15 November 2012
EMA/190568/2013
Committee for Medicinal Products for Human Use (CHMP)

Januvia

(sitagliptin)

Procedure No. EMEA/H/C/000722/P46 030

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

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

1.1. Type of application and aspects on development

This application concerns a follow-up measures P046 for Januvia/ Xelevia/Tesavel/Ristaben (CHMP adoption 21 February 2008) wherein the MAH committed to submit a proposal for a study design and timetable for paediatric studies.

A clinical study report (CSR) was submitted pertaining to study 081 – A Single-Dose Study to Assess the Pharmacokinetics, Safety and Tolerability of Sitagliptin in Adolescents (Januvia and related products, EMEA-000470-PIP01-08).

This submission is in accordance with Article 46 of Regulation (EC) No 1901/2006, which obliges the MAH to submit to the EMA any MAH-sponsored studies involving the use in the paediatric population of a centrally authorised medicinal product.

2. Clinical pharmacology

2.1. Pharmacokinetics

2.1.1. Introduction

Sitagliptin, an orally active, well-tolerated, potent and selective inhibitor of dipeptidyl peptidase IV (DPP-4), provides glycemic improvement by increasing the concentration of incretin hormones, including the key glucoregulatory hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which act to lower glucose through enhancement of insulin biosynthesis and release and suppression of glucagon secretion. Studies in the adult sitagliptin development program have shown that sitagliptin monotherapy improves HbA1c, fasting plasma glucose (FPG), and post-meal glucose (PMG) in a statistically significant and clinically meaningful manner. When coadministered with metformin, sulfonylurea, a PPAR-γ agonist, insulin, metformin plus a sulfonylurea, metformin plus a PPAR-γ agonist, and metformin plus insulin, sitagliptin results in statistically significant and clinically meaningful incremental glycemic improvements in HbA1c and FPG. Sitagliptin is presently indicated/approved for the treatment of adults with T2DM as monotherapy or in combination with metformin, sulfonylurea, PPAR-γ agonist, as well as part of triple combination therapy with metformin plus sulfonylurea or metformin plus PPAR-γ agonists. It has also been approved for use with insulin. Based upon its mechanisms of action and the similar pathophysiology underlying T2DM in youths and adults, the favorable safety and efficacy profiles of sitagliptin are predicted to be similar for youths relative to adults.

The study report included in this submission (MK-0431, PN081) presents data from the first clinical study in which sitagliptin was administered to subjects under the age of 18 years. This single-dose, placebo-controlled, double-blind study was conducted in 10 – 17 year old patients with T2DM, and evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of sitagliptin in this

pediatric patient population. Single oral doses of 50-, 100-, and 200-mg sitagliptin or matching placebo were administered to 35 adolescent patients (ages 10 – 17 years) with T2DM.

2.1.2. Methods

- **Study Design**

This was a multicenter, randomized, double-blind, placebo-controlled, multiple panel, single-dose study involving 10- to 17-year-old patients with type 2 diabetes mellitus (T2DM). Up to 3 panels (Panels A, B, and C) of up to 12 patients each were randomized to receive single oral doses of sitagliptin or placebo (in a 3:1 ratio, respectively). Panel A patients were administered single doses of 50 mg sitagliptin or placebo and Panel B subjects were administered single doses of 100 mg sitagliptin or placebo. There was a minimum of 48 hours between Panels A (after completion of 8 subjects) and B to allow for assessment of safety and tolerability. Initiation of Panel C was dependent on the review of safety and pharmacokinetic (PK) data from Panels A and B after completion of 16 subjects, which occurred at the completion of 8 subjects from Panel B. The dose of sitagliptin selected for administration in Panel C was 200 mg and was based upon the review of partial safety and PK data from Panels A and B.

The age of the subjects was 10 -17 years and the weight ranged from 50 to 180 kg.

Demographic information for the 35 patients is given in the Table 10-1

Table 10-1

Patient Demographics

AN	Gender	Race	Age (yr)	Height (cm)	Weight (kg)
0001	Male	White	16	172.4	92.0
0002	Female	White	17	157.2	75.4
0003	Female	White	14	156.5	74.2
0004	Female	White	17	161.0	74.0
0005	Male	White	16	166.0	102.6
0006	Female	Black	14	161.3	107.0
0007	Female	White	16	160.1	104.1
0008	Female	White	10	148.0	84.5
0009	Male	White	15	177.0	117.0
0010	Female	Black	15	158.0	81.1
0011	Female	White	16	175.3	92.6
0012	Male	White	13	177.0	95.6
0013	Female	White	15	158.5	56.0
0014	Male	White	14	165.5	58.6
0015	Male	White	16	171.5	85.5
0016	Female	White	13	173.0	129.5
0017	Female	White	16	154.2	59.1
0018	Female	White	16	162.0	98.2
0019	Female	White	13	165.0	125.9
0020	Female	Black	16	142.8	63.0
0021	Female	Black	12	160.7	66.2
0022	Female	Asian	10	151.0	50.4
0023	Male	Black	16	181.2	180.0
0024	Female	White	12	162.0	89.4
0025	Female	White	15	163.0	122.7
0026	Male	White	13	173.0	125.9
0027	Female	White	10	157.4	86.6
0028	Male	White	13	154.3	65.2
0029	Female	White	16	165.1	85.0
0030	Female	White	12	152.4	52.6
0031	Female	White	12	165.2	87.6
0032	Female	White	15	165.0	83.0
0033	Male	White	15	164.5	88.2
0034	Male	White	15	154.5	84.6
0035	Female	Black	15	171.6	101.0

Study Summary	Age (yr)	Height (cm)	Weight (kg)
N:	35	35	35
Range:	10 to 17	142.8 to 181.2	50.4 to 180.0
Mean:	14.3	162.9	89.8
Male N:	11	11	11
Male Range:	13 to 16	154.3 to 181.2	58.6 to 180.0
Male Mean:	14.7	168.8	99.6
Female N:	24	24	24
Female Range:	10 to 17	142.8 to 175.3	50.4 to 129.5
Female Mean:	14.0	160.3	85.4

There is a wide range in weight from 50 up to 180.0 kg. Included are 11 males and 24 females.

Baseline patient characteristics are given in Table 10-2

Table 10-2

Baseline Patient Characteristics

		Placebo (N = 9)		Sitagliptin 50 mg (N = 9)		Sitagliptin 100 mg (N = 9)		Sitagliptin 200 mg (N = 8)		Total (N = 35)	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender	Female	8	(88.9)	6	(66.7)	5	(55.6)	5	(62.5)	24	(68.6)
	Male	1	(11.1)	3	(33.3)	4	(44.4)	3	(37.5)	11	(31.4)
Age (years)	10 to <14	4	(44.4)	3	(33.3)	3	(33.3)	2	(25.0)	12	(34.3)
	14 to <18	5	(55.6)	6	(66.7)	6	(66.7)	6	(75.0)	23	(65.7)
	MEAN	14.1		13.9		14.3		14.8		14.3	
	SD	2.26		2.52		1.41		1.75		1.98	
	MEDIAN	15.0		14.0		15.0		15.5		15.0	
	RANGE	10 - 17		10 - 17		12 - 16		12 - 16		10 - 17	
Race	Asian	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.9)
	Black	1	(11.1)	1	(11.1)	1	(11.1)	3	(37.5)	6	(17.1)
	White	7	(77.8)	8	(88.9)	8	(88.9)	5	(62.5)	28	(80.0)

Data Source: [1.6.4]

In the placebo group there are 8 females versus one male. It could be of interest for interpretation of the study data whether the one male in the placebo-group weighed 180 kg, as might be concluded from Table 10-1.

None of the concomitant therapies could affect the study objectives.

Patients fasted for at least 8 hours prior to study drug administration. All doses were taken orally with approximately 240 mL of water, with water restricted 1 hour prior to and after study drug administration.

Blood samples (4 mL) for plasma sitagliptin and DPP-4 activity will be collected predose and at the following time points postdose: 0.5, 1, 1.5, 2, 3, 4 (pre-meal), 5, 6, 8, 10, 12, 24, 32, 48, and 72 hours.

The plasma pharmacokinetic parameters (e.g., $AUC_{0-\infty}$, C_{max}, T_{max}, and apparent $t_{1/2}$) of sitagliptin after oral administration of single doses were determined.

Urine for determination of sitagliptin concentrations was collected predose and at intervals up to 24-hours postdose in all panels.

Assessors Comments

The study design is considered acceptable. That the study was conducted as a multi centre (7 centres in the USA), parallel group design with only 8 patients in each group and the time span of the study was 28 months, this study is considered of low power and the results should be interpreted with care.

Analytical methods

Plasma samples were directly injected onto a High Turbulent Liquid Chromatography (HTLC) system. Analyte and internal standard were detected by MS/MS using selected reaction monitoring (SRM) with turbo-ionspray interface in the positive ion mode. The lower limit of quantitation (LLOQ) for the plasma assay was 0.50 ng/mL and the linear calibration range was 0.50 to 1000 ng/mL.

Urine samples were analyzed by MRL (Merck Research Laboratories) (West Point, PA, U.S.A.). Urine samples were diluted and injected directly onto a HPLC system. Analyte and its isotopic internal

standard were detected by MS/MS using SRM with turboionspray interface in the positive ion mode. The LLOQ for urine assay was 0.1 µg/mL and the linear calibration range was 0.10 to 50.0 µg/mL.

The long term stability was tested over a period of 527 days.

Assessor's comment
The analytical method used for determination of sitagliptin in plasma and urine is considered acceptable.

- **Pharmacokinetic data analysis**

Actual sampling times were used to estimate each patient's plasma sitagliptin pharmacokinetic parameters. $AUC_{0-\infty}$, C_{max}, C_{24hr}, T_{max}, and the apparent terminal $t_{1/2}$ were calculated for sitagliptin. Plasma sitagliptin concentrations were converted into molar units (nM) prior to analysis using the molecular weight of 407.32 g/mol. Values below the LLOQ (LLOQ = 0.50 ng/mL = 1.23 nM) were replaced with 0. The pharmacokinetic variables were calculated model independently.

Sitagliptin urine concentrations, urine volumes from individual collection intervals, and actual time of the total collection interval were used to calculate urinary pharmacokinetic parameters. The fraction of the sitagliptin dose that was excreted unchanged in urine over the dosing intervals was determined by the quotient of the sum of sitagliptin collected over all dosing intervals and the dose administered (corrected for assayed potency of the formulation).

Assessor's comment
The methods for estimation of the pharmacokinetic variables are acceptable.

2.1.3. Between Population Comparison

Between-Population Comparison

The appropriate dose-adjusted $AUC_{0-\infty}$ from MK-0431 PN005 (N=7 adult patients with T2DM, 25 mg and 200 mg doses) was used for comparison with adolescent patients with T2DM. Pharmacokinetics of sitagliptin in healthy adults obtained from MK-0431 PN033, a study to evaluate dose proportionality of MK-0431 final market image tablets in healthy volunteers, indicate that the range of doses to be studied here is dose proportional with respect to $AUC_{0-\infty}$. The dose-adjusted (to 100 mg) $AUC_{0-\infty}$ from MK- 0431 PN005 (N=7 diabetic patients, 25 mg and 200 mg doses) was used for comparison

with adolescent patients with T2DM.

The dose-adjusted $AUC_{0-\infty}$ (to 100 mg) for sitagliptin was analyzed using linear mixed effect model with treatment (25 mg, 50 mg, 100 mg and 200 mg) and population as fixed effects and patient as a random effect. The ninety percent confidence interval (90% CI) was generated for the least square mean ratio (GMR, adolescents/adults) for sitagliptin $AUC_{0-\infty}$, based upon the t-distribution. If this 90% CI of the GMR for $AUC_{0-\infty}$ fell within the pre-specified bounds [0.50, 2.00], similarity between the adults and the adolescents would be concluded.

In addition, since MK-0431 PN005 is a crossover study, the $AUC_{0-\infty}$ from 25 mg and 200 mg for each patient was dose-adjusted to 100 mg and the mean of these 2 readings for each patient was used as historic data in analysis. An ANOVA model with population (adolescent patients with T2DM vs. adult patients with T2DM) as a factor for the dose adjusted (to 100 mg) $AUC_{0-\infty}$ was performed as supplemental analysis.

Due to non-dose proportionality, sitagliptin C_{max} and C_{24hr} at 200 mg for both adolescents and adults were analyzed using an ANOVA model with population (diabetic adolescents vs. diabetic adults) as a factor.

By including the historic adult patients in the model, it was assumed that time and any differences between the protocols (site, country, etc.) have negligible effects on the sitagliptin pharmacokinetic comparisons.

Assessor's comment

The methods described for comparison the data in adolescent patients and historical data from adult patients are considered adequate. The assumptions made on the pharmacokinetic behaviour of sitagliptin as dose linearity, the influence of weight and the pre-specified range of 0.5 – 2.0 for clinical relevant differences are acceptable in comparison of the pharmacokinetic data.
However, as the number of possible covariables, e.g. the issues mentioned above and the differences between protocols like site, country analytical method etc., in this comparison is rather large the value of this comparison is of low significance.

2.1.4. Results

The pharmacokinetic results in plasma of this study are listed in the table and figure below.

Table 11-4

Summary of Pharmacokinetic Parameters and Assessment of Dose Proportionality for Sitagliptin after Single-Dose Administration of Sitagliptin 50, 100 and 200 mg in Adolescent Patients with T2DM

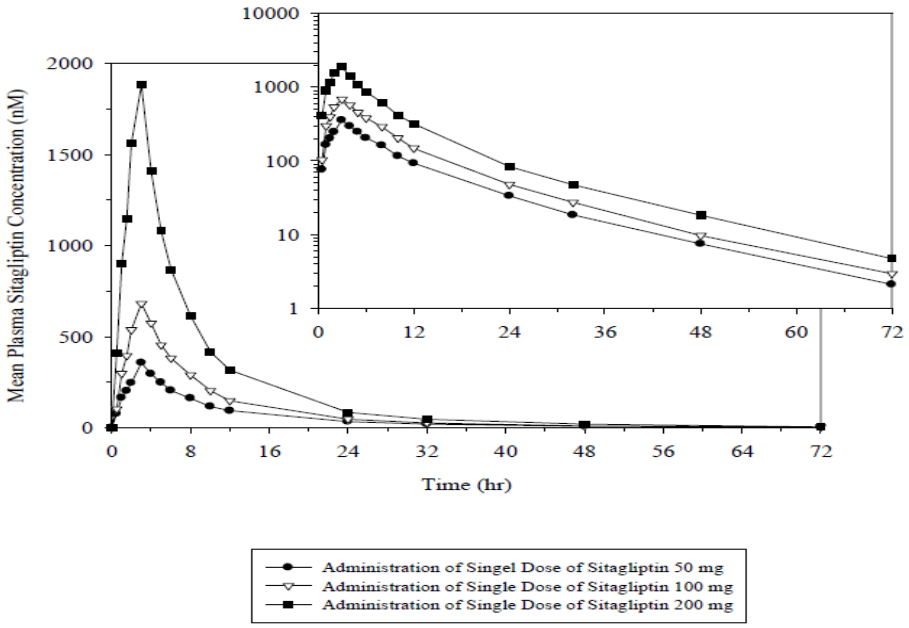
Pharmacokinetic	50 mg		100 mg		200 mg		
Parameter	N	GM (95% CI)‡	N	GM (95% CI)‡	N	GM (95% CI)‡	Slope (90% CI) †
$AUC_{0-\infty}$ (nM·hr)	9	3438 (2881,4103)	9	5869 (4918,7003)	8	12965 (10749,15638)	0.95 (0.80, 1.11)
C_{max} (nM)	9	366 (288,464)	9	666 (526,845)	8	1876 (1458,2413)	1.17 (0.96, 1.39)
C_{24hr} (nM)	9	32 (25,41)	9	43 (34,55)	8	78 (60,101)	0.63 (0.42, 0.85)
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)	

† The slope and 90% confidence interval from power-law model performed on natural log-transformed values.
‡ 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 $t_{1/2}$

Data Source: [16.4]

Figure 11-1

Arithmetic Mean Plasma Concentration-Time Profiles of Sitagliptin after Administration of a Single Dose of Sitagliptin 50 mg, 100 mg or 200 mg (n=9 for 50 mg and 100 mg; n=8 for 200 mg) in Adolescent Patients with T2DM (Insert: Semi-Log Scale)



The data found in urine are listed here.

Table 11-10

Summary Statistics of Fraction Recovered in Urine in 24 Hours for Sitagliptin after Single Dose Administration of Sitagliptin 50 mg. 100 mg and 200 mg in Adolescent Patients with T2DM

	50 mg		100 mg		200 mg	
	N	Mean (95% CI)†	N	Mean (95% CI)†	N	Mean (95% CI)†
Adolescent	9	0.57 (0.46, 0.68)	9	0.53 (0.41, 0.65)	8	0.53 (0.35, 0.71)
10 - <14 years old	3	0.48 (0.02, 0.94)	3	0.53 (0.21, 0.85)	2	0.55 (-1.36, 2.46)
14 - <18 years old	6	0.62 (0.51, 0.72)	6	0.53 (0.34, 0.71)	6	0.52 (0.27, 0.77)
Male	3	0.63 (0.52, 0.75)	4	0.53 (0.30, 0.75)	3	0.41 (-0.25, 1.06)
Female	6	0.54 (0.37, 0.71)	5	0.53 (0.30, 0.75)	5	0.60 (0.39, 0.81)

† Mean and confidence interval from univariate analysis performed on raw scale.
CI: Confidence Interval

Data Source: [16.4]

Table 11-6

Summary Statistics for Dose-Adjusted (to 100 mg) $AUC_{0-\infty}$ for Sitagliptin after Single Dose Administration of Sitagliptin 50, 100 and 200 mg to Adolescent and Adult Patients with T2DM

	GM (95% CI)‡							
	25 mg		50 mg		100 mg		200 mg	
Adolescent			9	6869 (5813, 8117)	8	5921 (4960, 7068)	8	6465 (5416, 7718)
Adult	7	7916 (6551, 9565)					7	7902 (6539, 9548)

Pooled across Doses

	N	GM (95% CI)‖	GMR (90% CI)§	rMSE ᵀ
Adolescent	25	6424 (5740, 7190)	0.82 (0.66, 1.01)	0.131
Adult §§	14	7851 (6360, 9691)		

ᵀ rMSE: Root mean square error on log-scale from mixed effect model. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
‡ GM = Geometric Least-Squares Mean for each dose strength. Back-transformed least-squares mean and confidence interval from ANOVA model performed on natural log-transformed values.
‖ GM = Geometric Least-Squares Mean across dose strengths. Back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
§ GMR = Geometric least-squares mean ratio (Adolescent/Adult).
CI: Confidence Interval.
§§ N=14 refers to 14 observations from 7 subjects.

Data Source: [16.4]

Table 11-7

Summary Statistics and Statistical Comparisons of Plasma C_{max} and C_{24hr} for Sitagliptin after Single Dose Administration of Sitagliptin 200 mg in Adolescent and Adult Patients with T2DM

	n	GM (95% CI)‡	GMR (90% CI)§	rMSE ᵀ
C_{max}				
Adolescent	8	1876 (1435, 2453)	1.04 (0.75, 1.44)	0.351
Adult	7	1803 (1354, 2401)		
C_{24hr}				
Adolescent	8	78 (54, 112)	0.74 (0.48, 1.14)	0.473
Adult	7	106 (72, 156)		

ᵀ rMSE: Root mean square error on log-scale from ANOVA model. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation
‡ GM = Geometric Least-Squares Mean. Back-transformed least-squares mean and confidence interval from ANOVA model performed on natural log-transformed values.
§ GMR = Geometric least-squares mean ratio (Adolescent/Adult).
CI: Confidence Interval

Data Source: [16.4]

The conclusions of the applicant on the pharmacokinetics of sitagliptin in adolescent subjects were:

- Single oral doses of sitagliptin up to 200 mg are generally safe and well-tolerated in 10 to 17 year old adolescent patients with T2DM.
- Adolescent patients with T2DM treated with single doses of sitagliptin have an approximately 18% lower $AUC_{0-\infty}$ as compared to adult patients with T2DM but this difference is not thought to be clinically meaningful.
- Adolescent patients with T2DM treated with a 200 mg single dose of sitagliptin have an approximately 4% higher C_{max} and 26% lower C_{24hr} compared to adult patients with T2DM treated with a 200 mg single dose of sitagliptin.

Assessors Comments
Considering the results from this study the conclusions of the applicant can be endorsed.

In adolescent subjects, despite the fact of the drawbacks of this study (parallel design, low number of subjects in each group, multi centre, long period of the study) the results showed acceptable variability and an acceptable comparison with the historical adult characteristics could be made.
In adolescent patients the pharmacokinetics showed also linear relationship with the dose with respect to the extent of absorption and a small deviation with respect to the rate of absorption. This is also in accordance with the data in adult patients.

In Conclusion
The exposure to sitagliptin in addolescent patients older than 10 years of age is considered not clinically significantly different from the exposure in adult patients.

2.2. Pharmacodynamics

Blood samples for determination of plasma DPP-4 activity were collected predose and at

selected time points through 72 hours postdose in all Panels**.**

DPP-4 enzyme activity was assessed in plasma by measuring the release of paranitroanaline (pNA) from the added substrate glylcyl-prolyl-paranitroaniline (Gly-PropNA).

The change in absorbance at 390 nm was determined at 30 second intervals over 20 minutes. The enzyme activity was defined as the slope (in mOD/min) from 4 to 14 minutes. The LLOQ for the DPP-4 assay was 0.6 mOD/min.

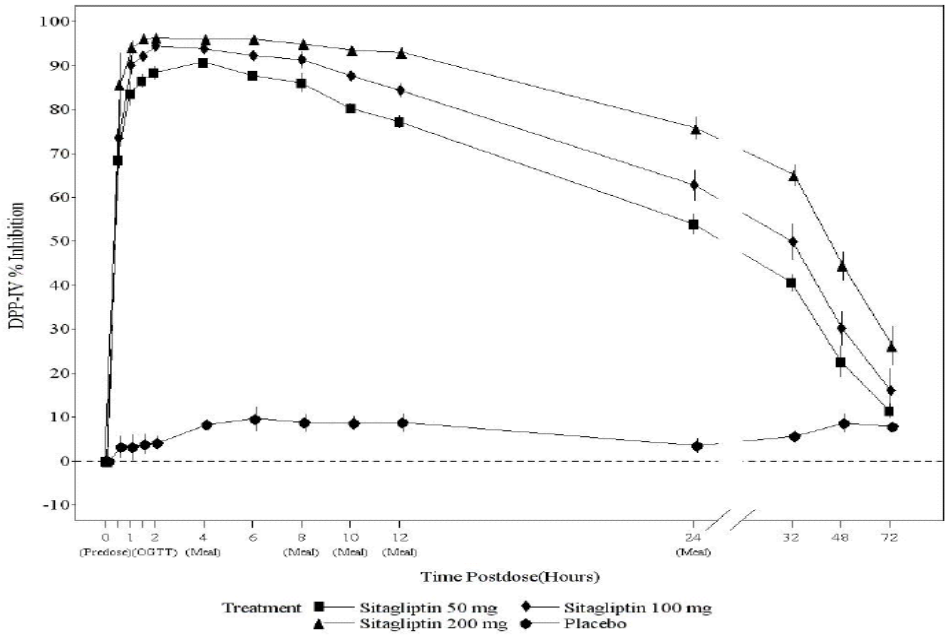
Percent Inhibition of Plasma DDP-4 Activity after sitagliptin
The geometric mean (± standard error) for % inhibition of DPP-4 activity after

administration of sitagliptin 50 mg, 100 mg, 200 mg or placebo is depicted in

Figure 11-8.

Figure 11-8

Geometric Mean (+/- SE) of DPP-4 % Inhibition versus Time (Hours) after Single Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Patients with T2DM



24-Hour Weighted Average Inhibition of Plasma DPP-4 Activity

The summary statistics and comparisons versus placebo for 24-hour weighted average inhibition (WAI) of DPP-4 activity by treatment are provided in Table 11-11.

Table 11-11

Summary Statistics of 24 Hours Weighted Average Inhibition (WAI) of DPP-4 Activity after Single-Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)[†]	Difference (95% CI)[††]	rMSE[‡]
Placebo	8	6.76 (-6.21, 18.14)		0.181
Sitagliptin 50 mg	9	73.98 (70.59, 76.99)	67.23 (58.26, 76.59)	
Sitagliptin 100 mg	9	80.53 (77.98, 82.78)	73.77 (65.32, 82.65)	
Sitagliptin 200 mg	8	87.96 (86.29, 89.43)	81.21 (73.09, 89.83)	

[†] LS Mean = Least-Square Geometric Mean; CI = Confidence Interval

[††] Difference = Difference of least-square geometric means (Active - Placebo)

[‡] Root mean square error on log-scale from ANOVA model. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation

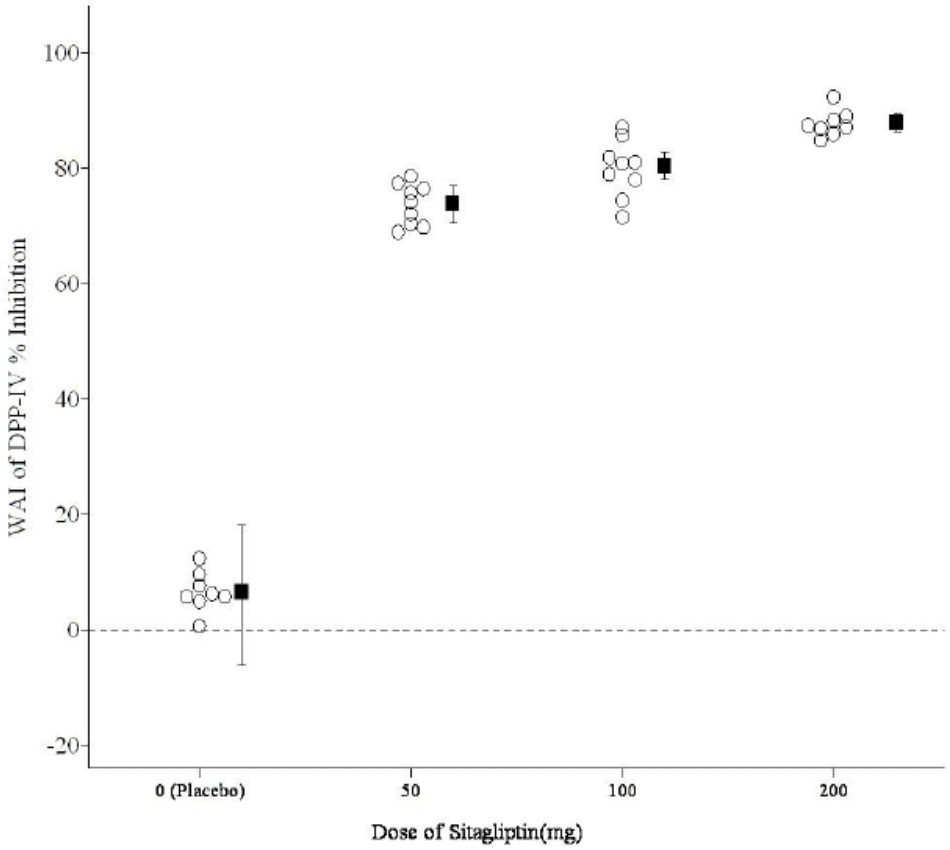
Data Source: [16.4]

In addition individual values, LS means and 95% CIs for 24 hours WAI of DPP-4 activity are displayed graphically in Figure 11-9.

After sitagliptin 50 mg, 100 mg and 200mg, the LS mean difference (active – placebo) and corresponding 95% CI for the WAI of DPP-4 activity was approximately 67.2% (58.3%, 76.6%), 73.8% (65.3%, 82.7%) and 81.2% (73.1%, 89.8%), respectively.

Figure 11-9

Individual Values, LSmeans and the Corresponding 95% CI of WAI of DPP-4 Activity versus Dose after Single Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Patients with T2DM



Percent Inhibition of Plasma DPP-4 Activity at 24 Hours Postdose

The summary statistics and comparisons versus placebo for percent inhibition of DPP-4 activity by treatment at 24 hours postdose are provided in Table 11-12. Individual values, LS means and 95% CIs for percent inhibition of DPP-4 activity at 24 hours postdose are displayed graphically in Figure 11-10.

After single dose administration of sitagliptin 50, 100 and 200 mg, the LS mean difference from placebo for the percent inhibition of DPP-4 activity at 24 hours postdose was approximately 50%, 59% and 72%, respectively.

Table 11-12

Summary Statistics of DPP-4 % Inhibition at 24 Hours Postdose after Single-Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)†	Difference (95% CI)††	rMSE‡
Placebo	8	3.57 (-12.60, 17.43)		0.215
Sitagliptin 50 mg	9	53.98 (46.74, 60.24)	50.41 (37.57, 63.67)	
Sitagliptin 100 mg	9	62.78 (56.92, 67.84)	59.21 (47.21, 71.70)	
Sitagliptin 200 mg	8	75.76 (71.70, 79.24)	72.19 (61.08, 83.94)	

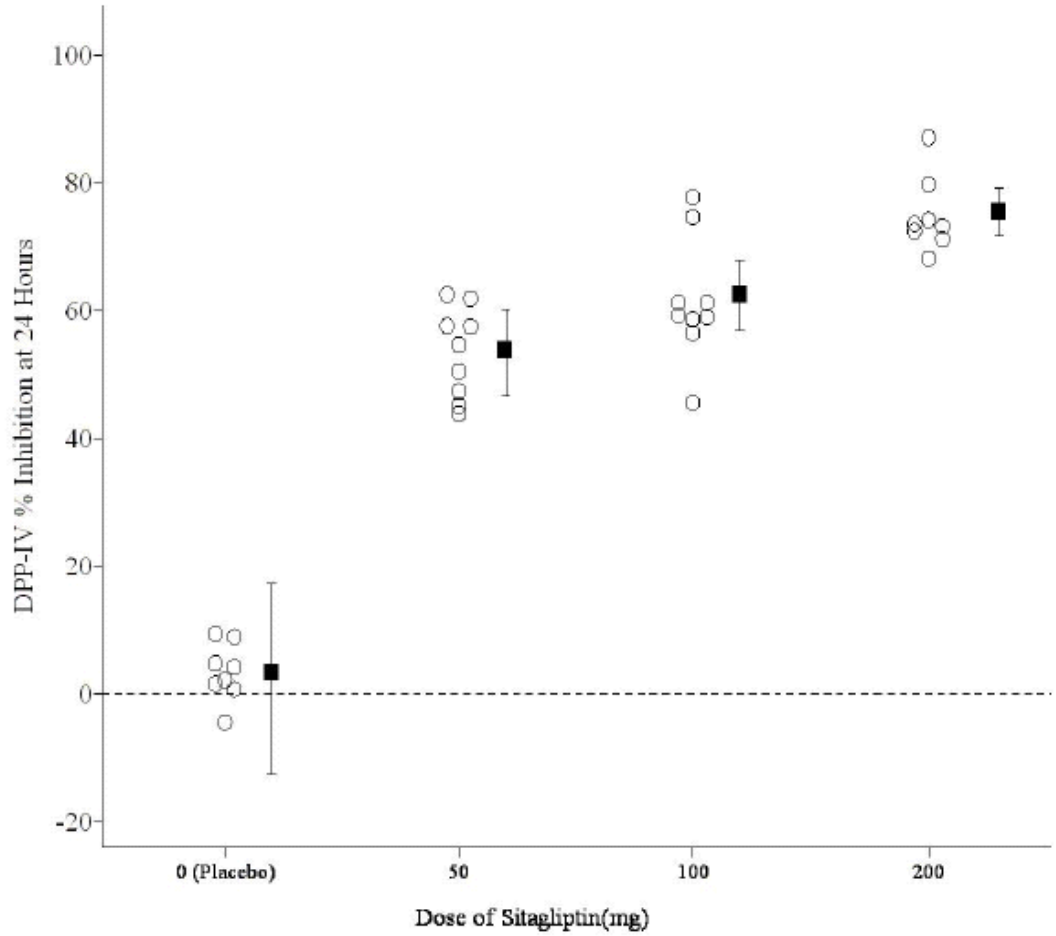
† LS Mean = Least-Square Geometric Mean; CI = Confidence Interval

†† Difference = Difference of least-square geometric means (Active - Placebo)

‡ Root mean square error on log-scale from ANOVA model. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation

Figure 11-10

Individual values and LSmeans (95% CI) of DPP-4 % Inhibition at 24 Hours Postdose versus Dose after Single Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo to Adolescent Patients with T2DM



Exploratory PK/PD Analysis

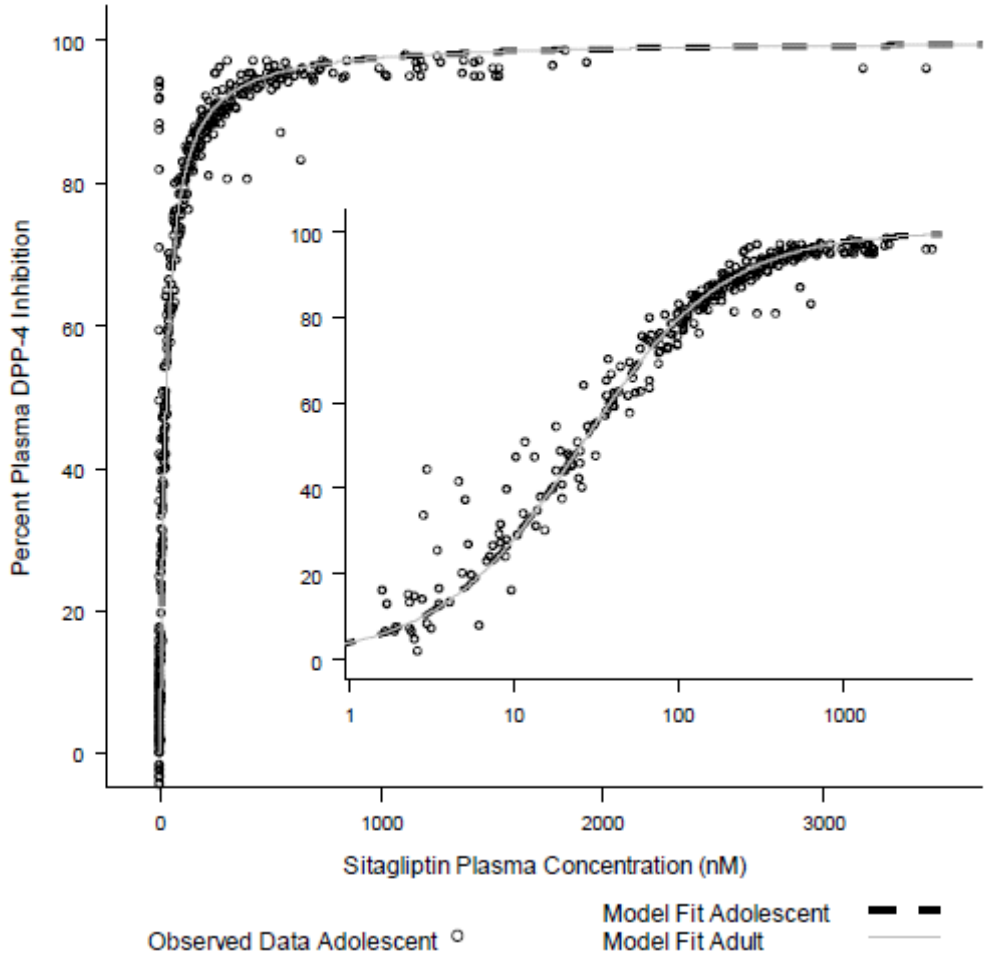
Time-matched DPP-4 inhibition and plasma concentration data were evaluated in an exploratory PK/PD analysis. Plotting the data (Figure 11-31) demonstrates that DPP-4 inhibition vs. plasma concentration follows a sigmoidal curve. An exploratory Emax model was fit to the adolescent data, shown with a dashed line. The estimated IC50 from this analysis was 25.4 +/- 1.5 nM. A similar analysis was performed with data generated in healthy adult subjects from protocol 001 and 002, receiving single oral doses of sitagliptin ranging from 1.5 to 600 mg. The estimated IC50 for adults in this previous study was 25.7 +/- 0.7 nM [16.1.12.46]. The Emax model fit for adults from P001/P002 is shown in Figure 11-31 with a solid gray line.

The PK/PD relationship between sitagliptin plasma concentration and DPP-4 inhibition was similar between adolescents and adults. The(modest) reduction in plasma sitagliptin exposure in adolescents translated to differences in plasma DPP-4 inhibition which were most marked at 24-hours post-dose. A single dose of 100 mg sitagliptin in healthy adult subjects achieves ~ 75% trough inhibition and ~ 83% change from placebo in weighted average inhibition (historical data from study MK-0431-PN001/002). The steady state trough DPP-4 inhibition in adults for 100 mg sitagliptin increases to ~80% following multiple dosing.

That a single dose of 100 mg sitagliptin in adolescent patients achieves a numerically lower placebo-adjusted DPP-4 inhibition, both on Day 1 "trough" inhibition (59.2%) and on weighted average inhibition (73.8%), reflects the small but observable differences in PK between adolescents and adults. However, it should be realised that this is a cross study comparison. In adults, sitagliptin dose-related reductions in trough DPP-4 inhibition have translated into only small differences in glycemic efficacy (historical data from MK-0431, PN001,PN002, PN014, PN07).

Figure 11-31

Percent Plasma DPP-4 Inhibition vs. Plasma Sitagliptin Concentration (nM), with Inhibitory E_{max} Model Fit Line (Inset: Semi-Log Plot)



Assessor's comments:
Considering the results of this pharmacodynamic study on the inhibition of DPP-4 activity the conclusions of applicant are endorsed.

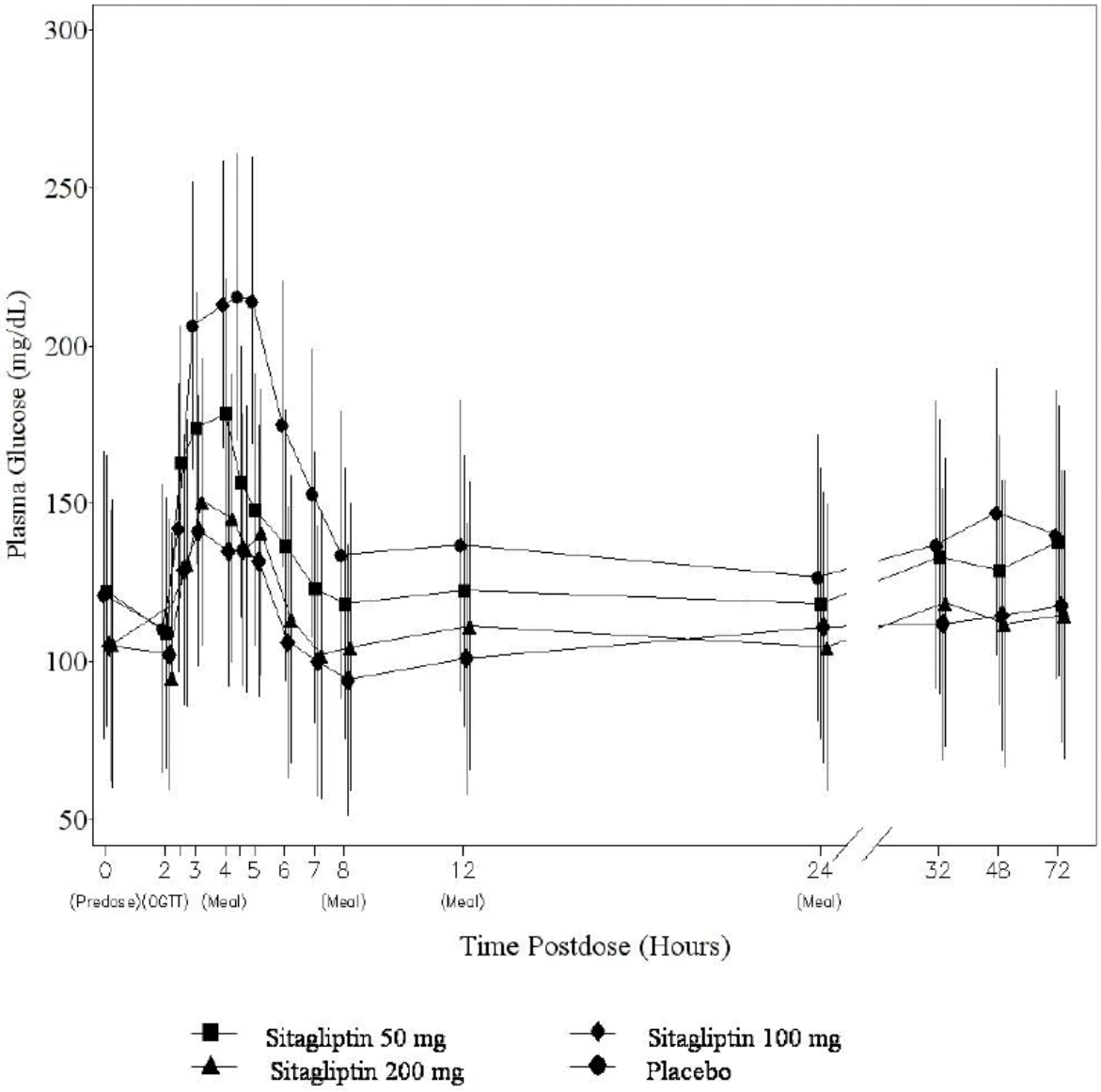
The pharmacodynamic effects of sitagliptin were evaluated further in an exploratory fashion. Plasma glucose, glucagon, insulin, C-peptide and GLP-1 (active and total) concentrations were measured in the context of an oral glucose tolerance test (OGTT) administered 2 hours postdose, and/or in the context of a standardized meal administered 4 hours postdose.

Glucose

The LS mean with corresponding 95% CI for plasma glucose concentrations (mg/dL) after single dose administration of sitagliptin 50 mg, 100 mg, 200 mg and placebo are given in Figure 11-11.

Figure 11-11

The LS Means with 95% Confidence Interval for Plasma Glucose (mg/dL) versus Time (Hours) after Single Dose Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo in Adolescent Patients with T2DM



Mean plasma glucose after sitagliptin wasa numerically lower than placebo over 72 hours.

2 Hours Post-OGTT Weighted Mean Glucose (WMG)

The LS mean (with 95% CIs) for plasma glucose concentrations (mg/dL) through 2 hours post OGTT, after administration of sitagliptin 50 mg, 100 mg, 200 mg and placebo, are in Figure 11-12. The summary statistics and comparisons with placebo for the 2-hour post-OGTT weighted mean glucose concentration are provided in Table 11-14.

The differences (sitagliptin - placebo) and 95% CI for the 2-hour post-OGTT weighted mean glucose concentration were -15.75 (-79.75, 48.27) mg/dL (-0.87 (-4.43, 2.68) mmol/L) for sitagliptin 50 mg, -

48.17 (-112.18, 15.84) mg /dL (-2.67 (-6.23, 0.88) mmol/L) for sitagliptin 100 mg, and -42.48 (-108.35, 23.38) mg/dL (-2.36 (-6.01, 1.30) mmol/L) for sitagliptin 200 mg.

Table 11-14

Summary Statistics of 2 Hours Post-OGTT Weighted Mean Glucose (mg/dL) after Single Doses Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo in Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)[†]	Difference (95% CI)[§]	rMSE[‡]
Placebo	8	180.14 (133.57,226.71)		64.501
Sitagliptin 50 mg	9	164.40 (120.49,208.31)	-15.74 (-79.75,48.27)	
Sitagliptin 100 mg	9	131.97 (88.06,175.88)	-48.17 (-112.18,15.84)	
Sitagliptin 200 mg	8	137.66 (91.08,184.23)	-42.48 (-108.35,23.38)	

[§] LS Mean = Least-Square Mean; CI = Confidence Interval

[†] Difference = Difference of least-square means (Active - Placebo)

[‡] Root mean square error on the raw scale from ANOVA model

The magnitude of the mean sitagliptin effect on post-OGTT WMG was smallest for the 50-mg dose, and larger for the 100- and 200-mg doses.

Glucagon

Mean plasma glucagon concentrations following the OGTT are given in Table 11-17. Mean plasma glucagon is similar between placebo and 50-mg sitagliptin, but lower for sitagliptin 100- and 200-mg doses.

Table 11-17

Summary Statistics of 2-Hour Post-OGTT Weighted Mean Glucagon (pg/mL) after Single Doses Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo in Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)[†]	Difference (95% CI)[§]	rMSE[‡]
Placebo	8	52.89 (42.45, 63.33)		14.459
Sitagliptin 50 mg	9	53.94 (44.10, 63.79)	1.05 (-13.29, 15.40)	
Sitagliptin 100 mg	9	41.43 (31.59, 51.27)	-11.46 (-25.81, 2.89)	
Sitagliptin 200 mg	8	34.55 (24.11, 44.99)	-18.34 (-33.11, -3.58)	

[§] LS Mean = Least-Square Mean; CI = Confidence Interval

[†] Difference = Difference of least-square means (Active - Placebo)

[‡] Root mean square error on the raw scale from ANOVA model

Insulin

The summary statistics and comparisons with placebo for the 2-hour post-OGTT weighted mean insulin concentration are provided in Table 11-19.

The differences (sitagliptin - placebo) and 95% CI for the 2-hour post-OGTT weighted mean insulin concentration were 75.25 (-49.22, 199.72) microIU/mL (522 (-341.86, 1387.04) pmol/L), 26.42 (-101.41, 152.25) microIU/mL (183.47 (-704.30, 1071.25) pmol/L) and 46.99 (-90.42, 184.40)

microIU/mL (326.34 (-627.99, 1280.66) pmol/L), respectively, for 50 mg, 100 mg and 200 mg sitagliptin.

Table 11-19

Summary Statistics of 2-Hour Post-OGTT Weighted Mean Insulin (microIU/mL) after Single Doses Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo in Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)[†]	Difference (95% CI)[§]	rMSE[‡]
Placebo	7	121.58 (28.23, 214.94)		120.159
Sitagliptin 50 mg	9	196.83 (114.50, 279.16)	75.25 (-49.22, 199.72)	
Sitagliptin 100 mg	8	148.00 (60.68, 235.32)	26.42 (-101.41, 154.25)	
Sitagliptin 200 mg	6	168.57 (67.74, 269.40)	46.99 (-90.42, 184.40)	

[§] LS Mean = Least-Square Mean; CI = Confidence Interval

[†] Difference = Difference of least-square means (Active - Placebo)

[‡] Root mean square error on the raw scale from ANOVA model

For the 2 hour period following the OGTT, the weighted mean insulin was greater than placebo for all three doses of sitagliptin.

GLP-1

After administration of sitagliptin 50 mg, 100 mg, 200 mg and placebo, the summary statistics and comparisons with placebo for the 2-hour post-OGTT weighted mean active GLP-1 concentration are provided in Table 11-23.

The GMRs (sitagliptin / placebo) and 95% CI for the 2-hour post-OGTT weighted average active GLP-1 concentration were 3.24 (1.81, 5.80), 2.38 (1.33, 4.25) and 1.89 (1.04, 3.43), respectively, for sitagliptin 50 mg, 100 mg and 200 mg.

Table 11-23

Summary Statistics of 2-Hour Post-OGTT Weighted Mean Active GLP-1 (pM) after Single Doses Administration of Sitagliptin 50 mg, 100 mg, and 200 mg or Placebo in Adolescent Patients with T2DM

Treatment	N	LS Mean (95% CI)[†]	GMR (95% CI)[§]	rMSE[‡]
Placebo	7	1.39 (0.90,2.14)		0.564
Sitagliptin 50 mg	9	4.49 (3.06,6.60)	3.24 (1.81,5.80)	
Sitagliptin 100 mg	9	3.30 (2.24,4.84)	2.38 (1.33,4.25)	
Sitagliptin 200 mg	8	2.62 (1.74,3.93)	1.89 (1.04,3.43)	

[§] Back-transformed from log scale; LS Mean = Geometric Least-Square Mean; CI = Confidence Interval

[†] GMR = Ratio of geometric least-square means (Active / Placebo)

[‡] Root mean square error on the log scale from ANOVA model

2.2.1. Assessor's overall conclusion on pharmacodynamics

This is a single-dose, placebo-controlled, double-blind in adolescents with T2DM. The term "adolescents" is used to refer to the 10-17 year old pediatric patient. The pharmacodynamic data in adolescents are consistent with those previously demonstrated in adults.

Based on the observed PK profile following single doses of 200 mg, increasing the daily sitagliptin dose in adolescents to above 100 mg in order to closely match adult trough DPP-4 inhibition would be accompanied by a sitagliptin Cmax in adolescents exceeding that associated with the usual 100 mg daily dose in adults. This daily dose exceeding 100 mg could induce risks in this vulnerable pediatric population.

Therefore, as based on the data presented, the balance of evidence indicates that 100 mg sitagliptin per day should be the dose for adolescent patients to be enrolled in Phase III studies.

3. Clinical safety

3.1. Assessor's overall conclusions on clinical safety

Discussion on clinical safety

All 35 patients were included in the assessment of safety and tolerability. Eight (8) patients reported a total of 18 clinical AEs (13 while on sitagliptin, 5 while on placebo), none of which was serious. Six (6) of the 18 clinical AEs were considered possibly related to study drug by the Investigator.

Seventeen (17) of the 18 reported clinical AEs were rated by the Investigator to be mild in intensity, and one was reported to be moderate in intensity (AN 0025, infusion site pain). All patients recovered from their adverse experiences.

There were no laboratory adverse experiences, serious adverse experiences (AEs) or deaths reported in this study. No patients were discontinued from the study due to an adverse experience. There were no consistent treatment-related changes in laboratory, vital sign, or ECG safety parameters.

Conclusions on clinical safety

In this single-dose, placebo-controlled, double-blind in adolescents with T2DM sitagliptin was safe and well tolerated. However, it should be noted that this is an exploratory PK/PD study of short duration.

4. Overall conclusion

As a corollary to the follow-up measures FUM 006 for Januvia/Xelevia and FUM 004 for Tesavel the clinical study report: "A single-dose study to assess the Pharmacokinetics, Safety and Tolerablity of Sitagliptin in Adolescents" has been sumitted. This is a single dose, placebo-controlled, double-blind study in adolescents with T2DM.

The exposure to sitagliptin in adolescents is clinically not significantly different from the exposure in adult patients.

Based on the data presented, the balance of evidence indicates that 100 mg per day should be the dose for adolescent patients with T2DM to be enrolled in Phase III studies.

In this exploratory PK/PD study of short duration sitaglitin was safe and well tolerated.

MAH confirms that in the context of this submission, no amendments to SmPC, labelling and/or PL are warranted.

P46.030 for Januvia and corresponding submissions for the clones Xelevia, Tesavel and Ristaben can be considered fulfilled.