Sponsor

Novartis

Generic Drug Name

LEZ763

Trial Indication(s)

Type 2 diabetes mellitus

Protocol Number

CLEZ763X2201

Protocol Title

A study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of LEZ763 following single and multiple ascending doses in healthy subjects and patients with type 2 diabetes

Clinical Trial Phase

Phase I/II

Phase of Drug Development

Phase I

Study Start/End Dates

01 Mar 2012 to 06 Sep 2013

Study Termination Date: 16 Sep 2013

Reason for Termination (If applicable)

Novartis terminated the study following the planned interim analysis in Part III. The study was not terminated because of a safety concern, but based on a perceived lack of efficacy.

Study Design/Methodology

This was a three part multicenter study. Parts I and II both used an interwoven, double-blind, randomized, placebo-controlled design of single and multiple ascending oral doses, respectively, of LEZ763 in healthy subjects. Part III, was a double-blind, double-dummy, placebo-controlled parallel design with six treatment groups including four LEZ763 groups, one placebo group and one comparator group treated with sitagliptin 100 mg q.d.

Centers

Eight centers in the United States

Publication

N/A

If the results may be considered material, then the clinical team/Medical Communication Leader should contact the Clinical Disclosure Office. A delayed disclosure form would have to be completed. The posting of the material results on the Novartis Clinical Trial results website would be delayed until the broad press release or publication.

Objectives:

Primary objectives

- Part I and Part II: to determine the safety, tolerability and pharmacokinetics of LEZ763 after single and multiple ascending doses of LEZ763 in healthy subjects

- Part III: to evaluate the effects of 4 weeks of treatment with LEZ763 on the glucose response following a standard MMT in patients with type 2 diabetes mellitus (T2DM)

Secondary objectives

- Part I and Part II: to assess the effect of LEZ763 on pharmacodynamic biomarkers in healthy subjects.
- Part III: to determine the safety, tolerability and pharmacokinetics of LEZ763 after single and multiple ascending doses of LEZ763 in patients with T2DM

Test Product (s), Dose(s), and Mode(s) of Administration

LEZ763 capsule (2.5 mg, 25 mg, 150 mg) and matching placebo capsule for oral administration. Sitagliptin capsule (100 mg) and matching placebo capsule for oral administration.

The following doses were administered in this study:

Single dose in healthy subjects (Part I), LEZ763: 10, 30, 100, 300, 600, 1200 mg, or matching placebo.

Multiple doses (once daily for 10 days) in healthy subjects (Part II), LEZ763: 30, 100, 300, 600, 1200 mg, or matching placebo

Multiple doses in patients with T2DM (Part III), LEZ763: 25, 100, 300, 600 mg or placebo once daily for 28 days plus a single dose of sitagliptin 100 mg on day 28, or sitagliptin 100 mg once daily for 27 days plus a single dose of placebo on day 28

Statistical Methods

Three analysis sets, a safety set, a pharmacokinetic set and a pharmacodynamic set were defined.

In Parts I and II, the primary safety and tolerability variables were the number and severity of AEs reported. The primary pharmacokinetic variables included AUCinf, AUClast, AUCtau, Cmax, T1/2, Tmax, CL/F and Racc, and were determined using non-compartmental method(s).

Part III, evaluated the effect of 4 weeks treatment with LEZ763 on the glucose AUC0-4h following a standard meal. A linear mixed effect model was applied to glucose AUC0-4h with treatment, Day (1 and 27), interaction of treatment and day, and baseline value as covariate, and subject as random effect. The primary analysis was the comparison of LEZ763 to placebo on Day 27 AUC0- 4h. The 20% and 80% quantiles of the percent reduction were obtained, and if the 20% quantile reduction was ≥15%, and the 80% quantile reduction was ≥25% on AUC0-4h, then a positive outcome was claimed based on the predefined decision criteria. The comparison of LEZ763 to placebo or sitagliptin on Day 1 or 27 was reported.

Prior to any statistical analysis, the data were log-transformed and the final results back transformed to the original scale. The baseline included in the analysis of covariance (ANCOVA) model was also log-transformed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

All Parts:

- Male or female subjects, 18 – 65 years old.
- Subjects weighed at least 50 kg to participate in the study, body mass index was within the range of 18 – 37 kg/m^2 (inclusive).
- Only postmenopausal females or female subjects who reported surgical sterilization (women without child bearing potential) were allowed in this study.
- Subjects with stable conventional sleep-wake cycle.

Parts I and II:

- Healthy male or female subjects
- Must be in good health (as determined by past medical history, physical examination, vital signs, ECG, and laboratory tests at Screening)

Part III:

- Type 2 diabetes diagnosed by ADA criteria for at least 3 months prior to screening.
- Patients either drug naïve or on stable dose of metformin (stable dose for at least 4 weeks prior to Screening). The metformin dose had to remain constant during the course of the study.
- HbA1c 6.5 to 9.5 % inclusive at screening.

Exclusion Criteria

All Parts:

- Smokers (use of tobacco products in the previous 3 months).
- Donation or loss of 400 mL or more of blood within 8 weeks prior to first dosing, or longer if required by local regulation.
- Significant illness within 2 weeks prior to dosing.
- Had (or had a history of) drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

Parts I and II:

- History of diabetes or adrenal disorders.

Part III:

- Type 1 diabetes mellitus; positive anti-GAD antibodies; acquired or secondary forms of diabetes such as those resulting from pancreatic surgery/injury, cystic fibrosis related diabetes.
- Evidence of clinically significant diabetic complications (such nephropathy, retinopathy, neuropathy).

Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow Table

Subject disposition – n (percent) (All subjects), Part I:

Disposition reason	LEZ763 10 mg N=8 n (%)	LEZ763 30 mg N=8 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=8 n (%)	LEZ763 1200 mg N=8 n (%)	Placebo N=13 n (%)	Total N=61 n (%)
Completed	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	12 (92.3)	60 (98.4)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (1.6)
Adverse Event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (1.6)

Subject disposition – n (percent) (All subjects), Part II:

Disposition reason	LEZ763 30 mg N=9 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=12 n (%)	LEZ763 1200 mg N=12 n (%)	Placebo N=12 n (%)	Total N=61 n (%)
Completed	8 (88.9)	8 (100)	8 (100)	12 (100)	12 (100)	12 (100)	60 (98.4)
Discontinued	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Subject withdrew consent	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Subject disposition – n (percent) (All subjects), Part III:

Disposition reason	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Completed	16 (100)	16 (100)	16 (100)	15 (93.8)	15 (93.8)	14 (87.5)	92 (95.8)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	2 (12.5)	4 (4.2)
Subject withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	2 (12.5)	3 (3.1)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)

Baseline Characteristics

Part I- Baseline characteristics by treatment group (Safety analysis set)

	LEZ763 10 mg N=8	LEZ763 30 mg N=8	LEZ763 100 mg N=8	LEZ763 300 mg N=8	LEZ763 600 mg N=8	LEZ763 1200 mg N=8	Placebo N=13	Total N=61
Age (years)								
Mean (SD)	53.9 (8.34)	48.9 (6.73)	45.0 (13.24)	55.8 (6.32)	40.0 (9.01)	41.4 (10.61)	40.0 (10.95)	45.9 (11.08)
Gender - n(%)								
Male	3 (37.5)	5 (62.5)	6 (75.0)	4 (50.0)	6 (75.0)	6 (75.0)	11 (84.6)	41 (67.2)
Female	5 (62.5)	3 (37.5)	2 (25.0)	4 (50.0)	2 (25.0)	2 (25.0)	2 (15.4)	20 (32.8)
Race - n(%)								
Caucasian	8 (100)	7 (87.5)	7 (87.5)	7 (87.5)	7 (87.5)	8 (100)	12 (92.3)	56 (91.8)
Black	0 (0.0)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	0 (0.0)	1 (7.7)	5 (8.2)

SD: standard deviation, BMI: body mass index

Part II- Baseline characteristics by treatment group (Safety analysis set)

Part II: Multiple ascending dose study in healthy subjects

	LEZ763 30 mg N=9	LEZ763 100 mg N=8	LEZ763 300 mg N=8	LEZ763 600 mg N=12	LEZ763 1200 mg N=12	Placebo N=12	Total N=61
Age (years)							
Mean (SD)	54.1 (9.41)	47.4 (13.82)	50.8 (9.56)	49.0 (4.29)	40.1 (10.77)	47.6 (11.57)	47.7 (10.65)
Gender - n(%)							
Male	3 (33.3)	4 (50.0)	5 (62.5)	10 (83.3)	10 (83.3)	7 (58.3)	39 (63.9)
Female	6 (66.7)	4 (50.0)	3 (37.5)	2 (16.7)	2 (16.7)	5 (41.7)	22 (36.1)
Race - n(%)							
Caucasian	9 (100)	7 (87.5)	7 (87.5)	12 (100)	12 (100)	12 (100)	59 (96.7)
Black	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)

Part III: Baseline characteristics by treatment group (All subjects)

	LEZ763 25 mg N = 16	LEZ763 100 mg N = 16	LEZ763 300 mg N = 16	LEZ763 600 mg N = 16	Placebo N = 16	Sitagliptin 100 mg N = 16	Total N = 96
Age (years)							
Mean (SD)	53.9 (6.42)	56.4 (6.63)	55.4 (4.86)	56.9 (5.53)	55.2 (8.18)	54.5 (7.11)	55.4 (6.46)
Gender - n(%)							
Male	12 (75.0)	11 (68.8)	8 (50.0)	6 (37.5)	8 (50.0)	10 (62.5)	55 (57.3)
Female	4 (25.0)	5 (31.3)	8 (50.0)	10 (62.5)	8 (50.0)	6 (37.5)	41 (42.7)
Race - n(%)							
Caucasian	14 (87.5)	14 (87.5)	13 (81.3)	11 (68.8)	13 (81.3)	12 (75.0)	77 (80.2)
Black	2 (12.5)	2 (12.5)	2 (12.5)	5 (31.3)	3 (18.8)	3 (18.8)	17 (17.7)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Native American	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Ethnicity - n(%)							
Hispanic/Latino	11 (68.8)	10 (62.5)	13 (81.3)	13 (81.3)	9 (56.3)	10 (62.5)	66 (68.8)
Other	5 (31.3)	6 (37.5)	3 (18.8)	3 (18.8)	7 (43.8)	6 (37.5)	30 (31.3)
Weight (kg)							
Mean (SD)	91.531 (15.0145)	88.763 (14.2720)	83.169 (17.9303)	79.838 (13.8860)	90.306 (12.7633)	82.438 (14.1076)	86.007 (15.0185)
Height (cm)							
Mean (SD)	171.36 (9.994)	169.59 (11.479)	166.71 (11.105)	164.38 (8.564)	166.95 (7.565)	165.66 (8.592)	167.44 (9.692)
BMI (kg/m^2)							
Mean (SD)	31.051 (4.1980)	30.779 (2.5915)	29.584 (4.6451)	29.525 (4.4425)	32.290 (3.4768)	30.010 (3.3106)	30.540 (3.8664)

Summary of Efficacy

Primary Outcome Results

Refer to Safety Result section for primary outcome result from Parts I and II

Part I – Summary statistics of pharmacokinetic parameters of LEZ763 (Safety analysis set)

	Visit	Statistics	AUCinf (h*ng/mL)	AUClast (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	CL/F (mL/h)
LEZ763 10 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	824 (374)	801 (365)	93.9 (33.4)	3.38 (1.94)	4.26 (1.15)	14900 (7690)
LEZ763 30 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	2250 (599)	2220 (602)	246 (27.5)	2.88 (2.36)	4.01 (0.673)	14100 (3370)
LEZ763 100 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	7790 (1330)	7740 (1310)	789 (161)	2.81 (0.753)	6.30 (3.61)	13200 (2440)
LEZ763 300 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	18700 (4390)	18600 (4360)	1640 (409)	4.38 (1.06)	7.24 (2.46)	16900 (4400)
LEZ763 600 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	28900 (9190)	28500 (8920)	1810 (591)	5.50 (2.78)	10.5 (4.01)	22900 (7860)
LEZ763 1200 mg	DAY1	n	8	8	8	8	8	8
		Mean (SD)	49500 (13600)	47300 (12400)	2940 (317)	4.75 (1.75)	15.9 (7.46)	25800 (6730)

Part II – Summary statistics of pharmacokinetic parameters of LEZ763 (Safety analysis set)

Treatment	Visit	Statistics	AUCtau (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	AF_AUC (1)	AF_Cmax (1)
LEZ763 30 mg	DAY1	n	8	8	8		
		Mean (SD)	2200 (667)	281 (78.5)	2.69 (1.58)		
	DAY10	n	8	8	8	8	8
		Mean (SD)	2450 (957)	275 (61.3)	2.63 (1.62)	1.09 (0.181)	1.00 (0.161)
LEZ763 100 mg	DAY1	n	8	8	8		
		Mean (SD)	5860 (976)	652 (202)	3.69 (1.65)		
	DAY10	n	8	8	8	8	8

Treatment	Visit	Statistics	AUCtau (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	AF_AUC (1)	AF_Cmax (1)
		Mean (SD)	6370 (1740)	610 (183)	1.94 (1.02)	1.09 (0.265)	0.980 (0.314)
LEZ763 300 mg	DAY1	n	8	8	8		
		Mean (SD)	13600 (3690)	1300 (267)	3.63 (0.694)		
	DAY10	n	8	8	8	8	8
		Mean (SD)	15200 (4630)	1360 (432)	3.38 (2.01)	1.11 (0.0846)	1.04 (0.192)
LEZ763 600 mg	DAY1	n	12	12	12		
		Mean (SD)	20600 (5740)	1810 (377)	4.50 (1.75)		
	DAY10	n	12	12	12	12	12
		Mean (SD)	23800 (6160)	2080 (558)	3.79 (1.32)	1.17 (0.210)	1.17 (0.314)
LEZ763 1200 mg	DAY1	n	12	12	12		
		Mean (SD)	27700 (9010)	2380 (590)	4.04 (1.44)		
	DAY10	n	12	12	12	12	12
		Mean (SD)	30400 (9890)	2750 (754)	3.58 (1.47)	1.15 (0.349)	1.20 (0.370)

(1) AF is the accumulation factor (equivalent to Racc; the accumulation ratio)

Part III - Analysis of LEZ763 pharmacodynamic effect for glucose AUC0-4h

PD variable	PD parameter [1]	Visit	Treatment	n	Baseline adjusted Estimate	Baseline adjusted 95% CI
Glucose	AUC0-4h	DAY1	LEZ763 25 mg	16	42.03	(40.04, 44.12)
			LEZ763 100 mg	16	42.09	(40.09, 44.18)
			LEZ763 300 mg	16	41.77	(39.79, 43.86)
			LEZ763 600 mg	16	41.27	(39.31, 43.33)
			Sitagliptin 100 mg	16	40.34	(38.43, 42.35)
			Placebo	16	41.83	(39.83, 43.92)
Glucose	AUC0-4h	DAY27	LEZ763 25 mg	16	39.87	(37.16, 42.79)
			LEZ763 100 mg	16	40.51	(37.75, 43.48)

PD variable	PD parameter [1]	Visit	Treatment	n	Baseline adjusted Estimate	95% CI
			LEZ763 300 mg	16	39.31	(36.62, 42.20)
			LEZ763 600 mg	15	38.54	(35.81, 41.47)
			Sitagliptin 100 mg	14	35.93	(33.31, 38.74)
			Placebo	15	41.70	(38.76, 44.87)
Glucose	AUC0-4h	DAY28	LEZ763 25 mg	16	36.66	(33.86, 39.69)
			LEZ763 100 mg	16	37.57	(34.70, 40.68)
			LEZ763 300 mg	16	36.37	(33.59, 39.39)
			LEZ763 600 mg	15	36.07	(33.21, 39.18)
			Sitagliptin 100 mg	14	36.06	(33.12, 39.25)
			Placebo	14	39.90	(36.64, 43.44)

Note: 1. Results are derived from an ANCOVA model with dose as the classification factor and the corresponding log(PD parameter) on Day -1 as the covariate. Changes from baseline in log-transformed PD data are analyzed. Analysis results are back transformed to the original scale.

[1] AUC0-4h refers to area under the curve over the 4-hour post dose period.

Secondary Outcome Results

Refer to Safety Result section for secondary outcome result from Part III

Part I – Analysis of LEZ763 pharmacodynamic effect for glucose

PD variable	PD parameter [1]	Visit	Treatment	n	Baseline adjusted Estimate	95% CI
Glucose (mmol/L)	AUC0-4h	DAY1	LEZ763 10 mg	8	22.29	(21.44, 23.17)
			LEZ763 30 mg	8	20.50	(19.71, 21.33)
			LEZ763 100 mg	8	19.93	(19.17, 20.72)
			LEZ763 300 mg	8	20.57	(19.78, 21.39)
			LEZ763 600 mg	8	21.00	(20.17, 21.86)
			LEZ763 1200 mg	8	21.23	(20.42, 22.07)

PD variable	PD parameter [1]	Visit	Treatment	n	Baseline adjusted Estimate	95% CI
			Placebo	12	21.86	(21.18, 22.57)
Glucose (mmol/L)	2hr postprandial	DAY1	LEZ763 10 mg	8	5.33	(4.99, 5.69)
			LEZ763 30 mg	8	4.93	(4.62, 5.27)
			LEZ763 100 mg	8	4.70	(4.41, 5.03)
			LEZ763 300 mg	8	4.70	(4.40, 5.02)
			LEZ763 600 mg	8	5.19	(4.85, 5.55)
			LEZ763 1200 mg	8	4.97	(4.65, 5.31)
			Placebo	12	4.91	(4.65, 5.18)

Note: 1. Results are derived from an ANCOVA model with dose as the classification factor and the corresponding log(PD parameter) on Day -1 as the covariate. Changes from baseline in log-transformed PD data are analyzed. Analysis results are back transformed to the original scale [1] AUC0-4h refers to area under the curve over the 4-hour post dose period. Concentrations below the lower limit of quantification (LLOQ) are imputed as 0.5*LLOQ

Part II - Analysis of LEZ763 pharmacodynamic effect for glucose

PD variable	PD parameter [1]	Visit	Treatment	n	Baseline adjusted Estimate	95% CI
Glucose (mmol/L)	AUC0-4h	DAY1	LEZ763 30 mg	8	21.37	(20.51, 22.28)
			LEZ763 100 mg	8	21.13	(20.27, 22.02)
			LEZ763 300 mg	8	21.23	(20.37, 22.12)
			LEZ763 600 mg	12	20.79	(20.10, 21.50)
			LEZ763 1200 mg	12	20.76	(20.07, 21.47)
			Placebo	12	22.35	(21.61, 23.11)
Glucose (mmol/L)	AUC0-4h	DAY10	LEZ763 30 mg	8	21.33	(20.55, 22.13)
			LEZ763 100 mg	8	21.40	(20.63, 22.20)
			LEZ763 300 mg	8	21.34	(20.57, 22.13)
			LEZ763 600 mg	12	21.27	(20.65, 21.92)
			LEZ763 1200 mg	12	21.37	(20.74, 22.02)
			Placebo	12	21.85	(21.21, 22.51)

Note: 1. Results are derived from an ANCOVA model with dose as the classification factor and the corresponding log(pharmacodynamic parameter) on Day -1 as the covariate. Changes from baseline in log-transformed pharmacodynamic data are analyzed. Analysis results are back transformed to the original scale. [1] AUC0-4h refers to area under the curve over the 4-hour post dose period. Concentrations below the lower limit of quantification (LLOQ) are imputed as 0.5*LLOQ.

Part III - Analysis of LEZ763 pharmacodynamic effect for glucose fasting value

					Baseline adjusted	
PD variable	**PD parameter**	**Visit**	**Treatment**	**n**	**Estimate**	**95% CI**
Glucose	Fasting value	DAY1	LEZ763 25 mg	16	9.05	(8.69, 9.43)
			LEZ763 100 mg	16	9.08	(8.71, 9.46)
			LEZ763 300 mg	16	9.02	(8.66, 9.40)
			LEZ763 600 mg	16	9.01	(8.65, 9.39)
			Sitagliptin 100 mg	16	9.21	(8.84, 9.59)
			Placebo	16	8.76	(8.41, 9.13)
Glucose	Fasting value	DAY27	LEZ763 25 mg	16	8.74	(8.12, 9.40)
			LEZ763 100 mg	16	8.54	(7.94, 9.19)
			LEZ763 300 mg	16	8.35	(7.76, 8.99)
			LEZ763 600 mg	15	8.10	(7.51, 8.74)
			Sitagliptin 100 mg	14	8.19	(7.58, 8.86)
			Placebo	15	8.77	(8.12, 9.46)
Glucose	Fasting value	DAY28	LEZ763 25 mg	16	8.44	(7.80, 9.13)
			LEZ763 100 mg	16	8.19	(7.57, 8.87)
			LEZ763 300 mg	16	8.15	(7.53, 8.82)
			LEZ763 600 mg	15	8.05	(7.41, 8.73)
			Sitagliptin 100 mg	14	7.95	(7.31, 8.65)
			Placebo	14	8.51	(7.82, 9.26)

Part III – Summary statistics of pharmacokinetic parameters for LEZ763 and sitagliptin (Safety analysis set)

		AUCtau (h*ng/mL)		Cmax (ng/mL)		Tmax (h)		AF_AUC (1)		AF_Cmax (1)	
Visit	**Statistics**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**
LEZ763 25 mg											
DAY1	n	16		16		16					
	Mean (SD)	1320 (314)		205 (46.9)		1.75 (0.876)					
DAY27	n	16		16		16		16		16	
	Mean (SD)	1350 (271)		229 (153)		1.90 (1.64)		1.07 (0.288)		1.25 (1.19)	
DAY28	n	16	16	16	16	16	16				
	Mean (SD)	1390 (463)	1440 (301)	195 (73.2)	230 (89.6)	1.75 (1.82)	1.16 (0.507)				
LEZ763 100 mg											
DAY1	n	16		16		16					
	Mean (SD)	6060 (2630)		746 (494)		2.59 (1.37)					
DAY27	n	16		16		16		16		16	
	Mean (SD)	6370 (3120)		710 (236)		3.81 (1.79)		1.06 (0.181)		1.10 (0.339)	
DAY28	n	16	15	16	15	16	15				
	Mean (SD)	6330 (1950)	1410 (349)	633 (160)	237 (98.1)	3.31 (2.10)	1.33 (0.556)				
LEZ763 300 mg											
DAY1	n	16		16		16					
	Mean (SD)	14800 (5970)		1340 (570)		3.47 (1.79)					
DAY27	n	16		16		16		16		16	
	Mean (SD)	17200 (5210)		1540 (387)		2.75 (1.52)		1.24 (0.480)		1.28 (0.581)	
DAY28	n	16	16	16	16	16	16				
	Mean (SD)	19500 (6010)	1450 (258)	1590 (493)	235 (102)	4.11 (2.26)	1.41 (1.05)				

		AUCtau (h*ng/mL)		Cmax (ng/mL)		Tmax (h)		AF_AUC (1)		AF_Cmax (1)	
Visit	**Statistics**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**	**LEZ763**	**Sitagliptin**
LEZ763 600 mg											
DAY1	n	16		16		16					
	Mean (SD)	22800 (5890)		2010 (595)		4.44 (1.96)					
DAY27	n	15		15		15		15		15	
	Mean (SD)	26400 (12200)		2230 (870)		3.07 (1.97)		1.16 (0.476)		1.12 (0.292)	
DAY28	n	15	15	15	15	15	15				
	Mean (SD)	29500 (13000)	1680 (389)	2250 (928)	294 (109)	4.24 (2.41)	1.10 (0.573)				
Placebo											
DAY28	n		13		13		13				
	Mean (SD)		1550 (286)		238 (99.9)		1.65 (1.13)				

(1) AF is the accumulation factor (equivalent to Racc; the accumulation ratio)

Summary of Safety

Safety Results

Part I - Incidence of AEs by primary system organ class - n (percent) of subjects (Safety analysis set)

	LEZ763 10 mg N=8 n (%)	**LEZ763 30 mg N=8 n (%)**	**LEZ763 100 mg N=8 n (%)**	**LEZ763 300 mg N=8 n (%)**	**LEZ763 600 mg N=8 n (%)**	**LEZ763 1200 mg N=8 n (%)**	**Placebo N=13 n (%)**	**Total N=61 n (%)**
Subjects with AE(s)	4 (50.0)	1 (12.5)	2 (25.0)	2 (25.0)	1 (12.5)	2 (25.0)	2 (15.4)	14 (23.0)
System organ class								
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (4.9)
General disorders and administration site conditions	3 (37.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	6 (9.8)
Infections and infestations	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (3.3)
Injury, poisoning and procedural complications	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

	LEZ763 10 mg N=8 n (%)	LEZ763 30 mg N=8 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=8 n (%)	LEZ763 1200 mg N=8 n (%)	Placebo N=13 n (%)	Total N=61 n (%)
Musculoskeletal and connective tissue disorders	1 (12.5)	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)
Nervous system disorders	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	3 (4.9)
Renal and urinary disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (3.3)

Part I - Incidence of AEs by preferred term (Safety analysis set)

	LEZ763 10 mg N=8 n (%)	LEZ763 30 mg N=8 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=8 n (%)	LEZ763 1200 mg N=8 n (%)	Placebo N=13 n (%)	Total N=61 n (%)
Subjects with AE(s)	4 (50.0)	1 (12.5)	2 (25.0)	2 (25.0)	1 (12.5)	2 (25.0)	2 (15.4)	14 (23.0)
Preferred term								
Back pain	1 (12.5)	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (4.9)
Escherichia urinary tract infection	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Haematuria	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Headache	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (3.3)
Muscle strain	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (1.6)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (1.6)
Urinary incontinence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (1.6)
Vessel puncture site pain	3 (37.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	6 (9.8)

Part II - Incidence of AEs by primary system organ class - n (percent) of subjects (Safety analysis set)

	LEZ763 30 mg N=9 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=12 n (%)	LEZ763 1200 mg N=12 n (%)	Placebo N=12 n (%)	Total N=61 n (%)
Subjects with AE(s)	2 (22.2)	3 (37.5)	5 (62.5)	2 (16.7)	5 (41.7)	5 (41.7)	22 (36.1)
System organ class							
Cardiac disorders	1 (11.1)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)

	LEZ763 30 mg N=9 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=12 n (%)	LEZ763 1200 mg N=12 n (%)	Placebo N=12 n (%)	Total N=61 n (%)
Eye disorders	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Gastrointestinal disorders	0 (0.0)	3 (37.5)	4 (50.0)	0 (0.0)	0 (0.0)	4 (33.3)	11 (18.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	2 (3.3)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	2 (16.7)	3 (4.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Nervous system disorders	0 (0.0)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (37.5)	0 (0.0)	2 (16.7)	2 (16.7)	1 (8.3)	8 (13.1)
Vascular disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Part II - Incidence of AEs by preferred term - n (percent) of subjects (Safety analysis set)

	LEZ763 30 mg N=9 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=12 n (%)	LEZ763 1200 mg N=12 n (%)	Placebo N=12 n (%)	Total N=61 n (%)
Subjects with AE(s)	2 (22.2)	3 (37.5)	5 (62.5)	2 (16.7)	5 (41.7)	5 (41.7)	22 (36.1)
Preferred term							
Body tinea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.6)
Chlamydial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.6)
Constipation	0 (0.0)	2 (25.0)	4 (50.0)	0 (0.0)	0 (0.0)	3 (25.0)	9 (14.8)
Dermatitis contact	0 (0.0)	3 (37.5)	0 (0.0)	2 (16.7)	2 (16.7)	1 (8.3)	8 (13.1)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.6)
Dizziness	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Ecchymosis	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.6)
Haematoma	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Headache	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

	LEZ763 30 mg N=9 n (%)	LEZ763 100 mg N=8 n (%)	LEZ763 300 mg N=8 n (%)	LEZ763 600 mg N=12 n (%)	LEZ763 1200 mg N=12 n (%)	Placebo N=12 n (%)	Total N=61 n (%)
Musculoskeletal pain	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Oral herpes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.6)
Palpitations	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Syncope	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Vessel puncture site pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.6)
Vision blurred	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Vomiting	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Part III - Incidence of AEs by primary system organ class - n (percent) of subjects (Safety analysis set)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Subjects with AE(s)	10 (62.5)	9 (56.3)	8 (50.0)	10 (62.5)	6 (37.5)	12 (75.0)	55 (57.3)
System organ class							
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	2 (2.1)
Gastrointestinal disorders	3 (18.8)	2 (12.5)	2 (12.5)	8 (50.0)	2 (12.5)	6 (37.5)	23 (24.0)
General disorders and administration site conditions	1 (6.3)	3 (18.8)	3 (18.8)	3 (18.8)	2 (12.5)	2 (12.5)	14 (14.6)
Immune system disorders	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Infections and infestations	1 (6.3)	2 (12.5)	1 (6.3)	4 (25.0)	0 (0.0)	0 (0.0)	8 (8.3)
Injury, poisoning and procedural complications	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	2 (2.1)
Investigations	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Metabolism and nutrition disorders	1 (6.3)	0 (0.0)	3 (18.8)	0 (0.0)	1 (6.3)	1 (6.3)	6 (6.3)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (6.3)	1 (6.3)	1 (6.3)	2 (12.5)	3 (18.8)	8 (8.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Nervous system disorders	2 (12.5)	3 (18.8)	1 (6.3)	3 (18.8)	2 (12.5)	2 (12.5)	13 (13.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	2 (2.1)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Respiratory, thoracic and mediastinal disorders	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	4 (4.2)
Skin and subcutaneous tissue disorders	1 (6.3)	3 (18.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	5 (5.2)
Vascular disorders	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (2.1)

Part III - Incidence of AEs by preferred term - n (percent) of subjects (Safety analysis set)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Subjects with AE(s)	10 (62.5)	9 (56.3)	8 (50.0)	10 (62.5)	6 (37.5)	12 (75.0)	55 (57.3)
Preferred term							
Abdominal distension	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Adnexa uteri pain	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Arthralgia	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (2.1)
Back pain	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	1 (6.3)	2 (12.5)	5 (5.2)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Blood pressure increased	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Cellulitis	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Constipation	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	1 (6.3)	0 (0.0)	4 (4.2)
Cough	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	3 (3.1)
Cystitis klebsiella	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Decreased appetite	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Dermatitis	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Dermatitis contact	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Diarrhoea	0 (0.0)	1 (6.3)	1 (6.3)	2 (12.5)	2 (12.5)	3 (18.8)	9 (9.4)
Dizziness	0 (0.0)	2 (12.5)	1 (6.3)	1 (6.3)	1 (6.3)	0 (0.0)	5 (5.2)
Dyspepsia	1 (6.3)	1 (6.3)	1 (6.3)	2 (12.5)	0 (0.0)	2 (12.5)	7 (7.3)
Ecchymosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Erectile dysfunction	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Furuncle	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Gastroenteritis	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Gastrooesophageal reflux disease	2 (12.5)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	4 (4.2)
Gingival pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.0)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	2 (2.1)
Haematuria	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Headache	2 (12.5)	1 (6.3)	0 (0.0)	3 (18.8)	1 (6.3)	0 (0.0)	7 (7.3)
Hot flush	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (2.1)
Hyperlipasaemia	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
Implant site haemorrhage	1 (6.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	5 (5.2)
Implant site pain	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Infusion site inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Ingrowing nail	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Injection site discolouration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.0)
Insomnia	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Medical device site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Muscle strain	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	2 (2.1)
Nasal congestion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Nausea	1 (6.3)	1 (6.3)	1 (6.3)	4 (25.0)	1 (6.3)	1 (6.3)	9 (9.4)
Oedema peripheral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	2 (2.1)
Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Paraesthesia oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.0)
Renal failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Seasonal allergy	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Skin irritation	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Transaminases increased	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	0 (0.0)	0 (0.0)	4 (4.2)
Vessel puncture site haemorrhage	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	2 (2.1)
Vessel puncture site pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.0)
Vessel puncture site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.0)
Vessel puncture site swelling	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	2 (2.1)

	LEZ763 25 mg N=16 n (%)	LEZ763 100 mg N=16 n (%)	LEZ763 300 mg N=16 n (%)	LEZ763 600 mg N=16 n (%)	Placebo N=16 n (%)	Sitagliptin 100 mg N=16 n (%)	Total N=96 n (%)
Vomiting	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	3 (3.1)

There were no deaths reported in this study. There were no SAEs reported in Parts I and II of this study

One AE was reported as an SAE in Part III; a patient in the LEZ763 600 mg arm experienced abdominal pain due to adenocarcinoma of the colon, the event occurred approximately 27 days after the last dose of study drug and was not suspected to be related to study drug. The SAE was assessed as severe but not suspected as related to study drug.

Other Relevant Findings

N/A

Conclusion:

All parts of this study assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of LEZ763 after single and multiple ascending doses. LEZ763 was generally safe and well tolerated in both healthy subjects and patients with T2DM. In this study, the highest dose of LEZ763 tested was 1200 mg, and was administered in Part II for 10 days. The incidence (41.7%) of AEs was equivalent to that of placebo treated group, and none were attributable to the LEZ763, indicating that the maximum tolerated dose was greater than 1200 mg.

In addition, 28 days of dosing LEZ763 (25 to 600 mg q.d) in patients with T2DM was also generally safe and well tolerated. The incidence of treatment-related AEs was higher (18 - 25%) in the LEZ763 treatment groups than in the placebo group (6%), but the AEs were mild or moderate in severity, no patient discontinued due to AE. One SAE was reported in one subject who received 600 mg LEZ763. Of the 96 patients with T2DM enrolled, 92 of them completed the entire study. Among the four patients who discontinued, three withdrew consent and one was discontinued for lack of compliance.

LEZ763 exposure (AUC and Cmax) increased with increasing dose in a less than dose proportional manner. The elimination half-life of LEZ763 was in the range of 4.3 to 15.9 hours over the dose range studied, which trended to increase with dose. Ten days of once daily LEZ763 dosing (30 - 1200 mg) led to minimal accumulation. Overall the pharmacokinetics of LEZ763 is similar between healthy subjects and subjects with T2DM. Neither sitagliptin nor LEZ763 significantly altered the pharmacokinetic parameters of the other.

Similar pharmacodynamic effects shown in Parts I and II were also observed in patients with T2DM in Part III. LEZ763 showed minimal effects on the key clinical surrogate endpoint of glucose excursion following a meal tolerance test. The reduction in glucose AUC was 3-8%, which was not statistically significant. The active comparator, sitagliptin, resulted in a significant glucose lowering effects of 14%, which is consistent with previous report. This further confirms the quality of the current study and confirms the validity of these study results.

Overall, LEZ763 was well tolerated by both the healthy volunteers at dose up to 1200 mg q.d. for 10 days and by patients with T2DM at dose up to 600 mg for 28 days. There were no dose-limiting toxicities observed even at the highest dose tested (1200 mg dosed q.d. for 10 days), indicating that the MTD is greater than 1200mg.

Date of Clinical Trial Report

02 September 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

02 September 2014

Date of Latest Update

Not Applicable

Reason for Update

Not applicable