Clinical trial results:
A Randomized, Double-blind, 2x2 Cross-over Euglycemic Clamp Study in Two Parallel Cohorts to Compare the Pharmacodynamic and Pharmacokinetic Properties of 0.4 and 0.6 U/kg/day Insulin Glargine (Toujeo®) with the Same Dose Levels of Insulin Degludec (Tresiba®) in Steady State After 8 Days Multiple Dosing Regimen in Patients with Diabetes Mellitus Type 1

Summary

EudraCT number	2015-004843-38
Trial protocol	DE
Global end of trial date	09 July 2016

Results information

Result version number	v1 (current)
This version publication date	23 July 2017
First version publication date	23 July 2017

Trial information

Trial identification

Sponsor protocol code	LPS14585

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sanofi-Aventis Groupe
Sponsor organisation address	54, rue de la Boetie , Paris, France, 75008
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pharmacodynamic (PD) profile of Toujeo with insulin degludec (Tresiba) in steady state in a euglycemic clamp after 8 days once-daily dosing regimen at 2 dose levels in Type 1 diabetes mellitus (T1DM) subjects. - To compare the pharmacokinetic (PK) profile of Toujeo with insulin degludec in steady state in a euglycemic clamp after 8 days once-daily dosing regimen at 2 dose levels in T1DM subjects. – To access safety and tolerability of Toujeo and insulin degludec over 8 days in once-daily dosing regimen at 2 dose levels in T1DM subjects.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2016
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	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a single center in Germany between 08 March 2016 and 09 July 2016.

Pre-assignment

Screening details:

A total of 48 subjects were randomized in 2 cohorts (cohort 1 and cohort 2) and were administered 2 treatments (Insulin glargine and Insulin degludec, both at 2 dose levels [0.4 U/kg/day and 0.6 U/kg/day for cohort 1 and cohort 2 respectively]) in a 2 treatment period-2 sequences cross-over design.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1:Insulin glargine 0.4 U/kg & Insulin degludec 0.4 U/Kg

Arm description:

Subjects received once daily dose of Insulin glargine (Test treatment 1 [T1]) or Insulin degludec (Reference treatment 1 [R1]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T1/R1 or R1/T1). A washout phase of 8-26 days was maintained between the two treatment periods.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901-U300
Other name	Toujeo®
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine (300 U/mL) 0.4 U/kg (T1) as subcutaneous injection over 8 days in either treatment period (period 1 and 2) according to the treatment sequence (T1/R1 or R1/T1).

Investigational medicinal product name	Insulin degludec
Investigational medicinal product code	
Other name	Tresiba®
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec (100 U/mL) 0.4 U/kg (R1) as subcutaneous injection over 8 days in either treatment period (period 1 and 2) according to the treatment sequence (T1/R1 or R1/T1).

Arm title	Cohort 2:Insulin glargine 0.6 U/kg & Insulin degludec 0.6 U/kg

Arm description:

Subjects received once daily doses of Insulin glargine (Test treatment 2 [T2]) or Insulin degludec (Reference treatment 2 [R2]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T2/R2 or R2/T2). A washout phase of 8-26 days was maintained between the two treatment periods.

Arm type	Experimental

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901-U300
Other name	Toujeo®
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine (300 U/mL) 0.6 U/kg (T2) as subcutaneous injection over 8 days in either treatment period (period 1 and 2) according to the treatment sequence (T2/R2 or R2/T2).

Investigational medicinal product name	Insulin degludec
Investigational medicinal product code	
Other name	Tresiba®
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec (100 U/mL) 0.6 U/kg (R2) as subcutaneous injection over 8 days in either treatment period (period 1 and 2) according to the treatment sequence (T2/R2 or R2/T2).

Number of subjects in period 1	Cohort 1:Insulin glargine 0.4 U/kg & Insulin degludec 0.4 U/Kg	Cohort 2:Insulin glargine 0.6 U/kg & Insulin degludec 0.6 U/kg
Started	24	24
Completed	23	23
Not completed	1	1
Consent withdrawn by subject	1	-
Withdrew due to adverse event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1:Insulin glargine 0.4 U/kg & Insulin degludec 0.4 U/Kg
Reporting group description:	
Subjects received once daily dose of Insulin glargine (Test treatment 1 [T1]) or Insulin degludec (Reference treatment 1 [R1]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T1/R1 or R1/T1). A washout phase of 8-26 days was maintained between the two treatment periods.	
Reporting group title	Cohort 2:Insulin glargine 0.6 U/kg & Insulin degludec 0.6 U/kg
Reporting group description:	
Subjects received once daily doses of Insulin glargine (Test treatment 2 [T2]) or Insulin degludec (Reference treatment 2 [R2]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T2/R2 or R2/T2). A washout phase of 8-26 days was maintained between the two treatment periods.	

Reporting group values	Cohort 1:Insulin glargine 0.4 U/kg & Insulin degludec 0.4 U/Kg	Cohort 2:Insulin glargine 0.6 U/kg & Insulin degludec 0.6 U/kg	Total
Number of subjects	24	24	48
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	43.7	41	
standard deviation	± 10.2	± 11.8	-
Gender categorical Units: Subjects			
Female	2	0	2
Male	22	24	46
Body mass index (BMI) Units: Kg/m^2			
arithmetic mean	25.42	25.99	
standard deviation	± 2.54	± 2.08	-
Glycohemoglobin (HbA1c) % Units: percentage of hemoglobin			
arithmetic mean	7.43	7.21	
standard deviation	± 1.01	± 0.8	-
Average Daily Basal Insulin Dose Units: U/Kg			
arithmetic mean	0.34	0.3	
standard deviation	± 0.14	± 0.08	-
Average Daily Prandial Insulin Dose Units: U/Kg			
arithmetic mean	0.33	0.29	
standard deviation	± 0.11	± 0.09	-
Average Daily Total Insulin Dose Units: U/Kg			
arithmetic mean	0.67	0.59	
standard deviation	± 0.16	± 0.14	-

End points

End points reporting groups

Reporting group title	Cohort 1:Insulin glargine 0.4 U/kg & Insulin degludec 0.4 U/Kg

Reporting group description:

Subjects received once daily dose of Insulin glargine (Test treatment 1 [T1]) or Insulin degludec (Reference treatment 1 [R1]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T1/R1 or R1/T1). A washout phase of 8-26 days was maintained between the two treatment periods.

Reporting group title	Cohort 2:Insulin glargine 0.6 U/kg & Insulin degludec 0.6 U/kg

Reporting group description:

Subjects received once daily doses of Insulin glargine (Test treatment 2 [T2]) or Insulin degludec (Reference treatment 2 [R2]) over 8 days in each treatment period (period 1 and 2) according to the treatment sequence (T2/R2 or R2/T2). A washout phase of 8-26 days was maintained between the two treatment periods.

Subject analysis set title	Insulin degludec 0.4 U/kg (R1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Insulin degludec (100 U/mL) 0.4 U/kg once daily over 8 days .

Subject analysis set title	Insulin glargine 0.4 U/kg (T1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Insulin glargine (300 U/mL) 0.4 U/kg once daily over 8 days.

Subject analysis set title	Insulin degludec 0.6 U/kg (R2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Insulin degludec (100 U/mL) 0.6 U/kg once daily over 8 days.

Subject analysis set title	Insulin glargine 0.6 U/kg (T2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Insulin glargine (300 U/mL) 0.6 U/kg once daily over 8 days.

Primary: Pharmacodynamics (PD): Fluctuation of the Glucose Infusion Rate (GIR) in Steady State Over the Dosing Interval of 24 Hours (GIR-smFL0-24)

End point title	Pharmacodynamics (PD): Fluctuation of the Glucose Infusion Rate (GIR) in Steady State Over the Dosing Interval of 24 Hours (GIR-smFL0-24)

End point description:

The individual fluctuation of the smoothed GIR 0-24 in steady state (GIR-smFL 0-24) after dosing on Day 8 was reported. It was calculated as the area between the individual smoothed GIR over time curve and the individual average GIR line from investigational medicinal product (IMP) administration on Day 8 until 24 hours after (within-day variability). It was measured by euglycemic clamp procedure in steady state. Analysis was performed on PD population defined as all subjects with no important deviations related to IMP intake and/or PD measurements for whom the PD parameters were available and evaluable. Clamps with less than 85% utility, incorrect dosing or a control deviation of more than 30 mg/dl during first 24 hours were excluded from the main PD analysis. A smoothing factor of 0.15 was used.

End point type	Primary

End point timeframe:

From start time of IMP administration up to 24 hours after dosing on Day 8

End point values	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)	Insulin glargine 0.6 U/kg (T2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	21	21	23
Units: mg/min/kg				
arithmetic mean (standard deviation)	0.46 (± 0.19)	0.38 (± 0.17)	0.48 (± 0.22)	0.45 (± 0.17)

Statistical analyses

Statistical analysis title	Test treatment 1 vs Reference treatment 1

Statistical analysis description:

For GIR-smFL 0-24, estimates and 90% confidence interval (CI) for the geometric means ratio of treatments (T1/R1) were obtained by computing estimate and 90% CI for the difference between treatment means within the linear mixed effects model framework, and then converting to ratio of geometric means by the antilog transformation. Total number of subjects in the analysis was 24 (21 evaluable for T1 and 24 evaluable for R1). Number of treatment ratios available for the analysis is 21.

Comparison groups	Insulin degludec 0.4 U/kg (R1) v Insulin glargine 0.4 U/kg (T1)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Geometric mean ratio
Point estimate	0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.66
upper limit	0.96

Notes:

[1] - PD profile of test treatment was compared to reference treatment.

Statistical analysis title	Test treatment 2 vs Reference treatment 2

Statistical analysis description:

For GIR-smFL 0-24, estimates and 90% confidence interval (CI) for the geometric means ratio of treatments (T2/R2) were obtained by computing estimate and 90% CI for the difference between treatment means within the linear mixed effects model framework, and then converting to ratio of geometric means by the antilog transformation. Total number of subjects in the analysis was 24 (23 evaluable for T2 and 21 evaluable for R2). Number of treatment ratios available for the analysis is 20.

Comparison groups	Insulin glargine 0.6 U/kg (T2) v Insulin degludec 0.6 U/kg (R2)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Geometric mean ratio
Point estimate	0.96

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.11

Notes:

[2] - PD profile of test treatment was compared to reference treatment.

Secondary: PD Profile in Steady state: Area under the GIR Over Time Curve up to 24 hours (GIR-AUC0-24); Maximum Smoothed Body Weight Standardized GIR (GIRmax) and Time to 50% of GIR AUC0-24 (T50%-GIR-AUC0-24)

End point title	PD Profile in Steady state: Area under the GIR Over Time Curve up to 24 hours (GIR-AUC0-24); Maximum Smoothed Body Weight Standardized GIR (GIRmax) and Time to 50% of GIR AUC0-24 (T50%-GIR-AUC0-24)

End point description:

The amount of glucose required (GIR-AUC) was a measure of insulin-mediated glucose uptake into tissues (glucose disposal or cumulative glucose lowering activity). GIR-AUC0-24 was a measure of area under the GIR over time curve up to 24 hours after dosing or end of clamp in case of premature termination or start of rescue insulin, whatever is earlier. T50%-GIR-AUC0-24 was the time to 50% of GIR-AUC0-24 and GIRmax was the maximum smoothed body weight standardized GIR. Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

From start time of IMP administration up to 24 h after dosing on day 8

End point values	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)	Insulin glargine 0.6 U/kg (T2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	21	21	23
Units: Provided in categories				
arithmetic mean (standard deviation)				
GIR-AUC0-24 (mg/kg)	1947.12 (± 1083.07)	1676.36 (± 1083.75)	3507.23 (± 1098.28)	2731.22 (± 1121.46)
T50%-GIR-AUC0-24 (hours)	12.79 (± 1.06)	12.6 (± 2)	12.24 (± 0.89)	11.96 (± 1.44)
GIRmax (mg/min/kg)	2.19 (± 0.97)	1.95 (± 0.98)	3.34 (± 0.91)	2.73 (± 0.99)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile (at Steady State) of Insulin Glargine 0.4 and 0.6 U/kg: Cmax, AUC0-24

End point title	PK Profile (at Steady State) of Insulin Glargine 0.4 and 0.6 U/kg: Cmax, AUC0-24

End point description:

Cmax: maximum concentration observed. AUC0-24: area under the serum concentration versus time curve was calculated using the trapezoidal method from time zero to 24 hours post dosing on Day 8. Analysis was performed on PK population defined as all subjects with no important deviations related to IMP intake and/or PK sampling for whom the PK parameters were available. During analysis, subjects

with missing data in 1 but not both periods were included in the analysis.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose on Day 8

End point values	Insulin glargine 0.4 U/kg (T1)	Insulin glargine 0.6 U/kg (T2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	24		
Units: Provided in categories				
arithmetic mean (standard deviation)				
Cmax (µU/mL)	13.2 (± 3.32)	19.3 (± 6.14)		
AUC0-24 (µU*h/mL)	265 (± 72.2)	391 (± 132)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile (at Steady State) of Insulin Degludec 0.4 and 0.6 U/kg: Cmax, AUC0-24

End point title	PK Profile (at Steady State) of Insulin Degludec 0.4 and 0.6 U/kg: Cmax, AUC0-24

End point description:

Cmax: maximum concentration observed. AUC0-24: area under the serum concentration versus time curve was calculated using the trapezoidal method from time zero to 24 hours post dosing on Day 8. Analysis was performed on PK population. During analysis, subjects with missing data in 1 but not both periods were included in the analysis.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose on Day 8

End point values	Insulin degludec 0.4 U/kg (R1)	Insulin degludec 0.6 U/kg (R2)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	23		
Units: specified in categories				
arithmetic mean (standard deviation)				
Cmax (µU/mL)	627 (± 128)	891 (± 147)		
AUC0-24 (µU*h/mL)	12400 (± 2620)	17600 (± 2970)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile (at Steady State): T50%-AUC0-24

End point title	PK Profile (at Steady State): T50%-AUC0-24

End point description:

T50%-AUC0-24: time to reach 50% of AUC0-24. Analysis was performed on PK population. During analysis, subjects with missing data in 1 but not both periods were included in the analysis.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose on Day 8

End point values	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)	Insulin glargine 0.6 U/kg (T2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	22	23	24
Units: hours				
arithmetic mean (standard deviation)	11.43 (± 0.43)	11.82 (± 0.63)	11.45 (± 0.54)	11.74 (± 0.59)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Profile: Relative Degree of Fluctuation (Frel)

End point title	PK Profile: Relative Degree of Fluctuation (Frel)

End point description:

Relative degree of fluctuation (percentage fluctuation) was calculated at steady state. Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

From start time of IMP administration up to 24 hours after dosing on day 8

End point values	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)	Insulin glargine 0.6 U/kg (T2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	22	23	24
Units: percentage fluctuation				
arithmetic mean (standard deviation)	48 (± 16)	44 (± 22)	49 (± 17)	42 (± 16)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (follow-up visit: up to Day 18 of treatment period 2) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events that is AEs that developed/worsened during on treatment phase, per period (time from the first IMP administration (included) until 3 days (Day 11) after the last dose of IMP). Safety population: all randomized subjects who were exposed to any IMP, regardless of the amount of treatment administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Insulin degludec 0.4 U/kg (R1)

Reporting group description:

Insulin degludec (100 U/mL) 0.4 U/kg once daily over 8 days.

Reporting group title	Insulin glargine 0.4 U/kg (T1)

Reporting group description:

Insulin glargine (300 U/mL) 0.4 U/kg once daily over 8 days.

Reporting group title	Insulin degludec 0.6 U/kg (R2)

Reporting group description:

Insulin degludec (100 U/mL) 0.6 U/kg once daily over 8 days.

Reporting group title	Insulin glargine 0.6 U/kg (T2)

Reporting group description:

Insulin glargine (300 U/mL) 0.6 U/kg once daily over 8 days.

Serious adverse events	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Insulin glargine 0.6 U/kg (T2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Insulin degludec 0.4 U/kg (R1)	Insulin glargine 0.4 U/kg (T1)	Insulin degludec 0.6 U/kg (R2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	20 / 23 (86.96%)	20 / 23 (86.96%)
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Drug Administered At Inappropriate Site			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Ligament Sprain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Procedural Dizziness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 24 (8.33%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	4	1	0
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pain In Extremity			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 23 (8.70%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Vestibular Neuronitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	14 / 24 (58.33%)	17 / 23 (73.91%)	20 / 23 (86.96%)
occurrences (all)	74	57	137

Non-serious adverse events	Insulin glargine 0.6 U/kg (T2)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 24 (91.67%)		

Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Drug Administered At Inappropriate Site			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Ligament Sprain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Procedural Dizziness			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		

Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 0 / 24 (0.00%) 0		
Psychiatric disorders Apathy subjects affected / exposed occurrences (all)	 0 / 24 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain In Extremity subjects affected / exposed occurrences (all)	 0 / 24 (0.00%) 0 0 / 24 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Vestibular Neuronitis subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 21 / 24 (87.50%) 102		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2016	Following changes were made: The vital signs and electrocardiogram (ECG) ranges for inclusion of T1DM subjects who were "otherwise healthy for T1DM by assessment of medical history and physical examination" were adjusted to known ranges in this population for systolic blood pressure (SBP) and diastolic blood pressure (DBP): 90 to 140 mmHg for SBP and 50 to 90 mmHg for DBP, and the upper limit for the QRS duration time to 110 ms.
21 March 2016	Following changes were made: Correction of inconsistence regarding the documentation of hypoglycemia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported