Clinical trial results:
A Randomized, Open-Label, Active-Controlled, 3-Arm Parallel-Group, 26-Week Study Comparing the Efficacy and Safety of Lixisenatide to That of Insulin Glulisine Once Daily and Insulin Glulisine Three Times Daily in Patients With Type 2 Diabetes Insufficiently Controlled With Insulin Glargine With or Without Metformin

Summary

EudraCT number	2012-004096-38
Trial protocol	CZ GB HU ES IT DE PL EE LV LT
Global end of trial date	03 December 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EFC12626

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01768559
WHO universal trial number (UTN)	U1111-1131-4936
Other trial identifiers	Study Name: GETGOAL DUO-2

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate in subjects with type 2 diabetes mellitus (T2DM) not adequately controlled on insulin glargine with or without metformin: The non-inferiority of lixisenatide versus insulin glulisine once daily (QD) (Basal Plus regimen) on glycated hemoglobin A1c (HbA1c) reduction at Week 26; The non-inferiority of lixisenatide versus insulin glulisine thrice daily (TID)(Basal Bolus regimen) on HbA1c reduction or superiority on body weight change at Week 26.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects received insulin glargine throughout the study. During the run-in phase, the dose of insulin glargine was titrated every 3 days to maintain a fasting self-monitored plasma glucose (SMPG) between 80 and 100 mg/dL (4.4 and 5.6 mmol/L, respectively). After randomization, except during the 4 weeks following randomization where a stable dose should be maintained, the dose was adjusted weekly as necessary to maintain a fasting SMPG in the same range. Subjects who were receiving metformin prior to entering the study, continued to receive metformin at a dose of ≥1.5 g/day or at the maximal tolerated dose throughout the study, at a stable dose unless there was a specific safety issue related to this treatment.

Evidence for comparator: -

Actual start date of recruitment	08 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Hungary: 54

Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Canada: 65
Country: Number of subjects enrolled	Chile: 50
Country: Number of subjects enrolled	Mexico: 100
Country: Number of subjects enrolled	Romania: 118
Country: Number of subjects enrolled	Russian Federation: 86
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	United States: 138
Worldwide total number of subjects	894
EEA total number of subjects	401

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	616
From 65 to 84 years	277
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 199 centers in 18 countries between January 08, 2013 and December 03, 2014.

Pre-assignment

Screening details:

A total of 2159 subjects were screened. Subjects underwent a 12 week run–in period with switch from other basal insulins to insulin glargine. 1265 subjects were screen failures/run-in failures; the most frequent reason for run-in failure was that HbA1C criteria were not met at the end of run-in phase. A total of 894 subjects were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lixisenatide

Arm description:

Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin.

Arm type	Experimental
Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	AVE0010
Other name	Lyxumia®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide was self-administered QD by subcutaneous injection 30 to 60 minutes before breakfast or dinner using disposable pre-filled pen.

Arm title	Insulin Glulisine QD

Arm description:

Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.

Arm type	Experimental
Investigational medicinal product name	Insulin glulisine
Investigational medicinal product code	
Other name	Apidra®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glulisine was administered QD within 15 minutes before breakfast or dinner. The initial dose was 3-5 units and then individually titrated to obtain the SMPG value >5.6 mmol/L (100 mg/dL) and ≤7.8 mmol/L (140 mg/dL) before lunch (if administered at breakfast) or at bedtime (if administered at dinner).

Arm title	Insulin Glulisine TID

Arm description:

Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.

Arm type	Experimental

Investigational medicinal product name	Insulin glulisine
Investigational medicinal product code	
Other name	Apidra®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glulisine was administered TID within 15 minutes before each meal. The initial dose was 3-5 units for each meal and then individually titrated to obtain the SMPG value >5.6 mmol/L (100 mg/dL) and ≤7.8 mmol/L (140 mg/dL) before the next meal (for injections at breakfast or at lunch) or at bedtime (for injection at dinner).

Number of subjects in period 1	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID
Started	298	298	298
Treated	298	298	297
Completed	268	281	285
Not completed	30	17	13
Randomized but not treated	-	-	1
Adverse event	15	2	5
Other than specified	9	8	5
Poor compliance to protocol	-	3	2
Lack of efficacy	6	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin.	
Reporting group title	Insulin Glulisine QD
Reporting group description:	
Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.	
Reporting group title	Insulin Glulisine TID
Reporting group description:	
Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.	

Reporting group values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID
Number of subjects	298	298	298
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.8	60.2	59.4
standard deviation	± 8.6	± 8.6	± 9.5
Gender categorical Units: Subjects			
Female	160	163	166
Male	138	135	132
Race Units: Subjects			
Caucasian/White	276	280	272
Black	13	11	12
Asian/Oriental	9	7	13
Other	0	0	1
Ethnicity Units: Subjects			
Hispanic	63	58	68
Non-Hispanic	235	240	230
Metformin use at screening Units: Subjects			
Yes	262	260	259
No	36	38	39
Number of Subjects with Categorical Body Mass Index (BMI) Units: Subjects			
<30 kg/m^2	97	118	97
≥30 kg/m^2	201	180	200
Subjects not analyzed for BMI	0	0	1

BMI			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline BMI analysis.			
Units: kg/m^2			
arithmetic mean	32.27	31.86	32.5
standard deviation	± 4.57	± 4.39	± 4.6
Weight			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline weight analysis.			
Units: kg			
arithmetic mean	90.06	88.45	90.08
standard deviation	± 17.31	± 15.84	± 17.18
HbA1c			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for HbA1c analysis.			
Units: Percentage of hemoglobin			
arithmetic mean	7.77	7.73	7.79
standard deviation	± 0.55	± 0.59	± 0.6
Fasting Plasma Glucose (FPG)			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for FPG analysis.			
Units: mmol/L			
arithmetic mean	6.58	6.84	6.65
standard deviation	± 1.82	± 1.98	± 1.89
2-Hour Postprandial Plasma Glucose (PPG)			
258 subjects (79 in lixisenatide arm; 77 in Insulin Glulisine QD and 102 in Insulin Glulisine TID) were included for PPG analysis.			
Units: mmol/L			
arithmetic mean	14.26	14.02	14.25
standard deviation	± 3.55	± 3.59	± 3.35
2-Hour Glucose Excursion			
243 subjects (73 in lixisenatide arm; 74 in Insulin Glulisine QD and 96 in Insulin Glulisine TID) were included for 2-hour glucose excursion analysis.			
Units: mmol/L			
arithmetic mean	7.31	7.31	7.35
standard deviation	± 3.19	± 3.63	± 3.34
Average 7-Point SMPG			
877 subjects (292 in lixisenatide arm; 291 in Insulin Glulisine QD and 294 in Insulin Glulisine TID) were included for average 7-point SMPG analysis.			
Units: mmol/L			
arithmetic mean	9.02	9.07	8.99
standard deviation	± 1.75	± 1.74	± 1.57
Insulin Glargine Dose			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for insulin glargine dose analysis.			
Units: Units (U)			
arithmetic mean	67.25	64.72	64.97
standard deviation	± 31.95	± 32.07	± 26.9
Duration of Diabetes Units: years			
arithmetic mean	11.89	12.33	12.41

standard deviation	± 6.43	± 6.75	± 6.8

Reporting group values	Total		
Number of subjects	894		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	489		
Male	405		
Race Units: Subjects			
Caucasian/White	828		
Black	36		
Asian/Oriental	29		
Other	1		
Ethnicity Units: Subjects			
Hispanic	189		
Non-Hispanic	705		
Metformin use at screening Units: Subjects			
Yes	781		
No	113		
Number of Subjects with Categorical Body Mass Index (BMI) Units: Subjects			
<30 kg/m^2	312		
≥30 kg/m^2	581		
Subjects not analyzed for BMI	1		
BMI			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline BMI analysis.			
Units: kg/m^2 arithmetic mean standard deviation	- -		
Weight			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline weight analysis.			
Units: kg arithmetic mean standard deviation	- -		
HbA1c			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for HbA1c analysis.			

Units: Percentage of hemoglobin arithmetic mean standard deviation	- 		
Fasting Plasma Glucose (FPG)			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for FPG analysis.			
Units: mmol/L arithmetic mean standard deviation	- 		
2-Hour Postprandial Plasma Glucose (PPG)			
258 subjects (79 in lixisenatide arm; 77 in Insulin Glulisine QD and 102 in Insulin Glulisine TID) were included for PPG analysis.			
Units: mmol/L arithmetic mean standard deviation	- 		
2-Hour Glucose Excursion			
243 subjects (73 in lixisenatide arm; 74 in Insulin Glulisine QD and 96 in Insulin Glulisine TID) were included for 2-hour glucose excursion analysis.			
Units: mmol/L arithmetic mean standard deviation	- 		
Average 7-Point SMPG			
877 subjects (292 in lixisenatide arm; 291 in Insulin Glulisine QD and 294 in Insulin Glulisine TID) were included for average 7-point SMPG analysis.			
Units: mmol/L arithmetic mean standard deviation	- 		
Insulin Glargine Dose			
893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for insulin glargine dose analysis.			
Units: Units (U) arithmetic mean standard deviation	- 		
Duration of Diabetes Units: years arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin.	
Reporting group title	Insulin Glulisine QD
Reporting group description:	
Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.	
Reporting group title	Insulin Glulisine TID
Reporting group description:	
Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.	
Subject analysis set title	Insulin Glulisine QD
Subject analysis set type	Safety analysis
Subject analysis set description:	
Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin. 4 subjects were randomized to Insulin glulisine TID group, but received insulin glulisine QD for more than 50% of treatment period. These subjects were included in QD arm for safety analysis.	
Subject analysis set title	Insulin Glulisine TID
Subject analysis set type	Safety analysis
Subject analysis set description:	
Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin. 1 subject was randomized to Insulin glulisine QD group, but received insulin glulisine TID for more than 50% of treatment period. This subject was included in TID arm for safety analysis.	

Primary: Change in HbA1c From Baseline to Week 26

End point title	Change in HbA1c From Baseline to Week 26
End point description:	
Change in HbA1C was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using last on-treatment observation carried forward (LOCF). On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. mITT population: all randomized subjects who received at least one dose of study drug; and had both baseline and at least one post-baseline efficacy assessment, irrespective of compliance with study protocol/procedures. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during on-treatment period.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	292	292	295	
Units: Percentage of hemoglobin				
least squares mean (standard error)	-0.63 (± 0.054)	-0.58 (± 0.054)	-0.84 (± 0.053)	

Statistical analyses

Statistical analysis title	Lixisenatide vs Insulin Glulisine QD

Statistical analysis description:

Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use, and country as fixed effects and baseline HbA1c value as a covariate. The non-inferiority was assessed using upper bound of 2-sided 95% CI.

Comparison groups	Lixisenatide v Insulin Glulisine QD
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[1] - Pre-specified non-inferiority margin of 0.4%

Statistical analysis title	Lixisenatide vs Insulin Glulisine TID

Statistical analysis description:

Analysis was performed using ANCOVA model as described above. Hochberg procedure was used to control type 1 error at significance level = 0.025 (1-sided) for comparison between lixisenatide vs insulin glulisine TID in HbA1c and body weight. If both comparisons were met, then both would be declared significant. Otherwise, if only one was met, then the one met should be tested at α=0.0125 (1-sided).

Comparison groups	Lixisenatide v Insulin Glulisine TID
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.095
upper limit	0.328
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[2] - Pre-specified non-inferiority margin of 0.4%

Primary: Change in Body Weight From Baseline to Week 26

End point title	Change in Body Weight From Baseline to Week 26

End point description:

Change in body weight was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period.

End point type	Primary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	295	295	
Units: kg				
least squares mean (standard error)	-0.63 (± 0.276)	1.03 (± 0.276)	1.37 (± 0.271)	

Statistical analyses

Statistical analysis title	Lixisenatide vs Insulin Glulisine TID

Statistical analysis description:

Analysis was performed using ANCOVA model as described above. Hochberg procedure was used to control type 1 error at α = 0.025 (1-sided) for comparison between lixisenatide vs insulin glulisine TID in HbA1c and body weight . If both comparisons were met, then both would be declared significant. Otherwise, if only one was met, then the one met should be tested at α=0.0125 (1-sided).

Comparison groups	Lixisenatide v Insulin Glulisine TID
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.593
upper limit	-1.396
Variability estimate	Standard error of the mean
Dispersion value	0.305

Notes:

[3] - The superiority was assessed by comparing the P-value at significance level = 0.025 or 0.0125.

[4] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects with HbA1c level <7% and ≤6.5% at Week 26

End point title	Percentage of Subjects with HbA1c level <7% and ≤6.5% at Week 26

End point description:

The on-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	292	292	295	
Units: Percentage of subjects				
number (not applicable)				
HbA1c ≤6.5%	20.5	17.8	30.8	
HbA1c <7.0%	42.1	38.4	49.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Body Weight from Baseline to Week 26- Lixisenatide arm versus Insulin Glulisine QD arm

End point title	Change in Body Weight from Baseline to Week 26- Lixisenatide arm versus Insulin Glulisine QD arm

End point description:

Change in body weight was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	295	295	
Units: kg				
least squares mean (standard error)	-0.63 (± 0.276)	1.03 (± 0.276)	1.37 (± 0.271)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with no Weight Gain at Week 26

End point title	Percentage of Subjects with no Weight Gain at Week 26

End point description:

The on-treatment period for this efficacy variable was the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	295	295	
Units: Percentage of subjects				
number (not applicable)	64.7	36.6	30.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average 7-point SMPG Profiles from Baseline to Week 26

End point title	Change in Average 7-point SMPG Profiles from Baseline to Week 26

End point description:

Subjects recorded a 7-point plasma glucose profile measured before and 2 hours after each meal and at bedtime three times in a week before baseline, before visit Week 12 and before visit Week 26 and the average value across the profiles performed in the week a visit for the 7-time points was calculated. Change in average 7-point SMPG was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline 7-point SMPG assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	270	268	278	
Units: mmol/L				
least squares mean (standard error)	-0.784 (± 0.1141)	-0.782 (± 0.1133)	-1.053 (± 0.1105)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FPG from Baseline to Week 26

End point title	Change in FPG from Baseline to Week 26

End point description:

Change in FPG was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline FPG assessment during on-treatment period

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	295	294	
Units: mmol/L				
least squares mean (standard error)	-0.23 (± 0.143)	-0.21 (± 0.142)	-0.06 (± 0.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PPG from Baseline to Week 26 (in Subjects who had an Injection of Investigational Medicinal Product [IMP] Before Breakfast)

End point title	Change in PPG from Baseline to Week 26 (in Subjects who had an Injection of Investigational Medicinal Product [IMP] Before Breakfast)

End point description:

The 2-hour PPG test measured blood glucose 2 hours after eating a standardized meal. Change in PPG

was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with IMP injection before breakfast and baseline and at least one post-baseline 2-hour PPG assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	55	68	
Units: mmol/L				
arithmetic mean (standard deviation)	-3.93 (± 4.29)	-1.62 (± 4.01)	-1.87 (± 3.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Glucose Excursions from Baseline to Week 26 (in Subjects who had an Injection of IMP Before Breakfast)

End point title	Change in Glucose Excursions from Baseline to Week 26 (in Subjects who had an Injection of IMP Before Breakfast)

End point description:

Glucose excursion = 2-hour PPG minus plasma glucose 30 minutes prior to the standardized meal test, before study drug administration. Change in glucose excursions was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with IMP injection before breakfast and baseline and at least one post-baseline glucose excursion assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	53	66	
Units: mmol/L				
arithmetic mean (standard deviation)	-3.42 (± 4.13)	-1.59 (± 3.42)	-1.56 (± 2.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Insulin Glargine Dose From Baseline to Week 26

End point title	Change in Insulin Glargine Dose From Baseline to Week 26

End point description:

Change in Insulin glargine dose was calculated by subtracting the baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline insulin glargine dose assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	292	294	294	
Units: U				
least squares mean (standard error)	0.7 (± 1.002)	-0.06 (± 0.999)	-3.13 (± 0.982)	

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Glulisine Dose at Week 26

End point title	Insulin Glulisine Dose at Week 26[5]

End point description:

The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline insulin glulisine dose assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting results only for the arms in which Insulin Glulisine was administered.

End point values	Insulin Glulisine QD	Insulin Glulisine TID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	293		
Units: U				
arithmetic mean (standard deviation)	9.97 (± 7.8)	20.24 (± 13.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Insulin Dose at Week 26

End point title	Total Insulin Dose at Week 26[6]

End point description:

The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline total insulin dose assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting results only of the arms in which Insulin Glulisine was administered, and therefore Total Insulin was derived by adding the Insuline Glulisine amount and Insulin Glargine amount.

End point values	Insulin Glulisine QD	Insulin Glulisine TID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	294		
Units: U				
arithmetic mean (standard deviation)	73.61 (± 39.13)	81.05 (± 33.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Documented Symptomatic and Severe Symptomatic Hypoglycemia

End point title	Percentage of Subjects with Documented Symptomatic and Severe Symptomatic Hypoglycemia[7]

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <60 mg/dL (3.3 mmol/L). Severe symptomatic hypoglycemia was symptomatic hypoglycemia event in which the subject required the assistance of another person and was associated with either a plasma glucose level below 36 mg/dL (2.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration, if no plasma glucose measurement was available. Safety population included all randomized subjects who were exposed to at least one dose of study drug, regardless of the amount of treatment administered.

End point type	Secondary

End point timeframe:

First dose of study drug up to 3 days after the last dose administration (maximum of 185 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for safety set.

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	298	301	294	
Units: Percentage of subjects				
number (not applicable)				
Documented Symptomatic hypoglycemia	31.5	37.5	44.6	
Severe symptomatic hypoglycemia	0	0.7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Reached the Target of HbA1c <7% at Week 26 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period

End point title	Percentage of Subjects who Reached the Target of HbA1c <7% at Week 26 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period

End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for symptomatic hypoglycemia assessment was defined as the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Subjects without any post-baseline on-treatment value for HbA1c were counted as non-responders if they experienced at least one symptomatic hypoglycemia. Otherwise, they were counted as missing.

End point type	Secondary

End point timeframe:

Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	296	293	295	
Units: Percentage of subjects				
number (not applicable)	29.4	24.2	26.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Reached the Target of HbA1c <7% and had no Weight Gain at Week 26

End point title	Percentage of Subjects who Reached the Target of HbA1c <7% and had no Weight Gain at Week 26

End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for body weight assessment was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Subjects without post-baseline on-treatment values (for HbA1c and body weight) that were no more than 30 days apart were counted as non-responders if at least one of the components (HbA1c and/or body weight) was available and showed non-response. Otherwise, they were counted as missing data.

End point type	Secondary

End point timeframe:

Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	293	295	
Units: Percentage of subjects				
number (not applicable)	31.2	16.7	17.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Reached the Target of HbA1c <7%, had no Weight Gain at Week 26, and did not Experience Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period

End point title	Percentage of Subjects who Reached the Target of HbA1c <7%, had no Weight Gain at Week 26, and did not Experience Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period

End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for body weight assessment was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. The on-treatment period for symptomatic hypoglycemia assessment was defined as the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Subjects without post-baseline on-treatment values (HbA1c and body weight) that were no more than 30 days apart were counted as non-responders if at least one of the components (HbA1c and/or body weight) was available and showed non-response, or if they experienced at least one documented symptomatic hypoglycemia during the on-treatment period. Otherwise, they were counted as missing data.

End point type	Secondary

End point timeframe:

Week 26

End point values	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	297	294	295	
Units: Percentage of subjects				
number (not applicable)	22.2	9.2	10.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 185) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent adverse events that is AEs that developed/worsened and death that occurred during the 'on treatment period' (time from the first dose of study drug up to 3 days after the last dose of study drug). Analysis was done on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lixisenatide

Reporting group description:

Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin (Median exposure of 182 days).

Reporting group title	Insulin Glulisine QD

Reporting group description:

Insulin glulisine QD subcutaneously on top of insulin glargine with or without metformin (Median exposure of 182 days). 4 subjects were randomized to Insulin glulisine TID group, but received insulin glulisine QD for more than 50% of treatment period. These subjects were included in QD arm for safety analysis.

Reporting group title	Insulin Glulisine TID

Reporting group description:

Insulin glulisine TID subcutaneously on top of insulin glargine with or without metformin (Median exposure of 182 days). 1 subject was randomized to Insulin glulisine QD group, but received insulin glulisine TID for more than 50% of treatment period. This subject was included in TID arm for safety analysis.

Serious adverse events	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 298 (3.69%)	11 / 301 (3.65%)	14 / 294 (4.76%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			

subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm Malignant			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Uterine Cancer			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 298 (0.00%)	2 / 301 (0.66%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional Hernia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Complete			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Chronic			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac Failure Congestive			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebrovascular Accident			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	2 / 294 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic Unconsciousness			
subjects affected / exposed	0 / 298 (0.00%)	2 / 301 (0.66%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuritis Cranial			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epigastric Discomfort			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Haemorrhage			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Mass			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic Bullosis			

subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer Haemorrhage			
subjects affected / exposed	0 / 298 (0.00%)	0 / 301 (0.00%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Acute			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	1 / 294 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile Infection			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Arthritis Staphylococcal			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	1 / 298 (0.34%)	0 / 301 (0.00%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 298 (0.34%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 301 (0.33%)	0 / 294 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 298 (61.41%)	186 / 301 (61.79%)	195 / 294 (66.33%)
Investigations			
Blood Glucose Decreased			
subjects affected / exposed	60 / 298 (20.13%)	67 / 301 (22.26%)	82 / 294 (27.89%)
occurrences (all)	153	254	344
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 298 (0.00%)	12 / 301 (3.99%)	20 / 294 (6.80%)
occurrences (all)	0	15	21
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 298 (6.71%)	8 / 301 (2.66%)	12 / 294 (4.08%)
occurrences (all)	22	15	14
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 298 (6.71%)	10 / 301 (3.32%)	4 / 294 (1.36%)
occurrences (all)	21	12	4
Nausea			

subjects affected / exposed	75 / 298 (25.17%)	5 / 301 (1.66%)	3 / 294 (1.02%)
occurrences (all)	97	6	3
Vomiting			
subjects affected / exposed	26 / 298 (8.72%)	5 / 301 (1.66%)	6 / 294 (2.04%)
occurrences (all)	40	6	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 298 (4.70%)	21 / 301 (6.98%)	18 / 294 (6.12%)
occurrences (all)	16	23	18
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	107 / 298 (35.91%)	140 / 301 (46.51%)	154 / 294 (52.38%)
occurrences (all)	455	630	844

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2013	It included following changes: - Revised inclusion/exclusion criteria as follows: Glinides were added as allowed previous oral antidiabetic medication within 3 months before the study entry; Previous use of glucagon-like peptide 1 (GLP-1) receptor agonist (except lixisenatide) was changed from forbidden to allowed, provided that GLP-1 receptor agonist treatment was stopped for other reason than safety/tolerability issue or lack of efficacy - A new safety committee was added, the pancreatic safety assessment committee (PSAC), to ensure the independent assessment of pancreatic event data by external experts. The PSAC reviewed pancreatic events reported on a specific adverse event form. -Clarified that alanine aminotransferase (ALT) increase was to be reported as an adverse event of special interest (AESI) with immediate notification to be in line with the updated requirements for safety information collection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27222510