Clinical trial results:
AN OPEN-LABEL, RANDOMIZED, MULTI-CENTER, PARALLEL GROUP CLINICAL TRIAL COMPARING THE EFFICACY AND SAFETY OF MYLAN' S INSULIN GLARGINE WITH LANTUS® IN TYPE 2 DIABETES MELLITUS PATIENTS

Summary

EudraCT number	2014-000881-23
Trial protocol	SK
Global end of trial date	24 December 2015

Results information

Result version number	v1
This version publication date	02 July 2017
First version publication date	02 July 2017

Trial information

Trial identification

Sponsor protocol code	MYL-GAI-3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02227875
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 105279

Notes:

Sponsors

Sponsor organisation name	Mylan GmbH
Sponsor organisation address	Thurgauerstrasse 40, Zurich, Switzerland, 8050
Public contact	Keri L. Vaughan, Director Global Clinical Operations, General Medicine, Mylan, Inc, keri.vaughan@mylan.com
Scientific contact	Keri L. Vaughan, Director Global Clinical Operations, General Medicine, Mylan, Inc, keri.vaughan@mylan.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	29 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2015
Global end of trial reached?	Yes
Global end of trial date	24 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test whether Mylan’s insulin glargine once daily is non-inferior to Lantus® once daily (both administered in combination with other anti-diabetic drugs) based on the change in HbA1c from baseline to 24 weeks

Protection of trial subjects:

All study participants signed an Informed Consent Form prior to study participation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2014
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	Slovakia: 67
Country: Number of subjects enrolled	United States: 453
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Jordan: 5
Worldwide total number of subjects	560
EEA total number of subjects	67

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)	534
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

· Gender: male or female;
· Age: 18-65 years, inclusive;
· Body mass index (BMI): 18.5-40.0 kg/m2, inclusive.

Pre-assignment

Screening details:

Nine hundred fifty-one (951) patients were screened to participate in the study, and 560 patients were randomized to study treatment. Of 560 randomized patients, 228 were insulin-naïve.

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	MYL IG

Arm description:

Mylan’s insulin glargine

Arm type	Experimental
Investigational medicinal product name	Insulin Glargine - new formulation
Investigational medicinal product code	MYL-1501D
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL once daily

Arm title	Lantus

Arm description:

Lantus

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	Lantus®
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL daily

Number of subjects in period 1	MYL IG	Lantus
Started	277	283
Completed	240	250
Not completed	37	33
Consent withdrawn by subject	12	13
Physician decision	1	-
Adverse event, non-fatal	3	-
Other	1	3
Lost to follow-up	10	10
Protocol deviation	10	7

Baseline characteristics

Reporting groups	
Reporting group title	MYL IG
Reporting group description:	
Mylan’s insulin glargine	
Reporting group title	Lantus
Reporting group description:	
Lantus	

Reporting group values	MYL IG	Lantus	Total
Number of subjects	277	283	560
Age categorical			
Units: Subjects			
Adults (18-64 years)	267	267	534
Adults (65 years)	10	16	26
Age continuous			
Units: years			
arithmetic mean	55	55.1	
standard deviation	± 7.91	± 7.5	-
Gender categorical			
Units: Subjects			
Female	130	118	248
Male	147	165	312
Insulin history			
Units: Subjects			
Yes	165	167	332
No	112	116	228
Dosing time			
Units: Subjects			
Morning	68	71	139
Evening	209	212	421
Previous exposure to Insulin			
The mean duration of diabetes prior to entry into the study was 11.64 ± 6.57 years, with 332 (59.3%) patients having previously used insulin and 228 (40.7%) having been insulin-naïve. Of the 560 randomized patients, 330 (58.9%) reported previous exposure to insulin, with 230 (41.1%) reported having been insulin-naïve (Table 11 2). This discrepancy in the proportion of patients with prior insulin use was a result of data entry errors during randomization.			
Units: Subjects			
Naive	114	116	230
Non-naive	163	167	330
Geographic region			
Units: Subjects			
East Asia	4	4	8
East Europe	34	33	67
Middle East and Africa	14	18	32
North America	225	228	453

Weight Units: kg arithmetic mean standard deviation	 90.08 ± 16.97	 90.65 ± 18.395	 -
Height Units: cm arithmetic mean standard deviation	 168.57 ± 9.476	 168.95 ± 10.646	 -
BMI			
Body Mass Index			
Units: kg/m2 arithmetic mean standard deviation	 31.591 ± 4.7907	 31.544 ± 4.4357	 -
Duration of Diabetes Units: years arithmetic mean standard deviation	 11.955 ± 7.0957	 11.337 ± 6.0104	 -
Baseline fasting plasma blood glucose Units: mmol/L arithmetic mean standard deviation	 8.6 ± 2.96	 8.6 ± 3.06	 -
Baseline HbA1c Units: percent arithmetic mean standard deviation	 8.14 ± 1.142	 8.13 ± 1.135	 -

End points

End points reporting groups

Reporting group title	MYL IG
Reporting group description:	
Mylan’s insulin glargine	
Reporting group title	Lantus
Reporting group description:	
Lantus	
Subject analysis set title	Randomized Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The Randomized population includes all patients who were enrolled and randomized to study drug. For analyses and displays based on the Randomized population, patients were classified according to their randomized Treatment.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients who received at least one dose of study drug.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients (including patients who may have received the incorrect treatment, did not complete the study, did not comply with the protocol, or who consumed prohibited medication) who had a Baseline (Randomization visit) and at least 1 post-Baseline primary efficacy value.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population includes patients who completed the study and had HbA1c measurements in accordance with the protocol, who discontinued, but had at least 12 weeks of HbA1c data and who do not have protocol violations that could impact the primary outcome measure.	

Primary: Change in HbA1c from Baseline to Week 24

End point title	Change in HbA1c from Baseline to Week 24
End point description:	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[1]	278[2]		
Units: percentage				
least squares mean (confidence interval 95%)	-0.6 (-0.779 to -0.414)	-0.66 (-0.837 to -0.475)		

Notes:

[1] - Intent-To-Treat Population

[2] - Intent-To-Treat Population

Statistical analyses

Statistical analysis title	Mylan's Insulin Glargine versus Lantus
Comparison groups	MYL IG v Lantus
Number of subjects included in analysis	552
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Mixed-Effect Model for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	0.218
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Change in HbA1c over Time

End point title	Change in HbA1c over Time
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[3]	278[4]		
Units: percentage				
arithmetic mean (standard deviation)				
week 12	-0.57 (± 0.88)	-0.59 (± 0.9)		
week 24	-0.42 (± 1.038)	-0.47 (± 1.061)		

Notes:

[3] - Intent-To-Treat Population

[4] - Intent-To-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FPG over time

End point title	Change from Baseline in FPG over time

End point description:

End point type	Secondary

End point timeframe:

week 12 and 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[5]	278[6]		
Units: mmol/L				
arithmetic mean (standard deviation)				
week 12	-0.98 (± 2.829)	-1.15 (± 3.077)		
week 24	-0.74 (± 3.105)	-1.05 (± 3.043)		

Notes:

[5] - Intent-To-Treat Population

[6] - Intent-To-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 7-point SMBG profile over time

End point title	Change from Baseline in 7-point SMBG profile over time

End point description:

Overall average of SMBG Profile. Number of subjects analyzed indicates the number of subjects in the Intent-to-treat Population.

End point type	Secondary

End point timeframe:

week 12 and week 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[7]	278[8]		
Units: mmol/L				
arithmetic mean (standard deviation)				
week 12	-1.133 (± 2.2187)	-1.214 (± 2.3124)		
week 24	-0.98 (± 2.3947)	-1.333 (± 2.4255)		

Notes:
[7] - Intent-To-Treat Population
[8] - Intent-To-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in basal insulin dose per unit body weight from baseline over time

End point title	Change in basal insulin dose per unit body weight from baseline over time

End point description:

End point type	Secondary

End point timeframe:
week 12 and 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[9]	278[10]		
Units: U/Kg				
arithmetic mean (standard deviation)				
week 12	0.1062 (± 0.1198)	0.1065 (± 0.13013)		
week 24	0.1244 (± 0.13864)	0.122 (± 0.14184)		

Notes:
[9] - Intent-To-Treat Population
[10] - Intent-To-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients with HbA1c <7%

End point title	Proportion of Patients with HbA1c <7%

End point description:

End point type	Secondary

End point timeframe:
24 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274[11]	278[12]		
Units: count	63	68		

Notes:

[11] - Intent-To-Treat Population

[12] - Intent-To-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of hypoglycemic events per 30 days over time

End point title	Rate of hypoglycemic events per 30 days over time

End point description:

End point type	Secondary

End point timeframe:

Week 12 and 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[13]	282[14]		
Units: Episodes/30 Days				
arithmetic mean (standard deviation)				
week 12	0.341 (± 1.8963)	0.24 (± 2.0551)		
week 24	-0.057 (± 0.919)	-0.102 (± 1.6791)		

Notes:

[13] - Safety Population

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemia occurrence

End point title	Hypoglycemia occurrence

End point description:

Overall incidence

End point type	Secondary

End point timeframe:

24 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[15]	282[16]		
Units: number				
Any nocturnal hypoglycemic event	41	49		
Severe Hypoglycemia	0	1		
Documented Symptomatic Hypoglycemia	27	29		
Asymptomatic Hypoglycemia	18	21		
Probable Symptomatic Hypoglycemia	2	1		
Relative Hypoglycemia	6	3		
Other Nocturnal	0	0		

Notes:

[15] - Safety Population

[16] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of local and systemic reactions

End point title	Occurrence of local and systemic reactions

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[17]	282[18]		
Units: patients				
Local	2	1		
Systemic	2	1		

Notes:

[17] - Safety Population

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Insulin Antibody Percent Binding for Mylan's Insulin Glargine Assay over time

End point title	Change in Total Insulin Antibody Percent Binding for Mylan's Insulin Glargine Assay over time

End point description:

Comparison of change from Baseline in Immunogenicity

End point type	Secondary

End point timeframe:

Week 12 and week 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[19]	282[20]		
Units: %SB				
arithmetic mean (standard deviation)				
week 12	1.9238 (± 12.54369)	0.6585 (± 8.05473)		
week 24	1.7802 (± 9.64745)	0.7838 (± 8.15086)		

Notes:

[19] - Safety Population

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Insulin Antibody Percent Binding for Lantus Assay over time

End point title	Change in Total Insulin Antibody Percent Binding for Lantus Assay over time

End point description:

Comparison of change from Baseline in Immunogenicity

End point type	Secondary

End point timeframe:

week 12 and week 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[21]	282[22]		
Units: %SB				
arithmetic mean (standard deviation)				
week 12	1.787 (± 11.67578)	0.6462 (± 7.56375)		
week 24	1.6866 (± 9.57132)	0.8212 (± 8.1084)		

Notes:

[21] - Safety Population

[22] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cross-Reactive Insulin Antibody Percent Binding for Mylan's

Insulin Glargine Assay over time

End point title	Change in Cross-Reactive Insulin Antibody Percent Binding for Mylan's Insulin Glargine Assay over time

End point description:

Comparison of change from Baseline in Immunogenicity

End point type	Secondary

End point timeframe:

week 12 and week 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[23]	282[24]		
Units: %SB				
arithmetic mean (standard deviation)				
week 12	1.7488 (± 11.68129)	0.5116 (± 7.25175)		
week 24	1.6301 (± 9.11098)	0.7524 (± 7.93317)		

Notes:

[23] - Safety Population

[24] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cross-Reactive Insulin Antibody Percent Binding for Lantus Assay over time

End point title	Change in Cross-Reactive Insulin Antibody Percent Binding for Lantus Assay over time

End point description:

Comparison of change from Baseline in Immunogenicity

End point type	Secondary

End point timeframe:

Week 12 and week 24

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[25]	282[26]		
Units: %SB				
arithmetic mean (standard deviation)				
week 12	1.5994 (± 10.64782)	0.5014 (± 6.72058)		
week 24	1.5648 (± 9.04243)	0.8361 (± 7.96308)		

Notes:
[25] - Safety Population
[26] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	MYL IG
Reporting group description: Mylan’s insulin glargine	
Reporting group title	Lantus
Reporting group description: Lantus	

Serious adverse events	MYL IG	Lantus	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 276 (2.90%)	9 / 282 (3.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Helicobacter test positive			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 276 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 276 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			

subjects affected / exposed	1 / 276 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	MYL IG	Lantus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 276 (64.13%)	164 / 282 (58.16%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 276 (2.17%)	2 / 282 (0.71%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 276 (1.45%)	2 / 282 (0.71%)	
occurrences (all)	4	2	
Injection site pain			

subjects affected / exposed	3 / 276 (1.09%)	2 / 282 (0.71%)	
occurrences (all)	4	3	
Oedema peripheral			
subjects affected / exposed	2 / 276 (0.72%)	6 / 282 (2.13%)	
occurrences (all)	2	6	
Immune system disorders			
Seasonal allergy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 276 (0.36%)	4 / 282 (1.42%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 276 (1.81%)	5 / 282 (1.77%)	
occurrences (all)	5	5	
Cough			
subjects affected / exposed	4 / 276 (1.45%)	10 / 282 (3.55%)	
occurrences (all)	4	10	
Respiratory tract congestion			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	3	0	
Investigations			
Lipase increased			
subjects affected / exposed	4 / 276 (1.45%)	1 / 282 (0.35%)	
occurrences (all)	4	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 276 (0.36%)	4 / 282 (1.42%)	
occurrences (all)	1	4	
Laceration			
subjects affected / exposed	0 / 276 (0.00%)	4 / 282 (1.42%)	
occurrences (all)	0	4	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 276 (2.90%)	10 / 282 (3.55%)	
occurrences (all)	9	11	

Tremor			
subjects affected / exposed	6 / 276 (2.17%)	1 / 282 (0.35%)	
occurrences (all)	9	3	
Dizziness			
subjects affected / exposed	4 / 276 (1.45%)	7 / 282 (2.48%)	
occurrences (all)	4	8	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 276 (2.17%)	4 / 282 (1.42%)	
occurrences (all)	6	4	
Vomiting			
subjects affected / exposed	5 / 276 (1.81%)	5 / 282 (1.77%)	
occurrences (all)	5	5	
Diarrhoea			
subjects affected / exposed	4 / 276 (1.45%)	5 / 282 (1.77%)	
occurrences (all)	4	10	
Abdominal pain			
subjects affected / exposed	4 / 276 (1.45%)	1 / 282 (0.35%)	
occurrences (all)	4	1	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	3	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 276 (0.36%)	3 / 282 (1.06%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 276 (0.72%)	3 / 282 (1.06%)	
occurrences (all)	3	3	
Pruritus			

subjects affected / exposed	1 / 276 (0.36%)	3 / 282 (1.06%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	3	0	
Dysuria			
subjects affected / exposed	0 / 276 (0.00%)	3 / 282 (1.06%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 276 (2.54%)	6 / 282 (2.13%)	
occurrences (all)	7	6	
Pain in extremity			
subjects affected / exposed	5 / 276 (1.81%)	4 / 282 (1.42%)	
occurrences (all)	5	4	
Arthralgia			
subjects affected / exposed	4 / 276 (1.45%)	5 / 282 (1.77%)	
occurrences (all)	4	7	
Musculoskeletal pain			
subjects affected / exposed	2 / 276 (0.72%)	5 / 282 (1.77%)	
occurrences (all)	2	5	
Infections and infestations			
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 276 (6.16%)	15 / 282 (5.32%)	
occurrences (all)	19	15	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 276 (4.35%)	8 / 282 (2.84%)	
occurrences (all)	13	8	
Nasopharyngitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	10 / 276 (3.62%)	13 / 282 (4.61%)	
occurrences (all)	11	14	
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 276 (2.90%)	4 / 282 (1.42%)	
occurrences (all)	9	5	
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 276 (2.17%)	3 / 282 (1.06%)	
occurrences (all)	7	3	
Bronchitis			
subjects affected / exposed	4 / 276 (1.45%)	6 / 282 (2.13%)	
occurrences (all)	4	6	
Gastroenteritis			
subjects affected / exposed	5 / 276 (1.81%)	1 / 282 (0.35%)	
occurrences (all)	5	1	
Pharyngitis			
subjects affected / exposed	3 / 276 (1.09%)	1 / 282 (0.35%)	
occurrences (all)	3	1	
Pneumonia			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	3	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	3 / 276 (1.09%)	0 / 282 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	75 / 276 (27.17%)	66 / 282 (23.40%)	
occurrences (all)	330	282	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2014	- Planned number of insulin-naïve patients changed to 224 - Inclusion criterion for insulin-naïve patients added: 7.5 to 10.5 %HbA1c - Recommended starting dose for insulin-naïve patients added - Retinal photography added - Clarification on recording Insulin dose added - Titration committee added - Clarification added regarding recording of device-related safety - Immunogenicity sampling added at visit 2 and visit 4 - Measurement and analysis of cross-reacting antibody added - Treatment compliance criteria modified - Clarification of analysis of insulin-naïve group added - Clarifications and minor editorial corrections
30 July 2015	• Planned number of insulin-naïve patients changed to 224 • Inclusion criterion for insulin-naïve patients added: 7.5 to 10.5% HbA1c • Recommended starting dose for insulin-naïve patients added • Clarification added regarding recording of device-related safety • Immunogenicity sampling added at visit 2 and visit 4 • Add other additional study related items
23 December 2015	- Text that refers to the extension study has been removed. - Clarification made that patients will go back to their prescribed medication after the treatment period. - The brief summary of the extension study has been removed from the Study Design section. - The addendum containing the extension study protocol has been removed. Logistical issues prevented the establishment in time of systems required to conduct the study. Hence the sponsor decided to halt the extension study, to maintain good clinical practice and a sound scientific approach. This step was not prompted by any known or suspected safety concerns.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes: