Clinical trial results:
Randomized, Double-blind, Placebo-controlled, Dose escalation, Study on Safety, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Pediatric Patients with Type 2 Diabetes Mellitus not Adequately Controlled With Metformin and/or Basal Insulin

Summary

EudraCT number	2015-005789-42
Trial protocol	ES Outside EU/EEA
Global end of trial date	27 January 2020

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	TDR14311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02803918
WHO universal trial number (UTN)	U1111-1176-6142

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000916-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate safety of 14-day repeated lixisenatide doses of 5 microgram [mcg], 10 mcg and 20 mcg as compared to placebo in paediatric subjects with Type 2 diabetes mellitus (T2DM).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy:

Metformin and/or basal insulin was used as non-investigational medicinal product and were administered according to local label.

Evidence for comparator: -

Actual start date of recruitment	17 May 2017
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	Spain: 1
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Mauritius: 5
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	South Africa: 1
Worldwide total number of subjects	23
EEA total number of subjects	1

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)	23
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 11 sites in 6 countries. A total of 23 subjects were screened between 17 May 2017 and 23 November 2019.

Pre-assignment

Screening details:

A total of 23 subjects were randomised and treated in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (matched to lixisenatide) was administered in abdominal area. Subjects were fasted for at least 1 hour prior to dosing.

Arm title	Lixisenatide

Arm description:

Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.

Arm type	Experimental
Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	AVE0010
Other name	Lyxumia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide was administered in abdominal area. Each subject underwent a dose escalation according to the following paradigm: 5 mcg (Day 1 to 14), then 10 mcg (Day 15 to 28) and 20 mcg (Day 29 to 42). Subjects were fasted for at least 1 hour prior to dosing.

Number of subjects in period 1	Placebo	Lixisenatide
Started	5	18
Completed	5	17
Not completed	0	1
Poor compliance to protocol	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.	
Reporting group title	Lixisenatide
Reporting group description:	
Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.	

Reporting group values	Placebo	Lixisenatide	Total
Number of subjects	5	18	23
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15.4	15.6	
standard deviation	± 1.5	± 1.0	-
Gender categorical Units: Subjects			
Female	3	13	16
Male	2	5	7
Body mass index (BMI) Units: Kilogram per square meter (kg/m^2)			
arithmetic mean	37.4	33.2	
standard deviation	± 3.6	± 4.8	-
Duration of diabetes Units: years			
arithmetic mean	3.5	1.6	
standard deviation	± 2.2	± 1.2	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.	
Reporting group title	Lixisenatide
Reporting group description:	
Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.	
Subject analysis set title	Lixisenatide 5 mcg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received a dose of lixisenatide 5 mcg as SC injection from Day 1 to Day 14.	
Subject analysis set title	Lixisenatide 10 mcg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received a dose of lixisenatide 10 mcg as SC injection from Day 15 to Day 28.	
Subject analysis set title	Lixisenatide 20 mcg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received a dose of lixisenatide 20 mcg as SC injection from Day 29 to Day 42.	

Primary: Safety profile: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Safety profile: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1][2]
End point description:	
Adverse event (AE): any untoward medical occurrence in a subject who received study drug and did not necessarily had a causal relationship with study treatment. Serious AEs (SAEs): Any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. AE of special interest (AESI): AE (serious/nonserious) of scientific and medical concern, specific to study drug or program, which were monitored and immediately notified to Sponsor. TEAEs: AEs that occurred or worsened or became serious during on-treatment phase (time from first study drug administration up to 3 days after last study drug administration [i.e., up to 45 days]). Analysis was performed on safety population which included subjects who were exposed to study drug regardless of amount of treatment administered.	
End point type	Primary
End point timeframe:	
From Baseline up to end-of-study (EOS; up to Day 45)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 5 mcg	Lixisenatide 10 mcg	Lixisenatide 20 mcg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	18	18
Units: subjects				
number (not applicable)				
Any TEAE	3	6	3	4
Severe TEAE	0	0	0	1
Ant TESAE	0	0	0	1
Any TEAE leading to death	0	0	0	0
Any TEAE leading to permanent discontinuation	0	0	0	0
Any TEAE of special interest (AESI)	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects by Anti-lixisenatide Antibodies (ADAs) Status (Positive/Negative)

End point title	Number of Subjects by Anti-lixisenatide Antibodies (ADAs) Status (Positive/Negative)[3][4]

End point description:

Number of subjects with ADAs status categorised as negative and positive were reported. Baseline was defined as the last values done on Baseline (Day -1) before first study drug administration. Analysis was performed on safety population.

End point type	Primary

End point timeframe:

Baseline (Day -1), Day 14, Day 28 and Day 42

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 5 mcg	Lixisenatide 10 mcg	Lixisenatide 20 mcg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	18	18
Units: subjects				
number (not applicable)				
Baseline: Negative	5	17	17	17
Baseline: Positive	0	1	1	1
Day 14: Negative	5	16	0	0
Day 14: Positive	0	2	0	0
Day 28: Negative	5	0	8	0
Day 28: Positive	0	0	9	0
Day 42: Negative	4	0	0	4
Day 42: Positive	1	0	0	14

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameter: Maximum Plasma Concentration Observed (Cmax) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point title	Pharmacokinetic (PK) Parameter: Maximum Plasma Concentration Observed (Cmax) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point description:

Cmax was defined as maximum plasma concentration observed during the respective treatment period, evaluated as per subject ADA status. Analysis was performed on PK population which included all subjects without any major deviations related to study drug administration and provided at least one blood sample for drug concentration measurement. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42

End point values	Lixisenatide 20 mcg			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: picogram/millilitre (pg/mL)				
arithmetic mean (standard deviation)				
ADA Negative (n = 4)	83.9 (± 25.2)			
ADA Positive (n = 11)	508 (± 453)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter : Time to Reach Maximum Plasma Concentration (tmax) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point title	Pharmacokinetic Parameter : Time to Reach Maximum Plasma Concentration (tmax) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point description:

tmax was defined as the time to reach Cmax, evaluated as per subject ADA status. Analysis was performed on the PK population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42

End point values	Lixisenatide 20 mcg			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: hours				
median (full range (min-max))				
ADA Negative (n = 4) ADA Positive (n = 11)	1.24 (0.98 to 2.50) 2.00 (0.50 to 4.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration (AUC) From Time 0 Hour to 4.5 Hours (AUC0-4.5) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point title	Area Under the Plasma Concentration (AUC) From Time 0 Hour to 4.5 Hours (AUC0-4.5) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

End point description:

AUC0-4.5 was defined as area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero (lixisenatide scale) to time 4.5 hours post-dose, evaluated as per subject ADA status. Analysis was performed on PK population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42

End point values	Lixisenatide 20 mcg			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: picogram*hour per millilitre (pg*h/mL)				
arithmetic mean (standard deviation)				
ADA Negative (n = 4) ADA Positive (n = 9)	267 (± 96.1) 2300 (± 1940)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Area Under the Plasma Glucose Concentration From Time 0 Hour to 4.5 Hours (AUC0-4.5) at Day 42

End point title	Change From Baseline in Area Under the Plasma Glucose Concentration From Time 0 Hour to 4.5 Hours (AUC0-4.5) at Day 42[5]

End point description:

AUC0-4.5 was defined as area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero (lixisenatide scale) to time 4.5 hours post-dose. Analysis was performed on pharmacodynamic (PD) population which included all randomised subjects without any important deviation related to study drug administration for whom the PD data was considered sufficient and interpretable. Here, 'number of subjects analysed' = subjects evaluable and had available data for this endpoint

End point type	Secondary

End point timeframe:

0.5 hour (prior to standardised breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours on Day -1 (baseline), pre-dose (0 hour), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 42

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 20 mcg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	17		
Units: millimoles*hour per litre (mmol*h/L)				
arithmetic mean (standard deviation)	13.84 (± 18.93)	-17.33 (± 12.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Day 14, Day 28 and Day 42

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Day 14, Day 28 and Day 42[6]

End point description:

Change in FPG was calculated by subtracting baseline value from Day 14, Day 28 and Day 42 values. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler and indicated that no subjects were involved in the PD analysis at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Days 14, 28 and 42

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 5 mcg	Lixisenatide 10 mcg	Lixisenatide 20 mcg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	18	18
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Day 14 (n = 5, 17, 0, 0)	1.73 (± 1.39)	-1.08 (± 1.84)	99999 (± 99999)	99999 (± 99999)
Day 28 (n = 5, 0, 18, 0)	2.35 (± 2.27)	99999 (± 99999)	-0.69 (± 2.76)	99999 (± 99999)
Day 42 (n = 5, 0, 0, 18)	2.91 (± 3.71)	99999 (± 99999)	99999 (± 99999)	-1.23 (± 2.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 1-Hour Postprandial Plasma Glucose (1-Hour-PPG) at Day 14, Day 28 and Day 42

End point title	Change From Baseline in 1-Hour Postprandial Plasma Glucose (1-Hour-PPG) at Day 14, Day 28 and Day 42[7]

End point description:

1-Hour PPG excursion was calculated as the difference between the plasma glucose value 1 hour post meal test (T1.5) and the plasma glucose value before time of injection (T0): 1-Hour-PPG excursion = PG-T1.5 - PG-T0. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler and indicated that no subjects were involved in the PD analysis at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Days 14, 28 and 42

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 5 mcg	Lixisenatide 10 mcg	Lixisenatide 20 mcg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	18	18
Units: mmol/L				
arithmetic mean (standard deviation)				
Day 14 (n = 5, 17, 0, 0)	0.42 (± 2.12)	-1.28 (± 2.36)	99999 (± 99999)	99999 (± 99999)
Day 28 (n = 5, 0, 18, 0)	-0.76 (± 3.45)	99999 (± 99999)	-3.12 (± 2.24)	99999 (± 99999)
Day 42 (n = 5, 0, 0, 16)	0.59 (± 2.33)	99999 (± 99999)	99999 (± 99999)	-3.19 (± 3.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 2-Hours Postprandial Plasma Glucose (2-Hours-PPG) at Day 14, Day 28 and Day 42

End point title	Change From Baseline in 2-Hours Postprandial Plasma Glucose (2-Hours-PPG) at Day 14, Day 28 and Day 42[8]

End point description:

2-Hours PPG excursion was calculated as the difference between the plasma glucose value 2 hours post meal test (T2.5) and the plasma glucose value before time of injection (T0): 2-Hours-PPG excursion = PG-T2.5 - PG-T0. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler at fields and indicated that no subjects were involved in the PD analysis at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Days 14, 28 and 42

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were planned to be collected and analysed for specified arms only.

End point values	Placebo	Lixisenatide 5 mcg	Lixisenatide 10 mcg	Lixisenatide 20 mcg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	18	18	18
Units: mmol/L				
arithmetic mean (standard deviation)				
Day 14 (n = 5, 17, 0, 0)	-1.43 (± 2.24)	-1.12 (± 1.73)	99999 (± 99999)	99999 (± 99999)
Day 28 (n = 5, 0, 18, 0)	-0.57 (± 2.36)	99999 (± 99999)	-2.75 (± 2.09)	99999 (± 99999)
Day 42 (n = 5, 0, 0, 17)	-0.08 (± 1.17)	99999 (± 99999)	99999 (± 99999)	-3.96 (± 3.17)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data were collected from signature of the informed consent form up to end-of-study (i.e. up to Day 45)

Adverse event reporting additional description:

TEAEs were defined as AEs that occurred or worsened or became serious during the on-treatment phase (the time from the first study drug administration up to 3 days after last study drug administration [i.e. up to Day 45]). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received a dose of placebo (matched to lixisenatide) as SC injection from Day 1 to Day 42.

Reporting group title	Lixisenatide

Reporting group description:

Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.

Serious adverse events	Placebo	Lixisenatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis Viral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
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: 0 %

Non-serious adverse events	Placebo	Lixisenatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	7 / 18 (38.89%)	
Investigations			

Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Weight Increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injection Site Pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	2 / 18 (11.11%)	
occurrences (all)	1	8	
Vomiting			

subjects affected / exposed	0 / 5 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 5 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2016	Following changes were made: -A part of the standard reporting text was deleted for unknown technical reasons in the finalisation procedure of the document. The reason for this Amendment was to re-include the standard reporting text. -Guidelines for reporting SAEs was updated.
19 July 2017	Following changes were made: - Inclusion Criterion: In order to accommodate local medical paediatric practice and clinical guidelines the global protocol did not specify the exact metformin dose. The other aspects of the Inclusion Criterion would not be changed as they were requirements. - Exclusion Criterion: Based on the local paediatric medical practice and clinical necessity, the utilisation of psychotropic agents would be accepted as long as the subjects were stabilised for at least three months on this therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported