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: AN EXTENSION STUDY

Summary

EudraCT number	2015-004353-40
Trial protocol	CZ SK LV HU EE DE
Global end of trial date	10 March 2017

Results information

Result version number	v1 (current)
This version publication date	18 May 2018
First version publication date	18 May 2018

Trial information

Trial identification

Sponsor protocol code	MYL-1501D-3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02666430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mylan GmbH
Sponsor organisation address	Thurgauerstrasse 40, Zurich, Switzerland, 8050
Public contact	David Gillogly, Head of Global CO, Mylan, Inc., +1 724485-6581, David.Gillogly@mylan.com
Scientific contact	David Gillogly, Head of Global CO, Mylan, Inc., +1 724485-6581, David.Gillogly@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	10 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2017
Global end of trial reached?	Yes
Global end of trial date	10 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the equivalence of changes in HbA1C between two treatment sequence groups, when Mylan's insulin glargine and Lantus® are interchanged (Mylan's insulin glargine and Lantus® are 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: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
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: 3
Country: Number of subjects enrolled	United States: 67
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Latvia: 10
Worldwide total number of subjects	127
EEA total number of subjects	57

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)	122
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The enrolment period ranged from 18 December 2015 to 10 March 2017. A total of 60 study sites enrolled patients: 32 sites in North America (United States and Canada) and 28 sites in the European Union (EU) (Czech Republic, Estonia, Germany, Hungary, Latvia, and Slovakia).

Pre-assignment

Screening details:

A total of 129 patients were screened and 127 patients were randomized.

Period 1

Period 1 title	Baseline visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Mylan Insulin Glargine Sequence

Arm description:

Mylan Insulin Glargine / Lantus® / Mylan Insulin Glargine

Arm type	Experimental
Investigational medicinal product name	Mylan Insulin Glargine / Lantus® / Mylan Insulin Glargine
Investigational medicinal product code	MYL-1501D / Lantus® / MYL-1501D
Other name	Insulin Glargine - New Formulation / Insulin Glargine / Insulin Glargine New Formulation
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Flexible dose

Arm title	Lantus® Sequence

Arm description:

Lantus® / Lantus® / Lantus®

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

Dosage and administration details:

Flexible dose

Number of subjects in period 1	Mylan Insulin Glargine Sequence	Lantus® Sequence
Started	64	63
Completed	64	63

Period 2	
Period 2 title	Period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Mylan Insulin Glargine Sequence

Arm description: -

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

Dosage and administration details:
Flexible dose

Arm title	Lantus® Sequence

Arm description: -

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

Dosage and administration details:
Flexible dose

Number of subjects in period 2	Mylan Insulin Glargine Sequence	Lantus® Sequence
Started	64	63
Completed	63	62
Not completed	1	1
Adverse event, non-fatal	-	1
Lost to follow-up	1	-

Period 3	
Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Mylan Insulin Glargine Sequence
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lantus®
Investigational medicinal product code	Insulin Glargine
Other name	Lantus®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details: Flexible dose	
Arm title	Lantus® Sequence
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Lantus®
Investigational medicinal product code	Insulin Glargine
Other name	Lantus®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details: Flexible dose	

Number of subjects in period 3	Mylan Insulin Glargine Sequence	Lantus® Sequence
Started	63	62
Completed	62	58
Not completed	1	4
Consent withdrawn by subject	1	4

Period 4	
Period 4 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Mylan Insulin Glargine Sequence
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Mylan Insulin Glargine
Investigational medicinal product code	MYL-1501D
Other name	Insulin Glargine New Formulation
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details: Flexible dose	
Arm title	Lantus® Sequence
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Lantus®
Investigational medicinal product code	Insulin Glargine
Other name	Lantus®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details: Flexible dose	

Number of subjects in period 4	Mylan Insulin Glargine Sequence	Lantus® Sequence
Started	62	58
Completed	61	58
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description: Mylan Insulin Glargine / Lantus® / Mylan Insulin Glargine	
Reporting group title	Lantus® Sequence
Reporting group description: Lantus® / Lantus® / Lantus®	

Reporting group values	Mylan Insulin Glargine Sequence	Lantus® Sequence	Total
Number of subjects	64	63	127
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44.8	43.2	
standard deviation	± 11.43	± 12.69	-
Gender categorical Units: Subjects			
Female	23	27	50
Male	41	36	77
Race Units: Subjects			
Asian	2	0	2
Black	2	2	4
Hispanic	1	0	1
White	59	61	120
Geographic region Units: Subjects			
Europe	30	27	57
North America	34	36	70
Dosing time Units: Subjects			
Morning	11	12	23
Evening	53	51	104
Baseline HIV status Units: Subjects			
Negative	64	62	126
Positive	0	1	1
Baseline HBsAg Units: Subjects			
Negative	64	63	127
Baseline HCVAb Units: Subjects			
Low positive	0	1	1
Negative	64	62	126

Weight			
Units: kilogram(s)			
arithmetic mean	80.712	82.415	
standard deviation	± 16.5393	± 15.2942	-
Height			
Units: centimeter(s)			
arithmetic mean	173.299	174.092	
standard deviation	± 9.9451	± 8.5502	-
Body mass index			
Units: kilogram(s)/square meter			
arithmetic mean	26.744	27.134	
standard deviation	± 4.1795	± 4.4084	-
Duration of diabetes			
Units: years			
arithmetic mean	21.369	20.212	
standard deviation	± 12.8879	± 8.9657	-
Baseline fasting plasma blood glucose			
Units: millimole(s)/litre			
arithmetic mean	9.82	9.51	
standard deviation	± 3.455	± 4.099	-
Baseline HbA1c			
Units: percent			
arithmetic mean	7.64	7.87	
standard deviation	± 0.997	± 0.913	-

End points

End points reporting groups

Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description:	
Mylan Insulin Glargine / Lantus® / Mylan Insulin Glargine	
Reporting group title	Lantus® Sequence
Reporting group description:	
Lantus® / Lantus® / Lantus®	
Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description: -	
Reporting group title	Lantus® Sequence
Reporting group description: -	
Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description: -	
Reporting group title	Lantus® Sequence
Reporting group description: -	
Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description: -	
Reporting group title	Lantus® Sequence
Reporting group description: -	
Subject analysis set title	Mylan Insulin Glargine Sequence
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified ITT (mITT) population included all randomized patients (including patients who received incorrect treatment sequence, did not complete the trial or did not comply with the protocol, or used prohibited medication) and had at least one baseline (Week 0 visit) HbA1c value and one post-baseline HbA1c value at treatment Period 3 (24 < Week ≤ 36). The mITT was used for primary analysis.	
Subject analysis set title	Lantus® Sequence
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified ITT (mITT) population included all randomized patients (including patients who received incorrect treatment sequence, did not complete the trial or did not comply with the protocol, or used prohibited medication) and had at least one baseline (Week 0 visit) HbA1c value and one post-baseline HbA1c value at treatment Period 3 (24 < Week ≤ 36). The mITT was used for primary analysis.	
Subject analysis set title	Mylan Insulin Glargine Sequence
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 sequence, did not complete the trial or did not comply with the protocol, or used prohibited medication) and had baseline (Week 0 visit) and at least one post-baseline visit. The patients in the ITT population were analyzed according to the planned treatment sequence.	
Subject analysis set title	Lantus® Sequence
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 sequence, did not complete the trial or did not comply with the protocol, or used prohibited medication) and had baseline (Week 0 visit) and at least one post-baseline visit. The patients in the ITT population were analyzed according to the planned treatment sequence.	
Subject analysis set title	Mylan Insulin Glargine Sequence
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. The safety analysis was conducted according to the treatment that a patient actually received.

Subject analysis set title	Lantus® Sequence
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. The safety analysis was conducted according to the treatment that a patient actually received.

Primary: Change in HbA1C from Baseline

End point title	Change in HbA1C from Baseline

End point description:

End point type	Primary

End point timeframe:

Week 36

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61[1]	57[2]		
Units: percent				
least squares mean (standard error)	-0.05 (± 0.032)	-0.06 (± 0.034)		

Notes:

[1] - modified Intent-to-Treat population

[2] - modified Intent-to-Treat population

Statistical analyses

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

An ANCOVA was performed on the primary outcome variable. The model included region and sequence group as fixed effect and baseline value as covariate using the mITT population. A 95% CI for the difference between the two treatment sequence groups for mean change from baseline HbA1c at endpoint was produced using the ANCOVA method.

Comparison groups	Lantus® Sequence v Mylan Insulin Glargine Sequence
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.101

Notes:

[3] - The pre-defined equivalence margins are +/- 0.4. The 95% confidence interval of treatment-sequence difference is (-0.085, 0.101) and is within the pre-defined margins. Therefore, equivalence of Mylan's insulin glargine sequence to Lantus® sequence was established.

Secondary: Change from Baseline in Fasting Plasma Glucose

End point title	Change from Baseline in Fasting Plasma Glucose

End point description:

End point type	Secondary

End point timeframe:

36 weeks

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[4]	63[5]		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	-0.56 (± 3.458)	0.10 (± 4.521)		

Notes:

[4] - Intent-to-Treat-population

[5] - Intent-to-Treat-population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Average of SMBG Change from Baseline

End point title	Overall Average of SMBG Change from Baseline

End point description:

SMBG = self-monitored blood glucose

End point type	Secondary

End point timeframe:

36 weeks

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[6]	63[7]		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	-0.144 (± 1.2569)	-0.426 (± 1.1243)		

Notes:

[6] - Intent-to-Treat-population

[7] - Intent-to-Treat-population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Total Daily Insulin Dose

End point title	Change from Baseline Total Daily Insulin Dose

End point description:

End point type	Secondary

End point timeframe:

36 weeks

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[8]	63[9]		
Units: Units per kilogram				
arithmetic mean (standard deviation)	0.0016 (± 0.09239)	0.0023 (± 0.07712)		

Notes:

[8] - Intent-to-Treat population

[9] - Intent-to-Treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Local and Systemic Allergic Reactions

End point title	Local and Systemic Allergic Reactions

End point description:

End point type	Secondary

End point timeframe:

40 weeks

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[10]	63[11]		
Units: patients				
Local	1	1		
Systemic	1	0		

Notes:

[10] - Safety Population

[11] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemic Rate

End point title	Hypoglycemic Rate
End point description: Change from Baseline	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[12]	63[13]		
Units: Episodes/30 Days				
arithmetic mean (standard deviation)	0.627 (± 2.7180)	0.410 (± 4.0911)		

Notes:

[12] - Safety Population

[13] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemic incidence

End point title	Hypoglycemic incidence
End point description: Overall incidence	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[14]	63[15]		
Units: events	58	57		

Notes:

[14] - Safety Population

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Total Insulin Antibodies - Mylan Insulin Glargine Assay

End point title	Total Insulin Antibodies - Mylan Insulin Glargine Assay
End point description: Change from Baseline	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[16]	63[17]		
Units: percent binding				
arithmetic mean (standard deviation)	-2.098 (± 5.3826)	-2.474 (± 5.2505)		

Notes:
[16] - Safety Population
[17] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Total Insulin Antibodies - Lantus® Assay

End point title	Total Insulin Antibodies - Lantus® Assay
End point description: Change from Baseline	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[18]	63[19]		
Units: percent binding				
arithmetic mean (standard deviation)	-1.288 (± 4.9617)	-2.351 (± 5.3774)		

Notes:
[18] - Safety Population
[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Cross-Reactive Insulin Antibody - Mylan Insulin Glargine Assay	
End point title	Cross-Reactive Insulin Antibody - Mylan Insulin Glargine Assay
End point description: Change from Baseline	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[20]	63[21]		
Units: percent binding				
arithmetic mean (standard deviation)	-2.051 (± 5.3697)	-2.252 (± 5.1904)		

Notes:

[20] - Safety Population

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Cross-Reactive Insulin Antibody - Lantus® Assay	
End point title	Cross-Reactive Insulin Antibody - Lantus® Assay
End point description: Change from Baseline	
End point type	Secondary
End point timeframe: 36 weeks	

End point values	Mylan Insulin Glargine Sequence	Lantus® Sequence		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64[22]	63[23]		
Units: percent binding				
arithmetic mean (standard deviation)	-1.232 (± 4.8965)	-2.192 (± 5.1741)		

Notes:

[22] - Safety Population

[23] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 40 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	Mylan Insulin Glargine Sequence
Reporting group description: Mylan Insulin Glargine / Lantus® / Mylan Insulin Glargine	
Reporting group title	Lantus® Sequence
Reporting group description: Lantus® / Lantus® / Lantus®	

Serious adverse events	Mylan Insulin Glargine Sequence	Lantus® Sequence	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 64 (3.13%)	5 / 63 (7.94%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			

Myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (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 detachment			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (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			
Ketoacidosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
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: 2 %

Non-serious adverse events	Mylan Insulin Glargine Sequence	Lantus® Sequence	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 64 (64.06%)	42 / 63 (66.67%)	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	0 / 63 (0.00%) 0	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 4	1 / 63 (1.59%) 1	
Eye disorders Diabetic retinopathy subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	4 / 63 (6.35%) 4	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2 2 / 64 (3.13%) 2	0 / 63 (0.00%) 0 1 / 63 (1.59%) 1	
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0 1 / 64 (1.56%) 1	2 / 63 (3.17%) 2 2 / 63 (3.17%) 2	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	0 / 63 (0.00%) 0	
Psychiatric disorders Stress subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	0 / 63 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	2 / 63 (3.17%) 2	

Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Gastroenteritis viral			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Herpes zoster			
subjects affected / exposed	0 / 64 (0.00%)	3 / 63 (4.76%)	
occurrences (all)	0	3	
Influenza			
subjects affected / exposed	3 / 64 (4.69%)	2 / 63 (3.17%)	
occurrences (all)	3	2	
Nasopharyngitis			
subjects affected / exposed	3 / 64 (4.69%)	4 / 63 (6.35%)	
occurrences (all)	3	8	
Sinusitis			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	7 / 64 (10.94%)	5 / 63 (7.94%)	
occurrences (all)	8	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2016	Clarifications made regarding wording of primary and secondary objective of immunogenicity, estimated number of patients, collection period for adverse events, collection of medical history and prior and concomitant medications and dilated ophthalmoscopy/retinal photography testing. Modifications were also made to throughout the data analysis/statistical methods section, and minor editorial and formatting corrections were made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported