Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group, Phase 3 Trial to Evaluate the Safety and Efficacy of Once Weekly Exenatide Therapy Added to Titrated Basal Insulin Glargine Compared to Placebo Added to Titrated Basal Insulin Glargine in Patients with Type 2 Diabetes Who Have Inadequate Glycemic Control on Basal Insulin Glargine with or without Metformin

Summary

EudraCT number	2014-003502-33
Trial protocol	SK HU
Global end of trial date	03 May 2017

Results information

Result version number	v1
This version publication date	03 September 2017
First version publication date	03 September 2017

Trial information

Trial identification

Sponsor protocol code	D5553C00002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
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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	07 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2016
Global end of trial reached?	Yes
Global end of trial date	03 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the change from baseline in hemoglobin A1c (HbA1c) achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Protection of trial subjects:

Treated in routine care.

Background therapy:

Insulin glargine titrated to achieve a target glucose of 4.0 to 5.5 mmol/L (72 to 99 mg/dL); metformin as prescribed by the Investigator.

Evidence for comparator: -

Actual start date of recruitment	06 September 2014
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	Hungary: 59
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Romania: 45
Country: Number of subjects enrolled	Slovakia: 38
Country: Number of subjects enrolled	United States: 253
Country: Number of subjects enrolled	South Africa: 22
Worldwide total number of subjects	464
EEA total number of subjects	189

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)	355
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 107 centers globally between 06 September 2014 and 29 August 2016.

Pre-assignment

Screening details:

The study had a Screening Visit, an 8-week insulin dose optimization phase, followed by a 28-week randomized, double-blind treatment phase. A total of 808 patients signed ICF and 464 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Exenatide

Arm description:

Exenatide 2 mg 1 time per week + titrated basal insulin glargine with or without metformin

Arm type	Experimental
Investigational medicinal product name	Exenatide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 mg one time per week, injection

Arm title	Placebo

Arm description:

Placebo 2 mg 1 time per week + titrated basal insulin glargine with or without metformin

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

Dosage and administration details:

one time per week, injection

Number of subjects in period 1	Exenatide	Placebo
Started	233	231
Received treatment	232	231
Completed	211	207
Not completed	22	24
Randomized in error	1	-
Adverse event, serious fatal	-	1
Consent withdrawn by subject	5	9
Adverse event, non-fatal	9	4
Fire at the study center	2	4
Investigator decision	1	4
Lost to follow-up	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Exenatide
Reporting group description:	
Exenatide 2 mg 1 time per week + titrated basal insulin glargine with or without metformin	
Reporting group title	Placebo
Reporting group description:	
Placebo 2 mg 1 time per week + titrated basal insulin glargine with or without metformin	

Reporting group values	Exenatide	Placebo	Total
Number of subjects	233	231	464
Age categorical Units: Subjects			
Adults (18-64 years)	181	172	353
From 65-74 years	41	49	90
75 years and over	9	9	18
Not recorded	2	1	3
Age Continuous Units: Years			
arithmetic mean	57.8	57.6	
standard deviation	± 9.02	± 10.28	-
Gender, Male/Female Units: Subjects			
Female	117	123	240
Male	114	107	221
Not recorded	2	1	3
Race, Customized Units: Subjects			
American Indian Or Alaska Native	1	0	1
Asian	4	2	6
Black Or African American	19	28	47
Native Hawaiian Or Other Pacific Islander	1	0	1
Other	1	4	5
White	205	196	401
Not recorded	2	1	3

End points

End points reporting groups	
Reporting group title	Exenatide
Reporting group description:	
Exenatide 2 mg 1 time per week + titrated basal insulin glargine with or without metformin	
Reporting group title	Placebo
Reporting group description:	
Placebo 2 mg 1 time per week + titrated basal insulin glargine with or without metformin	

Primary: Change in HbA1c from baseline to Week 28	
End point title	Change in HbA1c from baseline to Week 28
End point description:	
To compare the change from baseline in HbA1c achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.	
End point type	Primary
End point timeframe:	
Baseline to Week 28	

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: % HbA1c				
least squares mean (confidence interval 95%)	-0.96 (-1.11 to -0.8)	-0.23 (-0.38 to -0.07)		

Statistical analyses

Statistical analysis title	Change in HbA1c - baseline to Week 28
Statistical analysis description:	
To compare the change from baseline in HbA1c achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.	
Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.53
Variability estimate	Standard error of the mean
Dispersion value	0.101

Secondary: Change in body weight from baseline to Week 28

End point title	Change in body weight from baseline to Week 28

End point description:

To compare the change from baseline in body weight achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: kg				
least squares mean (confidence interval 95%)	-1.04 (-1.54 to -0.54)	0.46 (-0.03 to 0.96)		

Statistical analyses

Statistical analysis title	Change in body weight - baseline to Week 28

Statistical analysis description:

To compare the change from baseline in body weight achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	-0.84

Variability estimate	Standard error of the mean
Dispersion value	0.34

Secondary: Change from baseline to Week 28 in 2-hour postprandial glucose after a standard MTT

End point title	Change from baseline to Week 28 in 2-hour postprandial glucose after a standard MTT

End point description:

To compare the change from baseline in 2-hour postprandial glucose after a standard MTT achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: mg/dL				
least squares mean (confidence interval 95%)	-28.51 (-39.77 to -17.25)	-1.06 (-12.5 to 10.37)		

Statistical analyses

Statistical analysis title	Change in 2 hr PPG - baseline to Week 28

Statistical analysis description:

To compare the change from baseline in 2-hour postprandial glucose after a standard MTT achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-27.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.73
upper limit	-16.16
Variability estimate	Standard error of the mean
Dispersion value	5.74

Secondary: Proportion of patients achieving HbA1c <7.0% at Week 28

End point title	Proportion of patients achieving HbA1c <7.0% at Week 28

End point description:

To compare the proportion of patients achieving HbA1c <7.0% between EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: % of patients				
number (confidence interval 95%)	32.5 (26.4 to 38.5)	7.4 (4 to 10.8)		

Statistical analyses

Statistical analysis title	% Patients achieving HbA1c <7%

Statistical analysis description:

To compare the proportion of patients achieving HbA1c <7.0% between EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Change from baseline to Week 28 in daily insulin dose

End point title	Change from baseline to Week 28 in daily insulin dose

End point description:

To compare the change from baseline in daily insulin dose achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: units				
least squares mean (confidence interval 95%)	1.6 (0.1 to 3.1)	3.6 (2 to 5.1)		

Statistical analyses

Statistical analysis title	Change in daily insulin dose - baseline to Week 28

Statistical analysis description:

To compare the change from baseline in daily insulin dose achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.07

Secondary: Proportion of patients achieving HbA1c <7.0% at Week 28, no weight gain at Week 28, and no major hypoglycemia over 28 weeks

End point title	Proportion of patients achieving HbA1c <7.0% at Week 28, no weight gain at Week 28, and no major hypoglycemia over 28 weeks

End point description:

To compare the proportion of patients achieving HbA1c <7.0% at Week 28, no weight gain at Week 28, and no major hypoglycemia over 28 weeks between EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: % of patients				
number (confidence interval 95%)	22.1 (16.7 to 27.4)	2.6 (0.6 to 4.7)		

Statistical analyses

Statistical analysis title	HbA1c <7.0%, no weight gain or hypoglycemia

Statistical analysis description:

To compare the proportion of patients achieving HbA1c <7.0% at Week 28, no weight gain at Week 28, and no major hypoglycemia over 28 weeks between EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Change in seated SBP from baseline to Week 28

End point title	Change in seated SBP from baseline to Week 28

End point description:

To compare the change from baseline in seated systolic blood pressure achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Exenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	230		
Units: mmHg				
least squares mean (confidence interval 95%)	-2.6 (-4.4 to -0.7)	-0.7 (-2.6 to 1.1)		

Statistical analyses

Statistical analysis title	Change in SBP - baseline to Week 28

Statistical analysis description:

To compare the change from baseline in seated systolic blood pressure achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Comparison groups	Exenatide v Placebo
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	1.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of signature of informed consent to the end of the 28-week treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Exenatide

Reporting group description:

Exenatide 2 mg 1 time per week + titrated basal insulin glargine with or without metformin

Reporting group title	Placebo

Reporting group description:

Placebo 2 mg 1 time per week + titrated basal insulin glargine with or without metformin

Serious adverse events	Exenatide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 232 (4.74%)	11 / 231 (4.76%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (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			
Humerus fracture			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (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 unstable			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 232 (0.00%)	2 / 231 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 232 (0.43%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (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			
Psoriasis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neck obstruction			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
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			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 232 (0.00%)	2 / 231 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 232 (0.43%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Exenatide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 232 (17.24%)	36 / 231 (15.58%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 232 (2.16%)	13 / 231 (5.63%)	
occurrences (all)	6	15	
General disorders and administration site conditions			
Injection site nodule			
subjects affected / exposed	12 / 232 (5.17%)	1 / 231 (0.43%)	
occurrences (all)	14	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 232 (5.17%)	9 / 231 (3.90%)	
occurrences (all)	13	10	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 232 (7.76%)	15 / 231 (6.49%)	
occurrences (all)	25	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2014	Outcome measure of secondary objective was modified to specify "major" hypoglycemia. Insulin glargine, metformin, and rescue therapy would be sourced locally. Exclusion criterion #25 was included as inclusion criterion #9. Cut off for serum calcitonin concentration was decreased to 40 pg/mL. Tobacco, caffeine, and strenuous exercise were added to the list of restrictions 24 hours prior to each visit. Discontinuation procedures were amended to include a review when the Investigator deemed it necessary to temporarily stop and re-start study medication. Discontinued patients were required to complete the Follow-up visit (Visit 15). Discontinued patients who had symptoms of hypoglycemia were to record glucose measurements and episode details in the patient diary. Study Plan was updated to clarify when study diary was given out, procedures for collecting study diary, when study medication was dispensed and used/unused medication was collected. Text was added to differentiate procedures for Early Termination and Rescue Visits, to indicate IVRS should be called on the day of consent, to clarify that patients undergoing rescue therapy were to perform the 6 point SMBG profile before returning for Rescue Visit, to indicate that staff monitored study medication administration at study visits, and to indicate when MTTs should be performed. Text regarding the MTT was updated to include instruction on MTT timing and for how the MTT should have been performed. BP measurement instructions were modified. Investigators should contact medical monitor if a patient developed a liver function test abnormality. Hy's Law text was updated to state that cases meeting any of the identification criteria required an unscheduled laboratory draw. Hypoglycemia assessment was updated with criteria for classification. The Sponsor should have been contacted regarding hypoglycemia events. Added use of SU as a stratification factor for exploratory analyses. Clarified assessment of causality for AEs.
20 February 2015	The proportion of patients rescued or discontinued for lack of glycemic control at Week 28 was added as an exploratory outcome measure. Inclusion criterion #7 was clarified to state that patients may only take basal insulin glargine once daily. Exclusion criterion #32 was amended to include participation in an interventional clinical trial and to clarify that only administration of an investigational drug would have rendered a patient as ineligible. The Study Plan and Timing of Procedures was updated. This update clarified study visit windows, when used/unused study medication was to be collected, when training for study drug administration was to be received by the patient, and visits when rescue medication could have been dispensed. Review of potential CV event triggers was added to all visits where AEs and concomitant medication were reviewed. Text was added to indicate that metformin should be taken with the next meal, and does not need to be taken at the study center, and that urine should be collected right before time 0 of the meal tolerance test. Text was added to indicate that study medication may be dispensed at a Rescue Visit. Text was added to clarify that potential CV event triggers would be reviewed at specified study visits. Text was added to indicate that urine was collected right before time 0 of the MTT. Text was amended to indicate that antibody results would be presented in the CSR. Text was added to clarify that the baseline physical examination data are collection at Visit 1. Text was added to clarify that there is no restriction on fathering children during the study. Text was added to describe the adjudication of cardiovascular events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported