Clinical trial results:
A 21-Week, Open-label, Randomized, Controlled, Parallel-group, Multi-center Study Evaluating the Efficacy and Safety of HOE901-U300 Administered According to a Device-Supported Treat-to-target Regimen Versus Routine Titration in Patients with Type 2 Diabetes Mellitus

Summary

EudraCT number	2014-004533-13
Trial protocol	GB DE AT
Global end of trial date	30 November 2016

Results information

Result version number	v1 (current)
This version publication date	15 December 2017
First version publication date	15 December 2017

Trial information

Trial identification

Sponsor protocol code	EFC13470

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02585674
WHO universal trial number (UTN)	U1111-1165-9001
Other trial identifiers	Study Name: AUTOMATIX

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	19 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the MyStar DoseCoach (Long-acting Insulin Glargine Titration Meter) device-supported treat-to-target regimen relative to a routine titration regimen in the percentage of patients reaching glycemic target, ie, with a mean fasting self-monitored plasma glucose (FSMPG) value within the target range of 90-130 mg/dL (5.0-7.2 mmol/L) without a severe hypoglycemic episode during the 16-week on-treatment period.

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:

Glucose lowering therapy (such as metformin, sulphonylureas, thiazolidinediones, SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-IV inhibitors) kept stable for at least 3 months prior to screening and also, throughout the study unless there was a specific safety issue related to this treatment.

Evidence for comparator: -

Actual start date of recruitment	09 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	United Kingdom: 57
Country: Number of subjects enrolled	Germany: 94
Worldwide total number of subjects	151
EEA total number of subjects	151

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	85
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 19 centres in 2 countries. A total of 203 subjects were screened between 9 December 2015 and 12 July 2016 of whom 52 subjects were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

A total of 151 subjects were randomized in a 1:1 ratio to use either the Dose Helper function of the MyStar DoseCoach or the usual titration method provided by the investigator. The randomization was stratified by previous use of insulin (insulin-naïve versus non-insulin-naïve).

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	Dose Helper Titration

Arm description:

Subjects used the dose helper functionality of the MyStarDoseCoach device for basal insulin titration.

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 self-administered by deep SC injection at approximately the same time every day. Dose was individually titrated to achieve target fasting SMPG range equal to 90-130 mg/dL (5.0-7.2 mmol/L) while avoiding hypoglycemia.

Arm title	Routine Titration

Arm description:

Subjects followed the usual method of titration that was recommended by the investigator.

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 self-administered by deep SC injection at approximately the same time every day. Dose was individually titrated based on usual method recommended by investigator.

Number of subjects in period 1	Dose Helper Titration	Routine Titration
Started	75	76
Completed the Dose Helper period	58 [1]	0 [2]
Completed	70	76
Not completed	5	0
Consent withdrawn by subject	5	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of 75 subjects, 17 subjects stopped prematurely the dose helper.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone not applicable for this arm as subjects did not use the dose helper.

Baseline characteristics

Reporting groups	
Reporting group title	Dose Helper Titration
Reporting group description:	
Subjects used the dose helper functionality of the MyStarDoseCoach device for basal insulin titration.	
Reporting group title	Routine Titration
Reporting group description:	
Subjects followed the usual method of titration that was recommended by the investigator.	

Reporting group values	Dose Helper Titration	Routine Titration	Total
Number of subjects	75	76	151
Age categorical Units: Subjects			
<65 years	43	42	85
65-75 years	29	24	53
>=75 years	3	10	13
Age continuous Units: years			
arithmetic mean	61.2	62.9	
standard deviation	± 9.5	± 9.4	-
Gender categorical Units: Subjects			
Female	27	20	47
Male	48	56	104
Randomization strata of previous use of insulin			
According to interactive voice response system (IVRS) data.			
Units: Subjects			
Insulin-Naive	30	30	60
Insulin pre-treated	45	46	91
Body mass index (BMI) Units: kg/m^2			
arithmetic mean	33.2	33.3	
standard deviation	± 6.9	± 7.0	-
Duration of type 2 diabetes mellitus (T2DM) Units: years			
arithmetic mean	12.17	12.34	
standard deviation	± 7.21	± 6.37	-
Glycated Haemoglobin (HbA1c %) Units: percentage of hemoglobin			
arithmetic mean	8.80	8.59	
standard deviation	± 1.00	± 0.82	-
Mean fasting self-monitored plasma glucose (FSMPG)			
The baseline mean FSMPG was calculated by the mean of the last 5 readings recorded over the last 2 weeks preceding the first IMP intake			
Units: mg/dL			
arithmetic mean	183.40	177.64	

standard deviation	± 38.84	± 34.59	-
Fasting Plasma Glucose Units: mg/dL			
arithmetic mean	191.57	186.78	
standard deviation	± 39.83	± 47.15	-

End points

End points reporting groups

Reporting group title	Dose Helper Titration
Reporting group description:	
Subjects used the dose helper functionality of the MyStarDoseCoach device for basal insulin titration.	
Reporting group title	Routine Titration
Reporting group description:	
Subjects followed the usual method of titration that was recommended by the investigator.	

Primary: Percentage of Subjects Reaching Mean Fasting Self-Monitored Plasma Glucose (FSMPG) Target range of 90-130 mg/dL (5.0-7.2 mmol/L) at Week 16 Without Severe Hypoglycemia During the 16 Week On- Treatment Period

End point title	Percentage of Subjects Reaching Mean Fasting Self-Monitored Plasma Glucose (FSMPG) Target range of 90-130 mg/dL (5.0-7.2 mmol/L) at Week 16 Without Severe Hypoglycemia During the 16 Week On- Treatment Period

End point description:

Estimated percentages from multiple imputation approach. Mean FSMPG values at Week 16 time-point was calculated by the mean of the last 5 on-treatment readings recorded over the 2 weeks preceding the Week 16 time-point (Day 112), using the relative days from the first investigational medicinal product (IMP) dose. Severe hypoglycemia was an event that required assistance of another person to actively administered carbohydrate, glucagon, or other resuscitative actions. The 16-week on-treatment period for hypoglycemia occurs from first IMP up to 16 weeks defined by 112 days after the first IMP dose. Analysis was performed on modified intent-to-treat population (mITT) that included all randomized subjects treated with IMP and analysed according to the titration group allocated by randomization.

End point type	Primary
End point timeframe:	
First dose up to Day 112	

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)	45.92	36.84		

Statistical analyses

Statistical analysis title	Dose Helper Titration vs. Routine Titration

Statistical analysis description:

Estimated difference of percentage was obtained by combining the difference (diff.) in percentage, weighted by the randomization stratum of previous use of insulin (Insulin naive, Insulin pre-treated), between titration groups of all different imputed data sets, using Rubin's formulae.

Comparison groups	Routine Titration v Dose Helper Titration

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Estimated weighted percentage difference
Point estimate	9.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.748
upper limit	24.829

Notes:

[1] - To assess non-inferiority the lower bound of the two-sided 95% confidence interval (CI) for the difference in percentage of subjects between MyStar DoseCoach and routine titration of the primary endpoint must be strictly greater to the predefined non-inferiority margin of -15%. Only if non-inferiority of MyStar DoseCoach versus routine titration regimen had been demonstrated, step 2 was to test superiority of MyStar DoseCoach over routine titration.

Statistical analysis title	Dose Helper Titration vs Routine Titration

Statistical analysis description:

Step-2 was to test superiority of MyStar DoseCoach over routine titration. Only if non inferiority was demonstrated, the superiority of Dose Helper titration versus routine titration was demonstrated if the lower bound of the two-sided 95% CI for the weighted difference (diff.) in the percentage of subjects between titration arms was >0 (zero).

Comparison groups	Dose Helper Titration v Routine Titration
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2618
Method	Weighted diff. from multiple imputation
Parameter estimate	Estimated weighted percentage difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.748
upper limit	24.829

Secondary: Percentage of Subjects Reaching Mean FSMPG Target Range of 90-130 mg/dL (5.0-7.2 mmol/L) at Week 16 Without Severe and/or Confirmed Hypoglycemic Episode During the 16-Week On-Treatment Period

End point title	Percentage of Subjects Reaching Mean FSMPG Target Range of 90-130 mg/dL (5.0-7.2 mmol/L) at Week 16 Without Severe and/or Confirmed Hypoglycemic Episode During the 16-Week On-Treatment Period

End point description:

Estimated percentages from multiple imputation approach. Mean FSMPG values at Week 16 time-point was calculated by the mean of the last 5 on-treatment readings recorded over the 2 weeks preceding the Week 16 time-point (Day 112) using the relative days from the first IMP dose. Severe and/or Confirmed hypoglycemia event was a severe event or an event defined as plasma glucose ≤70 mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L). The 16-week on-treatment period for hypoglycemia occurs from first IMP up to 16 weeks defined by 112 days after the first IMP dose. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

First dose up to Day 112

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)				
At (≤70 mg/dL [3.9 mmol/L])	34.25	14.47		
At (<54 mg/dL [3.0 mmol/L])	39.96	34.21		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Mean FSMPG Target Range of 70-130 mg/dL (3.9-7.2 mmol/L) at Week 16 Without Severe Hypoglycemic Episode During the 16-Week On-Treatment Period

End point title	Percentage of Subjects Reaching Mean FSMPG Target Range of 70-130 mg/dL (3.9-7.2 mmol/L) at Week 16 Without Severe Hypoglycemic Episode During the 16-Week On-Treatment Period

End point description:

Estimated percentages from multiple imputation approach. Mean FSMPG values at Week 16 time-point was calculated by the mean of the last 5 on-treatment readings recorded over the 2 weeks preceding the Week 16 time-point (Day 112) using the relative days from the first IMP dose. The 16-week on-treatment period for hypoglycemia occurs from first IMP up to 16 weeks defined by 112 days after the first IMP dose. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

First dose up to Day 112

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)	46.07	39.47		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Mean FSMPG Target Range of 70-130 mg/dL (3.9-7.2 mmol/L) at Week 16 Without Severe and/or Confirmed Hypoglycemic Episode During 16-Week On-Treatment Period

End point title	Percentage of Subjects Reaching Mean FSMPG Target Range of 70-130 mg/dL (3.9-7.2 mmol/L) at Week 16 Without Severe and/or Confirmed Hypoglycemic Episode During 16-Week On-Treatment Period

End point description:

Estimated percentages from multiple imputation approach. Mean FSMPG values at Week 16 time-point was calculated by the mean of the last 5 on-treatment readings recorded over the 2 weeks preceding the Week 16 time-point (Day 112) using the relative days from the first IMP dose. The 16-week on-treatment period for hypoglycemia occurs from first IMP up to 16 weeks defined by 112 days after the first IMP dose. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

First dose up to Day 112

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)				
At ≤70 mg/dL [3.9 mmol/]	34.25	17.11		
At <54 mg/dL [3.0 mmol/L]	40.00	36.84		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean FSMPG at Week 16 During the On-Treatment Period

End point title	Change From Baseline in Mean FSMPG at Week 16 During the On-Treatment Period

End point description:

Change in FSMPG was calculated by subtracting baseline value from Week 16 time point value. Adjusted LS means from mixed-effect model with repeated measures. Mean FSMPG values were calculated by the mean of the last 5 on-treatment readings recorded over the 2 weeks preceding the corresponding time-point, using the relative days from the first IMP. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 16 time point

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: mg/dL				
least squares mean (standard error)	-41.70 (± 3.323)	-43.26 (± 3.175)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Reach Mean FSMPG Target Range During the On-Treatment Period

End point title	Time to First Reach Mean FSMPG Target Range During the On-Treatment Period

End point description:

The mean FSMPG was calculated by the mean of the last 5 on-treatment values recorded over each 2-weeks period defined by each time window of 14 consecutive days starting from first IMP date. Time to first mean FSMPG in target range was defined as the number of weeks from 1st IMP to the date of the first 2-weeks period where the mean FSMPG value was in the target. Median survival which corresponds to the duration for which 50% of the subjects reached the target, was estimated using Kaplan-Meier method. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: Weeks				
median (confidence interval 95%)	10 (8 to 10)	13 (6 to 16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Glycated Hemoglobin (HbA1c) at Week 16 During the On-Treatment Period

End point title	Change From Baseline in Glycated Hemoglobin (HbA1c) at Week 16 During the On-Treatment Period

End point description:

Change in HbA1c value from baseline to visit week 16 was analysed using all post-baseline values recorded from first IMP up to 7 days after last IMP dose. Adjusted LS means from ANCOVA. Analysis was performed on mITT population. Here, Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	73		
Units: percentage of HbA1c				
least squares mean (standard error)	-1.12 (± 0.086)	-1.07 (± 0.084)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Week 16 During the On-Treatment Period

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) at Week 16 During the On-Treatment Period

End point description:

Change in FPG value from baseline to visit Week 16 was analysed using all post-baseline values recorded from first IMP up to 1 day after last IMP dose. Adjusted LS means from mixed-effect model with repeated measures. Analysis was performed on mITT population. Here, Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	76		
Units: mg/dL				
least squares mean (standard error)				
Change at Week 16	-44.05 (± 4.255)	-49.46 (± 4.080)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c of <7.5% and <7% at Week 16 During the On-Treatment Period

End point title	Percentage of Subjects Reaching HbA1c of <7.5% and <7% at Week 16 During the On-Treatment Period

End point description:

Only HbA1c values recorded from the first IMP dose up to 7 days after the last IMP dose were considered in the analysis. Subjects who had no available on-treatment assessment for HbA1c at visit Week 16 were considered as non-responders. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)				
HbA1c of <7.5%	45.33	43.42		
HbA1c of <7.0%	30.67	27.63		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with FPG in the Target Range of [90-130 mg/dL] (5.0-7.2 mmol/L) at Week 16 Without Severe Hypoglycemia at Week 16 During the On-Treatment Period

End point title	Percentage of Subjects with FPG in the Target Range of [90-130 mg/dL] (5.0-7.2 mmol/L) at Week 16 Without Severe Hypoglycemia at Week 16 During the On-Treatment Period

End point description:

Only assessments reported from the first IMP dose up to 1 day after the last IMP dose for FPG values, and up to 2 days after the last IMP dose for hypoglycaemia events were considered in the analysis. Number of subjects with FPG in the target range of [90-130 mg/dL] (5.0-7.2 mmol/L) at visit Week 16 without severe hypoglycemia during the on-treatment period was analysed. Subjects who had no available on-treatment assessment for FPG at visit Week 16 were considered as non-responders . Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)	29.33	43.42		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hypoglycemic Events (Any Hypoglycemia, Severe Hypoglycemia, Documented Symptomatic Hypoglycemia, Asymptomatic Hypoglycemia and Severe and/or confirmed Hypoglycemia) During the On-Treatment Period

End point title	Percentage of Subjects with Hypoglycemic Events (Any Hypoglycemia, Severe Hypoglycemia, Documented Symptomatic Hypoglycemia, Asymptomatic Hypoglycemia and Severe and/or confirmed Hypoglycemia) During the On-Treatment Period

End point description:

Categories of hypoglycaemia event were based on ADA classification. Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=70 mg/dL (3.9 mmol/L). Asymptomatic hypoglycemia was an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration <=70 mg/dL (3.9 mmol/L). Hypoglycemic episodes with plasma glucose of 54 mg/dL (<3.0 mmol/L) were also analysed. Only events occurring from first IMP dose up to 2 days after last IMP dose were analysed. Analysis was performed on the safety population that included randomized population who actually received at least 1 dose or part of a dose of the IMP, analysed according to the titration regimen actually followed.

End point type	Secondary

End point timeframe:

First dose of study drug up to 2 days after the last dose administration

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia event	34.7	38.2		
Severe hypoglycemia	0	1.3		
Documented Symptomatic Hypoglycemia (≤3.9mmol/L)	13.3	13.2		
Documented Symptomatic Hypoglycemia (<3.0mmol/L)	4.0	3.9		
Asymptomatic hypoglycemia (≤3.9mmol/L)	20.0	27.6		
Asymptomatic hypoglycemia (< 3.0 mmol/L)	6.7	5.3		
Severe and/or confirmed hypoglycemia(≤ 3.9 mmol/L)	29.3	35.5		

Severe and/or confirmed hypoglycemia(< 3.0 mmol/L)	10.7	9.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 16

End point title	Change From Baseline in Total Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 16

End point description:

The DTSQs is a validated questionnaire to assess subject's satisfaction with their diabetes treatment. Total DTSQ score consists of the sum of 6 items (Q1 and Q4 - Q8), each rated on a 7-point scale (from 0 to 6). Total DTSQ score ranged from 0 (very dissatisfied) to 36 (very satisfied); higher score = more satisfaction. Change in total DTSQ score from baseline to visit Week 16 was performed on mITT population. Adjusted LS means from ANCOVA. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	67		
Units: Units on a scale				
least squares mean (standard error)	2.90 (± 0.612)	4.46 (± 0.596)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Total Hypoglycemia Fear Survey Score at Week 16

End point title	Change From Baseline in the Total Hypoglycemia Fear Survey Score at Week 16

End point description:

Hypoglycemia fear survey (HFS), is a validated tool to assess subject's fear and behavior relative to hypoglycemia. It consists of 33 items each rated on a 5-point scale ranges from 0= never to 4= always. Total HFS score (mean of the 33 items) ranged from 0 to 4 higher score reflects increasing fear of hypoglycaemia. Change in total HFS score from baseline to visit Week 16 was performed on mITT population. Adjusted LS means from ANCOVA. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	69		
Units: units on a scale				
least squares mean (standard error)	0.00 (± 0.050)	0.03 (± 0.048)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the World Health Organization-5 (WHO-5) Well-Being Index Score at Week 16

End point title	Change From Baseline in the World Health Organization-5 (WHO-5) Well-Being Index Score at Week 16

End point description:

The WHO-5 well-being index is a standardized test to evaluate emotional well-being and quality of life. It contains five items each rated on a 6-point scale (from 0 to 5). The total WHO-5 score (sum of the 5 items multiplied by 4) range from 0 to 100 where higher score indicated the best quality of life. Change in total WHO-5 score from baseline to visit Week 16 was performed on mITT population. Adjusted LS means from ANCOVA. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	69		
Units: units on a scale				
least squares mean (standard error)	-0.03 (± 1.788)	6.20 (± 1.750)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Diabetes Distress Scale Score to Week 16

End point title	Change From Baseline in Total Diabetes Distress Scale Score to Week 16

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 scale

(from 1 to 6). Total DDS score (mean of the 17 questions) ranged from 1 to 6. Higher score indicated greater emotional distress. Change in total DDS score from baseline to visit Week 16 was performed on mITT population. Adjusted LS means from ANCOVA. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	68		
Units: units on a scale				
least squares mean (standard error)	0.08 (± 0.060)	-0.04 (± 0.058)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Glucose Monitoring Satisfaction (GMS) Score to Week 16

End point title	Change From Baseline in Total Glucose Monitoring Satisfaction (GMS) Score to Week 16

End point description:

The GMS is a questionnaire assessing subject’s satisfaction with their glucose monitoring. It consists of 15 items, each rated on a 5-point scale (from 1 to 5). Total GMS score (mean of the 15 items) ranged from 1 to 5, higher score= greater level of satisfaction. Change in total GMS score from baseline to visit Week 16 was performed on mITT population. Adjusted LS means from ANCOVA. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 Visit

End point values	Dose Helper Titration	Routine Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	68		
Units: units on a scale				
least squares mean (standard error)	0.10 (± 0.071)	0.30 (± 0.069)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Helper Titration: Device Ease of Use Questionnaire at Week 16

End point title	Dose Helper Titration: Device Ease of Use Questionnaire at Week 16[2]

End point description:

The device ease of use questionnaires were administered to health care providers (1 question) and subjects randomized to the dose helper titration arm (3 questions) at visit Week 16. The 4 questions of the MyStar DoseCoach ease of use questionnaires were rated on a 7-point scale ranges from 1 (extremely difficult) to 7 (extremely easy). Descriptive analysis of each question was performed on mITT population. Number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Week 16 Visit

Notes:

[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: The end point is reporting results only for the arm applicable for this endpoint.

End point values	Dose Helper Titration			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: units on a scale				
arithmetic mean (standard deviation)				
How easy/difficult for subject to titrate?(n=71)	6.23 (± 1.36)			
To decide what dose to take? (n=70)	6.11 (± 1.36)			
To do the dose calculations correctly? (n=70)	6.07 (± 1.40)			
To adjust your insulin dose? (n=70)	6.24 (± 1.30)			

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 16) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Analysed AEs are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (The on-treatment period was defined as the time from the first injection of open-label IMP up to 2 days after the last injection of IMP).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Dose Helper Titration

Reporting group description:

Subjects used the dose helper functionality of the MyStarDoseCoach device for basal insulin titration.

Reporting group title	Routine Titration

Reporting group description:

Subjects followed the usual method of titration that was recommended by the investigator.

Serious adverse events	Dose Helper Titration	Routine Titration	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 75 (2.67%)	3 / 76 (3.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate Cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (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			
Dementia			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes Zoster			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
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: 5 %

Non-serious adverse events	Dose Helper Titration	Routine Titration	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 75 (20.00%)	9 / 76 (11.84%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 75 (6.67%)	1 / 76 (1.32%)	
occurrences (all)	5	1	
Vomiting			
subjects affected / exposed	4 / 75 (5.33%)	0 / 76 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 75 (9.33%)	8 / 76 (10.53%)	
occurrences (all)	7	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2015	Following changes were made: - To ensure that only adult subjects were included in this clinical trial, who were able to understand the nature, significance and implications of the clinical trial and to form their intention accordingly. - To ensure that no subjects with high risk hypoglycemia and hypoglycemia with particularly severe outcome should be included in the trial. - This included especially subjects with stenosis of coronary artery or vessels supplying the brain as well as subjects with proliferative retinopathy. - To clarify to use Investigator Brochure and its addenda for reference safety information. - To clarify that any protocol amendment or modification was submitted to Health Authorities (Competent Regulatory Authority) before implementation. - To implement an additional objective/endpoint of satisfaction with glucose monitoring via addition of the Glucose Monitoring Satisfaction Survey (GMS). - To implement changes related to the classification of MyStar DoseCoach.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported