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 1 DIABETES MELLITUS PATIENTS

Summary

EudraCT number	2014-000747-32
Trial protocol	SK CZ DE GB EE HU LV
Global end of trial date	07 July 2016

Results information

Result version number	v2 (current)
This version publication date	23 June 2018
First version publication date	21 July 2017
Version creation reason	• Correction of full data set Following CSR Amendment, Week 52 secondary endpoint values required update; Incident rate of adverse event 'Depression' did not have enough occurrences to meet reporting requirements

Trial information

Trial identification

Sponsor protocol code	MYL-GAI-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02227862
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 Vaughan, Director Global Clinical Operations, General Medicine, Mylan, Inc, keri.vaughan@mylan.com
Scientific contact	Keri 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	13 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2016
Global end of trial reached?	Yes
Global end of trial date	07 July 2016
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 (based on change in HbA1c from baseline to 24 weeks) when administered in combination with mealtime insulin lispro.

Protection of trial subjects:

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

Background therapy:

Humalog

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	Canada: 25
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	United States: 227
Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Slovakia: 66
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Hungary: 48
Country: Number of subjects enrolled	Latvia: 36
Worldwide total number of subjects	558
EEA total number of subjects	290

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)	547
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

· Gender: male or female;
· Age: 18-65 years, inclusive;
· Body mass index (BMI): 18.5-35.0 kg/m2, inclusive.

Pre-assignment

Screening details:

Eight hundred eighty-three (883) patients were screened to participate in the study, six hundred and nine (609) patients entered the run-in period, and Five Hundred fifty eight (558) patients were randomized to study treatment.

Pre-assignment period milestones

Number of subjects started	609[1]
Number of subjects completed	558

Pre-assignment subject non-completion reasons

Reason: Number of subjects	The Study Prematurely Terminated By Investigator: 1
Reason: Number of subjects	Lost to follow-up: 5
Reason: Number of subjects	Other: 2
Reason: Number of subjects	Protocol deviation: 5
Reason: Number of subjects	Failed To Meet Inclusion Or Exclusion Criteria: 13
Reason: Number of subjects	Consent withdrawn by subject: 19
Reason: Number of subjects	Reason not collected: 6

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects per country, from which the worldwide number enrolled in the trial is calculated, represent the subjects in the treatment period, which were randomized to study medication (see also Screening Details).

Period 1

Period 1 title	Active Treatment Phase (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 IU/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 IU/mL once daily

Number of subjects in period 1	MYL IG	Lantus
Started	280	278
Week24	269	263
Completed	261	256
Not completed	19	22
Consent withdrawn by subject	7	6
Adverse event, non-fatal	4	3
Other	-	2
Lost to follow-up	1	2
Protocol deviation	7	9

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	280	278	558
Age categorical Units: Subjects			
Adults (18-64 years)	275	272	547
From 65-84 years	5	6	11
Age continuous Units: years			
arithmetic mean	42	42.2	
standard deviation	± 12.03	± 11.97	-
Gender categorical Units: Subjects			
Female	116	106	222
Male	164	172	336
Race Units: Subjects			
Asian	2	2	4
Black	2	5	7
Caucasian	263	265	528
Hispanic	6	3	9
Other	7	3	10
Geographic Region Units: Subjects			
Europe	145	145	290
North America	126	126	252
South Africa	9	7	16
Insulin History Units: Subjects			
Yes	280	277	557
No	0	1	1
Dosing Time Units: Subjects			
Morning	38	40	78
Evening	242	238	480
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	26.435	26.636	
standard deviation	± 3.7058	± 4.2022	-
Duration of Diabetes			

Units: years			
arithmetic mean	18.685	19.697	
standard deviation	± 11.7771	± 11.2868	-
Baseline fasting plasma blood glucose			
Units: mg/dL			
arithmetic mean	167.4	163.9	
standard deviation	± 68.43	± 61.61	-
Baseline HbA1c			
Units: percent			
arithmetic mean	7.37	7.39	
standard deviation	± 0.869	± 0.843	-
Baseline fasting C-peptide			
Units: mmol/L			
arithmetic mean	0.298	0.291	
standard deviation	± 0.2291	± 0.2508	-

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:	
All patients who were enrolled and randomized to study drug.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population included patients who were randomized and took at least 1 dose of the study drug	
Subject analysis set title	Intent to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) Population included all randomized patients (including patients who received incorrect treatment, did not complete the study or did not comply with the protocol) and had ≥ 1 baseline (randomization visit) and 1 post-baseline value.	
Subject analysis set title	Per-protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol (PP) Population included patients who completed the study at Week 24, and had HbA1c measurements as per the protocol, or had at least 12week HbA1c data (for patients who discontinued prematurely), and did not have protocol violations (significant protocol deviations) that impacted the primary outcome.	

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	280[1]	277[2]		
Units: percent				
least squares mean (standard error)	0.14 (± 0.054)	0.11 (± 0.054)		

Notes:

[1] - Intent-to-Treat Population

[2] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Mixed Effect Repeated Measure model
Comparison groups	Lantus v MYL IG
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.117
Variability estimate	Standard error of the mean
Dispersion value	0.046

Secondary: Summary of Actual and Change from Baseline in HbA1c

End point title	Summary of Actual and Change from Baseline in HbA1c

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[3]	277[4]		
Units: percent				
arithmetic mean (standard deviation)				
week 24	0.12 (± 0.599)	0.09 (± 0.526)		
week 52	0.2 (± 0.633)	0.25 (± 0.595)		

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:
52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[5]	277[6]		
Units: mmol/L				
arithmetic mean (standard deviation)				
week 24	-0.81 (± 4.485)	0.09 (± 4.507)		
week 52	0.23 (± 4.281)	0.43 (± 4.455)		

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 8-point SMBG profile over time

End point title	Change from Baseline in 8-point SMBG profile over time

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[7]	277[8]		
Units: mmol/L				
arithmetic mean (standard deviation)				
week 24	0.038 (± 2.3751)	-0.095 (± 1.5012)		
week 52	-0.082 (± 1.5032)	-0.082 (± 1.5267)		

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in total daily insulin dose per unit body weight from

	baseline over time

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[9]	277[10]		
Units: U/Kg				
arithmetic mean (standard deviation)				
week 24	0.0203 (± 0.09962)	0.0127 (± 0.10871)		
week 52	0.0278 (± 0.1044)	0.0138 (± 0.11372)		

Notes:

[9] - Intent-to-Treat Population

[10] - 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:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[11]	278[12]		
Units: Episodes/30 Days				
arithmetic mean (standard deviation)				
week 24	-5.162 (± 9.0724)	-4.93 (± 8.3815)		
week 52	-6.241 (± 9.214)	-5.765 (± 8.3658)		

Notes:

[11] - Safety Population

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemia occurrence

End point title	Hypoglycemia occurrence

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[13]	278[14]		
Units: Number of patients				
Any hypoglycemic event	273	269		
Severe Hypoglycemia	11	13		
Documented Symptomatic Hypoglycemia	249	249		
Asymptomatic Hypoglycemia	246	243		
Probable Symptomatic Hypoglycemia	37	36		
Relative Hypoglycemia	35	44		
Other Hypoglycemia	19	19		
Unknown	77	71		

Notes:

[13] - Safety Population

[14] - 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:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[15]	278[16]		
Units: number of patients				
Local	3	4		
Systemic	2	2		

Notes:
[15] - Safety Population
[16] - 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: per cent Specific Binding (%SB)	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[17]	278[18]		
Units: %SB				
arithmetic mean (standard deviation)				
week 24	-0.3063 (± 7.22075)	0.3592 (± 7.16624)		
week 52	-0.9591 (± 8.51754)	-1.0634 (± 8.42794)		

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 Lantus Assay over time

End point title	Change in Total Insulin Antibody Percent Binding for Lantus Assay over time
End point description:	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[19]	278[20]		
Units: %SB				
arithmetic mean (standard deviation)				
week 24	-0.215 (± 7.3298)	0.157 (± 7.411)		
week 52	-0.896 (± 8.5610)	-1.233 (± 8.623)		

Notes:

[19] - Safety Population

[20] - 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:

End point type	Secondary

End point timeframe:

52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[21]	278[22]		
Units: %SB				
arithmetic mean (standard deviation)				
week 24	-0.363 (± 7.1081)	0.27 (± 7.1204)		
week 52	-1.132 (± 8.3911)	-1.21 (± 8.4096)		

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 Lantus Assay over time

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

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[23]	278[24]		
Units: %SB				
arithmetic mean (standard deviation)				
week 24	-0.265 (± 7.2543)	0.055 (± 7.3985)		
week 52	-1.060 (± 8.4414)	-1.367 (± 8.6848)		

Notes:
[23] - Safety Population
[24] - Safety 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:
52 Weeks

End point values	MYL IG	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[25]	277[26]		
Units: patients				
week 24	73	84		
week 52	65	61		

Notes:
[25] - Intent-to-Treat Population
[26] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

56 Weeks

Adverse event reporting additional description:

After Week 52, all the patients resumed treatment as per local standard of care. A safety follow up visit was done at Week 56.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Lantus

Reporting group description: -

Reporting group title	MYL IG

Reporting group description: -

Serious adverse events	Lantus	MYL IG	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 278 (7.91%)	18 / 280 (6.43%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant oligodendroglioma			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 278 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 278 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Retinal artery occlusion			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 278 (0.00%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis minimal lesion			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	2 / 278 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			

subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 278 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral rash			

subjects affected / exposed	1 / 278 (0.36%)	0 / 280 (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			
Hypoglycaemia			
subjects affected / exposed	10 / 278 (3.60%)	7 / 280 (2.50%)	
occurrences causally related to treatment / all	3 / 16	1 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Lantus	MYL IG	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	236 / 278 (84.89%)	222 / 280 (79.29%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 278 (2.16%)	9 / 280 (3.21%)	
occurrences (all)	6	9	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 278 (1.44%)	5 / 280 (1.79%)	
occurrences (all)	4	6	
Oedema peripheral			
subjects affected / exposed	3 / 278 (1.08%)	4 / 280 (1.43%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	2 / 278 (0.72%)	4 / 280 (1.43%)	
occurrences (all)	2	4	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 278 (1.08%)	2 / 280 (0.71%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	5 / 278 (1.80%)	6 / 280 (2.14%)	
occurrences (all)	5	6	
Oropharyngeal pain			
subjects affected / exposed	3 / 278 (1.08%)	6 / 280 (2.14%)	
occurrences (all)	3	6	
Sinus congestion			
subjects affected / exposed	4 / 278 (1.44%)	4 / 280 (1.43%)	
occurrences (all)	4	4	
Asthma			
subjects affected / exposed	0 / 278 (0.00%)	5 / 280 (1.79%)	
occurrences (all)	0	6	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 278 (1.08%)	2 / 280 (0.71%)	
occurrences (all)	3	2	
Anxiety			
subjects affected / exposed	1 / 278 (0.36%)	3 / 280 (1.07%)	
occurrences (all)	1	3	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 278 (1.44%)	1 / 280 (0.36%)	
occurrences (all)	4	1	
Blood pressure increased			
subjects affected / exposed	3 / 278 (1.08%)	0 / 280 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 278 (0.72%)	3 / 280 (1.07%)	
occurrences (all)	2	3	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 278 (1.08%)	0 / 280 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			

subjects affected / exposed	14 / 278 (5.04%)	5 / 280 (1.79%)	
occurrences (all)	20	5	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 278 (0.00%)	4 / 280 (1.43%)	
occurrences (all)	0	5	
Diabetic neuropathy			
subjects affected / exposed	3 / 278 (1.08%)	1 / 280 (0.36%)	
occurrences (all)	3	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 278 (0.00%)	3 / 280 (1.07%)	
occurrences (all)	0	3	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	5 / 278 (1.80%)	2 / 280 (0.71%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 278 (2.16%)	10 / 280 (3.57%)	
occurrences (all)	8	10	
Diarrhoea			
subjects affected / exposed	4 / 278 (1.44%)	11 / 280 (3.93%)	
occurrences (all)	4	12	
Toothache			
subjects affected / exposed	5 / 278 (1.80%)	4 / 280 (1.43%)	
occurrences (all)	5	7	
Vomiting			
subjects affected / exposed	2 / 278 (0.72%)	6 / 280 (2.14%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	4 / 278 (1.44%)	0 / 280 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Microalbuminuria			
subjects affected / exposed	0 / 278 (0.00%)	3 / 280 (1.07%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	2 / 278 (0.72%)	9 / 280 (3.21%)	
occurrences (all)	4	13	
Back pain			
subjects affected / exposed	6 / 278 (2.16%)	5 / 280 (1.79%)	
occurrences (all)	7	5	
Muscle spasms			
subjects affected / exposed	0 / 278 (0.00%)	4 / 280 (1.43%)	
occurrences (all)	0	4	
Osteoarthritis			
subjects affected / exposed	0 / 278 (0.00%)	3 / 280 (1.07%)	
occurrences (all)	0	3	
Trigger finger			
subjects affected / exposed	3 / 278 (1.08%)	0 / 280 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	39 / 278 (14.03%)	25 / 280 (8.93%)	
occurrences (all)	58	37	
Upper respiratory tract infection			
subjects affected / exposed	33 / 278 (11.87%)	27 / 280 (9.64%)	
occurrences (all)	44	38	
Influenza			
subjects affected / exposed	12 / 278 (4.32%)	12 / 280 (4.29%)	
occurrences (all)	14	12	
Urinary tract infection			
subjects affected / exposed	10 / 278 (3.60%)	9 / 280 (3.21%)	
occurrences (all)	11	13	
Bronchitis			
subjects affected / exposed	8 / 278 (2.88%)	9 / 280 (3.21%)	
occurrences (all)	8	9	
Gastroenteritis			
subjects affected / exposed	6 / 278 (2.16%)	10 / 280 (3.57%)	
occurrences (all)	6	10	
Sinusitis			

subjects affected / exposed	8 / 278 (2.88%)	8 / 280 (2.86%)	
occurrences (all)	8	10	
Gastroenteritis viral			
subjects affected / exposed	7 / 278 (2.52%)	6 / 280 (2.14%)	
occurrences (all)	7	6	
Viral infection			
subjects affected / exposed	6 / 278 (2.16%)	5 / 280 (1.79%)	
occurrences (all)	6	5	
Pharyngitis			
subjects affected / exposed	2 / 278 (0.72%)	5 / 280 (1.79%)	
occurrences (all)	2	5	
Fungal infection			
subjects affected / exposed	3 / 278 (1.08%)	3 / 280 (1.07%)	
occurrences (all)	4	3	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 278 (0.72%)	4 / 280 (1.43%)	
occurrences (all)	2	6	
Rhinitis			
subjects affected / exposed	5 / 278 (1.80%)	1 / 280 (0.36%)	
occurrences (all)	5	1	
Respiratory tract infection			
subjects affected / exposed	3 / 278 (1.08%)	2 / 280 (0.71%)	
occurrences (all)	3	2	
Onychomycosis			
subjects affected / exposed	3 / 278 (1.08%)	1 / 280 (0.36%)	
occurrences (all)	3	1	
Musculoskeletal pain			
subjects affected / exposed	3 / 278 (1.08%)	5 / 280 (1.79%)	
occurrences (all)	3	5	
Respiratory tract infection viral			
subjects affected / exposed	3 / 278 (1.08%)	1 / 280 (0.36%)	
occurrences (all)	4	1	
Tonsillitis			
subjects affected / exposed	1 / 278 (0.36%)	3 / 280 (1.07%)	
occurrences (all)	1	3	
Vulvovaginal mycotic infection			

subjects affected / exposed	3 / 278 (1.08%)	1 / 280 (0.36%)	
occurrences (all)	3	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 278 (0.00%)	3 / 280 (1.07%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	166 / 278 (59.71%)	151 / 280 (53.93%)	
occurrences (all)	3168	3037	
Hyperglycaemia			
subjects affected / exposed	5 / 278 (1.80%)	3 / 280 (1.07%)	
occurrences (all)	6	3	
Hyperlipidaemia			
subjects affected / exposed	3 / 278 (1.08%)	2 / 280 (0.71%)	
occurrences (all)	3	2	
Hyperkalaemia			
subjects affected / exposed	0 / 278 (0.00%)	3 / 280 (1.07%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2014	Retinal photography added Clarification regarding recording device-related safety Immunogenicity sampling added at visit 10 and visit 12 Titration committee added Measurement and analysis of crossreacting antibody added Treatment compliance criteria modified Clarifications and minor editorial corrections

22 July 2015	Key statistical analyses added to the synopsis, to make the synopsis more comprehensive (synopsis). Clarification made to inclusion criterion #1 that patient signature for authorization to use protected health information is part of the ICF; and will not be collected on a separate form Clarification made in inclusion criterion #10 to indicate that oral contraception alone is also acceptable; and that only women of childbearing potential need to perform pregnancy test Clarification made in exclusion criterion #9 that patients will be excluded for ECG or laboratory abnormalities only if they are considered by the investigator to be clinically significant enough to make the patient ineligible Clarification made to exclude glucocorticoids by all routes which have systemic effects; not only oral, inhaled and intravenous Clarification made that dose titration of insulin glargine/Lantus® should be kept to a minimum from 0 to 24 weeks. In the previous version, the period between 0 and 12 weeks was not covered; though implied "Serum"/"plasma" glucose corrected to "capillary" glucose where appropriate Clarification made that serious or severe hypoglycemia will be reported as an SAE (as per reporting guidelines), and recorded on the AE CRF page; while other types of hypoglycemia will be captured only on the hypoglycemia CRF page, and not on the AE page The use of basal insulin more than once daily, or at more than the prescribed dose (though this is rare) - for specified periods - have been added as non-compliance criteria Patients with glucose levels between 270 and 271 mg/dL were inadvertently not covered in the insulin dose titration guidance tables; this has been corrected; and "human insulin regular" has been removed from the table; as it is not permitted in the trial (Appendix II) The definition of per-protocol population has been modified

04 May 2016	In the section Contact Details For Reporting Serious Adverse Events, the sentence "Any SAE occurring in a subject from consent until 28 days after the last dose of the study drug must be reported" has been replaced with "Any SAE occurring in a subject from consent until his/her last study visit/phone visit (scheduled or unscheduled) must be reported". • The Synopsis and section 2.1, Secondary objectives, Immunogenicity, the sentence "change from baseline in titer, incidence of ADA, anti-HCP and neutralizing antibodies" has been replaced with "incidence and change from baseline in the relative levels of ADA, incidence and change from baseline the relative levels of anti-HCP antibodies". The Synopsis, Schedule of Activities, Section 3.1, Section 6.3 and Section 6.6 have been modified to clarify that the required number of patients who qualify for the MYL-1501D-3003 study will not go through the Follow-Up Visit of MYLGAI-3001, but will continue in MYL-1501D-3003 after the completion of 52 week visit (EOT). • Synopsis, Schedule of Activities, Section 3.1 and Section 6.3.The following statement has been added in the Schedule of Activities: Patients who qualify for the MYL-1501D-3003 study will be requested to sign a new ICF (for MYL-1501D-3003) prior to enrollment or any study activity. • In the Synopsis and Section 6.6, the withdrawal criteria have been modified to remove text on use of prohibited medications and non-compliance. • Section 3.5, figure 1, was updated to include the opportunity to enroll into the MYL-1501D-3003 study. • Section 7.2.1 has been rewritten to reflect methodological changes. • In Section 7.2.2, the following sentences have been removed: "All designated samples will undergo a screening assay that allows for a 5% false positive rate, to identify the presence of anti-HCP. Samples identified as positive in the screening assay will then be tested in a confirmatory assay that employs either

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: