjects in trial P083. Time points for efficacy assessments were previously described in section 6.1.1. Hemoglobin A1c was measured at a central laboratory using a NGSP certified assay, consistent with terms of the written request. Additional labs drawn at the screening visit for the purpose of eligibility included thyroid stimulating hormone, fasting C-peptide[90], and diabetes auto-antibody panel [glutamic acid decarboxylase 65 kDa autoantibody (GAD-65) and insulinoma associated protein 2 autoantibody (IA-2) antibody][91].

Reviewer Comment: Overall the safety assessments and frequency of monitoring were appropriate.

8.4. Safety Results

8.4.1. Deaths

There were 2 deaths reported in subjects who received sitagliptin in the clinical trials. Both deaths occurred more than 4 months after the last dose of study medication. Narratives for

[90] Drawn for all subjects in trial P083, but only for subjects with T2D duration < 2 years in trial P170 and P289.
[91] Diabetes autoantibody panel was drawn at screening for all subjects in trial P083, but only for subjects in India in trial P289. Diabetes autoantibody panel was not drawn at screening in trial P170.

subjects experiencing deaths are summarized below:

1. One death occurred in a subject in the Sitagliptin arm of trial P083. The subject was a 14-year-old female with a multi-racial background and Hispanic/Latino ethnicity. Duration of T2D was 21 days prior to first dose of study medication. Prior medical history included obesity, skin papilloma, hepatitis A, hepatic steatosis, irregular menses. The subject had completed both phase A and phase B of the study (entire 54-week period), with last dose of study medication administered on day 380 and study completion occurring on day 394. On day 381 (54-week visit), a CBC was notable for a high-normal total leukocyte count (10.9 x 10^9/L) and a low-normal neutrophil count (2.8 x 10^9/L). Review of prior hematologic testing during the study period did not reveal any clinically significant values. AEs recorded during the treatment period included seasonal rhinitis, bacteriuria, cold, back pain, shoulder pain, urinary tract infection, wart and drowsiness, all of which were categorized as mild. There were no serious adverse events during the treatment period. The subject was diagnosed with acute lymphoblastic leukemia (ALL) on day 451 (10 weeks after full study completion) after being admitted to the hospital with muscle pain and fever. ALL was recorded as a serious adverse event in the database. The subject was discharged from the hospital on day 544 with ongoing treatment for leukemia. The death occurred after the database lock on day 1094, a total of 714 days after last study medication dose. The cause of death was determined to be related to ALL and multi-organ dysfunction.

2. The second death occurred in a subject in the Sita/Met IR FDC arm of trial P170. The subject was a 15-year-old female of multi-racial background and Hispanic/Latino ethnicity. Subject had a T2D duration of 1 year 3 months prior to first dose of study medication. Prior medical history included drug hypersensitivity, hypothyroid goiter, gastritis, seasonal allergy and acanthosis nigricans. Subject was treated with cetirizine hydrochloride, levothyroxine, metformin (500 mg BID), ranitidine, omeprazole, dipyrone and sodium chloride prior to enrollment; treatment with cetirizine hydrochloride, levothyroxine sodium and omeprazole were continued during the study. The subject was randomized to receive Sita/Met IR FDC with total daily dose of 100 mg of sitagliptin and 1000 mg of metformin. This subject had participated in the base study only (because the extension study was unavailable), took the last dose of study medication on day 155 and completed the study on day 169. The subject had 12 AEs during the treatment period, which were categorized as mild or moderate, and included dysmenorrhea, hypoglycemia, nausea, vomiting, diarrhea, abdominal pain, worsening of gastritis, facial edema, drug hypersensitivity and acute tonsillitis (treated with penicillin). In total, the subject had 5 episodes of hypoglycemia during the treatment period (mostly asymptomatic, all related to delayed/missed/smaller meal or snack, and none requiring assistance). On day 277, the subject was found dead at home, 122 days after last dose of study medication. There were no reports of preceding clinical signs or

symptoms. Cause of death was determined via autopsy to be acute heart failure, due to arrhythmogenic right ventricular cardiomyopathy with fatty replacement and fibrosis of the right ventricle. ECGs performed during the study on day 1 and day 155 were normal.

Reviewer Comment: Based on my review, I do not believe that either of the 2 reported deaths (both occurring many months after study completion) were related to treatment with sitagliptin.

8.4.2. Serious Adverse Events

A total of 34 treatment-emergent serious adverse events (SAEs) occurring in 25 subjects were reported in the trials[92]. 10 SAEs occurred in 15 subjects in the sitagliptin arm, and 14 SAEs occurred in 10 subjects in the comparator arm.

Table 34 shows the number and proportion of subjects reporting specific SAEs by treatment group[93]. SAEs occurred at relatively low frequencies, mostly in no more than 1 subject in each treatment arm.

The two deaths discussed in section 8.4.1 are not included in Table 34, as one occurred following the database lock and both occurred more than 4 months after discontinuation of study medication and therefore are not considered treatment-emergent.

2 SAEs of acute lymphoblastic leukemia (ALL) occurred in the sitagliptin arm, both from trial P083. One subject who experienced ALL was previously discussed in section 8.4.1 (as this subject also experienced death). The ALL was recorded as an SAE due to being cancer but was not included in Table 34 as it occurred 10 weeks following study completion and thus was not treatment-emergent. Another SAE of ALL was diagnosed in a subject on day 348 of the trial (during phase B) and study medication was subsequently withdrawn; this SAE is also discussed in section 8.4.3 since it led to discontinuation of study medication. ALL is the most prevalent cancer among children and adolescents (representing 20% of all cancers diagnosed in persons < 20 years in the United States[94]), however, its occurrence in 2 subjects receiving sitagliptin treatment warrants further discussion. Given the relatively short duration of the trial and follow up, the exposure relative to the time of ALL diagnosis is likely too short to be consistent with a carcinogenic effect. Animal carcinogenicity studies conducted with sitagliptin had shown liver

[92] 15 SAEs from 14 subjects were reported in trial P083, 7 SAEs in 5 subjects were reported in trial P170 and 12 SAEs in 6 subjects were reported in trial P289.
[93] Subjects with duplicate SAEs based on dictionary-derived term were only counted once.
[94] Siegel DA, Henley SJ, Li J, Pollack LA, Van Dyne EA, White A. Rates and Trends of Pediatric Acute Lymphoblastic Leukemia — United States, 2001–2014. MMWR Morb Mortal Wkly Rep 2017;66:950–954.

tumors at approximately 20 times the human exposure in rats, but no increase in any tumors in mice up to 70 times the human exposure[79]. A metanalysis of human trials of DPP-IV inhibitors showed no statistically significant association with risk of cancer[95]. Postmarketing reports for sitagliptin have included pancreatic carcinoma, however a causal association has not been demonstrated[96].

SAEs related to hyperglycemia occurred in 3 (1.5%) subjects in the sitagliptin arm and in 1 (0.5%) subject in the comparator arm. One subject in the comparator arm had concurrent SAEs of diabetic ketoacidosis and acute kidney injury 38 days after last dose of study medication. These SAEs were not included in Table 34 as they were not treatment-emergent.

A review of the narratives for the SAEs in the sitagliptin arm was conducted. An SAE of diarrhea occurring following accidental overdose of study medication (total dose of 300 mg of sitagliptin and 3000 mg of metformin) was likely related to study treatment. I do not believe any of the other SAEs in the sitagliptin arm were related to study treatment.

Table 34: Subjects with Treatment-Emergent Serious Adverse Events

		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%

[95] Zhao M, Chen J, Yuan Y, et al. Dipeptidyl peptidase-4 inhibitors and cancer risk in patients with type 2 diabetes: a meta-analysis of randomized clinical trials [published correction appears in Sci Rep. 2017 Nov 24;7(1):16558]. Sci Rep. 2017;7(1):8273. Published 2017 Aug 15. doi:10.1038/s41598-017-07921-2

[96] Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment [published correction appears in N Engl J Med. 2014 Jun 5;370(23):2253]. N Engl J Med. 2014;370(9):794-797. doi:10.1056/NEJMp1314078

[97] Subject developed rash on face, chest, upper abdomen, back and upper limbs on day 37 of treatment leading to hospitalization and treatment with antihistamines. Treatment with study medication (Sita/Met IR FDC) was discontinued on day 46 but resumed on day 91. Type 1 hypersensitivity resolved on day 281. Subject remained in the study with last dose of study medication given on 371. Based on narrative, I do not believe the SAE was related to study medication.

	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%

[1] related to overdose of study medication. SAE of diarrhea occurred in a subject randomized to fixed dose combination of sitagliptin/metformin XR in trial P289. SAE of vomiting and abdominal pain upper occurred in the same subject randomized to metformin XR in trial P289.
SAEs included here are only those classified as treatment-emergent. See section 8.4.2 for description of other SAEs.

Source: Reviewer generated from ADAE dataset

Reviewer Comment: Serious adverse events occurred overall in low frequencies in both treatment arms. No clinically relevant imbalances in SAEs considered related to study treatment were noted.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuation criteria were previously discussed in section 6.1.1 and are considered reasonable.

No subjects dropped out of the study due to an adverse event. A total of 6 (2.9%) subjects in the comparator arm and 8 (4.0%) subjects in the sitagliptin arm discontinued study medication due to an adverse event that occurred either during weeks 0 to 20 or during weeks 20 to 54 of the trial.

AEs that led to discontinuation of study medication in the sitagliptin arm included acute lymphoblastic leukemia (1), ALT increase (3), abdominal pain (2), nausea (1)[98], vomiting (1), and

[98] AE of nausea and 1 AE of abdominal pain leading to discontinuation occurred in the same subject.

pruritis (1). AEs that lead to discontinuation of study medication in the comparator arm included ALT increase (4 subjects), hyperglycemia (1), and upper abdominal pain (1).

Following review of subject narratives, AEs leading to discontinuation of study medication in the sitagliptin arm that appeared related to treatment included pruritis, abdominal pain (occurring in 2 subjects), nausea and vomiting. Subjects in the sitagliptin arm who discontinued study medication due to increase in ALT had elevated ALT values prior to treatment (but below the exclusion criteria relating to ALT elevation). Based on the narrative review I felt that the ALT increase was unlikely related to sitagliptin treatment. The AE of ALL also appeared unrelated to study treatment (and was previously discussed in section 8.4.2 due to also being classified as an SAE).

Reviewer Comment: Slightly more subjects in the sitagliptin arm discontinued study medications due to an adverse event relative to the comparator arm (8 vs. 6 subjects). Adverse events leading to discontinuation of study medication in the sitagliptin arm that appeared related to study treatment included pruritis, abdominal pain, nausea, and vomiting. Except for abdominal pain (which occurred in 2 subjects), all other AEs related to sitagliptin treatment leading to discontinuation of study medication occurred in 1 subject only.

8.4.4. Significant Adverse Events (Hypoglycemia)

This section discusses hypoglycemia, see section 8.4.5 for discussion of adverse events by severity.

All episodes determined by the investigator to be hypoglycemia, and all glucose values $\leq$ 70 mg/dL were collected. Hypoglycemia episodes were categorized as severe (symptomatic hypoglycemia that required medical or non-medical assistance, whether or not such assistance was obtained), symptomatic (episode with clinical symptoms attributed to hypoglycemia, regardless of glucose level), asymptomatic (episode without symptoms but with measured plasma glucose $\leq$ 70 mg/dL), documented (< 54 mg/dL or $\leq$ 70 mg/dL), and hypoglycemia AEs.

Analyses of hypoglycemia conducted by the Applicant excluded data after initiation of glycemic rescue therapy. Separate hypoglycemia analyses were performed for subjects with and without background insulin therapy, for all subjects participating in weeks 0 to 20, and for all subjects participating in weeks 20 to 54. Table 35 shows hypoglycemia episodes in occurring from week 0 to week 54 in subjects that participated in the extension/phase B portion of the trials (weeks 20 to 54).

In subjects who were on background insulin, those receiving sitagliptin had higher frequency of hypoglycemia episodes, BG < 54 mg/dL, BG $\leq$ 70 mg/dL, symptomatic and asymptomatic hypoglycemia. Hypoglycemia AEs were also numerically quite higher in the sitagliptin arm in

subjects on background insulin, although the 95% confidence interval included 0.

In subjects who were not on background insulin, hypoglycemia episodes were overall higher, however no other categories had a 95% confidence interval that excluded 0. There were numerically more subjects with BG ≤ 70 mg/dL and asymptomatic hypoglycemia in the sitagliptin arm, however rates of severe hypoglycemia and BG < 54 mg/dL were similar between treatment arms.

Results of the hypoglycemia analysis for subjects participating only in weeks 0 to 20 of the trials were similar. In subjects not on background insulin rates of BG ≤ 70 mg/dL and asymptomatic hypoglycemia were similarly higher in the sitagliptin arm however in this case the 95% confidence interval excluded 0.

Table 35: Analysis of subjects with hypoglycemia episodes through week 54

	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).

Reviewer Comment: There appears to be a significantly increased risk of hypoglycemia in nearly all categories (BG < 54 mg/dL, BG ≤ 70 mg/dL, symptomatic and asymptomatic) in subjects treated with sitagliptin who were also on background insulin. In subjects who were not on background insulin, there was an increase in rates of hypoglycemia episodes categorized as BG ≤ 70 mg/dL or asymptomatic (and BG ≤ 70 mg/dL) but no difference in

episodes associated with BG <54 mg/dL. In all trial subjects, episodes of severe hypoglycemia were rare and there were no imbalances between treatment groups.

Based on current standards[11], hypoglycemia episodes associated with BG < 54 mg/dL or severe hypoglycemia (symptomatic hypoglycemia that required medical or non-medical assistance, whether or not such assistance was obtained) are considered most relevant in clinical trials and are typically used in product labeling. Using these updated definitions, there appears to be an increased risk of hypoglycemia (associated with BG < 54 mg/dL) in pediatric subjects only when sitagliptin is used with concomitant insulin therapy.

Current labeling of sitagliptin based on adult data includes a warning and precaution for increased hypoglycemia when sitagliptin is used with insulin or insulin secretagogues. However, it is important to note that adult clinical trials of sitagliptin were designed to collect only cases of symptomatic hypoglycemia, with or without concomitant BG measurement. Therefore, data on hypoglycemia episodes associated with BG < 54 mg/dL are not available in the adult clinical trials of sitagliptin. Due to differences in the definitions of hypoglycemia episodes captured in the pediatric and adult trials of sitagliptin, it is difficult to compare the hypoglycemia safety results.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In total, there were 1560 treatment-emergent AEs (TEAEs)[99] reported in the trial, including 846 in the sitagliptin arm and 714 in the comparator. 82.9% of TEAEs were mild, 15.2 % were moderate and 1.4% were severe[100]. TEAEs occurred in 161 subjects in the comparator arm, and in 156 subjects in the sitagliptin arm.

TEAEs by system organ class (SOC)
Table 36 shows the subjects with TEAEs categorized by SOC. In the comparator arm, there were a number of SOCs[101] with numerically higher frequency of subjects experiencing TEAEs versus the sitagliptin arm. In the sitagliptin arm, a numerically higher frequency of subjects experiencing TEAEs was seen in investigations (14.36 vs 13.94%), neoplasms benign, malignant

[99] For my analysis, I included all AEs in ADAE dataset for the 3-study pool with the treatment-emergent flag, excluding 9 subjects from the metformin arm of P083 and excluding phase B data from the 5 subjects in the placebo/metformin arm of P083. Note that safety analyses conducted by the Applicant were performed separately for all subjects that participated in weeks 0 to 20 (i.e., phase A for P083 and P289 or the base study for P170) and for subjects who entered the week 20 to 54 trial period (i.e., phase B for P083 and P289 or the extension study for P170). Methodological differences may account for slight numerical differences in my analyses compared to those conducted by the Applicant.
[100] 7 AEs (0.5%) did not have a severity classification
[101] gastrointestinal disorders, eye disorders, hepatobiliary disorders, infections and infestations, nervous system disorders, psychiatric disorders, renal and urinary disorders and skin and subcutaneous disorders

and unspecified (1.49 vs 0.96%), reproductive system and breast disorders (5.45 vs 2.40%) and in respiratory, thoracic and mediastinal disorders (11.39 vs 10.11%). Specific TEAEs driving these differences in SOC are discussed further below.

Table 36: Subjects with Treatment-Emergent AEs by System Organ Class

	Sitagliptin N=202		**Comparator N=208**	
System Organ Class	N	**% of total**	**N**	**% of total**
Blood and lymphatic system disorders	2	0.99%	3	1.44%
Congenital, familial and genetic disorders	1	0.50%	0	0.00%
Ear and labyrinth disorders	0	0.00%	3	1.44%
Endocrine disorders	0	0.00%	1	0.48%
Eye disorders	1	0.50%	6	2.88%
Gastrointestinal disorders	49	24.26%	63	30.29%
General disorders and administration site conditions	12	5.45%	17	8.17%
Hepatobiliary disorders	2	0.99%	5	2.40%
Immune system disorders	3	1.49%	0	0.00%
Infections and infestations	94	46.53%	109	52.40%
Injury, poisoning and procedural complications	12	5.94%	17	8.17%
Investigations	29	14.36%	29	13.94%
Metabolism and nutrition disorders	50	24.75%	55	26.44%
Musculoskeletal and connective tissue disorders	13	6.44%	14	6.73%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	1.49%	2	0.96%
Nervous system disorders	23	11.39%	34	16.35%
Psychiatric disorders	6	2.97%	12	5.77%
Renal and urinary disorders	5	2.48%	10	4.81%
Reproductive system and breast disorders	11	5.45%	5	2.40%
Respiratory, thoracic and mediastinal disorders	23	11.39%	21	10.10%
Skin and subcutaneous tissue disorders	15	7.43%	20	9.62%
Social circumstances	1	0.50%	0	0.00%
Vascular disorders	3	1.49%	3	1.44%
NOTE: Every subject counted single time for each applicable row and column				

Source: Reviewer generated based on ADAE dataset

Based on safety analyses conducted by the Applicant for the 3-study pool, there were no SOCs for which the 95% confidence interval for the between group difference excluded 0 through week 20. Through week 54, the only instance where the 95% confidence interval excluded 0

was in the case of eye disorders, which occurred at a lower incidence in the sitagliptin group versus the comparator group. Results of TEAEs by SOC in the individual studies were generally consistent with the 3-study pool.

Specific TEAEs
A numerically increased percentage of subjects with specific TEAEs were noted in the sitagliptin arm versus comparator for nasopharyngitis (11.4 vs. 7.2%), upper respiratory tract infections (12.9 vs. 10.1%), hypoglycemia (17.3 vs. 13.9%), AST increased (3.0 vs. 0.5%), cough (4.5 vs. 2.9%), creatinine renal clearance increased (3.0 vs. 0%), back pain (3.0 vs. 1.9%), dysmenorrhea (2.5 vs. 1.9%), blood glucose increased (4.5 vs. 1.9%), oropharyngeal pain (3.5 vs. 1.9%), gastritis (2.5 vs. 1.5%), asthma (2 vs. 0%) and epistaxis (2 vs. 0%). Headache occurred less frequently in the sitagliptin versus comparator arm (6.9 vs. 14.9% of subjects). For the remainder of specific TEAEs, numbers of subjects were similar between treatment arms or greater in the comparator group.

The Applicant also conducted safety analyses to determine specific TEAEs for which the 95% confidence interval for the between group difference excluded 0 through week 20 and through week 54. Based on these analyses, the incidences of AST increased, creatinine renal clearance increased, hypoglycemia and asthma through week 20; and the incidences of creatinine renal clearance increased and epistaxis through week 54 were higher in the sitagliptin arm versus the comparator arm. In the sitagliptin arm, all AEs of AST increase were mild or moderate in severity, and none led to discontinuation of study medication. Incidences of ALT increase were similar between groups. See section 8.4.6 for further discussion of changes in laboratory parameters. Increases in creatinine renal clearance may reflect hyperfiltration which can be seen early in the course of T2D, see section 8.5.5 for further discussion of renal-related adverse events. Hypoglycemia was previously discussed in section 8.4.4. Episodes of epistaxis in the sitagliptin arm were mild.

Reviewer Comment: Adverse reactions included in current labeling of sitagliptin based on occurring in >5% of subjects in adult clinical trials include upper respiratory tract infection, nasopharyngitis, headache and hypoglycemia (in subjects concurrently treated with insulin or insulin secretagogues). TEAEs occurring in >5% of subjects in the pediatric trials treated with sitagliptin were similar to known adult adverse reactions (i.e., nasopharyngitis, upper respiratory tract infection and hypoglycemia). When considering safety data only through week 20, small numerical differences were seen in several specific AEs, however many of these differences disappeared when considering safety data through week 54.

8.4.6. Laboratory Findings

Section 8.3.3 reviews the laboratory studies measured in the phase III trials.

Laboratory Values over Time

In the 3-study pool and among individual trials, there were no clinically meaningful differences in changes from baseline chemistry, hematology or lipids over time between the sitagliptin or comparator groups through week 20 or week 54. See section 8.5.5 for discussion of mean changes from baseline in serum creatinine.

Individual Subject Changes in Laboratory Values

The Applicant conducted analyses to compare differences in proportions of subjects meeting pre-defined laboratory criteria (PDLC) between treatment arms, including 95% confidence interval estimates. In the 3-study pool, similar proportions of subjects in both treatment arms met PDLC through week 20, however there were a few imbalances through week 54 where the 95% confidence interval for the difference versus comparator excluded 0:

1. A higher proportion of subjects in the sitagliptin arm exhibited one value of ALP > 1.5 x ULN (5.2 vs 1.2% in the comparator arm). This finding appears to have been completely driven by results in trial P083, in which 8 subjects in the sitagliptin arm versus 1 subject in the placebo/metformin arm had at least one ALP value > 1.5x ULN. No differences between treatment arms in PDLC for ALP were noted in trials P170 or P289. Upon review of ALP values for the aforementioned 8 subjects in the sitagliptin arm in trial P083, in nearly all cases the upper limit of the normal range for ALP declined over the course of the trial based on age-based reference ranges (and in at least 4 cases the decline in the upper limit of normal was by more than 50% from one time point to another). In the 8 cases noted, ALP values ranged from 144 to 388 IU/L (representing 1.6 to 2.08 x ULN for age). Review of the subject profiles did not reveal any AEs or other laboratory abnormalities suggestive of associated bone or hepatic disorders. ALP levels are known to rise during puberty but decline after age 12 in girls and after age 14 in boys[12]. In a number of the male subjects for whom this criterion was met, pubertal development appeared delayed compared to chronologic age. Pubertal delay may account for alkaline phosphatase levels above the reference range for age due to the pubertal rise in ALP occurring at an older age than would be expected.
2. A higher proportion of subjects in the sitagliptin arm had increased lymphocyte count > 20% and value > ULN (3.9 vs 0.6% in the comparator arm). Of the 6 subjects with this finding in the sitagliptin arm, the lymphocyte count ranged from 4.2 to 7.9 x 10^9 (representing 1.1 to 1.5 x ULN), and in 4 of 6 subjects the last value measured was below the ULN. A review of subject profiles revealed that in 2 cases, the rise in lymphocyte count corresponded to an ongoing AE for pharyngitis or lower respiratory tract infection. There were no differences between treatment arms between subjects meeting PDLCs for other hematologic parameters including leukocytes, neutrophils, platelets or hemoglobin. There were also no differences in changes from baseline in any

hematologic parameter, and no cases of AEs of increased lymphocyte count in either group.

Transaminases
In the Applicant's safety analyses based on 95% confidence intervals for the 3-study pool, trial P083 and trial P170, there were no imbalances between treatment arms in proportion of subjects meeting PDLC criteria for transaminases. In trial P289, more subjects in Sita/Met XR FDC group compared to the Met XR group had one value of ALT > 3 x ULN (5 vs 3 through phase A; 6 vs 3 through phase B). In the 3-study pool, 1 subject in each group had an ALT value >10 x ULN. The subject who met this criterion in the sitagliptin arm had a concurrent AE of hepatitis A, the subject who met this criterion in the comparator arm was withdrawn from the study due to transaminase elevation. No subjects in either treatment arm met biochemical criteria for drug-induced liver injury.

There were no clinically meaningful differences in transaminases over time between the sitagliptin and comparator arms in the 3-study pool or in individual trials. Mean change from baseline in in AST in the sitagliptin arm versus the comparator arm was 0.6 vs. 1.1 IU/L by week 20 and 0.3 vs. -1.9 IU/L by week 54. Mean change from baseline in ALT in the Sitagliptin arm versus the comparator arm was 0.8 vs 1.9 IU/L by week 20 and 1.0 vs -1.8 IU/L by week 54.

Other laboratory parameters
Findings related to markers of bone turnover and growth hormone dependent factors (IGF-1/IGF-BP3) are discussed in section 8.5.2 and 8.5.1 respectively.

The Applicant also conducted analyses to evaluate the change from baseline in the mean percent of peripheral blood mononuclear cells expressing CD26 (measured only in trial P083) through week 20 and through week 54[102]. At week 20, change from baseline in CD26 was 4.06% in the sitagliptin arm compared to -1.78% in the placebo/metformin arm. However, at week 54, there were no notable differences between treatment arms in change from baseline in CD26 (4.74% in the sitagliptin arm vs. 4.27% in the placebo/metformin arm).

Reviewer Comment: There were no clinically meaningful differences between treatment arms in changes in laboratory parameters from baseline to week 20 and to week 54. As discussed in section 8.4.5, there was an imbalance in TEAEs of AST increase through week 20 but not through week 54. However, numerical differences in mean changes from baseline in AST and

[102] In published literature, CD26 levels have been negatively associated with response to sitagliptin in adult subjects with T2D controlled inadequately by metformin and/or sulfonylurea therapy. (*Aso Y, Ozeki N, Terasawa T, et al. Serum level of soluble CD26/dipeptidyl peptidase-4 (DPP-4) predicts the response to sitagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes controlled inadequately by metformin and/or sulfonylurea. Transl Res. 2012;159(1):25-31)*

ALT were low and not clinically meaningful in both treatment arms.

There was an increased proportion of subjects in the sitagliptin arm with at least one value of ALP > 1.5 x ULN. This finding was driven by 8 subjects in the sitagliptin arm in trial P083 but was not seen in other individual trials. In the majority of cases, this finding appears to have been influenced by age-based reduction in ULN values over the course of the trial. There are no reports of DPP-IV inhibitors being associated with increase in ALP, and there were no signals in hepatic or bone-related TEAEs in the pediatric trials (see section 8.4.5).

There was also a slightly increased proportion of subjects in the sitagliptin arm (6 vs. 2 subjects in the comparator) with at least one increased lymphocyte count ≥20% and value > ULN, however in most cases lymphocyte values returned to normal by last measurement. No other imbalances hematologic laboratory parameters were noted between treatment groups. In adult clinical studies of sitagliptin, a small increase in neutrophils was observed that was not felt to be clinically relevant, however no changes in lymphocytes are discussed in product labeling.

Overall, I do not believe there are any laboratory findings suggestive of a new safety signal in pediatric patients.

8.4.7. Vital Signs and Measures of Adiposity

In the 3-study pool and in the individual studies, there were no notable differences between the sitagliptin and comparator groups in change over time in blood pressure, heart rate, weight, BMI, BMI percentile, waist circumference, waist circumference/height ratio and BMI percentile at week 20 and week 54. In adult clinical trials, no meaningful changes in vital signs were observed in subjects treated with sitagliptin.

8.4.8. Electrocardiograms (ECGs)

The number of subjects with ECG findings was evaluated in trial P083 only, based on an Applicant generated custom MedDRA query for ECG abnormalities. Through week 54, 4 subjects in the sitagliptin arm and 1 subject in the placebo/metformin arm had abnormal ECGs. ECG abnormalities in the sitagliptin arm included migration of pacemaker, incomplete right block, early repolarization, and sinus bradycardia. The subject with ECG abnormalities in the placebo/metformin arm had left ventricular hypertrophy. There were no ECG related TEAEs. In adult clinical trials, no meaningful changes in ECG (including QTc interval) were observed in subjects treated with sitagliptin. Overall, I do not believe that the ECG findings suggest a new safety signal.

8.4.9. QT

No QT studies were performed as part of the evaluation in the pediatric phase III studies.

8.4.10. Immunogenicity

Post-marketing reports of serious allergic and hypersensitivity reactions have been reported in patients using sitagliptin, including anaphylaxis, angioedema and exfoliative skin conditions such as Stephens-Johnson syndrome. This information is included under warnings and precautions in the product label. The written request specified that hypersensitivity reactions must be monitored during the pediatric phase III clinical trials of sitagliptin. The Applicant provided analyses of hypersensitivity AEs based on narrow standardized MedDRA query for hypersensitivity. In the 3-study pool, the incidences of hypersensitivity AEs were similar in sitagliptin and comparator groups through week 20 (3.5 vs 4.3%) and through week 54 (5.8 vs 8.6%). A subject in the sitagliptin arm experienced a SAE of type 1 hypersensitivity (previously discussed in section 8.4.2) which I reviewed and felt was unlikely related to study treatment[97]. Another subject in the comparator arm had an SAE of erythema nodosum. The incidences of hypersensitivity AEs were also similar between treatment arms in trial P083 and in the 2-study pool.

Reviewer Comment: No new immunogenicity safety signals were identified.

8.5. Analysis of Submission-Specific Safety Issues

The written request specified that the following adverse events must be monitored in the sitagliptin phase III pediatric trials: Linear growth and pubertal development, bone markers and calcitonin, dentition, gastrointestinal AEs, hypoglycemia, hypersensitivity reactions, infection by AE reporting, renal impairment by serum creatinine monitoring, and pancreatitis by AE reporting.

Hypoglycemia and hypersensitivity reactions were previously reviewed in in sections 8.4.4 and 8.4.10 respectively. The remainder of submission specific safety issues are discussed below.

8.5.1. Pubertal development and Linear Growth

Puberty:
Puberty was monitored by Tanner staging at baseline, week 20, week 54, and at rescue or discontinuation visits. Tanner staging was conducted for breast development in females, for genitalia in males, and for pubic hair development in both males and females. Given that pubic hair development reflects adrenarche rather than puberty, I focused my evaluation on Tanner stage assessment of breast development in females and genitalia development in males as most relevant for pubertal staging.

Table 37 displays the baseline Tanner stage for puberty (based on breast for females and genitalia for males) in the 3-study pool. Out of all subjects in the 3-study pool, majority were in puberty (Tanner stage II to V), with 1.3% of females and 4.4% of males being pre-pubertal (Tanner stage I). The most common baseline Tanner stage in females was Tanner stage V, with 73.5% of females estimated as having baseline Tanner stage IV or V. The most common baseline Tanner stage in males was Tanner stage IV, with 65.2% of males estimated as having baseline Tanner stage IV or V. There were no marked differences in baseline Tanner stage between treatment arms.

Table 37: Baseline Tanner Stage for Puberty in 3-study pool

Tanner stage for puberty at baseline[1]	Females			Males		
	Sitagliptin N=110	Comparator N=120	Total N=230	Sitagliptin N=70	Comparator N=65	Total N= 135
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
I	1 (0.9)	2 (1.7)	3 (1.3)	3 (4.3)	3 (4.6)	6 (4.4)
II	9 (8.2)	4 (3.3)	13 (5.7)	3 (4.3)	9 (13.8)	12 (8.9)
III	17 (15.5)	28 (23.3)	45 (19.6)	13 (18.6)	16 (24.6)	19 (21.5)
IV	35 (31.8)	42 (35.0)	77 (33.5)	30 (42.9)	21 (32.3)	51 (37.8)
V	47 (42.7)	45 (37.5)	92 (40.0)	21 (30.0)	16 (24.6)	37 (27.4)

[1] Tanner staging was based on breast for female and based on genitalia for male. This table does not include Tanner staging for pubic hair development.
NOTE: N indicates number of subjects with baseline Tanner stage. Not all treated subjects had baseline Tanner stage measurement.

Source: Reviewer generated based on ADTS dataset

In analyses conducted by the Applicant for the 3-study pool, changes over time in Tanner staging for breast development, genitalia and pubic hair were not notably different between the sitagliptin and comparator groups. Results in the individual studies were similar.

Bone age (BA):
Bone age was assessed only in trial P083, at baseline, week 20 and week 54. In analyses conducted by the Applicant, there was no difference in skeletal maturation (defined as change from baseline in bone age/change from baseline in chronologic age) between the sitagliptin and placebo/metformin arms. Given that most subjects had relatively advanced pubertal development at baseline, I conducted additional analyses on baseline bone age to better understand potential for further linear growth during the clinical trials. Based on analyses I conducted, the majority of females had nearly completed linear growth by the time of study entry (79.5 % had baseline BA $\geq$15 years, 83.0 % had baseline BA $\geq$14 years, with average baseline BA of 15.8 years). Around half of males had nearly completed linear growth by the

time of study entry (54.8 % with BA ≥16, 52.1% with BA ≥17, with average baseline BA of 16.2 years).

Reviewer Comment: Overall, there were no differences in changes from baseline in pubertal development or skeletal maturation between treatment arms. The majority of females had tanner stage V breast development at baseline, while the majority of males had Tanner stage IV to V genital development at baseline. Relatively few subjects had Tanner stage I pubertal development, consistent with the fact that pediatric T2D is most commonly coincides with onset of pubertal insulin resistance. The majority (close to 80%) of females and about half of males had nearly completed linear growth at baseline based on bone age estimation in trial P083. Baseline pubertal staging and bone age were similar to what was reported in Ellipse[103].

Linear growth and Growth-Hormone Dependent Factors:
In the majority of female subjects and in half of male subjects who had nearly fused epiphyses at baseline, significant changes in linear growth velocity would not be expected to occur over the course of the trial. Based on analyses conducted by the Applicant in the 3-study pool and in individual studies, no between-group differences were noted for changes from baseline in height, height SD score and growth velocity. Additionally, no differences were noted in changes from baseline in IGF-1 and IGF BP-3 in trial P083.

8.5.2. Markers of Bone turnover and Calcitonin

Markers of bone turnover and calcitonin were assessed in trial P083 at baseline, week 20 and week 54. Bone formation was assessed via bone-specific ALP and bone resorption was assessed by urine NTx/creatinine ratio. The Applicant conducted separate analyses by gender. **Changes from baseline in markers of bone turnover and calcitonin were not notably different between treatment arms through week 20 and through week 54.**

At week 54, mean change from baseline in bone specific alkaline phosphatase was -20.0 ug/dL in females and -16.2 ug/dL in males in the sitagliptin arm vs. -13.5 ug/dL in females and -15.0 ug/dL in males in the placebo/metformin arm. At week 54, mean change from baseline in urine NTx-creatinine ratio was -88.4 in females and -78.2 in males in the sitagliptin arm vs. -61.2 in females and -102.4 in males in the placebo/metformin arm. Markers of bone turnover are known to increase with the pubertal growth spurt and begin to decline towards adult levels in late puberty[13]. Given that the majority of subjects were in the later stages of puberty at baseline, it is not surprising that the markers of bone turnover declined over the course of the study. In contrast, calcitonin levels do not appear to change significantly during pubertal

[103] According to review by Dr. Tania Condarco for NDA 22341, in Ellipse, the majority of girls (~50-60% in each treatment arm) had Tanner V breast development at baseline, whereas the majority of boys were Tanner stage IV to V penis development at baseline. Additionally, the majority of the population had fused epiphyses at baseline.

development[14]. At week 54, mean change from baseline in calcitonin was -0.1 ng/L in females and 0.1 ng/L in males in the sitagliptin arm vs. -1.9 ng/L in females and -0.3 ng/L in males in the placebo/metformin arm.

8.5.3. Dentition

Dentition was assessed only in trial P083. As previously discussed, visual oral examination was performed at baseline, week 20 and week 54 in all trial subjects. In addition, a dental sub-study was added in amendment P083-12 to collect supplemental dental data (dental records from dental exam and dental photographs) for those who participated. Dental photographs for an individual subject per time point were reviewed in blinded random order by one independent reviewer. The same reviewer also reviewed dental and clinical data reports and visual oral examination reports for all subjects (including those who did not participate in the dental sub-study). A summary of subjects with worsening dental status at weeks 20 and at week 54 compared to baseline is shown in Table 38 below, as reported by the Applicant**. Overall, proportions of subjects with worsening dental status by defect category were similar between the sitagliptin and placebo/metformin groups.**

Table 38: Summary of Subjects with Worsening in Dental Status at Weeks 20 and at Weeks 54, Trial P083

	Sitagliptin		Placebo/Metformin	
	n	(%)	n	(%)
Week 20 vs. Baseline				
Subjects with dental data at Week 20	88		85	
Subjects with a DCDR Assessment by the independent reviewer	61	(69.3)	61	(71.8)
With one or more teeth with worsening[†]	32	(36.4)	25	(29.4)
Tooth fracture	5	(5.7)	5	(5.9)
Tooth discoloration	29	(33.0)	23	(27.1)
Enamel defect	7	(8.0)	4	(4.7)
With no teeth with worsening[‡]	1	(1.1)	1	(1.2)
Worsening could not be determined[§]	28	(31.8)	35	(41.2)
With one or more non-evaluable third molars excluded[‖]	2	(2.3)	0	(0.0)
Subjects without a DCDR Assessment[¶]	27	(30.7)	24	(28.2)
Week 54 vs. Baseline				

Subjects with dental data at Week 54[††]	79		78	
Subjects with a DCDR Assessment by the independent reviewer	59	(74.7)	59	(75.6)
With one or more teeth with worsening[†]	49	(62.0)	50	(64.1)
Tooth fracture	13	(16.5)	15	(19.2)
Tooth discoloration	45	(57.0)	48	(61.5)
Enamel defect	13	(16.5)	13	(16.7)
With no teeth with worsening[‡]	0	(0.0)	0	(0.0)
Worsening could not be determined[§]	10	(12.7)	9	(11.5)
With one or more non-evaluable third molars excluded[‖]	1	(1.3)	0	(0.0)
Subjects without a DCDR Assessment[¶]	20	(25.3)	19	(24.4)

[†]Includes subjects with worsening of tooth fracture, tooth discoloration, or enamel defect as determined by the independent reviewer.
[‡]Includes subjects for whom all available results fell into either of the following categories: (1) the independent reviewer was able to perform the worsening assessments and found no worsening, or (2) worsening assessments were not performed by the independent reviewer due to the absence of defects at the current time point.
[§]Includes subjects who had no worsening among teeth for which worsening could be assessed, but who had one or more teeth for which worsening could not be adequately assessed (e.g., due to braces, poor photographs, missing tooth).
[‖]Third molars = Teeth 1, 16, 17, and 32.
[¶]Subjects with only VOE dental data with no post-baseline defects reported by the investigator.
[††]Includes subjects with a prior worsening carried forward.
Worsening assessments are based upon the judgement of the independent reviewer, except where a worsening identified by the independent reviewer at Week 20 relative to baseline was no longer a worsening at Week 54 relative to baseline. In these cases, the Week 20 worsening was carried forward to Week 54.
DCDR = Dental Clinical and Data Review.

Source: P083 CSR 1, Applicant created table

8.5.4. Gastrointestinal Events

In pooled analyses of adult monotherapy studies of sitagliptin and add-on studies of sitagliptin to metformin and to pioglitazone, the incidence of selected gastrointestinal adverse reactions in subjects treated with sitagliptin were generally similar versus the comparator (abdominal pain: 2.3 vs 2.1%, nausea: 1.4 vs 0.6%, diarrhea 3.0 vs 2.3%)[79]. However, AEs of diarrhea and nausea are among the most commonly reported preferred terms in post-marketing safety data in adults (see section 8.9.1).

For the pediatric phase III trials, consistent with the written request, the Applicant conducted analyses of selected gastrointestinal AEs (for abdominal pain[104], diarrhea, nausea and vomiting) through week 20 and through week 54 to evaluate the difference in percentage of subjects experiencing these AEs in the sitagliptin versus the comparator arm. For all selected gastrointestinal AEs in the 3-study pool through week 20 and week 54, the 95% confidence

[104] Includes abdominal pain lower, abdominal pain upper, abdominal pain, abdominal discomfort and epigastric discomfort

interval for the difference in percentage between treatment arms included 0. Numerical percentages of subjects experiencing selected AEs were also similar between treatment arms. Results of analyses of selected gastrointestinal AEs were similar in trial P083 and in the 2-study pool.

As previously discussed in section 8.4.5, the percentage of subjects experiencing TEAEs in the gastrointestinal disorders SOC in the 3-study pool was numerically higher in the comparator arm compared to the sitagliptin arm (30.3 vs. 24.3 %). Additionally, the 95% confidence interval of the treatment arm difference in percentage of TEAEs in the gastrointestinal disorders SOC arms included 0. Among specific TEAEs, gastritis occurred in numerically higher frequency in the sitagliptin arm in the 3-study pool (2.5 vs 1.5%), however, based on Applicant-conducted analyses no gastrointestinal specific TEAEs had a 95% confidence interval excluding 0 for between group differences. Gastrointestinal AEs leading to discontinuation of study medication occurred in both treatment arms (see section 8.4.3). One subject in each treatment arm also had a gastrointestinal AE that was considered serious due to being associated with overdose of medication in trial P283 (see Table 34 in section 8.4.2).

Overall, I do not believe that there is evidence of a new safety signal related to gastrointestinal events.

8.5.5. Renal Impairment

Approved prescribing information for sitagliptin includes a warning and precaution regarding post-marketing reports of acute renal failure sometimes requiring dialysis[79]. Consistent with the terms of the written request, the Applicant monitored for renal impairment by serum creatinine in all three trials. As previously discussed in section 8.4.6, there were no clinically meaningful differences in changes from baseline chemistry (including serum creatinine) over time between the sitagliptin or comparator groups through week 20 or week 54. Mean change from baseline in serum creatinine was 0 mg/dL in both the sitagliptin and comparator arms through week 20 and through week 54. Among individual subjects with laboratory findings meeting PDLC, 3 subjects in the sitagliptin arm (2.0%) had a last value of creatinine > 0.3 mg/dL compared to 2 subjects in the comparator arm (1.2%) through week 54.

The percentage of subjects experiencing TEAEs in the renal and urinary disorders SOC[105] was numerically higher in the comparator arm versus the sitagliptin arm (Table 36). However, among the SOC of investigations, percentages of subjects with renal-related TEAEs reported in

[105] Included terms of acute kidney injury (1 subject in comparator arm only), diabetic nephropathy (2 subjects in sitagliptin arm, 1 subject in comparator arm), dysuria (2 subjects in comparator arm), glycosuria (1 subject in each arm), hematuria (1 subject in comparator arm), ketonuria (1 subject in each arm), microalbuminuria (1 subject in sitagliptin arm and 3 subjects in comparator arm), nephrolithiasis (1 subject in comparator arm), proteinuria (1 subject in sitagliptin arm and 4 subjects in comparator arm), ureterolithiasis (1 subject in sitagliptin arm)

were higher in the sitagliptin arm versus the comparator, including for albumin urine (1% vs. 0%), albumin urine present (1% vs. 0.5%), creatinine renal clearance increased (3% vs 0% in comparator), creatinine urine increased (1% vs 0%) and urine albumin/creatinine ratio increased (2% vs 0%). As discussed previously, increase in creatinine renal clearance may reflect hyperfiltration. Both hyperfiltration and urinary albumin to creatinine ratio are known early indicators of diabetic nephropathy, which may have accelerated onset in youth-onset T2D compared to adults (as previously discussed in section 2.1). In total, 10 subjects in the sitagliptin arm experienced renal-related investigation TEAEs[106] compared to 3 subjects in the comparator arm. I conducted a separate review of the 10 subject profiles in the sitagliptin arm with renal-related investigation TEAEs. In nearly all cases, estimated GFR was elevated at baseline suggesting that hyperfiltration may have been present prior to study entry. For those cases that involved increase in urine albumin/creatinine ratio during the study, the baseline value was often high-normal, and values measured during the study varied but did not indicate a progressive increase. Overall, I suspect these renal-related findings reflect underlying T2D disease progression rather than a drug-related AE.

1 subject in the comparator group had an SAE of acute kidney injury which occurred 38 days after the last dose of study medication concurrently with an SAE of diabetic ketoacidosis. No renal-related AEs led to discontinuation of study medication.

Reviewer Comment: There was no evidence of treatment differences in serum creatinine changes over time. An imbalance was seen in some investigations related to renal impairment including increase in creatinine renal clearance and in urine creatinine/albumin ratio occurring in more subjects in the sitagliptin versus comparator arms. Based on review of the subjects with these specific TEAEs, I believe these reflect underlying T2D disease progression rather than an adverse reaction. No cases of acute renal failure were reported in subjects treated with sitagliptin. Overall, I do not believe that there is evidence to suggest any new renal-related safety signal.

8.5.6. Infections

In the 3-study pool, there were no notable differences between the sitagliptin and comparator arms in the incidences of infections. The percentage of subjects with TEAEs in the SOC of infections and infestations was 46.5% in the sitagliptin arm and 52.4 % in the comparator arm. Among specific TEAEs, there was a numerically higher percentage of subjects in the sitagliptin arm versus comparator for nasopharyngitis (11.4 vs. 7.2%) and for upper respiratory tract infections (12.9 vs. 10.1%); both of these are currently included in prescribing information as adverse reactions occurring in $\geq$5% of adult subjects in clinical trials of sitagliptin. Urinary tract infections occurred in fewer subjects in the sitagliptin arm versus the comparator (3.5 vs. 7.2%).

[106] Several subjects experienced multiple renal investigation TEAEs

No infection-related AEs led to discontinuation of study medication. The number of SAEs related to infections and infestations were generally balanced between groups (Table 34).

Reviewer Comment: Among pediatric subjects treated with sitagliptin, similar adverse reactions related to infections were seen as compared to adults.

8.5.7. Pancreatitis

The product label for sitagliptin includes a warning and precaution regarding post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis[79]. Monitoring for pancreatitis was specified in the written request for the phase III pediatric studies. **No AEs of pancreatitis were reported in any of the phase III pediatric trials.**

8.6. Safety Analyses by Demographic Subgroups

A review of the percentage of subjects with TEAEs by SOC between treatment arms did not identify any difference in safety results by sex, age (<14 or ≥14 years), or race (white or non-white) (results not shown). Formal statistical assessments for interactions on safety signals have not been conducted given the overall small subgroup sizes.

8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies or clinical trials to evaluate a specific safety concern in this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in this submission

8.8.2. Human Reproduction and Pregnancy

A formal assessment of sitagliptin use during pregnancy and lactation was not included in this submission.

1 subject in the sitagliptin group in trial P170 and 2 subjects in the comparator group (in trials P083 and P170) became pregnant during the double-blind treatment period. The subject in the sitagliptin group was followed and delivered a baby with “no apparent abnormalities. Among the pregnancies in the comparator group, 1 resulted in a baby with macrosomia, but the other subject was lost to follow up so data on the pregnancy outcome is unknown.

8.8.3. Pediatrics and Assessment of Effects on Growth

These issues were previously discussed in section 8.5.1.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

A formal assessment of overdose, drug abuse potential, withdrawal and rebound was not included in this submission.

In total, overdose was reported in 3 subjects in trial P083 (2 in sitagliptin arm and 1 in placebo/metformin arm), in 1 subject in the metformin IR arm of trial P170, and in 1 subject in the Sita/Met XR arm of trial P289[107]. AEs related to overdose were reported only for the 1 subject in the metformin IR arm of trial P170 (abdominal pain upper and vomiting) and for the 1 subject in the Sita/Met XR arm of trial P289 (diarrhea). These AEs were classified as SAEs and were previously discussed in section 8.4.2. Following a review of the SAEs related to overdose in the sitagliptin arm, I concluded that the SAE of diarrhea occurring following accidental overdose of study medication in trial P289 (total dose of 300 mg of sitagliptin and 3000 mg of metformin) was likely related to study treatment. Overall, no new information regarding overdose was obtained from this submission.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As part of the evaluation of the postmarking setting, I reviewed the cumulative postmarketing exposure and safety data provided by the Applicant for sitagliptin through December 31st, 2019. I agree with the Applicant's assessment that over the total patient-year exposure to date (64.2 million years), no new safety concerns have been identified that are not already described in the product label for sitagliptin.

8.9.2. Expectations on Safety in the Postmarket Setting

This section is not relevant since a pediatric indication is not being granted.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The safety of sitagliptin was assessed across all three pediatric phase III studies, including a

[107] This subject had two events of overdose, but 1 event was reported in error.

total of 410 subjects. 202 subjects were treated with sitagliptin and 208 subjects were treated with a comparator (placebo/metformin, metformin IR or metformin XR) for up to 54 weeks.

There were 2 deaths in subjects receiving sitagliptin that were unrelated to study treatment, both occurring more than 4 months after discontinuation of the study medication. The frequency of SAEs was overall low, with no clinically relevant imbalances between treatment arms. Adverse events leading to study medication discontinuation in the sitagliptin arm included pruritis, abdominal pain, nausea, and vomiting.

An increased risk of hypoglycemia episodes involving BG < 54 mg/dL was found only when sitagliptin used with concomitant insulin therapy. Episodes of severe hypoglycemia were rare and not imbalanced between treatment groups. The sitagliptin product label includes a warning and precaution for increased risk of hypoglycemia when sitagliptin is used concurrently with insulin or insulin secretagogues, based on adult clinical trial data that captured episodes of symptomatic hypoglycemia (with or without concurrent BG measurement). Hypoglycemia episodes involving BG < 54 mg/dL were not captured in adult clinical studies.

Common adverse reactions occurring in >5% of subjects were similar to adult studies, and included nasopharyngitis, upper respiratory tract infection and hypoglycemia. No events of pancreatitis were reported in the pediatric studies, and there was no evidence of any new safety signal related to gastrointestinal events. Mean changes in laboratory parameters over time were similar between groups.

Most study participants were in the later stages of puberty at baseline. Nearly 80% of female subjects and half of male subjects had nearly completed linear growth at baseline, therefore effects on height were difficult to interpret. No treatment arm differences were identified in markers of bone turnover or dentition.

Overall, sitagliptin therapy appeared to be well tolerated in the pediatric trials with a safety profile that appeared generally similar to adults. Due to the differences in the definitions of hypoglycemia episodes in adult and pediatric trials, comparison of hypoglycemia safety results is limited. No new safety concerns were identified in the pediatric population.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this efficacy supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

We recommend the following major labeling changes for JANUVIA, JANUMET and JANUMET XR:

Section 1:
- Recommend removal of diabetic ketoacidosis from limitations of use[108]

Section 5:
- Recommend removal of the warning and precaution "there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction"[10]
- Recommend edits to the warning and precaution for acute renal failure and hypoglycemia to be consistent with updated labeling practices

Section 8.4:
- Recommend including the statement that safety and effectiveness of sitagliptin has not been established in pediatric patients
- Recommend including relevant details of the all three pediatric phase III trials including brief description of trial population studied and results of primary efficacy analyses that did not support efficacy indication[109].
- Consistent with labeling guidelines to avoid an implication of a pediatric indication, given that no new safety signals were identified in the pediatric population as compared to adults, no specific discussion of pediatric safety information is recommended.

Section 12.3:
- Recommend deletion of the statement "studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed", to avoid the implication that there is an indication.

For JANUMET and JANUMET XR, we recommend updates to sections 2, 4, 5 and 7 to reflect metformin labeling[110].

Updates to the medication guide for JANUVIA, JANUMET and JANUMET XR were also

[108] Consistent with updating labeling practices for oral antihyperglycemic products
[109] Trial P083 was a monotherapy study of sitagliptin, whereas trials P170 and P289 involved combination therapy of sitagliptin with metformin. While monotherapy glycemic control trials are typically not used to support indications for combination products, in this case an indication is not being granted for any of the products. Additionally, the slight numerical differences in outcomes between the studies are not felt to represent true differences between the products. Therefore, we recommend inclusion of results of all three trials in all three labels to provide a complete description of the data that did not support the efficacy indication.
[110] Changes include rewording of dosage and administration, removal of warning and precaution regarding "change in clinical status of patients with previously controlled type 2 diabetes" and regarding "loss of control of blood glucose", presentation of drug interactions in the form of a table, updates to patient counseling information.

recommended to be consistent with changes to the prescribing information and recent labeling practices.

10.2. Nonprescription Drug Labeling

This section is not applicable to this application

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no REMS recommended

12. Postmarketing Requirements and Commitments

No new post marketing requirement or commitment is recommended.

The following is postmarketing requirements (PMR) are considered fulfilled based on this submission:

1. NDA 021995/S47 JANUVIA (sitagliptin) Tablets:
PMR 224-1*: "Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive"*

2. NDA 022044/S48 JANUMET(sitagliptin and metformin) Tablets
PMR 856-1: *"Deferred pediatric study under PREA for the treatment of type 2 diabetes in pediatric patients ages 11 to 16, inclusive."*

3. NDA 202270/S22 JANUMET XR Tablets (sitagliptin and metformin extended release) tablets
PMR 1802-04: *"A 54-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of JANUMET XR versus metformin extended-release in pediatric patients who are inadequately controlled on metformin immediate release."*

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): P083

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 293		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): P170

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 176		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

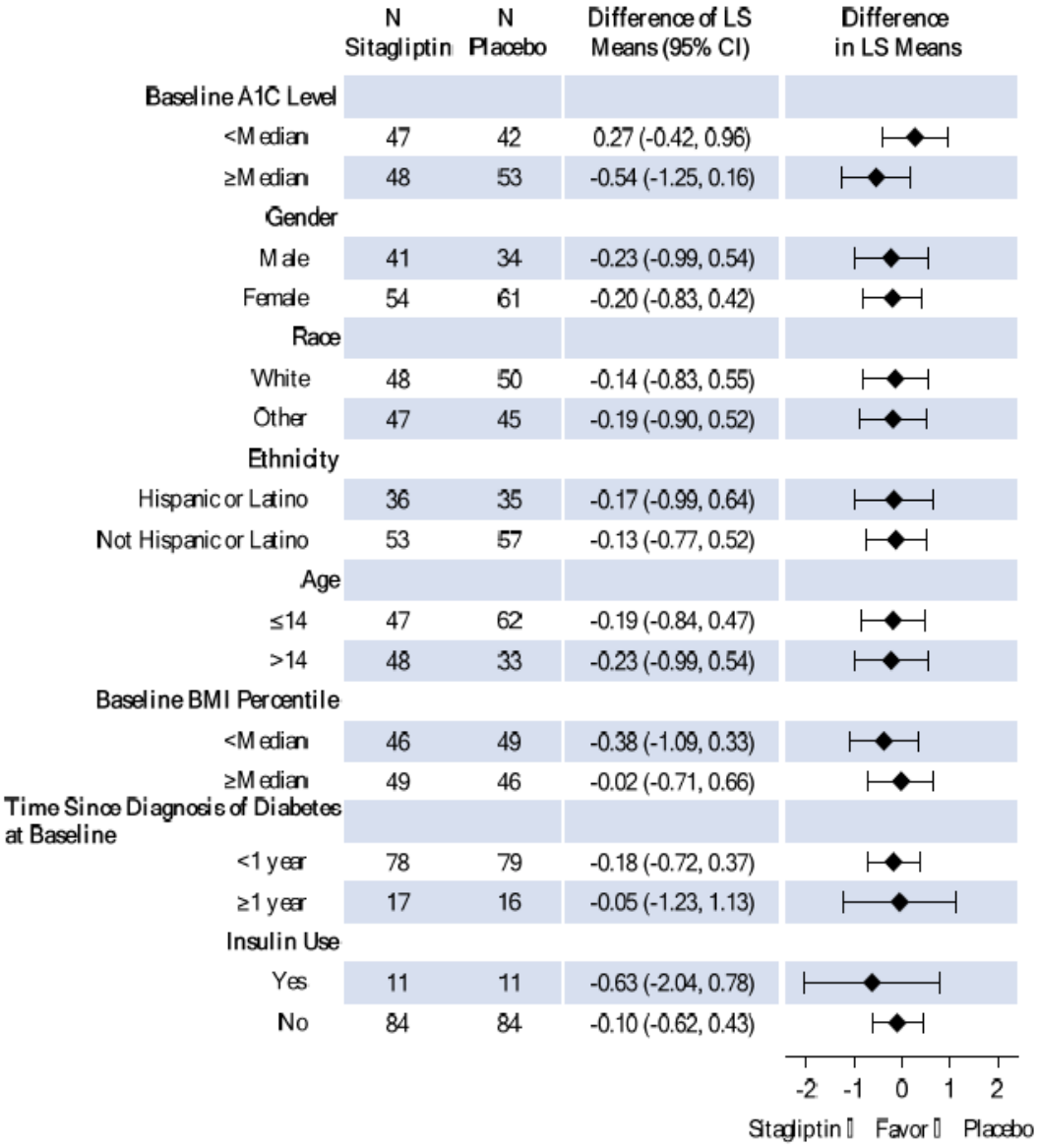
Covered Clinical Study (Name and/or Number): P289

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 240		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

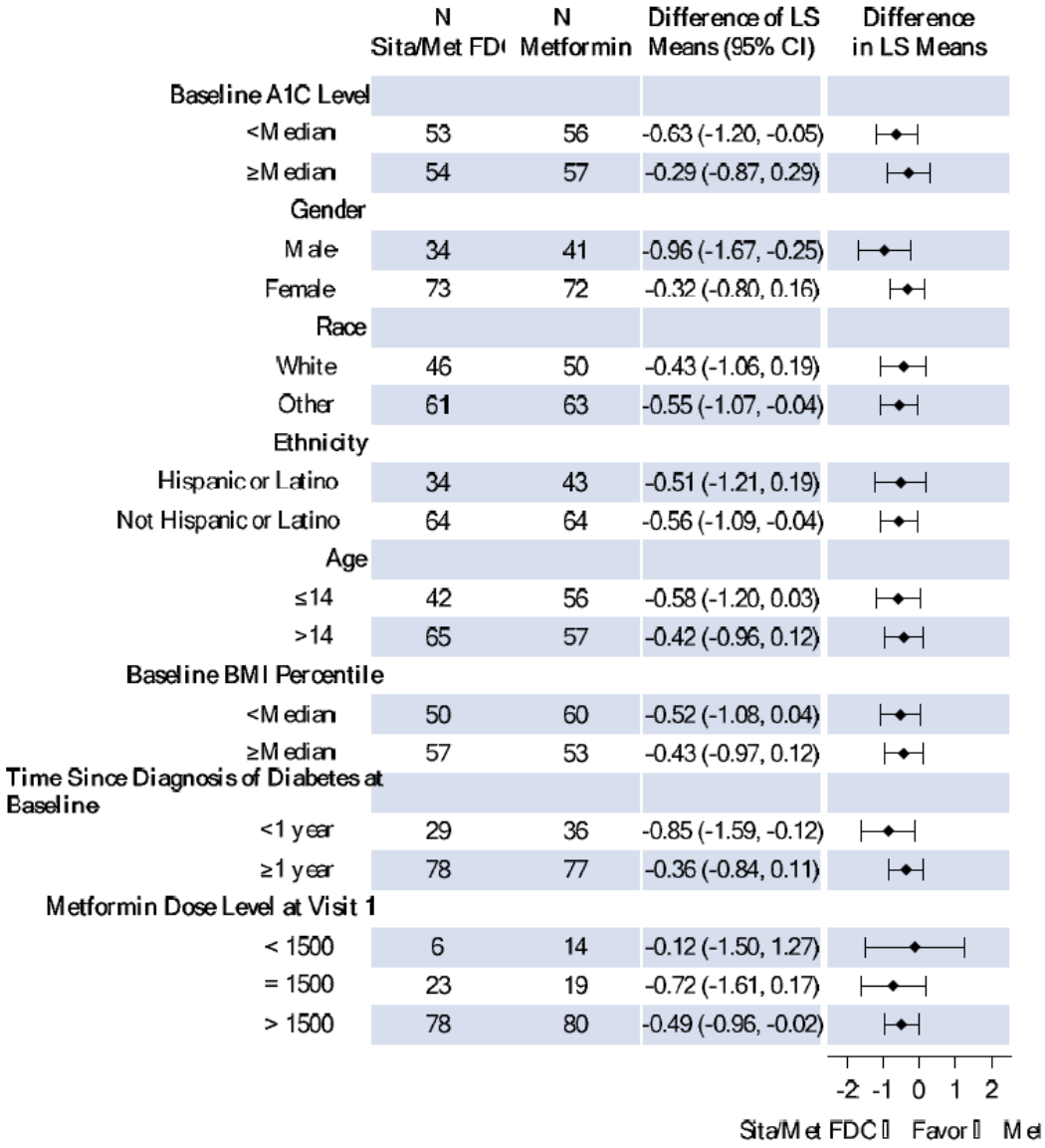
13.2. Additional Efficacy Analyses

Figure 9: Forest Plot showing change in HbA1c (%) from baseline to week 20, using repeated measures analysis of covariance subgroup analysis, TE estimand, Trial P083.



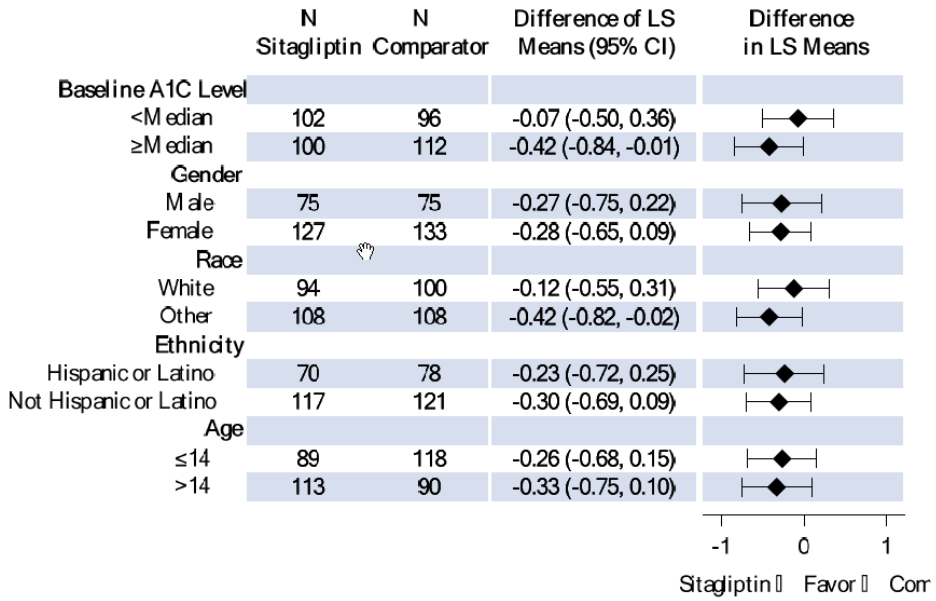
Source: CSR1 for P083, analysis provided by Applicant

Figure 10: Forest Plot showing change in HbA1c (%) from baseline to week 20, using repeated measures analysis of covariance subgroup analysis, TE estimand, 2-study pool (P170 + P289)



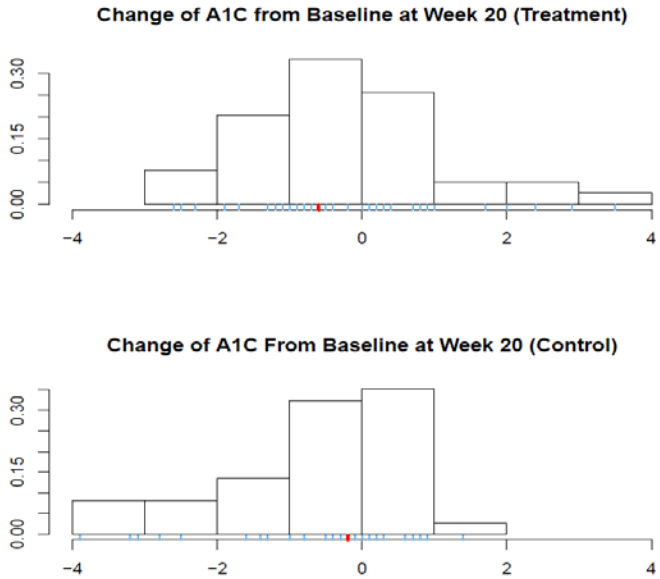
Source: Summary of clinical efficacy for 2-study pool, analysis provided by Applicant

Figure 11: Forest Plot showing change in HbA1c (%) from baseline to week 20 in subgroups, using analysis of covariance subgroup, TP estimand, 3-study pool (P083+ P170 + P289)



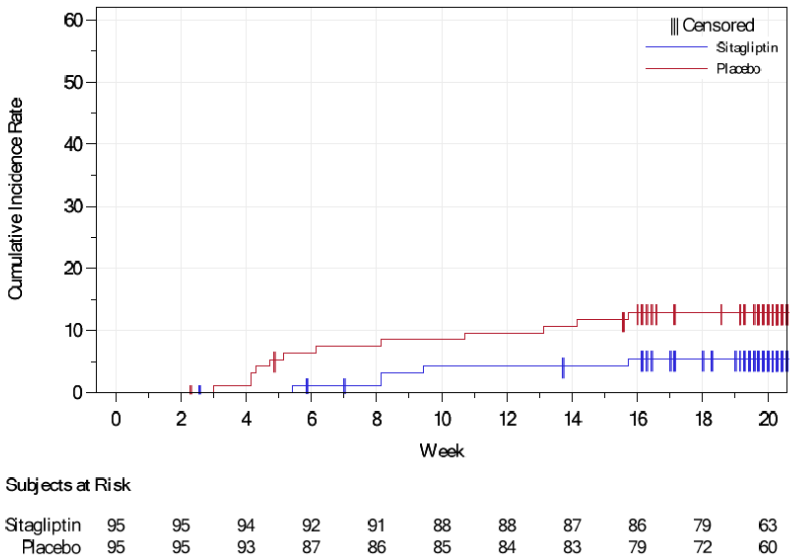
Source: Summary of clinical efficacy, 3-study pool

Figure 12: Trial P289, Treatment Effect Estimand: Distribution of Change in HbA1c from baseline at Week 20



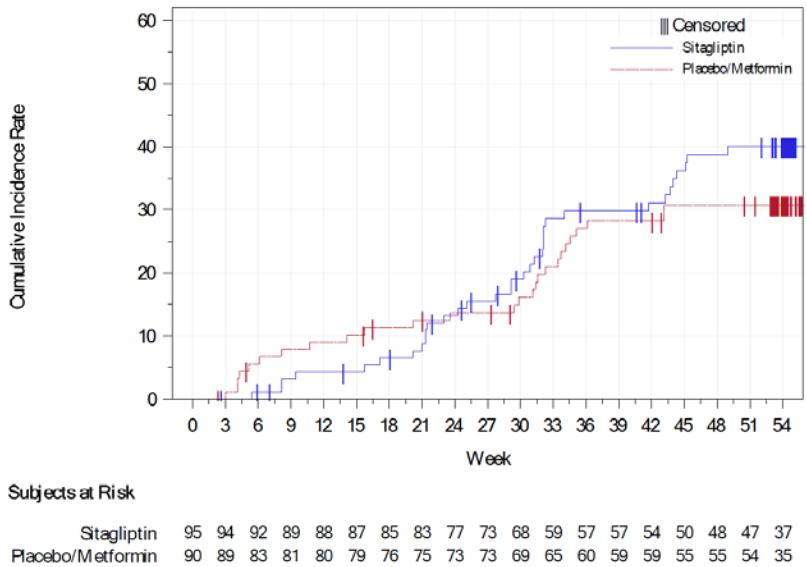
Treatment= Sita/Met XR; Control= Met XR
Source: Dr. Wenda Tu, Statistical Reviewer

Figure 13: Kaplan-Meier plot for Time to Initiation of Glycemic Rescue Therapy, Weeks 0 to 20, Treatment Effect Estimand, Trial P083



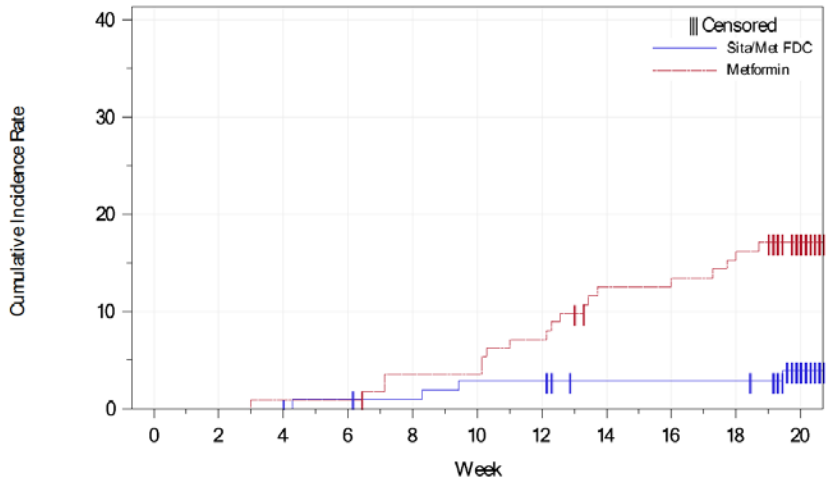
Source: P083 CSR

Figure 14: Kaplan-Meier plot for Time to Initiation of Glycemic Rescue Therapy, Weeks 0 to 54, Treatment Effect Estimand, Trial P083



Source: P083 CSR

Figure 15: Kaplan-Meier plot for Time to Initiation of Glycemic Rescue Therapy, Weeks 0 to 20, Treatment Effect Estimand, 2-Study Pool

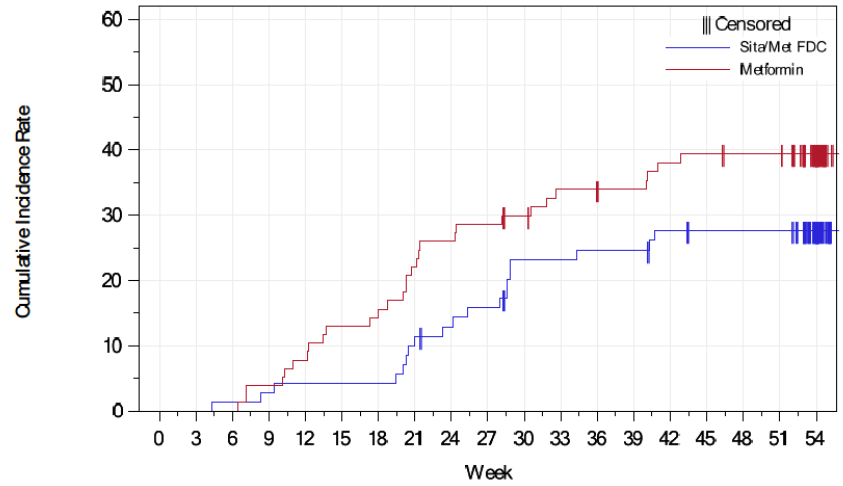


Subjects at Risk

Sita/Met FDC	107	107	107	105	104	102	102	99	99	99	81
Metformin	113	113	112	112	108	108	104	96	96	93	74

Source: Summary of clinical efficacy, 2-study pool

Figure 16: Kaplan-Meier plot for Time to Initiation of Glycemic Rescue Therapy, Weeks 0 to 54, Treatment Effect Estimand, 2-Study Pool



Subjects at Risk

Sita/Met FDC	70	70	69	68	67	67	67	63	60	58	52	52	51	51	48	47	47	47	32
Metformin	77	77	77	74	71	67	66	60	57	55	53	49	49	48	45	44	43	43	27

Source: Summary of clinical efficacy, 2-study pool

Table 39: Change from Baseline in HbA1c from Weeks 0 to 20 in Trials P083, P170, P289, 2-Study Pool and 3-Study Pool using Summary Statistics for Treatment Policy Estimand

Trial	Arm	Change from Baseline HbA1c %: Unadjusted Mean (SD)[1]		
		Week 6 or 8	Week 12 or 14	Week 20
P083	Sitagliptin	-0.40 (0.66)	-0.26 (1.09)	-0.15 (1.56)
	Placebo	-0.14 (1.03)	0.01 (1.42)	0.03 (1.46)
P170	Sita/Met IR FDC	-0.93 (0.86)	-0.97 (1.16)	-0.91 (1.34)
	Met IR	-0.39 (1.03)	-0.31 (1.44)	-0.29 (1.62)
P289	Sita/Met XR FDC	-0.60 (0.79)	-0.40 (1.21)	-0.21 (1.38)
	Met XR	-0.15 (0.89)	-0.23 (1.49)	-0.21 (1.50)
2-study pool (P170+P289)	Sita/Met FDC	-0.79 (0.84)	-0.73 (1.21)	-0.62 (1.40)
	Metformin	-0.23 (097)	-0.27 (1.46)	-0.25 (1.56)
3 study pool (P083+P170+P289)	Sitagliptin	-0.62 (0.79)	-0.51 (1.17)	-0.40 (1.49)
	Comparator	-0.19 (1.00)	-0.15 (1.45)	-0.13 (1.52)

HbA1c, hemoglobin A1c; Sita/Met IR FDC, fixed dose combination of sitagliptin and metformin immediate release; Sita/Met XR FDC, fixed dose combination of sitagliptin and metformin extended release; Sita/Met FDC, fixed dose combination of sitagliptin and metformin; Met IR, metformin immediate release; Met XR, metformin extended release

[1] Treatment Policy estimand: All post-baseline data was included regardless of treatment discontinuation or rescue therapy

Trial P083: assessed HbA1c at week 8, 12, 20 and 54

Trial P170 and P289: assessed HbA1c at week 6, 12, 20 and 54.

Source: Reviewer generated, based on CSRs for P083, P170, P289 and summaries of clinical efficacy for 2-study pool and 3-study pool

13.1. References

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