Amsterdam, 27 March 2025
EMADOC-1700519818-1838618
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xelevia

INN: Sitagliptin

Xelevia Procedure number.: EMA/PAM/0000244508

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 8 January 2025, the MAH submitted a completed paediatric study for Januvia and duplicates (Xelevia, Tesavel and Ristaben), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Sitagliptin is a selective DPP-4 inhibitor. DPP-4 inhibitors improve glycemic control by preventing the enzymatic degradation and inactivation of GLP-1 and GIP, the major incretins involved in glucose homeostasis. These hormones lower glucose levels through enhancement of insulin biosynthesis and release when blood glucose levels are elevated, and through suppression of glucagon.

Indication
Januvia was approved in the EU in 2007 for the following indications:

For adult patients with type 2 diabetes mellitus, Januvia is indicated to improve glycaemic control:
as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARg) agonist (i.e. a thiazolidinedione) when use of a PPARg agonist is appropriate and when diet and exercise plus the PPARg agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARg agonist and metformin when use of a PPARg agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

Sitagliptin is not registered for paediatric patients with T2DM due to lack of efficacy in patients aged 10 to 17 years of age and has not been studied in patients under 10 years of age, and no indication is sought for this population.

Clinical development program
The current report concerns a submission in accordance with the requirements of Article 46 of Regulation No. 1901/2006 of the European Commission and includes results of the MK-0431 Protocol

351 study (hereinafter referred to as P351), a noninterventional follow-up study of participants from the MK-0431 Protocol 083 study (hereinafter referred to as P083). P083 was a 54-week, 2-part (Phases A and B), multinational, placebo-controlled, double-blind, parallel-group study assessing the safety and efficacy of sitagliptin once daily in pediatric participants (aged 10 to 17 years, inclusive at initiation of therapy) with T2DM and inadequate glycemic control.

P351 was designed to provide an up to 5-year noninterventional observational assessment of the safety of participants who participated in P083. In P083, participants were randomized to receive sitagliptin ± insulin (in Phases A and B), metformin (in Phases A and B), placebo in Phase A followed by sitagliptin in Phase B (placebo/sitagliptin) or placebo ± insulin in Phase A followed by metformin in Phase B (placebo ± insulin/metformin).

P351 was conducted at the request of the PDCO of the EMA as a required component of the PIP (EMEA-C-00470-PIP01-08-M11).provides an overview of each clinical trial in the sitagliptin pediatric program, including P351. P351 is the last Sponsor-planned study in the clinical development program of sitagliptin.

Table 1 provides an overview of each clinical trial in the sitagliptin pediatric program, including P351. P351 is the last Sponsor-planned study in the clinical development program of sitagliptin.

Regulatory guidance and advice

No scientific advice was received from the EU regulatory authorities regarding the conduct of this noninterventional study. This follow-up study has been conducted at the request of the PDCO of the EMA and was part of the 28-FEB-2020 positive opinion of the PDCO in compliance with the sitagliptin PIP EMEA-C-000470-PIP01-08-M11 (EMA/PDCO/98616/2020).

Table 1: Overview of the Sitagliptin Pediatric Clinical Development Program

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	**Design**	**Number of Participants by Intervention Group**	**Study Population (N)**	**Primary Endpoints/Results**
Phase 1 Study				
MK-0431-081 (completed-previously submitted) 7 sites (1 country)	Randomized, double-blind, placebo-controlled, multiple panel, single-dose	Sitagliptin 50 mg: N=9 Sitagliptin 100 mg: N=9 Sitagliptin 200 mg: N=8 Placebo: N=9	Gender: 11 males and 24 females Mean age (years): 14.3 Percentage 10 to <14 years old: 34.3 Percentage 14 to <18 years old: 65.7 Adolescent participants with T2DM, 10 to 17 years old.	The 90% CI (0.66, 1.01) of the GMR (adolescent/adult) for dose-normalized (to 100 mg) sitagliptin $AUC_{0-\infty}$ was contained within the prespecified bounds, (0.50, 2.00), supporting the primary hypothesis that the plasma $AUC_{0-\infty}$ following single oral doses of sitagliptin in adolescents with T2DM and adults with T2DM is similar. Single doses of sitagliptin up to 200 mg were generally well tolerated in 10- to 17-year-old male and female participants with T2DM.
Phase 3 Studies				
MK-0431-083 (completed-previously submitted) 213 sites (42 countries)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sitagliptin in pediatric participants (aged 10 to 17 years) with T2DM and inadequate glycemic control (±insulin). The 54-week treatment period consisted of a 20-week Phase A and 34-week Phase B.	Sitagliptin 100 mg/day: N=95 Placebo/Metformin: N=90 Placebo/Sitagliptin: N=5 Metformin: N=9 Participants randomized to placebo/metformin or placebo/sitagliptin switched (in a blinded manner) to their predefined active therapy (metformin or sitagliptin) in Phase B (or during Phase A for participants who met glycemic rescue criteria).	Gender: 75 males and 115 females Mean age (years): 14.0 Percentage ≥10 and <15 years old: 57.4 Percentage ≥15 and <18 years old: 42.6 Mean A1C (%): 7.5 Mean BMI (kg/m^2): 32.3 Participants on background insulin (N): 22 This column excludes data from the 9 participants in the metformin group.	Change from baseline in A1C at Week 20 The effect of treatment with sitagliptin was not significantly different from that of placebo on A1C reduction at Week 20 (placebo-adjusted difference of -0.19%, p=0.448).
MK-0431A-170 (completed-previously submitted) 100 sites (25 countries)	Multicenter, randomized, double-blind, parallel-group study that compared the efficacy and safety of the addition of sitagliptin (as the Sita/Met IR FDC) with the addition of placebo to metformin IR (±insulin) in pediatric participants (aged 10 to 17 years) with T2DM and inadequate glycemic control. The 54-week treatment period consisted of a	<u>Base Study</u>: Sita/Met IR FDC: N=62 Metformin IR: N=62 <u>Extension Study</u>: Sita/Met IR FDC: N=28 Metformin IR: N=30	<u>Base Study Population</u>: Gender: 43 males and 81 females Mean age (years): 14.1 Percentage ≥10 and <15 years old: 53.2 Percentage ≥15 and <18 years old: 46.8 Mean A1C (%): 8.1 Mean BMI (kg/m^2): 31.1 Participants on background insulin (N): 16 <u>Subset Who Entered the Extension Study</u>: Gender: 23 males and 35 females	Change from baseline in A1C at Week 20. The observed mean (SD) reduction from baseline in A1C at Week 20 was greater in the Sita/Met IR FDC group (-0.90 [1.34]) compared with the Metformin IR group (-0.33 [1.53]).

Study Number (Status) [CTD Location] **Number of Study Sites (Countries)**	**Design**	**Number of Participants by Intervention Group**	**Study Population (N)**	**Primary Endpoints/Results**
	20-week base study and a 34-week extension study. Participants who completed the base study before the extension study was available (N=43) were not eligible to enter the extension study.		Mean age (years): 14.3 Percentage ≥10 and <15 years: 53.4 Percentage ≥15 and <18 years old: 46.6 Mean A1C (%): 7.9 Mean BMI (kg/m^2): 31.8 Participants on background insulin (N): 9	
MK-0431A-289 (completed-previously submitted) 139 sites (31 countries)	Multicenter, randomized, double-blind, parallel-group study that compared the efficacy and safety of the addition of sitagliptin (as the Sita/Met XR FDC) with the addition of placebo to metformin XR (±insulin) in pediatric participants (aged 10 to 17 years) with T2DM and inadequate glycemic control The 54-week treatment period consisted of a 20-week Phase A and 34-week Phase B.	Sita/Met XR FDC: N=45 Metformin XR: N=51	Gender: 32 males and 64 females Mean age (years): 14.8 Percentage ≥10 and <15 years old: 33.3 Percentage ≥15 and <18 years old: 66.7 Mean A1C (%): 7.9 Mean BMI (kg/m^2): 30.6 Participants on background insulin (N): 17	Change from baseline in A1C at Week 20. The observed mean (SD) reduction from baseline in A1C at Week 20 was smaller in the Sita/Met XR FDC group (-0.19 [1.40]) compared with the Metformin XR group (-0.54 [1.30]).
Phase 4 Study				
MK-0431-351 (completed) [Ref. 5.3.5.1: P351MK0431] 39 sites (16 countries)	Multicenter, safety, observational, noninterventional, multinational, 5-year follow-up study	Exposed to Sitagliptin in P083: N=36 Not Exposed in P083: N=44	Gender: 29 males and 51 females Mean age (years): 14.9 Percentage ≥10 and <15 years old: 40.0 Percentage ≥15 and <18 years old: 45.0 Percentage ≥18 years old: 15.0 Mean BMI at Year 0 of P351 (kg/m^2): 31.1	Safety: AEs, BMI, height, body weight, Tanner staging (pubertal progression), growth velocity, blood pressure, and heart rate. Safety was generally similar in participants exposed to sitagliptin and those not exposed in P083.

A1C=hemoglobin A1c; AE=adverse event; $AUC_{0-\infty}$=predicted area under the plasma concentration vs time curve from time after last dose zero extrapolated to infinity; BMI=body mass index; CI=confidence interval; CTD=Common Technical Document; FDC=fixed-dose combination; GMR=geometric mean ratio; IR=immediate release; Met=metformin; SD=standard deviation; Sita=sitagliptin; T2DM=type 2 diabetes mellitus; XR=extended release

2.2. Information on the pharmaceutical formulation used in the study

Not applicable in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study P351: A Five-year, Observational, Non-interventional Follow-up to: 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

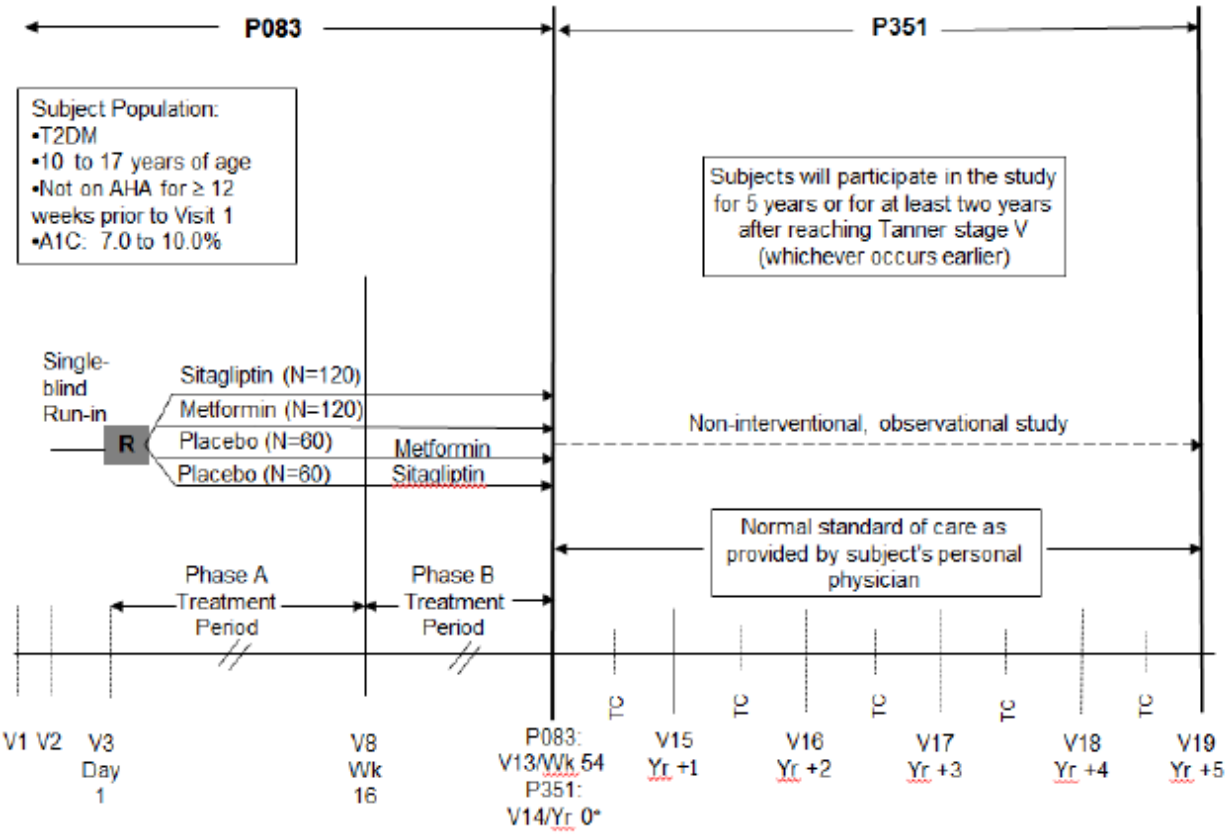
2.3.2. Clinical study

Study P351: A Five-year, Observational, Non-interventional Follow-up to: 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

Description

P351 was an observational, noninterventional, multisite, follow-up study to provide an up to 5-year observational assessment of safety for participants with T2DM who were 10 to 17 years of age (inclusive) when randomized to therapy in the MK-0431-083 (hereinafter referred to as P083).
P083 is a multinational, placebo- and metformin-controlled, double-blind, parallel-group study of approximately 56 weeks' duration. Subjects are randomized to receive sitagliptin and metformin-placebo, metformin and sitagliptin-placebo, or the sequence of placebo (for the 16-week Phase A period) followed by metformin (for either rescue or the 38-week Phase B period, whichever came first), or the sequence of placebo (for the 16-week Phase A period) followed by sitagliptin (for either rescue or the 38-week Phase B period, whichever comes first). P083 will be completed at Visit 13/Week 54. A telephone contact is performed 14 days after the last dose of study medication to assess for any serious adverse events (SAEs).
The request of the PDCO for P351 stated: "Patients included in the study must be offered at least annual follow-up examinations, to include assessment of all infections, auxological and pubertal parameters, for at least 5 years or for at least two years after reaching Tanner stage V (whichever occurs first)."
Participants who completed P083 were eligible to provide assent/consent for P351 at or within 6 months of the Week-54 visit of P083; participants who did not complete P083 were eligible to provide assent/consent for P351 at the time or within 6 months of when their Week-54 visit for P083 would have occurred.
Participants observed in P351 received standard of care as provided by their usual care physician. During P351, participants attended annual onsite visits and received telephone calls at 6-month intervals between visits for up to 5 years or for 2 years after reaching Tanner Stage V, whichever occurred earlier. Regardless of when the assent/consent for P351 was obtained, the last possible visit (Year +5) occurred no later than 5 years after the participant was scheduled to complete the Week-54 visit for P083. (Figure 1)

Figure 1: Study design



*Subjects who have completed P083 or stopped study medication during P083 and satisfy all enrollment criteria are eligible to enter the follow-up study.

Following the implementation of amendment P083-05, the duration of the placebo-controlled Phase A was modified to 20 weeks and the number of treatment groups to which subjects could be randomized was reduced from 4 to 2: sitagliptin and placebo/metformin. Randomization of subjects to the metformin group and to the placebo/sitagliptin group was discontinued with amendment P083-05 due to recruitment challenges and because the safety and efficacy profiles of metformin in paediatric patients had already been established. Subjects randomized to receive metformin or to placebo/sitagliptin before the implementation of amendment P083-05 continued in the study according to their originally planned treatment assignment.

Methods

Study participants

Inclusion criteria:

- Participant and/or parent/guardian provided documented informed assent and/or consent for the study..
- Completed P083 or stopped study medication during P083.

Exclusion criteria:

- Did not agree to refrain from participating in any double-blind interventional study while participating in P351.
- Was unlikely to adhere to the study procedures and appointment schedule.

Treatments

This was a noninterventional study, there was no exposure to study intervention.

Objective(s)

Primary Objective: To assess safety for up to a 5-year period in pediatric subjects (ages 10 to 17 years at initiation of therapy in P083) with T2DM who participated for up to one year in P083.

Endpoints

Adverse events (AEs), BMI (body mass index), BMI SDS (body mass index standard deviation score), height, body weight, Tanner Staging (pubertal progression), growth velocity, blood pressure, and heart rate.

Sample size

P083 is scheduled to enroll approximately 360 pediatric subjects with T2DM who were 10-17 years of age (inclusive) at initiation of therapy in P083. Randomized subjects from P083 (both those who have completed P083 and those who stopped study medication during P083) are eligible to participate in the follow-up study P351 if they meet enrollment criteria. The number of subjects enrolled in this study is not pre-specified. Subjects and/or their parent/legal guardians who are unable to or choose not to provide assent/consent when the subject completes or discontinues from P083, may do so at a later date.

Randomisation and blinding (masking)

This was a noninterventional study, participants retained their randomization numbers assigned for study P083. Participants in P351 remained blinded to treatment assignment from P083 while P083 was ongoing. Investigators could inform participants about treatment assignment in P083 after P083 was completed.

Statistical Methods

Statistical summaries by originally-assigned treatment groups from P083 were provided for the follow-up study only (i.e., without pooling with P083) because the follow-up study is an observational study with no treatment. The treatment group assignments from P083 are: sitagliptin, metformin, placebo/sitagliptin, and placebo/metformin.
Safety endpoints for the follow-up study were summarized by treatment group from P083, with no between-group comparisons. Safety endpoints were analysed descriptively.

Results

Participant flow

A total of 80 participants enrolled in P351 across 39 study sites in 16 countries. All participants enrolled in P351 completed P083 on or off study medication. Of the 80 participants enrolled in P351, 36 were in the Exposed to Sitagliptin in P083 group and 44 in the Not Exposed in P083 group (Table 1).
A total of 57/80 (71.3%) of the enrolled participants completed P351 per protocol. In the Exposed to Sitagliptin in P083 group 12/36 (33.3%) participants and in the Not Exposed in P083 group 11/44 (25.0%) participants, discontinued the study. The specific reasons for discontinuation were not notably different between the groups. The most commonly reported reason for study discontinuation in both groups was withdrawal by participant.

Table 2: Disposition of Participants

	Exposed to Sitagliptin in P083[a] n (%)	Not Exposed in P083[b] n (%)	Total n (%)
Enrolled in P351	36	44	80
Completed	24 (66.7)	33 (75.0)	57 (71.3)
Discontinued	12 (33.3)	11 (25.0)	23 (28.8)
Death	1 (2.8)	0 (0.0)	1 (1.3)
Lost To Follow-Up	4 (11.1)	2 (4.5)	6 (7.5)
Physician Decision	1 (2.8)	1 (2.3)	2 (2.5)
Withdrawal By Parent/Guardian	1 (2.8)	3 (6.8)	4 (5.0)
Withdrawal By Subject	5 (13.9)	5 (11.4)	10 (12.5)

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Recruitment

Clinical investigator study sites were located in 16 countries: Argentina, Canada, Colombia, Dominican Republic, Guatemala, Honduras, Hungary, Israel, Italy, Malaysia, Mexico, Philippines, Poland, Romania, Russia, and the US.

Baseline data

Baseline demographics and disease characteristics were generally comparable between groups. The mean duration of T2DM at Year 0 in P351 was 2.0 years. The mean age was 14.9 years and the majority of participants (85.0%) were <18 years of age at Year 0. The proportion of female participants was lower in the Exposed to Sitagliptin in P083 group compared with the Not Exposed in P083 group, while baseline body weight and baseline BMI were higher in the Exposed to Sitagliptin in P083 group compared with the Not Exposed in P083 group. The proportion of participants from EU and EU-like countries was similar between the Exposed to Sitagliptin in P083 group and the Not Exposed in P083 group.

Table 3: Demographic and anthropometric characteristics

	Exposed to Sitagliptin in P083[a]		Not Exposed in P083[b]		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	36		44		80	
Gender						
Male	16	(44.4)	13	(29.5)	29	(36.3)
Female	20	(55.6)	31	(70.5)	51	(63.8)
Age at Year 0 of P351 (Years)						
≥10 and <15	13	(36.1)	19	(43.2)	32	(40.0)
≥15 and <18	15	(41.7)	21	(47.7)	36	(45.0)
≥18	8	(22.2)	4	(9.1)	12	(15.0)
Mean	15.1		14.7		14.9	
SD	2.3		2.0		2.1	
Median	15.0		15.0		15.0	
Range	11 to 19		11 to 18		11 to 19	
Race						
American Indian Or Alaska Native	2	(5.6)	3	(6.8)	5	(6.3)
Asian	5	(13.9)	8	(18.2)	13	(16.3)
Black Or African American	1	(2.8)	1	(2.3)	2	(2.5)
Multiple	13	(36.1)	14	(31.8)	27	(33.8)
American Indian Or Alaska Native, Black Or African American	1	(2.8)	0	(0.0)	1	(1.3)
American Indian Or Alaska Native, White	8	(22.2)	9	(20.5)	17	(21.3)
Black Or African American, White	4	(11.1)	5	(11.4)	9	(11.3)
White	15	(41.7)	18	(40.9)	33	(41.3)
Ethnicity						
Hispanic Or Latino	18	(50.0)	19	(43.2)	37	(46.3)
Not Hispanic Or Latino	18	(50.0)	24	(54.5)	42	(52.5)
Not Reported	0	(0.0)	1	(2.3)	1	(1.3)
Body Mass Index at Year 0 of P351 (kg/m^2)						
Mean	32.7		29.7		31.1	
SD	8.2		6.9		7.6	
Median	31.7		27.6		28.8	
Range	20.9 to 57.2		21.4 to 47.6		20.9 to 57.2	
Duration of Type 2 Diabetes Mellitus at Year 0 of P351 (years) (derived based on P083 medical history)						
Mean	1.8		2.0		2.0	
SD	1.6		1.7		1.6	
Median	1.3		1.5		1.4	
Range	1.1 to 10.1		1.1 to 9.0		1.1 to 10.1	

SD=Standard deviation.
Based on P083 enrollment:
Gender, Race, Ethnicity.
Age at baseline = (Number of days from date of birth to first day of this follow-up study + 1)/365.25.
Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.
[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.
[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Efficacy results

N/A. No efficacy data were included in this study.

Safety results

Summary measures of AEs were generally similar between groups (Table 2). The FAIRs of SAEs were generally similar for both groups. No participant discontinued this study due to an AE. One participant death was reported during this study and occurred in the Exposed to Sitagliptin in P083 group. The death was due to leukaemia and was considered not related to study intervention by the investigator.

Table 4: Adverse event summary

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Participants in population	36	44
with one or more adverse events	15/72.6 (20.7)	20/99.2 (20.2)
with serious adverse events	3/103.0 (2.9)	3/140.3 (2.1)
who died	1/107.7 (0.9)	0/143.7 (0.0)
discontinued follow-up due to an adverse event	0/110.0 (0.0)	0/143.7 (0.0)

FAIR: Follow-up adjusted incidence rate = (Number of participants with ≥1 event during the follow-up study) / (Total participant-years of follow-up).

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

For participants who have an event, the participant-years of follow-up will be calculated as (Date of the first event - First day of the follow-up study + 1)/365.25. For participants without an event, the participant-years of follow-up will be calculated as (Last day of the follow-up window - First day of the follow-up study + 1)/365.25. The total participant-years for a treatment group will be the sum of the participant-years of follow-up of all participants in the treatment group.

The FAIRs of AEs by SOC were generally similar between the groups in P351. AEs in the Infections and Infestations SOC were the most frequent in both groups. The FAIR for this SOC was higher in the Exposed to Sitagliptin in P083 group than in the Not Exposed in P083 group; however, there was no clinically relevant pattern or remarkable imbalance in specific AEs reported under this SOC.

Seven unique participants (3 in the Exposed to Sitagliptin in P083 group and 4 in the Not Exposed in P083 group) reported AEs of upper respiratory infections (a composite of AE terms of laryngopharyngitis, nasopharyngitis, acute otitis media, pharyngitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection) Four AEs were in the Exposed to Sitagliptin in P083 group and 6 were in the Not Exposed in P083 group.

Two AEs initially reported during P083 were reported as having worsened during P351. Both AEs (hypertriglyceridemia [1 participant in the Exposed to Sitagliptin in P083 group] and granuloma annulare [1 participant in the Not Exposed in P083 group]) were nonserious and moderate in intensity.

Serious adverse events

One death, in the Exposed to Sitagliptin in P083 group, was reported during P351. This participant had an SAE of leukaemia reported on Day 71 of P351 (Day 451 of P083) and died on Day 714 of P351 (Day 1094 of P083). This death was considered not related to study intervention by the investigator.

The FAIR of SAEs reported in P351 was low and similar in both groups. Appendicitis was the only SAE reported by more than 1 participant (2 in the Not Exposed in P083 group). No specific SAE was reported in >1 participant in the Exposed to Sitagliptin in P083 group. No participant discontinued the study due to an SAE (Table 3).

Discontinuation due to adverse events

No participant reported an AE that led to discontinuation in P351.

Adverse Events of Special Interest

No AEs of special interest were identified for this study.

Vital Signs, Physical Examinations, and Other Observations Related to Safety

Vital signs:

No meaningful differences in blood pressure and heart rate between patients exposed to sitagliptin and patients not exposed to sitagliptin were observed. (Table 5, Table 6, Table 7)

Physical examination

Auxological and pubertal parameters
There were no clinically meaningful differences in weight, height and BMI between patients exposed to sitagliptin and patients not exposed to sitagliptin, although the number of patients in each group was small over time (Table 8, Table 9, Table 10, Table 11).
Tanner Stage progression (percentage of participants that reached Tanner Stage V by year) was similar between groups throughout this study (Table 12). At study initiation, most participants (67/80 [31/36 in the Exposed to Sitagliptin in P083 group and 36/44 in the Not Exposed in P083 group]) were in late puberty (ie, Tanner Stage IV or Tanner Stage V). Tanner Stage V was not reported for 13 participants when they completed or discontinued prematurely; of these, 8 discontinued or were lost to follow-up. Pubertal progression (yearly proportion of participants progressing to Tanner V) showed minor variations between the 2 groups, but by Year 5, all male participants in both groups had progressed to Tanner V. Slightly higher growth velocities were observed in females in the Exposed to Sitagliptin in P083 group compared with the Not Exposed in P083. This may reflect the slightly lower yearly proportion of female participants progressing to Tanner Stage V in the Exposed to Sitagliptin in P083 group compared with the Not Exposed in P083. The variability observed across groups in growth velocity and pubertal progression is not considered clinically meaningful.

Pregnancy

Pregnancies were reported for 3 participants in this study (1 in the Exposed to Sitagliptin in P083 and 2 in the Not Exposed in P083 group), none of the participants were exposed to sitagliptin during pregnancy.

Table 5: Participants with Specific Adverse Events (Incidence >0% in One or More Treatment Groups)

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Participants in population	36	44
with one or more adverse events	15/72.6 (20.7)	20/99.2 (20.2)
Blood and lymphatic system disorders	**0/110.0 (0.0)**	**1/142.7 (0.7)**
Hypochromic anaemia	0/110.0 (0.0)	1/142.7 (0.7)
Cardiac disorders	**0/110.0 (0.0)**	**1/138.7 (0.7)**
Wandering pacemaker	0/110.0 (0.0)	1/138.7 (0.7)
Endocrine disorders	**0/110.0 (0.0)**	**1/141.9 (0.7)**
Hypothyroidism	0/110.0 (0.0)	1/141.9 (0.7)
Eye disorders	**0/110.0 (0.0)**	**2/139.3 (1.4)**
Accommodation disorder	0/110.0 (0.0)	1/140.4 (0.7)
Diabetic retinopathy	0/110.0 (0.0)	1/142.7 (0.7)
Retinal vascular disorder	0/110.0 (0.0)	1/140.4 (0.7)
Gastrointestinal disorders	**3/104.1 (2.9)**	**6/133.3 (4.5)**
Abdominal pain	1/108.3 (0.9)	1/141.9 (0.7)
Abdominal pain lower	0/110.0 (0.0)	1/142.1 (0.7)
Diarrhoea	0/110.0 (0.0)	2/140.3 (1.4)
Dyspepsia	0/110.0 (0.0)	1/143.7 (0.7)
Food poisoning	1/108.9 (0.9)	0/143.7 (0.0)
Gastritis	1/107.0 (0.9)	2/139.1 (1.4)
Lip ulceration	1/108.8 (0.9)	0/143.7 (0.0)
General disorders and administration site conditions	**1/105.2 (1.0)**	**1/143.7 (0.7)**
Non-cardiac chest pain	1/105.2 (1.0)	0/143.7 (0.0)
Pyrexia	0/110.0 (0.0)	1/143.7 (0.7)
Infections and infestations	**10/86.7 (11.5)**	**10/129.4 (7.7)**
Appendicitis	0/110.0 (0.0)	2/141.3 (1.4)
Bacteriuria	1/107.5 (0.9)	0/143.7 (0.0)
Body tinea	1/108.3 (0.9)	0/143.7 (0.0)
Bronchitis	0/110.0 (0.0)	1/142.6 (0.7)

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Infections and infestations	**10/86.7 (11.5)**	**10/129.4 (7.7)**
COVID-19	1/109.9 (0.9)	0/143.7 (0.0)
Conjunctivitis	1/107.8 (0.9)	1/142.0 (0.7)
Cystitis	0/110.0 (0.0)	1/141.7 (0.7)
Enterovirus infection	0/110.0 (0.0)	2/141.0 (1.4)
Folliculitis	0/110.0 (0.0)	1/141.5 (0.7)
Fungal skin infection	1/109.7 (0.9)	0/143.7 (0.0)
Gastroenteritis	0/110.0 (0.0)	2/143.5 (1.4)
Gastrointestinal infection	1/106.1 (0.9)	0/143.7 (0.0)
Herpes simplex	1/108.0 (0.9)	0/143.7 (0.0)
Impetigo	1/109.4 (0.9)	0/143.7 (0.0)
Influenza	1/108.7 (0.9)	0/143.7 (0.0)
Laryngopharyngitis	0/110.0 (0.0)	1/141.7 (0.7)
Nasopharyngitis	2/105.9 (1.9)	1/141.2 (0.7)
Onychomycosis	1/109.8 (0.9)	0/143.7 (0.0)
Otitis media acute	0/110.0 (0.0)	1/142.2 (0.7)
Pharyngitis	0/110.0 (0.0)	1/143.1 (0.7)
Pilonidal disease	1/105.1 (1.0)	0/143.7 (0.0)
Respiratory tract infection viral	1/109.5 (0.9)	1/142.7 (0.7)
Rotavirus infection	1/108.3 (0.9)	0/143.7 (0.0)
Sinusitis	0/110.0 (0.0)	1/142.2 (0.7)
Upper respiratory tract infection	2/104.5 (1.9)	0/143.7 (0.0)
Urinary tract infection	1/108.7 (0.9)	1/142.2 (0.7)
Varicella	1/108.8 (0.9)	0/143.7 (0.0)
Viral upper respiratory tract infection	0/110.0 (0.0)	1/142.1 (0.7)
Vulvovaginal mycotic infection	0/110.0 (0.0)	1/142.2 (0.7)
Vulvovaginitis	0/110.0 (0.0)	1/143.7 (0.7)
Investigations	**2/103.9 (1.9)**	**1/140.3 (0.7)**
Blood calcium increased	1/108.9 (0.9)	0/143.7 (0.0)
High density lipoprotein decreased	1/105.0 (1.0)	0/143.7 (0.0)
Urine analysis abnormal	1/105.0 (1.0)	0/143.7 (0.0)
Weight increased	0/110.0 (0.0)	1/140.3 (0.7)
Metabolism and nutrition disorders	**4/99.8 (4.0)**	**5/134.6 (3.7)**

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Metabolism and nutrition disorders	**4/99.8 (4.0)**	**5/134.6 (3.7)**
Diabetes mellitus inadequate control	1/105.4 (0.9)	2/140.1 (1.4)
Hypercholesterolaemia	0/110.0 (0.0)	1/143.7 (0.7)
Hyperglycaemia	1/107.0 (0.9)	2/138.2 (1.4)
Hypertriglyceridaemia	1/108.0 (0.9)	0/143.7 (0.0)
Hypoglycaemia	1/109.4 (0.9)	0/143.7 (0.0)
Musculoskeletal and connective tissue disorders	**1/107.2 (0.9)**	**1/141.7 (0.7)**
Arthralgia	1/107.2 (0.9)	0/143.7 (0.0)
Muscle spasms	0/110.0 (0.0)	1/141.7 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2/106.4 (1.9)**	**0/143.7 (0.0)**
Haemangioma of liver	1/108.7 (0.9)	0/143.7 (0.0)
Leukaemia	1/107.7 (0.9)	0/143.7 (0.0)
Nervous system disorders	**3/100.2 (3.0)**	**3/137.7 (2.2)**
Autonomic neuropathy	0/110.0 (0.0)	1/142.7 (0.7)
Burning sensation	0/110.0 (0.0)	1/142.0 (0.7)
Diabetic neuropathy	0/110.0 (0.0)	1/140.4 (0.7)
Headache	2/105.1 (1.9)	0/143.7 (0.0)
Petit mal epilepsy	1/105.2 (1.0)	0/143.7 (0.0)
Polyneuropathy	0/110.0 (0.0)	1/142.7 (0.7)
Psychiatric disorders	**1/109.7 (0.9)**	**2/140.0 (1.4)**
Anxiety	0/110.0 (0.0)	1/142.0 (0.7)
Insomnia	0/110.0 (0.0)	1/141.7 (0.7)
Intentional self-injury	1/109.7 (0.9)	0/143.7 (0.0)
Renal and urinary disorders	**3/107.8 (2.8)**	**0/143.7 (0.0)**
Microalbuminuria	1/110.0 (0.9)	0/143.7 (0.0)
Nephrolithiasis	2/107.8 (1.9)	0/143.7 (0.0)
Reproductive system and breast disorders	**0/110.0 (0.0)**	**2/137.2 (1.5)**
Menstruation irregular	0/110.0 (0.0)	1/141.5 (0.7)

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Reproductive system and breast disorders	**0/110.0 (0.0)**	**2/137.2 (1.5)**
Ovarian cyst	0/110.0 (0.0)	1/139.9 (0.7)
Polycystic ovaries	0/110.0 (0.0)	1/141.0 (0.7)
Respiratory, thoracic and mediastinal disorders	**2/104.3 (1.9)**	**1/143.7 (0.7)**
Productive cough	1/108.1 (0.9)	0/143.7 (0.0)
Respiratory tract inflammation	0/110.0 (0.0)	1/143.7 (0.7)
Rhinitis allergic	1/106.2 (0.9)	0/143.7 (0.0)
Skin and subcutaneous tissue disorders	**1/106.8 (0.9)**	**2/138.7 (1.4)**
Acne	0/110.0 (0.0)	1/141.5 (0.7)
Dermatitis	1/107.7 (0.9)	0/143.7 (0.0)
Eczema	1/106.8 (0.9)	0/143.7 (0.0)
Granuloma annulare	0/110.0 (0.0)	1/140.9 (0.7)
Necrobiosis lipoidica diabeticorum	0/110.0 (0.0)	1/140.9 (0.7)

FAIR: Follow-up adjusted incidence rate = (Number of participants with ≥1 event during the follow-up study) / (Total participant-years of follow-up).

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

For participants who have an event, the participant-years of follow-up will be calculated as (Date of the first event - First day of the follow-up study + 1)/365.25. For participants without an event, the participant-years of follow-up will be calculated as (Last day of the follow-up window - First day of the follow-up study + 1)/365.25. The total participant-years for a treatment group will be the sum of the participant-years of follow-up of all participants in the treatment group.

Table 6: Participants with Serious Adverse Events (Incidence >0% in One or More Treatment Groups)

	Exposed to Sitagliptin in P083[a] n (FAIR in 100-participant-years)	Not Exposed in P083[b] n (FAIR in 100-participant-years)
Participants in population	36	44
with serious adverse events	3/103.0 (2.9)	3/140.3 (2.1)
Infections and infestations	**0/110.0 (0.0)**	**3/140.3 (2.1)**
Appendicitis	0/110.0 (0.0)	2/141.3 (1.4)
Urinary tract infection	0/110.0 (0.0)	1/142.7 (0.7)
Metabolism and nutrition disorders	**1/107.0 (0.9)**	**0/143.7 (0.0)**
Hyperglycaemia	1/107.0 (0.9)	0/143.7 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1/107.7 (0.9)**	**0/143.7 (0.0)**
Leukaemia	1/107.7 (0.9)	0/143.7 (0.0)
Renal and urinary disorders	**1/108.3 (0.9)**	**0/143.7 (0.0)**
Nephrolithiasis	1/108.3 (0.9)	0/143.7 (0.0)

FAIR: Follow-up adjusted incidence rate = (Number of participants with ≥1 event during the follow-up study) / (Total participant-years of follow-up).

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

For participants who have an event, the participant-years of follow-up will be calculated as (Date of the first event - First day of the follow-up study + 1)/365.25. For participants without an event, the participant-years of follow-up will be calculated as (Last day of the follow-up window - First day of the follow-up study + 1)/365.25. The total participant-years for a treatment group will be the sum of the participant-years of follow-up of all participants in the treatment group.

Table 7: Summary of Change from Baseline in Systolic Blood Pressure (mmHg) over Time

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	36	114.0 (9.8)				
Not Exposed in P083	44	117.0 (11.4)				
Year 1						
Exposed to Sitagliptin in P083	33	113.8 (10.1)	115.8 (11.1)	2.0 (11.4)	1.0	-18.0 to 30.0
Not Exposed in P083	40	117.0 (11.6)	117.0 (11.1)	0.0 (10.8)	0.5	-25.0 to 31.0
Year 2						
Exposed to Sitagliptin in P083	28	113.3 (10.3)	115.2 (8.5)	1.9 (13.0)	-1.5	-17.0 to 27.0
Not Exposed in P083	38	117.0 (11.9)	117.6 (10.2)	0.6 (12.8)	0.0	-40.0 to 25.0
Year 3						
Exposed to Sitagliptin in P083	19	113.9 (8.8)	118.2 (11.5)	4.2 (13.9)	1.0	-15.0 to 31.0
Not Exposed in P083	28	116.4 (12.0)	118.7 (7.8)	2.3 (10.2)	2.0	-28.0 to 23.0
Year 4						
Exposed to Sitagliptin in P083	12	112.3 (10.0)	116.2 (5.5)	3.9 (11.6)	5.0	-11.0 to 28.0
Not Exposed in P083	19	116.3 (13.8)	118.2 (9.8)	1.9 (11.2)	3.0	-23.0 to 24.0
Year 5						
Exposed to Sitagliptin in P083	9	111.8 (11.4)	115.4 (9.9)	3.7 (17.2)	-4.0	-23.0 to 29.0
Not Exposed in P083	13	114.5 (10.3)	120.8 (9.9)	6.3 (14.5)	6.0	-12.0 to 34.0

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

One participant had their blood pressure measured in a semi-recumbent position that did not align with the protocol at Year 2 and Year 3 visits.

Table 8: Summary of Change from Baseline in Diastolic Blood Pressure (mmHg) over Time

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	36	70.4 (9.0)				
Not Exposed in P083	44	73.0 (8.5)				
Year 1						
Exposed to Sitagliptin in P083	33	70.1 (9.3)	71.9 (10.2)	1.8 (8.2)	1.0	-14.0 to 23.0
Not Exposed in P083	40	73.0 (8.8)	72.6 (7.9)	-0.4 (8.8)	-0.5	-19.0 to 17.0
Year 2						
Exposed to Sitagliptin in P083	28	69.8 (8.9)	71.8 (8.8)	2.1 (9.4)	2.0	-16.0 to 20.0
Not Exposed in P083	38	73.4 (8.6)	73.5 (7.8)	0.1 (9.2)	0.0	-18.0 to 18.0
Year 3						
Exposed to Sitagliptin in P083	19	69.2 (8.8)	75.4 (7.2)	6.3 (9.5)	5.0	-6.0 to 29.0
Not Exposed in P083	28	73.1 (8.8)	75.6 (7.4)	2.5 (7.0)	3.0	-12.0 to 19.0
Year 4						
Exposed to Sitagliptin in P083	12	69.3 (8.4)	75.0 (4.7)	5.8 (11.0)	4.5	-14.0 to 31.0
Not Exposed in P083	19	72.3 (9.2)	75.1 (7.6)	2.8 (9.0)	3.0	-15.0 to 21.0
Year 5						
Exposed to Sitagliptin in P083	9	69.0 (9.6)	76.9 (7.6)	7.9 (9.1)	8.0	-3.0 to 21.0
Not Exposed in P083	13	71.4 (9.2)	74.4 (10.4)	3.0 (10.1)	1.0	-15.0 to 21.0

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

One participant had their blood pressure measured in a semi-recumbent position that did not align with the protocol at Year 2 and Year 3 visits.

Table 9: Summary of Change from Baseline in Heart Rate (beats/min) over Time

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	36	80.5 (8.8)				
Not Exposed in P083	44	80.7 (9.7)				
Year 1						
Exposed to Sitagliptin in P083	33	80.3 (8.5)	79.3 (9.3)	-1.0 (8.9)	0.0	-22.0 to 18.0
Not Exposed in P083	40	79.9 (9.5)	80.8 (10.3)	0.8 (10.3)	1.0	-25.0 to 24.0
Year 2						
Exposed to Sitagliptin in P083	27	80.2 (8.7)	78.2 (11.0)	-2.0 (10.8)	-2.0	-25.0 to 29.0
Not Exposed in P083	38	80.6 (9.1)	82.5 (11.2)	1.9 (11.5)	1.0	-28.0 to 36.0
Year 3						
Exposed to Sitagliptin in P083	19	81.9 (8.3)	84.8 (10.4)	2.9 (12.2)	-2.0	-13.0 to 30.0
Not Exposed in P083	28	80.7 (9.9)	80.0 (10.4)	-0.7 (8.0)	-1.5	-15.0 to 18.0
Year 4						
Exposed to Sitagliptin in P083	12	82.2 (8.3)	84.7 (8.8)	2.5 (10.1)	1.5	-10.0 to 21.0
Not Exposed in P083	19	81.4 (10.6)	81.6 (9.6)	0.2 (11.2)	1.0	-25.0 to 25.0
Year 5						
Exposed to Sitagliptin in P083	9	83.0 (9.5)	81.3 (11.7)	-1.7 (8.7)	-3.0	-12.0 to 14.0
Not Exposed in P083	13	81.3 (12.5)	80.2 (12.3)	-1.1 (13.4)	0.0	-25.0 to 27.0

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Table 10: Summary of Change from Baseline in Weight (kg) over Time

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	36	85.7 (19.6)				
Not Exposed in P083	44	77.5 (22.1)				
Year 1						
Exposed to Sitagliptin in P083	33	84.3 (19.1)	84.6 (19.1)	0.2 (5.4)	0.4	-20.2 to 12.1
Not Exposed in P083	40	78.0 (22.6)	79.2 (23.1)	1.2 (4.6)	1.9	-15.8 to 10.3
Year 2						
Exposed to Sitagliptin in P083	28	84.0 (20.4)	84.4 (17.9)	0.3 (9.7)	0.5	-39.5 to 14.2
Not Exposed in P083	38	77.9 (22.9)	81.1 (22.7)	3.3 (6.1)	2.8	-6.7 to 17.4
Year 3						
Exposed to Sitagliptin in P083	19	80.4 (18.5)	83.2 (17.5)	2.9 (6.6)	0.8	-6.2 to 17.7
Not Exposed in P083	28	76.1 (23.5)	81.1 (22.0)	5.0 (8.5)	4.5	-7.7 to 32.2
Year 4						
Exposed to Sitagliptin in P083	12	75.1 (19.9)	80.2 (21.0)	5.1 (8.5)	2.2	-5.9 to 19.5
Not Exposed in P083	19	77.9 (27.2)	83.4 (25.2)	5.5 (10.9)	3.5	-9.3 to 41.5
Year 5						
Exposed to Sitagliptin in P083	9	75.6 (23.0)	81.7 (23.0)	6.1 (8.5)	4.5	-4.3 to 17.9
Not Exposed in P083	13	73.1 (22.4)	83.4 (24.2)	10.3 (16.2)	7.8	-8.4 to 55.8

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Table 11: Summary of Change from Baseline in BMI (kg/m2) over Time

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	26	33.2 (8.5)				
Not Exposed in P083	28	30.4 (7.9)				
Year 1						
Exposed to Sitagliptin in P083	23	33.2 (8.8)	32.3 (8.3)	-0.9 (2.4)	-0.2	-9.7 to 1.9
Not Exposed in P083	26	31.0 (7.8)	31.2 (7.9)	0.2 (1.3)	0.2	-3.0 to 2.8
Year 2						
Exposed to Sitagliptin in P083	18	33.3 (9.4)	31.7 (7.9)	-1.5 (4.3)	-0.6	-16.6 to 3.9
Not Exposed in P083	26	31.0 (7.8)	31.6 (7.7)	0.6 (2.2)	0.4	-2.6 to 6.8
Year 3						
Exposed to Sitagliptin in P083	13	31.1 (7.1)	30.5 (6.6)	-0.6 (1.4)	-0.5	-3.0 to 2.5
Not Exposed in P083	18	31.0 (9.0)	31.9 (8.8)	0.9 (3.5)	0.6	-4.9 to 7.9
Year 4						
Exposed to Sitagliptin in P083	8	30.5 (7.9)	29.8 (7.0)	-0.7 (2.3)	-0.8	-2.9 to 4.0
Not Exposed in P083	13	32.4 (10.2)	32.2 (10.3)	-0.2 (4.4)	-0.6	-7.5 to 10.6
Year 5						
Exposed to Sitagliptin in P083	6	31.3 (9.2)	30.8 (7.5)	-0.4 (2.5)	-0.5	-3.9 to 3.0
Not Exposed in P083	8	30.4 (10.1)	31.4 (11.9)	1.0 (5.3)	0.9	-7.9 to 11.6

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Table 12: Summary of Change from Baseline in Height (cm) over Time (female)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	20	157.1 (7.0)				
Not Exposed in P083	31	159.7 (8.4)				
Year 1						
Exposed to Sitagliptin in P083	19	157.0 (7.2)	158.4 (6.7)	1.4 (1.5)	1.0	-0.2 to 5.2
Not Exposed in P083	27	158.9 (8.6)	159.6 (8.5)	0.7 (1.3)	0.0	-1.4 to 5.0
Year 2						
Exposed to Sitagliptin in P083	17	157.0 (6.9)	159.2 (7.0)	2.2 (2.4)	1.0	-0.2 to 7.4
Not Exposed in P083	26	158.8 (8.7)	160.4 (8.5)	1.6 (2.2)	1.0	-0.2 to 9.2
Year 3						
Exposed to Sitagliptin in P083	13	157.6 (6.7)	161.1 (6.7)	3.5 (2.8)	4.0	0.0 to 7.5
Not Exposed in P083	19	156.9 (8.0)	158.9 (7.9)	2.0 (2.5)	1.5	-3.3 to 8.0
Year 4						
Exposed to Sitagliptin in P083	9	156.7 (7.4)	160.2 (6.9)	3.5 (2.9)	2.0	0.0 to 8.3
Not Exposed in P083	12	157.9 (7.2)	159.9 (8.0)	1.9 (3.1)	1.0	-3.3 to 7.2
Year 5						
Exposed to Sitagliptin in P083	7	155.0 (7.4)	159.7 (7.4)	4.7 (3.3)	6.0	0.0 to 9.3
Not Exposed in P083	8	158.5 (6.1)	161.3 (6.1)	2.9 (3.6)	2.5	-1.6 to 9.0

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Table 13: Summary of Change from Baseline in Height (cm) over Time (male)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline		
				Mean (SD)	Median	Range
Baseline (Year 0)						
Exposed to Sitagliptin in P083	16	169.2 (11.1)				
Not Exposed in P083	13	163.1 (13.1)				
Year 1						
Exposed to Sitagliptin in P083	14	167.3 (10.6)	169.2 (8.7)	1.9 (3.3)	0.8	-0.7 to 11.5
Not Exposed in P083	13	163.1 (13.1)	164.9 (12.3)	1.8 (1.7)	1.3	-0.5 to 5.7
Year 2						
Exposed to Sitagliptin in P083	11	167.3 (10.6)	170.6 (8.2)	3.3 (4.2)	2.0	-0.5 to 13.5
Not Exposed in P083	12	165.1 (11.6)	168.5 (9.5)	3.4 (3.5)	2.8	0.0 to 12.2
Year 3						
Exposed to Sitagliptin in P083	6	163.9 (11.5)	170.4 (7.9)	6.6 (7.1)	4.0	1.0 to 18.5
Not Exposed in P083	9	162.5 (12.1)	167.9 (9.5)	5.4 (5.5)	3.6	0.1 to 18.0
Year 4						
Exposed to Sitagliptin in P083	3	159.3 (14.0)	172.2 (3.3)	13.0 (10.8)	15.1	1.3 to 22.5
Not Exposed in P083	7	160.1 (11.5)	167.5 (8.9)	7.4 (5.9)	4.8	2.5 to 19.7
Year 5						
Exposed to Sitagliptin in P083	2	161.1 (19.2)	173.4 (4.8)	12.3 (14.4)	12.3	2.1 to 22.5
Not Exposed in P083	5	157.4 (12.8)	167.4 (11.0)	10.0 (8.0)	6.0	3.6 to 22.2

N = Number of subjects with both baseline and timepoint measurements.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

Exposed to Sitagliptin in P083 = The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

Not Exposed in P083 = The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

Table 14: Participants reaching Tanner stage V

Tanner Stage at Year 0	Participants Who Reached Tanner Stage V					
	At Year 0 n/m (%)	By Year 1 n/m (%) [d]	By Year 2 n/m (%) [d]	By Year 3 n/m (%) [d]	By Year 4 n/m (%) [d]	By Year 5 n/m (%) [d]
Exposed to Sitagliptin in P083[a]						
Stage II						
Male	0/2 (0.0%)	0/2 (0.0%) [0]	0/2 (0.0%) [0]	0/2 (0.0%) [0]	1/2 (50.0%) [0]	1/1 (100.0%) [1]
Stage III						
Female	0/3 (0.0%)	0/3 (0.0%) [0]	0/3 (0.0%) [0]	2/3 (66.7%) [0]	2/3 (66.7%) [0]	2/3 (66.7%) [0]
Stage IV						
Male	0/6 (0.0%)	4/6 (66.7%) [0]	5/6 (83.3%) [0]	6/6 (100.0%) [0]	6/6 (100.0%) [0]	6/6 (100.0%) [0]
Female	0/12 (0.0%)	3/11 (27.3%) [1]	4/10 (40.0%) [2]	7/10 (70.0%) [2]	7/10 (70.0%) [2]	8/10 (80.0%) [2]
Stage V						
Male	8/8 (100.0%)	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]
Female	5/5 (100.0%)	5/5 (100.0%) [0]	5/5 (100.0%) [0]	5/5 (100.0%) [0]	5/5 (100.0%) [0]	5/5 (100.0%) [0]
Overall						
Male	8/16 (50.0%)	12/16 (75.0%) [0]	13/16 (81.3%) [0]	14/16 (87.5%) [0]	15/16 (93.8%) [0]	15/15 (100.0%) [1]
Female	5/20 (25.0%)	8/19 (42.1%) [1]	9/18 (50.0%) [2]	14/18 (77.8%) [2]	14/18 (77.8%) [2]	15/18 (83.3%) [2]
Not Exposed in P083[b]						
Stage II						
Female	0/1 (0.0%)	0/1 (0.0%) [0]	0/1 (0.0%) [0]	0/1 (0.0%) [0]	1/1 (100.0%) [0]	1/1 (100.0%) [0]
Stage III						
Male	0/4 (0.0%)	0/4 (0.0%) [0]	1/4 (25.0%) [0]	2/4 (50.0%) [0]	2/4 (50.0%) [0]	4/4 (100.0%) [0]
Female	0/3 (0.0%)	0/3 (0.0%) [0]	1/3 (33.3%) [0]	1/2 (50.0%) [1]	2/2 (100.0%) [1]	2/2 (100.0%) [1]

Tanner Stage at Year 0	Participants Who Reached Tanner Stage V					
	At Year 0 n/m (%)	By Year 1 n/m (%) [d]	By Year 2 n/m (%) [d]	By Year 3 n/m (%) [d]	By Year 4 n/m (%) [d]	By Year 5 n/m (%) [d]
Stage IV						
Male	0/6 (0.0%)	2/6 (33.3%) [0]	3/5 (60.0%) [1]	4/5 (80.0%) [1]	5/5 (100.0%) [1]	5/5 (100.0%) [1]
Female	0/19 (0.0%)	6/17 (35.3%) [2]	10/17 (58.8%) [2]	13/16 (81.3%) [3]	14/16 (87.5%) [3]	14/16 (87.5%) [3]
Stage V						
Male	3/3 (100.0%)	3/3 (100.0%) [0]	3/3 (100.0%) [0]	3/3 (100.0%) [0]	3/3 (100.0%) [0]	3/3 (100.0%) [0]
Female	8/8 (100.0%)	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]	8/8 (100.0%) [0]
Overall						
Male	3/13 (23.1%)	5/13 (38.5%) [0]	7/12 (58.3%) [1]	9/12 (75.0%) [1]	10/12 (83.3%) [1]	12/12 (100.0%) [1]
Female	8/31 (25.8%)	14/29 (48.3%) [2]	19/29 (65.5%) [2]	22/27 (81.5%) [4]	25/27 (92.6%) [4]	25/27 (92.6%) [4]

n = Number of participants with a Tanner Stage V at Year x or with a Tanner Stage V prior to Year x.

m = Number of participants at Year x or with a Tanner Stage V prior to Year x.

d = Cumulative number of dropouts who did not reach Tanner Stage V by Year x. Participants reaching Tanner Stage V by Year x are not considered as dropouts.

Number (%) of participants who reached Tanner Stage V (genitalia for male and breasts for female) by each follow-up year were summarized.

Treatment groups in this follow-up study (P351) reflect the originally assigned treatment groups in P083.

[a] The Exposed to Sitagliptin in P083 includes 35 participants who were randomized to the Sitagliptin +/- insulin group, and 1 participant who was randomized to the Placebo followed by Sitagliptin group in P083. 1 participant from this group received sitagliptin as concomitant medication during P351.

[b] The Not Exposed in P083 includes 39 participants who were randomized to the Placebo +/- insulin followed by metformin group, and 5 participants who were randomized to the Metformin group in P083. 4 participants from this group received a DPP-4 inhibitor (sitagliptin or vildagliptin) as concomitant medication during P351.

2.3.3. Discussion on clinical aspects

The present study P351 was an observational, noninterventional, multisite, follow-up study to provide an up to 5-year observational assessment of safety for participants with T2DM who were 10 to 17 years of age (inclusive) when randomized to therapy in P083. In study P083, participants were randomised to receive sitagliptin and metformin-placebo, metformin and sitagliptin-placebo, or the sequence of placebo, followed by metformin), or the sequence of placebo followed by sitagliptin.
This study was to provide follow-up of patients who participated in study P083, without (new) interventions, patients received only standard of care as provided by their usual care physician. Therefore, it was considered to be appropriate that the study was designed as an observational study.
Only patients who participated in study P083 were eligible for inclusion in the current study, therefore the inclusion and exclusion criteria seem appropriate. The primary objective was to assess safety or up to a 5-year period in pediatric subjects (ages 10 to 17 years at initiation of therapy in P083) with T2DM who participated for up to one year in P083. The study design and inclusion criteria are considered appropriate for the study objective.
Baseline criteria were generally comparable between groups, which is expected as these patients were previously included in an RCT.
The study does not contain efficacy data, since no intervention was studied.
Safety data were derived from the patients included in this study over 5 years of follow-up or for 2 years after reaching Tanner Stage V, whichever occurred first. Safety data of patients who were exposed to sitagliptin were compared with patients have not been exposed to sitagliptin. The number of adverse events and serious adverse events is comparable between the two groups. One death was reported in the study (in the Sitagliptin group), this was considered not related to the intervention.
The number and type of adverse events were comparable between the patients exposed to sitagliptin and not exposed to sitagliptin. Thus, no new safety issues arise from the current study. Sitagliptin is currently not authorised for paediatric patients, therefore no amendments to the SmPC are needed.

3. CHMP's overall conclusion and recommendation

The results of the present study P351 do not raise new issues regarding the safety of sitagliptin in paediatric patients with T2DM. The MAH's commitment is fulfilled, and no regulatory action is required at this stage.