



Clinical trial results:

A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes

Summary

EudraCT number	2015-000408-24
Trial protocol	HU BG
Global end of trial date	

Results information

Result version number	v1
This version publication date	18 November 2020
First version publication date	18 November 2020

Trial information

Trial identification

Sponsor protocol code	D5551C00002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01554618
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000689-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	06 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect on glycemetic control, as measured by glycosylated hemoglobin (HbA1c), of exenatide once weekly following 24 weeks of treatment compared with placebo in children and adolescents with type 2 diabetes mellitus.

The Extended Safety Follow-up Period was continued for up to 3 years or until the increase in height between two 6 month interval visits was less than 5 millimeter (mm) (whichever came first). No study medication was administered during the Extended Safety Follow-up Period.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	United States: 53
Country: Number of subjects enrolled	Kuwait: 3
Worldwide total number of subjects	83
EEA total number of subjects	5

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)	4
Adolescents (12-17 years)	79
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in adolescents (aged 10 to 17 years inclusive) with type 2 diabetes treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening. 27 study centers in 6 countries randomized patients during the study.

Pre-assignment

Screening details:

Study had a screening period (5 weeks), controlled assessment period (24 weeks; patients randomized 5:2 to exenatide or placebo), open-label extension period (28 weeks) and post-treatment follow-up period (10 weeks). 84 patients were randomized but 1 due to clinical error and immediately discontinued, thus, 83 patients were included in the study.

Period 1

Period 1 title	Randomized Through Start of Treatment
Is this the baseline period?	No
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:

Patients randomized to the exenatide treatment group.

Arm type	Experimental
Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW; BYDUREON™
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Period is prior to the start of treatment; no study medication administered.

Arm title	Placebo
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Arm description:

Patients randomized to the placebo treatment group.

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

Dosage and administration details:

Period is prior to the start of treatment; no study medication administered.

Number of subjects in period 1	Exenatide	Placebo
Started	59	24
Completed	58	24
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Controlled Assessment Period
Is this the baseline period?	Yes ^[1]
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:

Patients received exenatide 2 milligrams (mg) subcutaneous (SC) injection once weekly for 24 weeks during the controlled assessment period.

Arm type	Experimental
Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW; BYDUREON™
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Exenatide once weekly was administered by the caregiver (or the patient self-administered if the medically qualified site staff member assessed that this was appropriate) for 24 weeks using prefilled syringes or dual chamber pens (dual chamber pen was intended for use in all patients recruited from August 2018 onwards).

Arm title	Placebo
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Arm description:

Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period.

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

Dosage and administration details:

Placebo matching with exenatide once weekly was administered by the caregiver (or the patient self-administered if the medically qualified site staff member assessed that this was appropriate) for 24 weeks using prefilled syringes or dual chamber pens (dual chamber pen was intended for use in all patients recruited from August 2018 onwards).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 presents data for all patients randomized until the start of treatment and Period 2 presents data for all patients who received study medication during the controlled assessment period. Baseline characteristics are based on patients who were randomized and who received at least one dose of the study medication; Period 2 is therefore the baseline period.

Number of subjects in period 2 ^[2]	Exenatide	Placebo
Started	58	24
Completed	50	23
Not completed	8	1
Consent withdrawn by subject	6	-
Lost to follow-up	2	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomized and who received at least one dose of the study medication.

Period 3

Period 3 title	Open-Label Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Exenatide

Arm description:

Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period (from Week 25 to Week 52). Patients in this treatment group had previously received exenatide during the controlled assessment period.

Arm type	Experimental
Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW; BYDUREON™
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Open-label exenatide once weekly was administered by the caregiver (or the patient self-administered if the medically qualified site staff member assessed that this was appropriate) for 28 weeks during the extension period using prefilled syringes or dual chamber pens (dual chamber pen was intended for use in all patients recruited from August 2018 onwards).

Arm title	Placebo to Exenatide
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Arm description:

Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period (from Week 25 to Week 52). Patients in this treatment group had previously received placebo during the controlled assessment period.

Arm type	Experimental
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Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW; BYDUREON™
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Open-label exenatide once weekly was administered by the caregiver (or the patient self-administered if the medically qualified site staff member assessed that this was appropriate) for 28 weeks during the extension period using prefilled syringes or dual chamber pens (dual chamber pen was intended for use in all patients recruited from August 2018 onwards).

Number of subjects in period 3^[3]	Exenatide	Placebo to Exenatide
Started	49	23
Completed	46	18
Not completed	3	5
Consent withdrawn by subject	2	3
Physician decision	-	1
Lost to follow-up	1	1

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1 patient who was noncompliant with study medication did not enter the open-label extension period.

Baseline characteristics

Reporting groups

Reporting group title	Exenatide
Reporting group description:	
Patients received exenatide 2 milligrams (mg) subcutaneous (SC) injection once weekly for 24 weeks during the controlled assessment period.	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period.	

Reporting group values	Exenatide	Placebo	Total
Number of subjects	58	24	82
Age Categorical			
Age group (years)			
Units: participants			
< 10	0	0	0
≥ 10 to ≤ 12	8	3	11
≥ 13 to ≤ 16	36	12	48
> 16	14	9	23
Age Continuous			
Units: years			
arithmetic mean	14.9	15.6	
standard deviation	± 1.88	± 1.66	-
Sex: Female, Male			
Units: participants			
Female	31	17	48
Male	27	7	34
Race/Ethnicity, Customized			
Units: Subjects			
White	23	12	35
Black or African American	17	8	25
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	4	1	5
Other	12	2	14
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	25	8	33
Not Hispanic or Latino	29	13	42
Unknown or Not Reported	4	3	7
Region of Enrollment			
Units: Subjects			
Bulgaria	1	0	1
Hungary	3	1	4
Israel	4	3	7
Mexico	13	2	15
United States	35	17	52

Kuwait	2	1	3
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End points

End points reporting groups

Reporting group title	Exenatide
Reporting group description: Patients randomized to the exenatide treatment group.	
Reporting group title	Placebo
Reporting group description: Patients randomized to the placebo treatment group.	
Reporting group title	Exenatide
Reporting group description: Patients received exenatide 2 milligrams (mg) subcutaneous (SC) injection once weekly for 24 weeks during the controlled assessment period.	
Reporting group title	Placebo
Reporting group description: Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period.	
Reporting group title	Exenatide
Reporting group description: Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period (from Week 25 to Week 52). Patients in this treatment group had previously received exenatide during the controlled assessment period.	
Reporting group title	Placebo to Exenatide
Reporting group description: Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period (from Week 25 to Week 52). Patients in this treatment group had previously received placebo during the controlled assessment period.	
Subject analysis set title	Controlled Assessment Period - Exenatide
Subject analysis set type	Full analysis
Subject analysis set description: Patients received exenatide 2 mg SC injection once weekly for 24 weeks during the controlled assessment period.	
Subject analysis set title	Controlled Assessment Period - Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period.	
Subject analysis set title	Treatment Period - Exenatide
Subject analysis set type	Full analysis
Subject analysis set description: Patients received exenatide 2 mg SC injection once weekly for 24 weeks during the controlled assessment period and continued to receive exenatide 2 mg SC once weekly during the open-label extension period for a further 28 weeks (from Week 0 to Week 52 overall).	
Subject analysis set title	Treatment Period - Placebo then Exenatide
Subject analysis set type	Full analysis
Subject analysis set description: Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period and then received exenatide 2 mg SC once weekly beginning at the start of the open-label extension period for 28 weeks (from Week 25 to Week 52).	

Primary: Change from Baseline in HbA1c to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in HbA1c to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in HbA1c (%) to Week 24 during the controlled assessment period is reported as adjusted least square (LS) mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A mixed model with repeated measures (MMRM) analysis was performed, excluding data collected after initiation of rescue medication or premature discontinuation of study medication. The Evaluable Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and post-baseline HbA1c assessment.

End point type	Primary
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End point timeframe:

Baseline (Week 0) and Week 24

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: percentage (% HbA1c)				
least squares mean (standard error)	-0.36 ($\pm$ 0.184)	0.49 ($\pm$ 0.273)		

Statistical analyses

Statistical analysis title	Treatment difference in HbA1c at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, and treatment group by visit interaction, baseline HbA1c value (continuous) and baseline HbA1c by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[1] - Exenatide versus Placebo

Primary: Percentage of Patients with On-Treatment Adverse Events (AEs) up to Week 24 (Controlled Assessment Period)

End point title	Percentage of Patients with On-Treatment Adverse Events (AEs) up to Week 24 (Controlled Assessment Period) ^[2]
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End point description:

A controlled assessment period AE was defined as an AE starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the extension period. For patients not entering the extension period, the period was defined up to and including last dose of study medication + 7 days (+ 90 days for serious AEs [SAEs] and other clinically significant or related AEs). The Investigator assessed AEs for causal relationship to study drug medication. The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. One patient who was randomized to placebo received a dose of exenatide in error and was subsequently reassigned to the exenatide treatment group for analyses based on actual treatment (ie, for analyses based on the Safety Analysis Set).

End point type	Primary
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End point timeframe:

Day 1 (Week 0) up to Week 24, plus up to a maximum of 90 days follow up

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were reported for this primary endpoint.

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	23		
Units: percentage of participants				
number (not applicable)				
Any AE	61.0	73.9		
Any AE with outcome of death	0	0		
Any SAE	3.4	4.3		
Any AE leading to discontinuation of treatment	0	0		
Any AE leading to discontinuation from study	0	0		
Any AE related to treatment	25.4	21.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Patients Positive for Anti-Drug Antibodies (ADAs) to Exenatide up to Week 24

End point title	Percentage of Patients Positive for Anti-Drug Antibodies (ADAs) to Exenatide up to Week 24 ^[3]
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End point description:

Percentage of patients positive for ADAs up to Week 24 is reported. Data were only available for the exenatide treatment group. Baseline was the antibody measurement at Week 0 (Day 1). A negative or missing antibody measurement was considered negative at baseline. High positive = antibody titers

≥625, including baseline assessment. Low positive = antibody titers <625, including baseline assessment. A patient was said to have treatment-emergent ADA positive at a visit if the antibody test was positive after first dose of exenatide following a negative or missing antibody measurement, or the titer increased by at least 1 titration category from a detectable measurement prior to first dose of randomized study medication. The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. Only patients receiving exenatide in the controlled assessment period were included in the analysis.

End point type	Primary
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End point timeframe:

Samples were collected on Day 1 (Week 0), Week 4, Week 8, Week 12 and Week 24

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were reported for this primary endpoint.

End point values	Treatment Period – Exenatide			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: percentage of participants				
number (not applicable)				
Week 4: High Positive (n=55)	16.4			
Week 4: Low Positive (n=55)	29.1			
Week 4: Treatment-Emergent ADA Positive (n=55)	43.6			
Week 8: High Positive (n=52)	53.8			
Week 8: Low Positive (n=52)	38.5			
Week 8: Treatment-Emergent ADA Positive (n=52)	92.3			
Week 12: High Positive (n=51)	58.8			
Week 12: Low Positive (n=51)	37.3			
Week 12: Treatment-Emergent ADA Positive (n=51)	96.1			
Week 24: High Positive (n=49)	40.8			
Week 24: Low Positive (n=49)	55.1			
Week 24: Treatment-Emergent ADA Positive (n=49)	95.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) Concentration to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) Concentration to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in FPG to Week 24 during the controlled assessment period is reported as adjusted LS mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A MMRM analysis was performed, excluding data collected after initiation of rescue medication or after premature discontinuation of study medication. The Intent-to-Treat (ITT) Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 24

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)	-5.2 (± 7.65)	16.5 (± 11.32)		

Statistical analyses

Statistical analysis title	Treatment difference in FPG at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, and treatment group by visit interaction, baseline fasting plasma glucose value, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline fasting plasma glucose by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.119
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	13.7

Notes:

[4] - Exenatide versus Placebo

Secondary: Change from Baseline in Body Weight to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Body Weight to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in body weight to Week 24 during the controlled assessment period is reported as adjusted LS mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A MMRM analysis was performed, excluding data collected after initiation of rescue medication or after premature discontinuation of study medication. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 24	

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: kilogram (kg)				
least squares mean (standard error)	-0.59 ($\pm$ 0.665)	0.63 ($\pm$ 0.982)		

Statistical analyses

Statistical analysis title	Treatment difference in body weight at Week 24
Statistical analysis description:	
Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, and treatment group by visit interaction, baseline body weight, screening HbA1c ($< 9.0\%$ or $\geq 9.0\%$), and baseline body weight by visit interaction as fixed effects, using an unstructured covariance matrix.	
Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.307
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.59
upper limit	1.15
Variability estimate	Standard error of the mean
Dispersion value	1.189

Notes:

[5] - Exenatide versus Placebo

Secondary: Change from Baseline in Fasting Insulin to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Fasting Insulin to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in fasting insulin to Week 24 during the controlled assessment period is reported as adjusted LS mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A MMRM analysis was performed, excluding data collected after initiation of rescue medication or after premature

discontinuation of study medication. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 24	

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: picomoles per liter (pmol/L)				
least squares mean (standard error)	79.6 (± 52.28)	-15.3 (± 78.49)		

Statistical analyses

Statistical analysis title	Treatment difference in fasting insulin at Week 24
Statistical analysis description:	
Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline fasting insulin, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline fasting insulin by visit interaction as fixed effects, using an unstructured covariance matrix.	
Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.323
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	94.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-95.6
upper limit	285.5
Variability estimate	Standard error of the mean
Dispersion value	95.26

Notes:

[6] - Exenatide versus Placebo

Secondary: Percentage of Patients Achieving HbA1c Goals of < 6.5%, ≤ 6.5%, and < 7.0% at Week 24 (Controlled Assessment Period)

End point title	Percentage of Patients Achieving HbA1c Goals of < 6.5%, ≤ 6.5%, and < 7.0% at Week 24 (Controlled Assessment Period)
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End point description:

The percentage of patients achieving HbA1c goals of < 6.5%, ≤ 6.5%, and < 7.0% at Week 24 during

the controlled assessment period is reported. A Cochran-Mantel-Haenszel (CMH) analysis was performed with missing data treated as non-responder, and excluding data collected after initiation of rescue medication or after premature discontinuation of study medication. The Evaluable Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and post-baseline HbA1c assessment. Only patients with data available were included in the analysis.

End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	22		
Units: percentage of participants				
number (confidence interval 95%)				
HbA1c <6.5%	19.0 (8.9 to 29.1)	4.2 (0.0 to 12.2)		
HbA1c ≤ 6.5%	19.0 (8.9 to 29.1)	4.2 (0.0 to 12.2)		
HbA1c < 7.0%	31.0 (19.1 to 42.9)	8.3 (0.0 to 19.4)		

Statistical analyses

Statistical analysis title	Treatment difference in HbA1c < 6.5% at Week 24
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Statistical analysis description:

Treatment group comparison was based on CMH test stratified by screening HbA1c (<9.0% or ≥9.0%). P-value was from the general association statistic.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.077
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	27.7

Notes:

[7] - Exenatide versus Placebo. Difference was the risk difference of the 2 proportions.

Statistical analysis title	Treatment difference in HbA1c ≤ 6.5% at Week 24
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Statistical analysis description:

Treatment group comparison was based on CMH test stratified by screening HbA1c (<9.0% or ≥9.0%). P-value was from the general association statistic.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period – Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.077
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	27.7

Notes:

[8] - Exenatide versus Placebo. Difference was the risk difference of the 2 proportions.

Statistical analysis title	Treatment difference in HbA1c < 7.0% at Week 24
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Statistical analysis description:

Treatment group comparison was based on CMH test stratified by screening HbA1c (<9.0% or ≥9.0%). P-value was from the general association statistic.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period – Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.02
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	22.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	39

Notes:

[9] - Exenatide versus Placebo. Difference was the risk difference of the 2 proportions.

Secondary: Change from Baseline in Lipid Profiles to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Lipid Profiles to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in lipid profiles to Week 24 during the controlled assessment period is reported as mean values (Standard International [SI] units). The following lipids were assessed: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. All lipids presented were taken in a fasted state. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with data available were included in the

analysis (n denotes number of patients analyzed for each parameter).

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 24	

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Total Cholesterol (n=46, 21)	-0.117 (± 0.7124)	-0.114 (± 0.5819)		
HDL-C (n=46, 21)	-0.035 (± 0.1950)	-0.047 (± 0.1039)		
LDL-C (n=43, 20)	-0.050 (± 0.5618)	-0.110 (± 0.5983)		
Triglycerides (n=46, 21)	-0.122 (± 1.0303)	0.094 (± 0.6626)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) to Week 24 (Controlled Assessment Period)
End point description:	
Change from baseline in SBP and DBP to Week 24 during the controlled assessment period is reported as adjusted LS mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A MMRM analysis was performed, excluding data collected after initiation of rescue medication or after premature discontinuation of study medication. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication.	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 24	

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: millimeters mercury (mmHg)				
least squares mean (standard error)				
SBP	-0.7 (± 1.48)	2.2 (± 2.15)		
DBP	0.2 (± 1.00)	-1.3 (± 1.45)		

Statistical analyses

Statistical analysis title	Treatment difference in SBP at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline SBP, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline SBP by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.284
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	2.61

Notes:

[10] - Exenatide versus Placebo

Statistical analysis title	Treatment difference in DBP at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline DBP, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline DBP by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
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Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.376
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	5.1
Variability estimate	Standard error of the mean
Dispersion value	1.77

Notes:

[11] - Exenatide versus Placebo

Secondary: Number of Patients Needing Rescue Medication Due to Failure to Maintain Glycemic Control up to Week 24 (Controlled Assessment Period)

End point title	Number of Patients Needing Rescue Medication Due to Failure to Maintain Glycemic Control up to Week 24 (Controlled Assessment Period)
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End point description:

Number of patients needing rescue medication at Week 24 and at each intermediate visit during the controlled assessment period is reported. Patients with a loss of glycemic control, defined as either an increase from baseline in HbA1c values by $\geq 1.0\%$ at 2 consecutive clinic visits that were at least 1 month apart, or a fasting plasma glucose value ≥ 250 mg/dL or random blood glucose value > 300 mg/dL for 4 days during a 7 day period, received rescue medication. Data collected after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with data available were included in the analysis (n denotes number of patients analyzed at each time point).

End point type	Secondary
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End point timeframe:

At Week 4, Week 8, Week 12, Week 18 and Week 24

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	24		
Units: participants				
Week 4 (n=57, 24)	0	0		
Week 8 (n=55, 24)	0	0		
Week 12 (n=51, 24)	0	0		
Week 18 (n=50, 24)	1	0		
Week 24 (n=49, 24)	0	0		

Statistical analyses

Secondary: Change from Baseline in Homeostasis Model Assessments – Beta-Cell Function (HOMA-B) and Insulin Sensitivity (HOMA-S) to Week 24 (Controlled Assessment Period)

End point title	Change from Baseline in Homeostasis Model Assessments – Beta-Cell Function (HOMA-B) and Insulin Sensitivity (HOMA-S) to Week 24 (Controlled Assessment Period)
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End point description:

Change from baseline in HOMA-B and HOMA-S in patients who were not taking insulin to Week 24 during the controlled assessment period is reported as adjusted LS mean values. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. A MMRM analysis was performed, excluding data collected after initiation of rescue medication or after premature discontinuation of study medication. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Homeostasis model assessments were only performed in patients who were not taking insulin.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 24

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	7		
Units: percentage (%HOMA-B and %HOMA-S)				
least squares mean (standard error)				
HOMA-B	63.98 (± 39.552)	-26.39 (± 56.138)		
HOMA-S	0.62 (± 3.607)	7.37 (± 4.914)		

Statistical analyses

Statistical analysis title	Treatment difference in HOMA-B at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline HOMA-B, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline HOMA-B by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period - Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.211
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	90.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.27
upper limit	238
Variability estimate	Standard error of the mean
Dispersion value	69.207

Notes:

[12] - Exenatide versus Placebo

Statistical analysis title	Treatment difference in HOMA-S at Week 24
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Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline at Week 24 were modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline HOMA-S, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline HOMA-S by visit interaction as fixed effects, using an unstructured covariance matrix.

Comparison groups	Controlled Assessment Period - Exenatide v Controlled Assessment Period – Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.289
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-6.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	6.29
Variability estimate	Standard error of the mean
Dispersion value	6.173

Notes:

[13] - Exenatide versus Placebo

Secondary: Percentage of Patients Reporting AEs of Injection Site Reactions up to Week 24 (Controlled Assessment Period)

End point title	Percentage of Patients Reporting AEs of Injection Site Reactions up to Week 24 (Controlled Assessment Period)
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End point description:

Percentage of patients reporting injection site reactions at Week 24 and at each intermediate visit during the controlled assessment period is reported. Injection site reactions were presented from the AE case report form (CRF), based on the "Injection site reactions" higher level term. A controlled assessment period AE was defined as an AE starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the extension period. For patients not entering the extension period, the period was defined up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs). The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. Only patients with data available were included in the analysis (n denotes number of patients analyzed at each time point).

End point type	Secondary
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End point timeframe:

At Week 4, Week 8, Week 12, Week 18 and Week 24

End point values	Controlled Assessment Period - Exenatide	Controlled Assessment Period - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	23		
Units: percentage of participants				
number (not applicable)				
Week 4 (n=59, 23)	8.5	8.7		
Week 8 (n=57, 23)	3.5	4.3		
Week 12 (n=53, 23)	1.9	0		
Week 18 (n=51, 22)	0	0		
Week 24 (n=51, 22)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HbA1c to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in HbA1c to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
End point description:	
Change from baseline in HbA1c (%) to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The Evaluable Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and post-baseline HbA1c assessment. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 52	

End point values	Treatment Period - Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	17		
Units: percentage (% HbA1c)				
arithmetic mean (standard deviation)	-0.10 (± 1.711)	0.53 (± 2.123)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FPG Concentration to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in FPG Concentration to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in FPG to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 52

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	16		
Units: mg/dL				
arithmetic mean (standard deviation)	-1.8 (± 62.64)	10.6 (± 75.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Weight to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in Body Weight to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in body weight to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study

medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 52	

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	18		
Units: kg				
arithmetic mean (standard deviation)	0.04 (± 6.088)	-0.04 (± 4.687)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Insulin to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in Fasting Insulin to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in fasting insulin to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 52	

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	16		
Units: pmol/L				
arithmetic mean (standard deviation)	-32.4 (± 273.57)	121.5 (± 379.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving HbA1c Goals of < 6.5%, ≤ 6.5%, and < 7.0% to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Percentage of Participants Achieving HbA1c Goals of < 6.5%, ≤ 6.5%, and < 7.0% to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

The percentage of patients achieving HbA1c goals of < 6.5%, ≤ 6.5%, and < 7.0% at Week 52 among patients who received open-label exenatide during the treatment period is reported. The treatment period was defined as the controlled assessment period and extension period combined. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The Evaluable Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and post-baseline HbA1c assessment. Only patients who received open-label exenatide and with data available were included in the analysis.

End point type	Secondary
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End point timeframe:

At Week 52

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	17		
Units: percentage of participants				
number (not applicable)				
HbA1c < 6.5%	30.8	23.5		
HbA1c ≤ 6.5%	30.8	23.5		
HbA1c < 7.0%	35.9	29.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lipids Profiles to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in Lipids Profiles to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in lipid profiles to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values (SI units). The treatment period was defined as the controlled assessment period and extension period combined. The following lipids were assessed: total cholesterol, HDL-C, LDL-C, and triglycerides. All lipids presented were taken in a fasted state. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis (n denotes number of patients analyzed for each parameter).

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 52	

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	15		
Units: mmol/L				
arithmetic mean (standard deviation)				
Total Cholesterol (n=37, 15)	-0.188 (± 0.4199)	-0.255 (± 0.9075)		
HDL-C (n=37, 15)	0.004 (± 0.1740)	-0.076 (± 0.2327)		
LDL-C (n=33, 15)	-0.175 (± 0.4025)	-0.152 (± 0.7682)		
Triglycerides (n=37, 15)	-0.155 (± 1.1108)	-0.043 (± 0.5971)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Pressure (Systolic and Diastolic) to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in Blood Pressure (Systolic and Diastolic) to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in SBP and DBP to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.

End point type	Secondary
End point timeframe:	
Baseline (Week 0) and Week 52	

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	18		
Units: mmHg				
arithmetic mean (standard deviation)				
SBP	-0.7 (± 13.09)	-0.6 (± 8.73)		
DBP	1.1 (± 8.65)	-2.5 (± 10.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Needing Rescue Medication Due to Failure to Maintain Glycemic Control up to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Number of Patients Needing Rescue Medication Due to Failure to Maintain Glycemic Control up to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Number of patients needing rescue medication at Week 52 and at each intermediate visit during the treatment period is reported. The treatment period was defined as the controlled assessment period and extension period combined. Patients with a loss of glycemic control, defined as either an increase from baseline in HbA1c values by $\geq 1.0\%$ at 2 consecutive clinic visits that were at least 1 month apart, or a fasting plasma glucose value ≥ 250 mg/dL or random blood glucose value > 300 mg/dL for 4 days during a 7 day period, received rescue medication. Data collected after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients who received open-label exenatide and with data available were included in the analysis (n denotes number of patients analyzed at each time point).

End point type	Secondary
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End point timeframe:

At Week 4, Week 8, Week 12, Week 18, Week 24, Week 28, Week 40 and Week 52

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	23		
Units: participants				
Week 4 (n=49, 23)	0	0		
Week 8 (n=49, 23)	0	0		
Week 12 (n=49, 23)	0	0		
Week 18 (n=49, 23)	1	0		
Week 24 (n=49, 23)	0	0		

Week 28 (n=49, 23)	2	1		
Week 40 (n=47, 20)	2	0		
Week 52 (n=45, 18)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HOMA-B and HOMA-S to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Change from Baseline in HOMA-B and HOMA-S to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Change from baseline in HOMA-B and HOMA-S to Week 52 among patients who received open-label exenatide during the treatment period is reported as mean values. The treatment period was defined as the controlled assessment period and extension period combined. Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of randomized study medication. Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded. The ITT Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication. Only patients with observed baseline and Week 52 values, and who received open-label exenatide were included in the analysis.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and Week 52

End point values	Treatment Period - Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	5		
Units: percentage (%HOMA-B and %HOMA-S)				
arithmetic mean (standard deviation)				
HOMA-B	-2.58 (± 130.435)	42.02 (± 183.869)		
HOMA-S	9.85 (± 12.366)	2.36 (± 7.631)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Reporting AEs of Injection Site Reactions up to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Percentage of Patients Reporting AEs of Injection Site Reactions up to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Percentage of patients reporting injection site reactions at Week 52 and at each intermediate visit among patients who received open-label exenatide during the treatment period is reported. The treatment period was defined as the controlled assessment period and extension period combined. Injection site reactions were presented from the AE CRF, based on the "Injection site reactions" higher level term. An Extension Period AE was defined as an AE starting on or after day of first dose of open-label exenatide to last dose + 7 days (+ 90 days for SAEs and other clinically significant or related AEs). The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. Only patients with data available at each specified visit were included in the analysis (n denotes number of patients analyzed at each time point).

End point type	Secondary
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End point timeframe:

At Week 4, Week 8, Week 12, Week 18, Week 24, Week 28, Week 40 and Week 52

End point values	Treatment Period – Exenatide	Treatment Period - Placebo then Exenatide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	22		
Units: percentage of participants				
number (not applicable)				
Week 4 (n=50, 22)	10.0	9.1		
Week 8 (n=50, 22)	4.0	4.5		
Week 12 (n=50, 22)	2.0	0		
Week 18 (n=50, 22)	0	0		
Week 24 (n=50, 22)	0	0		
Week 28 (n=50, 22)	4.0	0		
Week 40 (n=48, 19)	0	0		
Week 52 (n=46, 17)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Exenatide Concentrations to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)

End point title	Plasma Exenatide Concentrations to Week 52 Among Patients who Received Open-Label Exenatide (Treatment Period)
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End point description:

Geometric mean plasma exenatide concentrations up to Week 52 during the treatment period are reported. The treatment period was defined as the controlled assessment period and extension period combined. Data were only available for the exenatide treatment group. Data collected after initiation of rescue medication were included. Data collected after discontinuation of study medication were excluded. The Pharmacokinetic (PK) Analysis Set consisted of all patients who received at least 1 dose of exenatide, for whom any postdose data were available and who did not deviate from the protocol in ways that would significantly affect the PK analyses. Only patients who received open-label exenatide and with data available were included in the analysis (n denotes number of patients analyzed at each time point). 99999 = Not calculated as below the lower limit of quantification.

End point type	Secondary
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End point timeframe:

Samples were collected on Day 1 (Week 0), Week 4, Week 8, Week 12, Week 24 and Week 52

End point values	Treatment Period – Exenatide			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: mmol/L				
geometric mean (geometric coefficient of variation)				
Baseline (n=54)	99999 (± 99999)			
Week 4 (n=54)	41.51 (± 91.9)			
Week 8 (n=49)	130.60 (± 83.8)			
Week 12 (n=44)	163.58 (± 92.3)			
Week 24 (n=33)	140.81 (± 84.0)			
Week 52 (n=28)	88.88 (± 79.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After first dose of study medication in period through end of treatment in period +90 days for SAEs (or +7 days for non-serious AEs). Overall timeframe: up to maximum of ~37 weeks and 41 weeks for controlled assessment and extension periods, respectively.

Adverse event reporting additional description:

The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. One patient who was randomized to placebo received a dose of exenatide in error and was subsequently reassigned to the exenatide treatment group for analyses based on actual treatment (ie, for analyses based on the Safety Analysis Set).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Controlled Assessment Period – Exenatide
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Reporting group description:

Patients received exenatide 2 mg SC injection once weekly for 24 weeks during the controlled assessment period.

Reporting group title	Controlled Assessment Period – Placebo
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Reporting group description:

Patients received placebo (matching with exenatide) SC injection once weekly for 24 weeks during the controlled assessment period.

Reporting group title	Extension Period - Exenatide
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Reporting group description:

Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period. Patients in this treatment group had previously received exenatide during the controlled assessment period.

Reporting group title	Extension Period – Placebo to Exenatide
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Reporting group description:

Patients received open-label exenatide 2 mg SC injection once weekly for 28 weeks during the extension period. Patients in this treatment group had previously received placebo during the controlled assessment period.

Serious adverse events	Controlled Assessment Period – Exenatide	Controlled Assessment Period – Placebo	Extension Period - Exenatide
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 59 (3.39%)	1 / 23 (4.35%)	3 / 50 (6.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 23 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Irritable bowel syndrome			
subjects affected / exposed	0 / 59 (0.00%)	1 / 23 (4.35%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 59 (1.69%)	0 / 23 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 23 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 59 (1.69%)	0 / 23 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 23 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 23 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension Period – Placebo to Exenatide		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Irritable bowel syndrome			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Controlled Assessment Period – Exenatide	Controlled Assessment Period – Placebo	Extension Period – Exenatide
Total subjects affected by non-serious adverse events subjects affected / exposed	25 / 59 (42.37%)	10 / 23 (43.48%)	10 / 50 (20.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 5	2 / 23 (8.70%) 3	2 / 50 (4.00%) 2
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	1 / 23 (4.35%) 1	0 / 50 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 5 3 / 59 (5.08%) 3 5 / 59 (8.47%) 5 4 / 59 (6.78%) 4 3 / 59 (5.08%) 3	3 / 23 (13.04%) 3 0 / 23 (0.00%) 0 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 0 / 23 (0.00%) 0	1 / 50 (2.00%) 1 1 / 50 (2.00%) 1 1 / 50 (2.00%) 1 0 / 50 (0.00%) 0 2 / 50 (4.00%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 5	1 / 23 (4.35%) 1	0 / 50 (0.00%) 0
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 23 (0.00%) 0	0 / 50 (0.00%) 0
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 5	2 / 23 (8.70%) 3	1 / 50 (2.00%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 6	0 / 23 (0.00%) 0	2 / 50 (4.00%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4	2 / 23 (8.70%) 2	0 / 50 (0.00%) 0
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 2	1 / 23 (4.35%) 1	0 / 50 (0.00%) 0
Hypoglycaemia subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4	0 / 23 (0.00%) 0	1 / 50 (2.00%) 2

Non-serious adverse events	Extension Period – Placebo to Exenatide		
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 22 (18.18%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Vomiting subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2011	- Inclusion criterion updated to specify that patients aged 10 to 17, inclusive, at Screening visit were eligible to participate in the study. - Study plan and procedures updated to include assessment of study medication compliance. - Additional guidance provided for rescue treatment following the loss of glycemic control.
20 June 2012	- Study design amended to include extended safety follow-up period. - Primary, secondary and safety objectives and corresponding endpoints updated. Exploratory safety endpoints added. - Descriptions of the analysis methods for the study endpoints also updated. - An inclusion criterion and an exclusion criterion were updated and another exclusion criterion was removed. - Additional information provided regarding dispensing of study medication. - Randomization strata updated to include country. - Procedures for rescue treatment updated. - Certain screening procedures revised. - For the controlled assessment period, certain laboratory assessments were amended and guidance for returning used/unused medication was updated. - For the open-label extension period, certain laboratory assessments were amended. - For study termination/early termination, a procedure was added requiring patients to fast overnight and certain laboratory assessments were amended. - Ethical safety considerations updated. - Blood glucose threshold for determination of hypoglycemia event updated. - Total blood draw volume increased. - Description of analysis populations updated.

09 April 2015	- Information was transferred into AstraZeneca format, including transferal of the mixed meal substudy addenda. - Study population description expanded to specify both children and adolescents. The study objectives, plan, and an inclusion criterion were updated to reflect this. - Study duration and plan updated as follows: controlled assessment period updated to 24 weeks, open-label extension period updated to 28 weeks, and 10-week post-treatment follow-up period added. - Observation periods for variables related to the primary and secondary objectives updated to align with the revised study plan. - Procedures for rescue treatment updated. - Updates/additions for 4 inclusion criteria and 3 exclusion criteria. - Procedures for patient enrollment and randomization, and for handling patients incorrectly enrolled or randomized in the study, and blinding/unblinding procedures were updated and expanded. - Dosing guidance generalized to remove specific reference to abdomen for route of injection. - Guidance for the concomitant use of insulin, as well as other medications, updated. - Text added to clarify treatment compliance procedures. - Text added to clarify the procedures for discontinuing from study medication, and withdrawing from the study. - Visit schedule and procedures were updated to reflect the updated study duration/plan. - Collection of safety variables updated. - Analysis sets expanded to include Per Protocol population. - Interim analysis details, including the timing of the analysis, were updated. - The study sample size was adjusted. - Study plan and procedures modified to include injection site reaction assessments. - Safety assessments related to markers of bone turnover updated from deoxypyridinoline to N telopeptide. - Formulation of study medication updated to include a dual chamber pen. Instructions for study medication administration were clarified. - Procedures regarding paternal exposure were removed.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Indicated as interim analysis to allow submission of results while trial is ongoing, but all reported endpoint data is considered the final analysis. Due to limited sample size, statistical inference for HOMA-B and HOMA-S is difficult to interpret.

Notes: