Clinical trial results:
Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

Summary

EudraCT number	2011-005196-16
Trial protocol	Outside EU/EEA
Global end of trial date	01 April 2020

Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020

Trial information

Trial identification

Sponsor protocol code	D5550C00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00658021
WHO universal trial number (UTN)	-
Other trial identifiers	AstraZeneca: H8O-MC-GWBQ

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparredsleden 1, Mölndal, Sweden, 431 83
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, 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)	EMEA-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	Final
Date of interim/final analysis	01 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that glycemic control, as measured by change in glycated hemoglobin A1c (HbA1c) from baseline to endpoint, with exenatide 5 microgram (mcg) twice daily or 10 mcg twice daily is superior to that of placebo, after 28 weeks of treatment in adolescent participants with type 2 diabetes who are naïve to antidiabetes agents, or participants who were treated with metformin, an sulfonylurea (SU), or a combination of metformin and an SU.

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.

Background therapy:

Participants who were naïve to antidiabetic treatment, or who were receiving metformin and/or an SU, were enrolled in this study.

Evidence for comparator: -

Actual start date of recruitment	30 May 2008
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	Brazil: 2
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Mexico: 27
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	122
EEA total number of subjects	0

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)	14
Adolescents (12-17 years)	108
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 who were naïve to antidiabetics, or were receiving metformin, an SU or a combination of metformin and an SU in 7 countries between 30 May 2008 and 01 April 2020.

Pre-assignment

Screening details:

The study commenced with a 1-week, single-blind, injectable placebo lead-in period before participants were randomized to 1 of 3 treatment groups: exenatide 5 mcg twice daily, exenatide 10 mcg twice daily, or placebo twice daily. A total of 122 participants were randomized in this study.

Period 1

Period 1 title	28-Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Exenatide 5 mcg

Arm description:

Adolescent participants received exenatide 5 mcg subcutaneous (SC) injection twice daily for 28 weeks.

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

Dosage and administration details:

Exenatide 5 mcg was self-administered twice daily by SC injection using prefilled pens for 28 weeks.

Arm title	Exenatide 10 mcg

Arm description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.

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

Dosage and administration details:

Exenatide 5 mcg was self-administered twice daily by SC injection using prefilled pens for 4 weeks after randomization. At the end of 4 weeks post-randomization, the dose increased to 10 mcg twice daily for next 24 weeks.

Arm title	Placebo

Arm description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching with exenatide 5 mcg or 10 mcg was self-administered twice daily by SC injection using prefilled pens for 28 weeks.

Number of subjects in period 1	Exenatide 5 mcg	Exenatide 10 mcg	Placebo
Started	42	38	42
Received treatment	40	38	42
Completed	31	25	25
Not completed	11	13	17
Consent withdrawn by subject	1	1	3
Physician decision	1	2	1
Adverse event, non-fatal	3	1	-
Loss of glucose control	1	1	10
Unspecified	2	3	1
Did not receive treatment	2	-	-
Withdrawal by parent/guardian	1	1	1
Developed study withdrawal criteria	-	2	-
Protocol deviation	-	2	1

Period 2

Period 2 title	Long-term Safety Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Exenatide 5 mcg

Arm description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 28 weeks. Participants with a height difference of at least 5 millimeter (mm) between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

Arm type	Experimental

Investigational medicinal product name	Exenatide
Investigational medicinal product code	
Other name	BYETTA®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Exenatide 5 mcg was self-administered twice daily by SC injection using prefilled pens for 28 weeks. Study treatment was not received in the Safety Follow-up Period.

Arm title	Exenatide 10 mcg

Arm description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks. Participants with a height difference of at least 5 mm between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

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

Dosage and administration details:

Exenatide 5 mcg was self-administered twice daily by SC injection using prefilled pens for 4 weeks after randomization. At the end of 4 weeks post-randomization, the dose increased to 10 mcg twice daily for next 24 weeks. Study treatment was not received in the Safety Follow-up Period.

Arm title	Placebo

Arm description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks. Participants with a height difference of at least 5 mm between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching with exenatide 5 mcg or 10 mcg was self-administered twice daily by SC injection using prefilled pens for 28 weeks. Study treatment was not received in the Safety Follow-up Period.

Number of subjects in period 2[1]	Exenatide 5 mcg	Exenatide 10 mcg	Placebo
Started	7	5	7
Completed	7	2	7
Not completed	0	3	0
Consent withdrawn by subject	-	1	-
Physician decision	-	2	-

Notes:

[1] - 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: Only participants entering safety follow-up period are presented.

Baseline characteristics

Reporting groups	
Reporting group title	Exenatide 5 mcg
Reporting group description:	
Adolescent participants received exenatide 5 mcg subcutaneous (SC) injection twice daily for 28 weeks.	
Reporting group title	Exenatide 10 mcg
Reporting group description:	
Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.	

Reporting group values	Exenatide 5 mcg	Exenatide 10 mcg	Placebo
Number of subjects	42	38	42
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	5	4
Adolescents (12-17 years)	37	33	38
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	13.7	14.0	14.4
standard deviation	± 1.94	± 1.95	± 1.82
Sex: Female, Male Units: participants			
Female	31	22	29
Male	11	16	13
Race/Ethnicity, Customized			
Ethnicity not collected and Hispanic was collected as a Race in this study.			
Units: Subjects			
White	7	5	13
Black or African American	14	8	7
Asian	3	2	5
American Indian or Alaska Native	0	1	0
Hispanic	18	22	17

Reporting group values	Total		
Number of subjects	122		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	14		
Adolescents (12-17 years)	108		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	82		
Male	40		
Race/Ethnicity, Customized			
Ethnicity not collected and Hispanic was collected as a Race in this study.			
Units: Subjects			
White	25		
Black or African American	29		
Asian	10		
American Indian or Alaska Native	1		
Hispanic	57		

Subject analysis sets

Subject analysis set title	Total Exenatide twice daily (EBID)
Subject analysis set type	Full analysis

Subject analysis set description:

Efficacy data from participants from both exenatide groups (Total EBID) was pooled for comparison with placebo.
Adolescent participants received exenatide 5 mcg SC injection twice daily for 28 weeks; or Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.

Reporting group values	Total Exenatide twice daily (EBID)	Placebo	
Number of subjects	78	42	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	10	4	
Adolescents (12-17 years)	68	38	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	13.9	14.4	
standard deviation	± 1.96	± 1.82	
Sex: Female, Male			
Units: participants			
Female	51	29	
Male	27	13	
Race/Ethnicity, Customized			
Ethnicity not collected and Hispanic was collected as a Race in this study.			
Units: Subjects			
White	12	13	
Black or African American	20	7	
Asian	5	5	
American Indian or Alaska Native	1	0	
Hispanic	40	17	

End points

End points reporting groups

Reporting group title	Exenatide 5 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg subcutaneous (SC) injection twice daily for 28 weeks.

Reporting group title	Exenatide 10 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.

Reporting group title	Placebo

Reporting group description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.

Reporting group title	Exenatide 5 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 28 weeks. Participants with a height difference of at least 5 millimeter (mm) between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

Reporting group title	Exenatide 10 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks. Participants with a height difference of at least 5 mm between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

Reporting group title	Placebo

Reporting group description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks. Participants with a height difference of at least 5 mm between Day 1 and Week 28 visits returned for study visits every 6 months for up to 3 years after completion of the treatment period.

Subject analysis set title	Total Exenatide twice daily (EBID)
Subject analysis set type	Full analysis

Subject analysis set description:

Efficacy data from participants from both exenatide groups (Total EBID) was pooled for comparison with placebo.
Adolescent participants received exenatide 5 mcg SC injection twice daily for 28 weeks; or Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.

Primary: Adjusted Change From Baseline in HbA1c at Week 28

End point title	Adjusted Change From Baseline in HbA1c at Week 28

End point description:

Change from baseline in HbA1c is reported as adjusted least square (LS) mean values at Week 28. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. A mixed model with repeated measures (MMRM) analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Evaluable Analysis Set included all randomized participants who received at least 1 dose of randomized study medication and had a baseline and at least 1 post-baseline HbA1c assessment.

End point type	Primary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[1]	42[2]		
Units: percentage (%HbA1c)				
least squares mean (standard error)	0.11 (± 0.215)	0.38 (± 0.293)		

Notes:

[1] - All participants in Evaluable Analysis set population.

[2] - All participants in Evaluable Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference in HbA1c at Week 28

Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline values at visit are obtained from a MMRM including treatment, baseline HbA1c, background diabetes therapy strata, week of visit, baseline HbA1c-by-visit interaction and treatment-by-visit interaction as fixed effects using an unstructured covariance matrix.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.363

Primary: Number of Participants With Post-Treatment Adverse Events of Special Interest (AESI) During Safety Follow-up Period

End point title	Number of Participants With Post-Treatment Adverse Events of Special Interest (AESI) During Safety Follow-up Period[3]

End point description:

Post-treatment adverse events (AEs) were defined as AEs that started or worsened during the off-treatment period (Safety Follow-up Period), which was defined as the day after the Week 28/early discontinuation (ED) visit to the date of completion of the Safety Follow-up Period. The AESIs recorded were as follows: hematological malignancies, thyroid neoplasms, pancreas neoplasms, aplastic anemia, pancreatitis, pregnancy and pregnancy outcomes (including congenital anomalies). The Safety Follow-up Analysis Set included all participants who had at least 1 safety follow-up period assessment visit.

End point type	Primary

End point timeframe:

From 1 day after the Week 28/ED visit to 3 years after Week 28/ED visit.

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 determined for this endpoint.

End point values	Exenatide 5 mcg	Exenatide 10 mcg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	7	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving HbA1c Goals of < 7%, <= 6.5%, and < 6.5% Through Week 28

End point title	Percentage of Participants Achieving HbA1c Goals of < 7%, <= 6.5%, and < 6.5% Through Week 28

End point description:

The percentage of participants achieving HbA1c goals of < 7%, <= 6.5%, and < 6.5% through Week 28 were compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which screening HbA1c strata and background diabetes therapy strata served as the stratification factors. The CMH analysis excluded measurements after initiation of rescue medication and study drug discontinuation with missing data treated as non-responder. The Evaluable Analysis Set included all randomized participants who received at least 1 dose of randomized study medication and had a baseline and at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Weeks 0, 4, 12, 20 and 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[4]	42[5]		
Units: percentage of participants				
number (confidence interval 95%)				
HbA1c < 7%: Week 0	37.2 (26.5 to 47.9)	38.1 (23.4 to 52.8)		
HbA1c < 7%: Week 4	44.9 (33.8 to 55.9)	42.9 (27.9 to 57.8)		
HbA1c < 7%: Week 12	43.6 (32.6 to 54.6)	33.3 (19.1 to 47.6)		
HbA1c < 7%: Week 20	35.9 (25.3 to 46.5)	35.7 (21.2 to 50.2)		
HbA1c < 7%: Week 28	33.3 (22.9 to 43.8)	28.6 (14.9 to 42.2)		

HbA1c <=6.5%: Week 0	17.9 (9.4 to 26.5)	16.7 (5.4 to 27.9)		
HbA1c <=6.5%: Week 4	29.5 (19.4 to 39.6)	23.8 (10.9 to 36.7)		
HbA1c <=6.5%: Week 12	33.3 (22.9 to 43.8)	23.8 (10.9 to 36.7)		
HbA1c <=6.5%: Week 20	24.4 (14.8 to 33.9)	19.0 (7.2 to 30.9)		
HbA1c <=6.5%: Week 28	23.1 (13.7 to 32.4)	19.0 (7.2 to 30.9)		
HbA1c <6.5%: Week 0	15.4 (7.4 to 23.4)	7.1 (0.0 to 14.9)		
HbA1c <6.5%: Week 4	26.9 (17.1 to 36.8)	21.4 (9.0 to 33.8)		
HbA1c <6.5%: Week 12	30.8 (20.5 to 41.0)	19.0 (7.2 to 30.9)		
HbA1c <6.5%: Week 20	21.8 (12.6 to 31.0)	19.0 (7.2 to 30.9)		
HbA1c <6.5%: Week 28	23.1 (13.7 to 32.4)	14.3 (3.7 to 24.9)		

Notes:

[4] - All participants in Evaluable Analysis set population.

[5] - All participants in Evaluable Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference in HbA1c < 7% at Week 28
Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.562 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Treatment group comparison is based on CMH test stratified by screening HbA1c and background diabetes therapy strata. P-value is from the general association statistics.

Statistical analysis title	Treatment difference in HbA1c <= 6.5% at Week 28
Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621 [7]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - Treatment group comparison is based on CMH test stratified by screening HbA1c and background diabetes therapy strata. P-value is from the general association statistics.

Statistical analysis title	Treatment difference in HbA1c < 6.5% at Week 28
Comparison groups	Total Exenatide twice daily (EBID) v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - Treatment group comparison is based on CMH test stratified by screening HbA1c and background diabetes therapy strata. P-value is from the general association statistics.

Secondary: Adjusted Change From Baseline in Body Weight Through Week 28

End point title	Adjusted Change From Baseline in Body Weight Through Week 28

End point description:

Change from baseline in body weight is reported as adjusted LS mean values at Weeks 4, 12, 20 and 28. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. A MMRM analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Full Analysis Set included all randomized participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[9]	42[10]		
Units: kilogram				
least squares mean (standard error)				
Week 4	-0.89 (± 0.196)	0.04 (± 0.260)		
Week 12	-1.09 (± 0.401)	-0.42 (± 0.534)		
Week 20	-0.71 (± 0.559)	-0.33 (± 0.755)		
Week 28	-0.81 (± 0.632)	-0.36 (± 0.857)		

Notes:

[9] - All participants in Full Analysis set population.

[10] - All participants in Full Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference in body weight at Week 4

Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline values at visit are obtained from a MMRM including treatment, baseline body weight, screening HbA1c strata, background diabetes therapy strata, week of visit, baseline body weight-by visit interaction and treatment-by-visit interaction as fixed effects using an unstructured covariance matrix.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.327

Statistical analysis title	Treatment difference in body weight at Week 12

Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline values at visit are obtained from a MMRM including treatment, baseline body weight, screening HbA1c strata, background diabetes therapy strata, week of visit, baseline body weight-by visit interaction and treatment-by-visit interaction as fixed effects using an unstructured covariance matrix.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.669

Statistical analysis title	Treatment difference in body weight at Week 20

Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline values at visit are obtained from a MMRM including treatment, baseline body weight, screening HbA1c strata, background diabetes therapy strata, week of visit, baseline body weight-by visit interaction and treatment-by-visit interaction as fixed effects using an unstructured covariance matrix.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.692
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.94

Statistical analysis title	Treatment difference in body weight at Week 28

Statistical analysis description:

Adjusted LS mean and treatment group difference in the change from baseline values at visit are obtained from a MMRM including treatment, baseline body weight, screening HbA1c strata, background diabetes therapy strata, week of visit, baseline body weight-by visit interaction and treatment-by-visit interaction as fixed effects using an unstructured covariance matrix.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	1.68
Variability estimate	Standard error of the mean
Dispersion value	1.065

Secondary: Adjusted Change From Baseline in Fasting Serum Glucose (FSG) at Week 28

End point title	Adjusted Change From Baseline in Fasting Serum Glucose (FSG) at Week 28

End point description:

Change from baseline in FSG is reported as adjusted LS mean values at Week 28. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. An analysis of covariance (ANCOVA) analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Full Analysis Set included all randomized participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[11]	42[12]		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)	0.791 (± 0.4010)	1.072 (± 0.5466)		

Notes:

[11] - All participants in Full Analysis set population.

[12] - All participants in Full Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference in FSG

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline fasting serum glucose, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.614
upper limit	1.052
Variability estimate	Standard error of the mean
Dispersion value	0.68

Secondary: Adjusted Change From Baseline in Self-Monitored Blood Glucose (SMBG) at Week 28

End point title	Adjusted Change From Baseline in Self-Monitored Blood Glucose (SMBG) at Week 28

End point description:

Change from baseline in SMBG measurements are reported as adjusted LS mean values at Week 28. SMBG measurements were taken before (pre-prandial) and 2 hours after (post-prandial) the 2 main meals of the day on 3 separate days during the week before baseline (Day 1) and Week 28. Post-prandial excursions were calculated as the difference between the pre-prandial and post-prandial blood glucose concentrations (post-prandial – pre-prandial) and averaged (mean) over the 2 main meals over the 3 separate days in each period. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. An ANCOVA analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Full

Analysis Set included all randomized participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Pre-meal and 2 hours post-meal on Baseline (Day 1) and Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[13]	42[14]		
Units: mmol/L				
least squares mean (standard error)				
Pre-meal SMBG	-0.699 (± 0.2709)	-0.888 (± 0.4511)		
Post-meal SMBG	-1.029 (± 0.2722)	-1.542 (± 0.4503)		
Post-prandial excursion SMBG	-0.181 (± 0.2107)	-0.391 (± 0.3418)		
Overall SMBG	-0.877 (± 0.2468)	-1.193 (± 0.4117)		

Notes:

[13] - All participants in Full Analysis set population.

[14] - All participants in Full Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference for pre-meal SMBG

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline SMBG measure, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.714
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.821
upper limit	1.199
Variability estimate	Standard error of the mean
Dispersion value	0.5151

Statistical analysis title	Treatment difference for post-meal SMBG

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline SMBG measure, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.513
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.516
upper limit	1.541
Variability estimate	Standard error of the mean
Dispersion value	0.5245

Statistical analysis title	Treatment difference post-prandial excursion SMBG

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline SMBG measure, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.601
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.577
upper limit	0.997
Variability estimate	Standard error of the mean
Dispersion value	0.4015

Statistical analysis title	Treatment difference for overall SMBG

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline SMBG measure, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.316
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.615
upper limit	1.248
Variability estimate	Standard error of the mean
Dispersion value	0.4749

Secondary: Adjusted Change From Baseline in Fasting Serum Insulin at Week 28

End point title	Adjusted Change From Baseline in Fasting Serum Insulin at Week 28

End point description:

Change from baseline in fasting serum insulin is reported as adjusted LS mean values at Week 28. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. An ANCOVA analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Full Analysis Set included all randomized participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[15]	42[16]		
Units: picomoles per liter				
least squares mean (standard error)	1.67 (± 25.323)	12.49 (± 34.825)		

Notes:

[15] - All participants in Full Analysis set population.

[16] - All participants in Full Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference in fasting serum insulin

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline fasting serum insulin, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-10.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-95.48
upper limit	73.84
Variability estimate	Standard error of the mean
Dispersion value	43.187

Secondary: Adjusted Change From Baseline in Homeostasis Model Assessments – Beta-Cell Function (HOMA-B) and Insulin Sensitivity (HOMA-S) at Week 28

End point title	Adjusted Change From Baseline in Homeostasis Model Assessments – Beta-Cell Function (HOMA-B) and Insulin Sensitivity (HOMA-S) at Week 28

End point description:

Change from baseline in HOMA-B and HOMA-S are reported as adjusted LS mean values at Week 28. Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to the first dose of study medication. An ANCOVA analysis was performed, excluding measurements after initiation of rescue medication and study drug discontinuation. The Full Analysis Set included all randomized participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[17]	42[18]		
Units: percentage (%HOMA-B and %HOMA-S)				
least squares mean (standard error)				
HOMA-B	-25.93 (± 10.404)	-22.10 (± 14.885)		
HOMA-S	-3.18 (± 2.172)	-2.90 (± 3.117)		

Notes:

[17] - All participants in Full Analysis set population.

[18] - All participants in Full Analysis set population.

Statistical analyses

Statistical analysis title	Treatment difference for HOMA-B

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline %HOMA-B, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.836
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.19
upper limit	32.51
Variability estimate	Standard error of the mean
Dispersion value	18.542

Statistical analysis title	Treatment difference for HOMA-S

Statistical analysis description:

Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline %HOMA-S, screening HbA1c strata and background diabetes therapy strata as fixed effects.

Comparison groups	Total Exenatide twice daily (EBID) v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.941
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.82
upper limit	7.26
Variability estimate	Standard error of the mean
Dispersion value	3.846

Secondary: Percentage of Participants Discontinuing the Study Due to Failure to Maintain Glycemic Control Through Week 28

End point title	Percentage of Participants Discontinuing the Study Due to Failure to Maintain Glycemic Control Through Week 28

End point description:

Participants were discontinued from the study due to failure to maintain glycemic control if either discontinuation reason on summary case report form was "Loss of glucose control" or AE with lower level Medical Dictionary for Regulatory Activities (MedDRA) term "Loss of control of blood sugar" or

"Hyperglycaemia" leading to study drug discontinuation, using MedDRA Version 23.0. The Full Analysis Set included all randomized participants who received at least 1 dose of randomized study medication. Here, "n" is defined as number of participants analysed at each time point.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24 and 28

End point values	Total Exenatide twice daily (EBID)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78[19]	42[20]		
Units: percentage of participants				
number (not applicable)				
Week 2 (n= 40, 38, 42)	0	0		
Week 4 (n= 40, 38, 42)	0	2.4		
Week 8 (n= 39, 38, 41)	0	0		
Week 12 (n= 37, 35, 40)	1.4	5.0		
Week 16 (n= 36, 33, 36)	1.4	0		
Week 20 (n= 35, 30, 34)	0	14.7		
Week 24 (n= 35, 30, 29)	0	6.9		
Week 28 (n= 33, 28, 26)	1.6	0		

Notes:

[19] - All participants in Full Analysis set population.

[20] - All participants in Full Analysis set population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious AEs: From first dose of study drug (Day 1) up to 30 days after last dose of study drug, approximately 32 weeks.
Non-serious AEs: From first dose of study drug (Day 1) up to 1 day after last dose of study drug, approximately 28 weeks.

Adverse event reporting additional description:

The Safety Analysis Set included all participants who received at least 1 dose of randomized study medication.
Treatment-emergent AEs are reported for the 28-week treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Exenatide 5 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 28 weeks.

Reporting group title	Exenatide 10 mcg

Reporting group description:

Adolescent participants received exenatide 5 mcg SC injection twice daily for 4 weeks after randomization. At the end of 4 weeks post-randomization, participants received exenatide 10 mcg SC injection twice daily for next 24 weeks.

Reporting group title	Placebo

Reporting group description:

Adolescent participants received placebo matching with exenatide 5 mcg or 10 mcg SC injection twice daily for 28 weeks.

Serious adverse events	Exenatide 5 mcg	Exenatide 10 mcg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 41 (7.32%)	1 / 37 (2.70%)	1 / 42 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 37 (2.70%)	0 / 42 (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			
Intentional self-injury			

subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	0 / 42 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	0 / 42 (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
Gastroenteritis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal abscess			
subjects affected / exposed	1 / 41 (2.44%)	0 / 37 (0.00%)	0 / 42 (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

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

Non-serious adverse events	Exenatide 5 mcg	Exenatide 10 mcg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 41 (63.41%)	24 / 37 (64.86%)	23 / 42 (54.76%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 41 (4.88%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	2	3	2
Headache			
subjects affected / exposed	9 / 41 (21.95%)	9 / 37 (24.32%)	11 / 42 (26.19%)
occurrences (all)	14	15	27
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 37 (2.70%)	3 / 42 (7.14%)
occurrences (all)	2	1	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 41 (4.88%)	2 / 37 (5.41%)	3 / 42 (7.14%)
occurrences (all)	2	2	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 41 (2.44%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	1	5	4
Diarrhoea			
subjects affected / exposed	2 / 41 (4.88%)	3 / 37 (8.11%)	5 / 42 (11.90%)
occurrences (all)	3	3	9
Nausea			
subjects affected / exposed	4 / 41 (9.76%)	11 / 37 (29.73%)	7 / 42 (16.67%)
occurrences (all)	4	15	10
Vomiting			
subjects affected / exposed	2 / 41 (4.88%)	8 / 37 (21.62%)	3 / 42 (7.14%)
occurrences (all)	2	10	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 41 (4.88%)	3 / 37 (8.11%)	4 / 42 (9.52%)
occurrences (all)	3	4	6
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 41 (7.32%)	0 / 37 (0.00%)	3 / 42 (7.14%)
occurrences (all)	3	0	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	1	4	2
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 41 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0

Influenza			
subjects affected / exposed	3 / 41 (7.32%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences (all)	3	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 41 (19.51%)	2 / 37 (5.41%)	3 / 42 (7.14%)
occurrences (all)	10	4	3
Pharyngitis			
subjects affected / exposed	4 / 41 (9.76%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences (all)	6	5	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 41 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	4 / 41 (9.76%)	1 / 37 (2.70%)	2 / 42 (4.76%)
occurrences (all)	4	1	2
Upper respiratory tract infection			
subjects affected / exposed	5 / 41 (12.20%)	3 / 37 (8.11%)	5 / 42 (11.90%)
occurrences (all)	8	3	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2008	Protocol addendum (dated: 15-Jan-2008) was added to allow collection (at Visits 3 and 11) and banking of biological samples for genomic/proteomic/biochemical research. Modification of the inclusion criteria to clarify that drug naïve participants be limited to participants with a confirmed diagnosis of type 2 diabetes who were receiving treatment with diet and exercise only. The Schwartz equation for calculating glomerular filtration rate in children and adolescents was substituted for the Cockcroft-Gault creatinine clearance equation.
09 February 2011	Protocol addendum (dated: 21-May-2008) was added to mention the following exclusions: use of warfarin and other coumarol derivatives, certain conditions known to be associated with improper functioning of the pancreas, and uncontrolled hypertension. Protocol addendum (dated: 01-Feb-2011) was added to allow thorough quantification of the pharmacokinetics disposition of exenatide in adolescents and allow assessment of safety endpoints relative to maximum plasma exenatide concentrations observed in adolescent participants. Updated objectives/statistical measures related to proportion of participants achieving HbA1c milestones. Broadening of HbA1c inclusion criteria was added. The age-related inclusion criterion was expanded to limit the number of participants >= 17 years of age.
29 May 2012	Added references to a required Safety Follow-up addendum. In the secondary objectives, the HbA1c endpoints were amended to < 7%, <= 6.5%, and < 6.5%.
16 May 2013	Protocol addendum (dated: 29-May-2012) was added to include a long-term Safety Follow-up in which participants were observed following discontinuation of study drug administration. Change in Sponsor from Eli Lilly and Company to Amylin Pharmaceuticals, LLC.
13 October 2017	Added explanation for the switch of current reusable injection pen (Ypsopen U100) to BYETTA commercial like clinical prefilled injection pen. Updated the study Sponsor as Amylin Pharmaceuticals, LLC, a wholly owned subsidiary of AstraZeneca PLC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported