Clinical trial results:
A 24-Week, Multicenter, Randomized, Open-Label, 2-Arm Parallel-Group Study Evaluating the Efficacy and Safety of Patient- Versus Physician-Managed Titration of Insulin Glargine U300 in Type 2 Diabetes Mellitus

Summary

EudraCT number	2015-001626-42
Trial protocol	CZ GB ES SK DK GR SI PL HR
Global end of trial date	08 June 2017

Results information

Result version number	v1 (current)
This version publication date	17 June 2018
First version publication date	17 June 2018

Trial information

Trial identification

Sponsor protocol code	LPS14409

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: TAKE Control

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
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	09 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority in terms of glycemic control, measured as change from baseline to Week 24 in glycated hemoglobin (HbA1c), of a subject - versus a physician-managed titration algorithm, for the treatment with HOE901-U300 (insulin glargine U300), in subjects with inadequately controlled type-2 diabetes mellitus (T2DM).

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:

Non-insulin antihyperglycemic background therapy administered at a stable dose for at least 12 weeks prior to the screening and was continued throughout the study. Doses were to be kept stable throughout the study unless there was a specific safety issue related to these treatments. Basal insulin taken prior to the study (if any) was discontinued and switched to study IMP at randomization.

Evidence for comparator: -

Actual start date of recruitment	19 February 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	Switzerland: 16
Country: Number of subjects enrolled	Poland: 200
Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	Spain: 89
Country: Number of subjects enrolled	United Kingdom: 49
Country: Number of subjects enrolled	Croatia: 28
Country: Number of subjects enrolled	Czech Republic: 78
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Greece: 117
Worldwide total number of subjects	631
EEA total number of subjects	615

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)	329
From 65 to 84 years	301
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 79 centres in 10 countries. A total of 771 subjects were screened between 19 February 2016 & 30 November 2016, of which 140 subjects were screen failures. Screen failures were mainly due to HbA1c <7.0% or >10% for subjects taking basal insulin & 7.5% or >11.0% for insulin-naïve subjects at the screening visit.

Pre-assignment

Screening details:

A total of 631 subjects were randomized in 1:1 ratio to either of the 2 titration modality arms. Randomization was stratified by HbA1c at screening (<8.5% vs >=8.5%), by previous use of insulin (yes vs no) & by use of sulfonylurea at screening (yes vs no).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Subject-Managed Titration

Arm description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

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

Dosage and administration details:

HOE901-U300 (Insulin glargine, 300 U/mL) self-administered by deep subcutaneous (SC) injection at approximately the same time every day. Insulin-naïve subjects were started with an initial dose of 0.2 U/kg HOE901-U300. In insulin-pretreated subjects, switching from once-daily basal insulin products to once-daily HOE901-U300 was done unit-to-unit based on the previous basal insulin dose; in case of switching from twice daily basal insulin products to once-daily HOE901-U300, the recommended initial HOE901-U300 dose had to be 80% of the total daily dose of basal insulin that was discontinued.

Arm title	Physician-Managed Titration

Arm description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 8 weeks, bi-weekly until Week 12 and then monthly until end of treatment) to achieve fasting SMPG in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901
Other name	Toujeo®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

HOE901-U300 (Insulin glargine, 300 U/mL) was self-administered by deep SC injection at approximately the same time every day. Insulin-naïve subjects were started with an initial dose of 0.2 U/kg HOE901-

U300. In insulin-pretreated subjects, switching from once-daily basal insulin products to once-daily HOE901-U300 was done unit-to-unit based on the previous basal insulin dose; in case of switching from twice daily basal insulin products to once-daily HOE901-U300, the recommended initial HOE901-U300 dose had to be 80% of the total daily dose of basal insulin that was discontinued.

Number of subjects in period 1	Subject-Managed Titration	Physician-Managed Titration
Started	314	317
Completed	307	311
Not completed	7	6
Randomized but not treated	2	1
Adverse event	-	1
Other than specified	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Subject-Managed Titration
Reporting group description:	
Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).	
Reporting group title	Physician-Managed Titration
Reporting group description:	
Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 8 weeks, bi-weekly until Week 12 and then monthly until end of treatment) to achieve fasting SMPG in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).	

Reporting group values	Subject-Managed Titration	Physician-Managed Titration	Total
Number of subjects	314	317	631
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.69	62.97	
standard deviation	± 8.84	± 9.00	-
Gender categorical			
Units: Subjects			
Female	156	158	314
Male	158	159	317
Body mass index (BMI)			
Units: kg/m^2			
arithmetic mean	31.68	31.75	
standard deviation	± 5.53	± 5.43	-
Duration of type 2 diabetes mellitus (T2DM)			
Units: years			
arithmetic mean	12.9	12.8	
standard deviation	± 7.2	± 6.9	-
Glycated Haemoglobin (HbA1c %)			
Units: percentage (%)			
arithmetic mean	8.40	8.42	
standard deviation	± 0.89	± 0.92	-
Fasting Plasma Glucose			
Units: mg/dL			
arithmetic mean	172.92	167.17	
standard deviation	± 48.13	± 47.18	-
Median fasting pre-breakfast Self Monitored Plasma Glucose (SMPG)			
Baseline median fasting pre-breakfast SMPG refers to the median of all available fasting pre-breakfast SMPG collected during the 7 day preceding Day 1 (Day 1 included).			
Units: mg/dL			

arithmetic mean	150.94	148.84	
standard deviation	± 37.85	± 37.37	-

End points

End points reporting groups

Reporting group title	Subject-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

Reporting group title	Physician-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 8 weeks, bi-weekly until Week 12 and then monthly until end of treatment) to achieve fasting SMPG in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

Primary: Change in HbA1c From Baseline to Week 24

End point title	Change in HbA1c From Baseline to Week 24

End point description:

Analysis was performed on intent-to-treat (ITT) population that included all randomized subjects, irrespective of the titration arm actually being used at the time of the analysis. Change in HbA1c was calculated by subtracting baseline value from Week 24 value. Adjusted least square (LS) means and standard errors (SE) were obtained from a mixed-effect model with repeated measures (MMRM), using all post-baseline HbA1c data available on the 24-week on-treatment period (defined as the time from the first dose of investigational medicinal product [IMP] up to 7 days after the last dose of IMP or up to the introduction of rescue therapy, whichever was earlier). Here, number of subjects analyzed = subjects with both baseline and at least one post-baseline HbA1c assessment during the 24-week on-treatment period.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	311		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.97 (± 0.05)	-0.84 (± 0.05)		

Statistical analyses

Statistical analysis title	Subject-managed vs Physician-managed Titration

Statistical analysis description:

Analysis was performed using a MMRM approach with fixed categorical effects of titration modality arm, visit, titration modality arm-by-visit interaction, randomization strata (sulfonylurea use [Yes/No], previous use of insulin[Yes/No]), as well as continuous fixed covariates of baseline HbA1c & baseline HbA1c value-by-visit interaction.

Comparison groups	Physician-Managed Titration v Subject-Managed Titration

Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS mean difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2619
upper limit	-0.0004
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[1] - Non-inferiority comparison was demonstrated if upper bound of 2-sided 95% confidence interval (CI) was <0.3%.

Statistical analysis title	Subject-managed vs Physician-managed Titration

Statistical analysis description:

Analysis was performed using a MMRM approach. A hierarchical step-down testing procedure was applied to control the Type I error. If non inferiority was established then step 2 was to test superiority of subject managed titration over physician managed titration.

Comparison groups	Subject-Managed Titration v Physician-Managed Titration
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	LS Mean Difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2619
upper limit	-0.0004
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[2] - Superiority was demonstrated if the upper bound of the 2-sided 95% CI was <0 (zero).

Secondary: Percentage of Subjects Reaching Targeted Fasting SMPG (80-130 mg/dL [4.4 -7.2 mmol/L)] at Week 12 and Week 24

End point title	Percentage of Subjects Reaching Targeted Fasting SMPG (80-130 mg/dL [4.4 -7.2 mmol/L)] at Week 12 and Week 24

End point description:

Median pre-breakfast SMPG at Week 12 and week 24 were derived using the median value of fasting pre-breakfast SMPGs collected between days [79, 85] and days [163,169] respectively. The 24-week on-treatment period occurred from the first dose of IMP up to 1 day after the last dose of IMP or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12 and Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: percentage of subjects				
number (not applicable)				
Week 12	74.8	68.8		
Week 24	72.9	65.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Targeted Fasting SMPG (80-130 mg/dL [4.4 -7.2 mmol/L]) Without Experiencing Severe and/or Confirmed Hypoglycemia <54 mg/dL (3.0 mmol/L) at Week 12 and Week 24

End point title	Percentage of Subjects Achieving Targeted Fasting SMPG (80-130 mg/dL [4.4 -7.2 mmol/L]) Without Experiencing Severe and/or Confirmed Hypoglycemia <54 mg/dL (3.0 mmol/L) at Week 12 and Week 24

End point description:

Severe and/or Confirmed hypoglycemia event was an event requiring assistance from another person for corrective measurements
or an event with measured plasma glucose =<70 mg/dL (3.9 mmol/L). For hypoglycaemia, the 24-week on-treatment period occurred from the first dose of IMP up to 2 days after the last dose of IMP or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12 and Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: percentage of subjects				
number (not applicable)				
Week 12	71.7	65.6		
Week 24	67.5	58.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c From Baseline to Week 12

End point title	Change in HbA1c From Baseline to Week 12

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 12 value. Adjusted least square (LS) means and standard errors (SE) were obtained from MMRM using all post-baseline values recorded from first dose of IMP up to 7 days after last IMP dose or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on ITT population. Here, Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	310		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.88 (± 0.04)	-0.78 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose to Week 12 and Week 24

End point title	Change From Baseline in Fasting Plasma Glucose to Week 12 and Week 24

End point description:

Change in fasting plasma glucose was calculated by subtracting baseline value from Week 12 and Week 24 values. Adjusted LS means and SE were obtained from MMRM using all post-baseline values recorded from first dose of IMP up to 1 day after last IMP dose or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on ITT population. Here, "n"= subjects with both baseline and at least one post-baseline fasting plasma glucose assessment at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: mg/dL				
least squares mean (standard deviation)				
Change at Week 12 (n= 296, 296)	-34.15 (± 1.98)	-32.80 (± 1.98)		
Change at Week 24 (n= 287, 288)	-30.98 (± 2.03)	-29.59 (± 2.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Baseline to Reach Targeted Fasting SMPG (80-130 mg/dL [4.4 –7.2 mmol/L]) During the 24 Week on Treatment Period

End point title	Time from Baseline to Reach Targeted Fasting SMPG (80-130 mg/dL [4.4 –7.2 mmol/L]) During the 24 Week on Treatment Period

End point description:

Cumulative incidence of subjects reaching SMPG target range was estimated using the Kaplan-Meier method (curve over time). Data below was expressed as the percentage of subjects reaching SMPG at least once during the 24 week treatment period. The censoring time is the number of weeks composing the 24-week on-treatment period for SMPG. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: percentage of subjects				
number (not applicable)	97.5	95.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight to Week 12 and Week 24

End point title	Change From Baseline in Body Weight to Week 12 and Week 24

End point description:

Change in body weight was calculated by subtracting baseline value from Week 12 and Week 24 values. Adjusted LS means and SE were obtained from MMRM using all post-baseline values recorded from first dose of IMP up to 2 days after last IMP dose or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on safety population which included all randomized subjects treated with at least one dose of IMP. Here, "n"= subjects with both baseline and at least one post-baseline body weight assessment at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	316		
Units: kg				
least squares mean (standard error)				
Change at Week 12 (n= 307, 312)	0.36 (± 0.13)	0.12 (± 0.12)		
Change at Week 24 (n= 308, 309)	0.84 (± 0.17)	0.50 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Hypoglycemia Event (Any Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During On-treatment Period

End point title	Percentage of Subjects With At Least One Hypoglycemia Event (Any Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During On-treatment Period

End point description:

Severe hypoglycemia was an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe and/or confirmed hypoglycemia event was a severe event or an event associated with plasma glucose =<70 mg/dL (=<3.9 mmol/L). Hypoglycemic episodes with plasma glucose of <54 mg/dL (<3.0 mmol/L) were also analyzed. On-treatment period was defined as the time from first dose of IMP to 2 days after the last dose of IMP or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

First dose of study drug up to 24 weeks (or 2 days after the last dose administration)

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	316		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	36.2	37.0		
Severe and/or confirmed hypoglycemia(=<70 mg/dL)	33.3	34.2		
Severe and/or confirmed hypoglycemia(<54 mg/dL)	7.4	7.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Nocturnal Hypoglycemia Event (Any Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During On-treatment Period

End point title	Percentage of Subjects With At Least One Nocturnal Hypoglycemia Event (Any Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During On-treatment Period

End point description:

Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time), regardless the subject was awake or woke up because of the event. Severe hypoglycemia was an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe and/or confirmed hypoglycemia event was a severe event or an event associated with plasma glucose =<70 mg/dL (=<3.9 mmol/L). Hypoglycemic episodes with plasma glucose of <54 mg/dL (<3.0 mmol/L) were also analyzed. On-treatment period was defined as the time from first dose of IMP to 2 days after the last dose of IMP or up to the introduction of rescue therapy, whichever was earlier. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

First dose of study drug up to 24 weeks (or 2 days after the last dose administration)

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	316		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	8	11.4		
Severe and/or confirmed hypoglycemia (=<70 mg/dL)	6.7	10.1		
Severe and/or confirmed hypoglycemia(<54 mg/dL)	1.3	2.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Diabetes Distress Scale at Week 12 and Week 24

End point title	Change From Baseline in Total Diabetes Distress Scale at Week 12 and Week 24

End point description:

The Diabetes distress scale (DDS) is a validated questionnaire that evaluates subject's emotional distress related to diabetes disease burden. It consists of 17 questions, each rated on a 6-point Likert scale (from 1 to 6). Total DDS score (mean of the 17 questions) ranged from 1 (no problem) to 6 (a serious problem). Higher score indicated greater emotional distress. Analysis was performed on ITT population. Here, "n"= subjects with both baseline and at least one post baseline DDS assessment at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 12 (n= 298, 295)	-0.24 (± 0.04)	-0.22 (± 0.04)		
Change at Week 24 (n= 292, 293)	-0.24 (± 0.04)	-0.16 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Diabetes Empowerment Scale at Week 12 and Week 24

End point title	Change From Baseline in Total Diabetes Empowerment Scale at Week 12 and Week 24

End point description:

The Diabetes Empowerment scale (DES) is a validated measure with 28 items which evaluates diabetes-related psychosocial self-efficacy. The scale includes three subscales: managing the psychosocial aspect of diabetes, assessing dissatisfaction and readiness to change, setting and achieving diabetes goals. The total DES score was the mean of the 28 items ranging from 1 (strongly disagree) to 5 (strongly agree) on a Likert scale, higher score indicated better quality of life. Analysis was performed on ITT population. Here, "n"= subjects with both baseline and at least one post baseline DES assessment at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Subject-Managed Titration	Physician-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	317		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 301, 303)	0.14 (± 0.43)	0.06 (± 0.47)		
Change at Week 24 (n= 298, 298)	0.19 (± 0.45)	0.12 (± 0.49)		

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 (Week 25) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs that developed/worsened during 'on treatment period' (time from first dose of IMP up to 2 days after last dose of IMP, regardless of introduction of rescue therapy).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Physician-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit (weekly for the first 8 weeks, bi-weekly until Week 12 and then monthly until end of treatment to achieve fasting SMPG in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

Reporting group title	Subject-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 7.2 mmol/L (80-130 mg/dL).

Serious adverse events	Physician-Managed Titration	Subject-Managed Titration	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 316 (3.80%)	10 / 312 (3.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Breast Carcinoma			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (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			
Lumbar Vertebral Fracture			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute Coronary Syndrome			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 316 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (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			
Cerebral Circulatory Failure			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
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 / 316 (0.32%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures			

subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar Insufficiency			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Age-Related Macular Degeneration			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Strangulated Hernia			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical Polyp			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval Leukoplakia			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Lichen Sclerosus			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Psoriatic Arthropathy			
subjects affected / exposed	1 / 316 (0.32%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 316 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 316 (0.63%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Physician-Managed Titration	Subject-Managed Titration	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 316 (6.65%)	22 / 312 (7.05%)	
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	21 / 316 (6.65%)	22 / 312 (7.05%)	
occurrences (all)	24	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported