10 December 2020
EMA/104840/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

BYETTA

exenatide

Procedure no: EMEA/H/C/000698/P46/048

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Introduction

On 21 Sep 2020, the MAH submitted a completed paediatric study for Byetta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a paediatric program based on an agreed Paediatric Investigational Plan (PIP); (PIP number: EMEA-000689-PIP01-09-M10).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study H80-MC-GWBQ has been conducted as part of a paediatric program based on an agreed Paediatric Investigational Plan (PIP); (PIP number: EMEA-000689-PIP01-09-M10) which is ongoing to assess the treatment of type 2 diabetes mellitus as monotherapy or in combination with metformin, and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies, or in combination with insulin with or without other oral antidiabetic agents. The submitted paediatric study does not support the proposed paediatric indication for Byetta and therefore the benefit/risk for Byetta is unaffected and there are no regulatory consequences identified.

The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by Q1 2021. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Exenatide twice daily (Byetta; hereafter referred to as EBID) is administered by subcutaneous injection. It was approved for use in the US on 28 April 2005 and on 20 November 2006 for use in the EU. In the EU, EBID is indicated for adults who have not achieved adequate glycaemic control on maximally tolerated doses of oral therapies or as an adjunct treatment with insulin glargine.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study H8O-MC-GWBQ (hereafter referred to as study GWBQ): "A Phase 3, double-blind, randomized, placebo-controlled, clinical safety and efficacy study of exenatide 5 µg and 10 µg BID as monotherapy and as add-on to metformin, an SU, or a combination of metformin and an SU in children with type 2 diabetes mellitus"

2.3.2. Clinical study

Study H8O-MC-GWBQ: "A Phase 3, double-blind, randomized, placebo-controlled, clinical safety and efficacy study of exenatide 5 µg and 10 µg BID as monotherapy and as add-on to metformin, an SU, or a combination of metformin and an SU in children with type 2 diabetes mellitus"

Description

This was a multicentre study performed in adolescents (aged 10 to 17 years) with T2DM, evaluating the glycaemic control with exenatide compared to placebo. This study has been conducted as part of a paediatric programme based on an agreed PIP (number: EMEA-000480-PIP01-08-M10, which assessed the potential therapeutic benefits of exenatide in adolescents with T2DM.

Methods

Objective

The primary efficacy objective of the study was to test the hypothesis that glycaemic control, as measured by change in HbA1c from baseline to endpoint, with exenatide 5 µg twice daily or 10 µg twice daily (Total EBID) is superior to that of placebo, after 28 weeks of treatment in adolescent patients with type 2 diabetes who are naïve to anti-diabetes agents, or patients who are being treated with metformin, an SU, or a combination of metformin and an SU.

The primary safety objective of the study was to assess ongoing development and growth following up to 28 weeks of study drug treatment in adolescent patients with type 2 diabetes.

CHMP comment

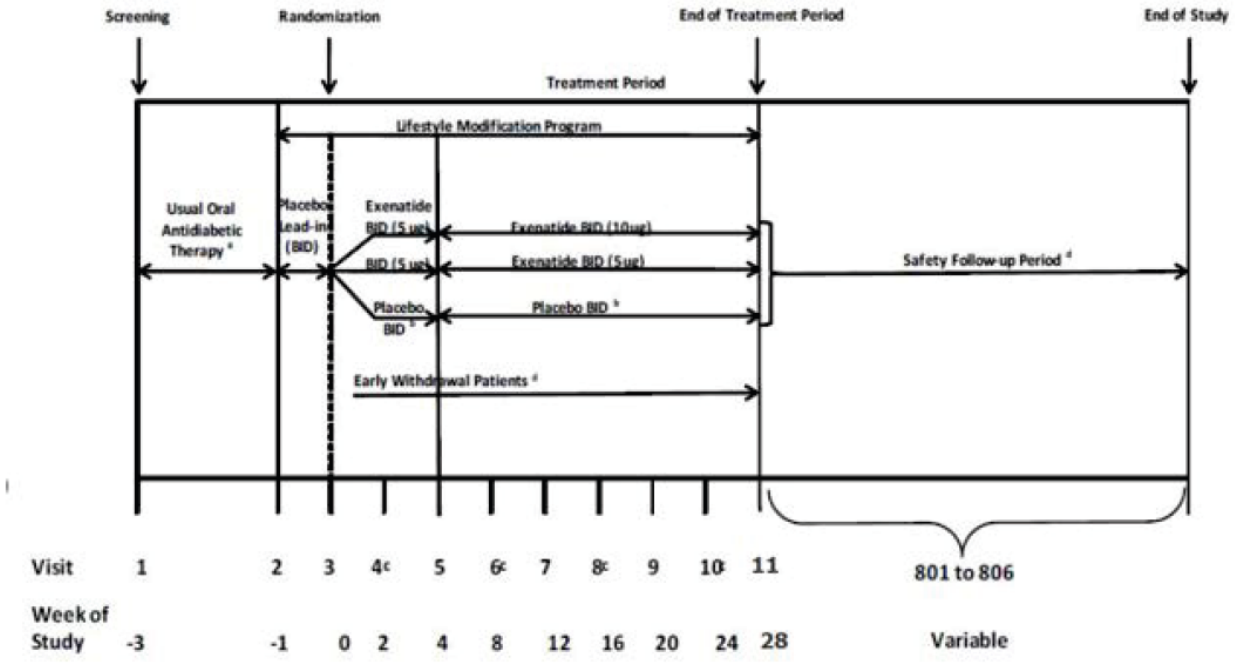
The original aim of the study was to separately assess exenatide 5 µg twice daily or 10 µg twice daily versus placebo, however due to slow recruitment due to ongoing clinical paediatric studies using other more conveniently administered therapies, the objective was changed to assess pooled data from both exenatide groups versus placebo. This change was made with agreement by the EMA and the FDA.

Study design

This was a multicenter, double-blind, placebo-controlled, randomized, parallel, 3-arm study performed in adolescents (10 to 17 years of age inclusive) with type 2 diabetes (Figure 1).

Patients were naïve to antidiabetic agents, or were receiving oral treatment with metformin, a sulfonylurea (SU), or a combination of metformin and an SU at the time of enrolment.

Figure 1 Flow chart of study design



a Metformin or SU or combination of MET and SU, with or without diet and exercise, or naïve to antidiabetic agents as being treated with diet and exercise alone.

b The volume of placebo was equivalent to 5 µg or 10 µg exenatide.

c Scheduled telephone visit.

d Patients returned to the study site at approximately 6-month intervals for a period of up to 3 years or until the difference between 2 height measurements over a 6-month interval was less than 5 mm (whichever came first). Patients who had a height change of less than 5 mm over a 6-month interval during the treatment period did not enter the Safety Follow-up Period. Patients who did not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication entered the Safety Follow-up Period. Patients did not receive any study drug but could be treated with a diabetes treatment regimen deemed appropriate by the Investigator or healthcare provider.

BID, twice daily; MET, metformin; SU, sulfonylurea.

CHMP comment

The overall design of the study as well as the study duration was adequate. The study included an extended safety follow-up period of up to three years. During this period, no study medication was administered, and patients were treated as deemed appropriate by the Investigator or health care provider.

Study population /Sample size

The study included adolescents (aged 10 to 17 years) with T2DM (screening HbA1c 6.5% to 10.5%). Patients were naïve to antidiabetic agents, or were receiving oral treatment with metformin, an SU, or a combination of metformin and an SU at the time of enrolment. The American Diabetes Association diagnostic criteria for T2DM were applied.

The number of patients ≥ 17 years of age was limited to no more than 10% of patients in each treatment arm.

CHMP comment

The selection of patients was adequate, in order to recruit a representative study population. The exclusion criteria included concomitant medications and conditions that might have rendered the interpretation of data difficult. Other exclusion criteria were in place to for the safety of the patients.

Initial sample size calculation

Approximately 195 patients diagnosed with type 2 diabetes were planned to be enrolled. Approximately 65 patients were to be randomized to receive placebo and 130 patients were to be randomized to receive exenatide (65 per exenatide treatment group). A sample of 65 patients per treatment group would provide > 95% power to reject the null hypothesis of no difference among treatments assuming true mean changes in HbA1c of -0.7, -0.5, and 0 for patients receiving exenatide 10 µg twice daily, exenatide 5 µg twice daily, and placebo twice daily, respectively.

Final sample size calculation

Due to the availability of other more conveniently administered therapies, eg, oral, QD, or QW recruitment to this study has been slow/difficult despite extensive efforts by the Sponsor.

A decision was made with agreement by the European Medicines Agency and FDA to stop recruitment and to pool patients from both exenatide groups and compare the pooled group with placebo. With a total of 122 patients randomized (Total EBID:Placebo 2:1), the study should have had approximately 87% power to detect a difference between Total EBID and placebo assuming the true mean changes in HbA1c were -0.7, -0.5, and 0 for patients receiving exenatide 10 µg BID, exenatide 5 µg BID, and placebo BID, respectively. The combined effect of the Total EBID doses compared with placebo (mean difference) was assumed to be -0.6 with a common standard deviation of 1% at the 5% significance level without consideration of patient discontinuation and impact on effect size. If a lower Total EBID effect size of -0.455 was to be assumed as a result of patient discontinuations, this would correspond to 64% power.

CHMP comment

The original aim of the study was to separately assess 5 µg EBID and 10 µg EBID versus placebo, and 195 patients were to be recruited. However, because of slow recruitment to the study (first patient enrolled in May 2008, last patient visit in April 2020), due to the emergence of other more convenient therapies, it was decided to pool the data for the two EBID arms and to stop recruitment when 122 patients had been randomised. This was made with agreement by the EMA and the FDA.

Treatments

Patients received single-blind placebo by subcutaneous (SC) injection during a 1-week lead-in period. Once randomized, patients received either 5 or 10 µg exenatide SC twice daily, or matched placebo.

Patients remained on their background antidiabetic treatment during the study (metformin, SU, metformin and SU, or no antidiabetic treatment), and all patients were expected to participate in a simplified lifestyle modification program.

Duration of treatment

Patients received single-blind placebo by SC injection during a 1-week lead-in period. Patients were then randomized and received either 5 or 10 µg exenatide SC twice daily, or matched placebo for 28 weeks.

Patients assigned to 10 µg exenatide SC twice daily received 5 µg exenatide SC twice daily for 4 of the 28 weeks before being titrated to 10 µg exenatide SC twice daily.

Rescue medication

Rescue therapy was defined as any new antidiabetic concomitant medication or changes to background oral-diabetic medication, for exacerbation of diabetes. Treatment with insulin could be given for emergency reasons during the treatment period.

CHMP comment

Exenatide was given in accordance with the recommendations in the SmPC for Byetta, which states that treatment should be started with 5 µg exenatide SC twice daily for at least 4 weeks after which the dose may be increased to 10 µg twice daily.

Rescue medication was allowed. If prolonged insulin therapy was necessary, the patient was to discontinue from the study.

Outcomes/endpoints

Primary endpoints (efficacy)

The change in HbA1c from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

Primary endpoints (safety)

- Adverse events of special interest
- Prescription medications
- Body weight, height, and Tanner pubertal stage
- Carcinoembryonic antigen concentration
- Calcitonin concentration

Secondary endpoints (efficacy)

- Proportion of patient achieving HbA1c goals of < 7%, ≤ 6.5%, and < 6.5% at Visit 11 (Week 28) and each intermediate visit as applicable
- Change in body weight from baseline Visit 3 (Week 0) to Visit 11 (Week 28), and to each intermediate visit as applicable
- Change in FSG from baseline Visit 3 (Week 0) to Visit 11 (Week 28)
- Change in SMBG measurements before and 2 hours after the 2 main meals of the day on 3 days during the week before Visit 3 (Week 0) and Visit 11 (Week 28)
- Change in fasting serum insulin from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

- Change in HOMA-B and HOMA-S as measured by homeostasis model assessment from baseline Visit 3 (Week 0) to Visit 11 (Week 28)
- Proportions of patients discontinuing the study, due to failure to maintain glycaemic control at Visit 11 (Week 28), and to each intermediate visit as applicable

Secondary endpoints (safety)

- Adverse events (serious and nonserious)
- Incidence and frequency of hypoglycaemic events
- Laboratory measurements (including clinical chemistry, calcitonin, CEA and haematology and urinalysis)
- Antibodies to exenatide
- Electrocardiograms
- Vital signs
- Pubertal assessment
- Height

CHMP comment

Primary and secondary endpoints were adequate.

Statistical Methods

- Initially, statistical comparisons were planned between each exenatide group and the placebo group separately. However, as a result of the reduced sample size, final analyses and comparisons to placebo were performed on a pooled exenatide group (exenatide 5 and 10 µg twice daily; Total EBID).
- All efficacy and safety variables were summarized using descriptive statistics as appropriate. Continuous variables were summarized by descriptive statistics including number of patients with available data (n), arithmetic mean, standard deviation (SD), median, minimum value, and maximum value.
- Statistical tests, where performed, were conducted at a 2-sided significance level of 5%. Where appropriate, model-based point estimates, together with their 95% confidence intervals were presented along with the 2-sided p-values for the tests. No adjustments for multiplicity (including hierarchical testing) were made for the primary, secondary and exploratory variables.
- The primary efficacy analysis compared treatment groups (Total EBID versus placebo) with respect to change in HbA1c from baseline Visit 3 (Week 0) to Visit 11 (Week 28) using the mixed model repeated measures (MMRM) approach. The model included change in HbA1c as the dependent variable and treatment, baseline HbA1c, background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin + SU), week of visit, baseline HbA1c-by-visit interaction and treatment-by-visit interaction as the fixed effects.

- Secondary efficacy analyses were performed using a MMRM if multiple post-baseline measurements were collected. If only an endpoint measurement is collected, analysis of covariance (ANCOVA) was used. The MMRM/ANCOVA analysis was treated as the primary analysis method for continuous efficacy endpoints. The statistical analysis of categorical variables was done using a stratified Cochran-Mantel-Haenszel (CMH) test.
- Adverse events (AEs) were classified in accordance to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 23.0.

CHMP comment

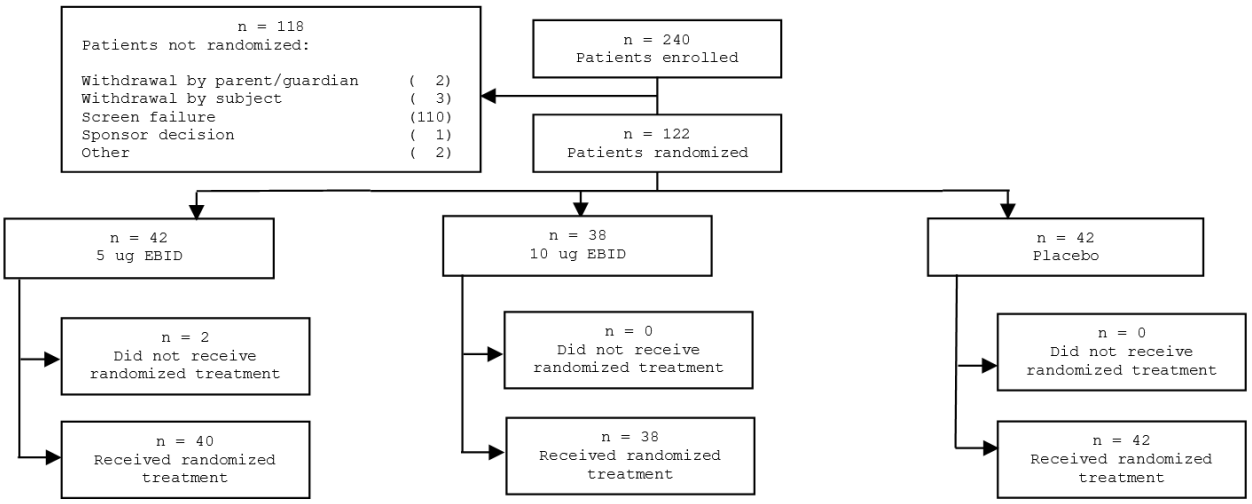
Statistical methods were adequate.

Results

Recruitment/ Number analysed

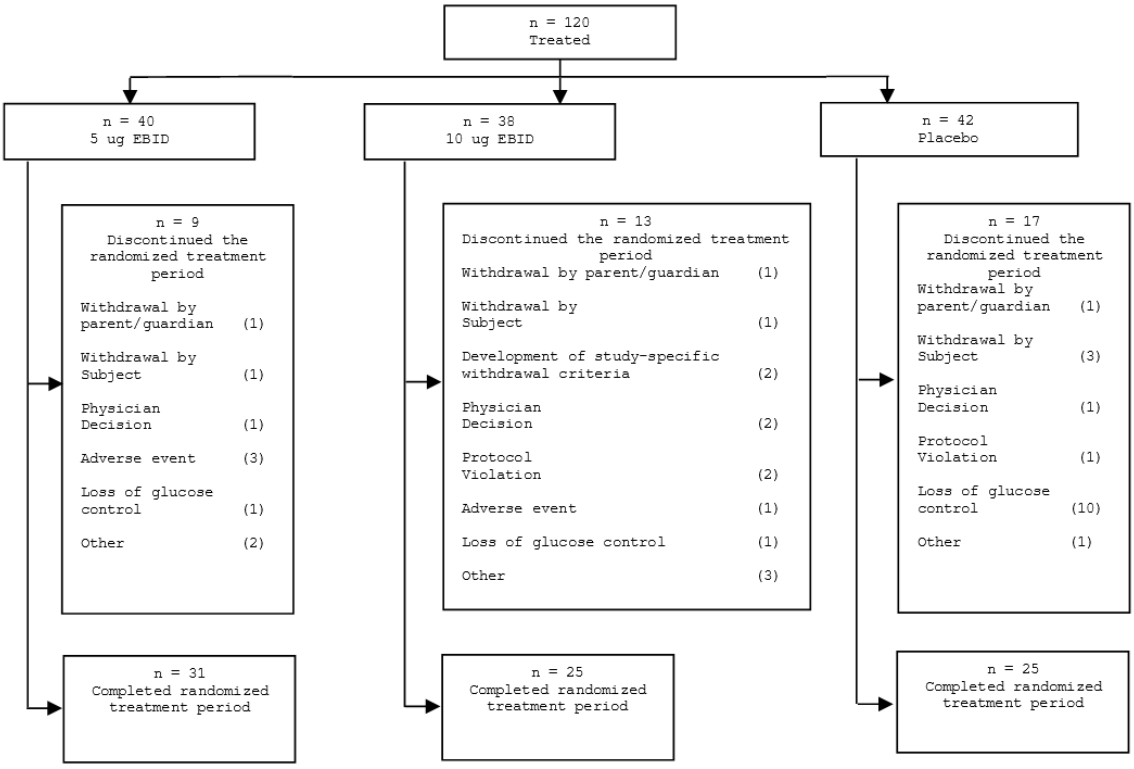
A total of 240 patients were enrolled, of which 124 entered the placebo lead-in and 122 were randomized. A total of 120 patients received study treatment: 78 patients received EBID (patients assigned to 5 µg EBID: 40; patients assigned to 10 µg EBID: 38) and 42 patients received placebo. The majority of Total EBID and placebo patients completed 28 weeks of study treatment (71.8% and 59.5%, respectively). A total of 19 patients (15.8% of those who received randomized study treatment) entered the Safety Follow-up Period, the majority of these (16 patients) completed the Safety Follow-up Period as a result of reaching their final height.

Figure 2 Patient Disposition – Randomisation (All Patients Analysis Set)



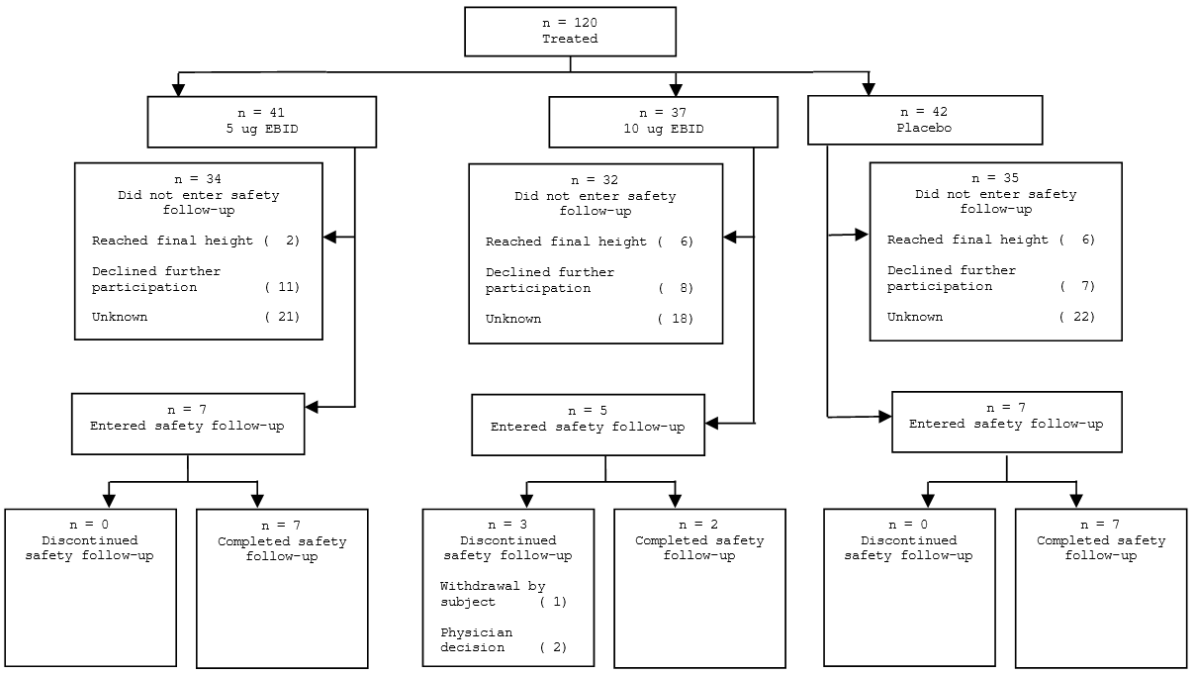
EBID, Exenatide twice daily; n, Number of patients included in analysis.

Figure 3 Patient Disposition – Treatment Period (Safety Analysis Set)



EBID, Exenatide twice daily; n, Number of patients included in analysis.

Figure 4 Patient Disposition – Safety Follow-up Period (Safety Analysis Set)



EBID, Exenatide twice daily; n, Number of patients included in analysis.

CHMP comment

As already stated, recruitment was slow with the first patient enrolled in May 2008 and the last patient last visit occurred in April 2020. A large proportion of the enrolled patients (110/240) were screen failures. The drop-out rate was higher in the placebo treated group and the most common reason for discontinuation in this group was loss of glycaemic control (10/17) compared to Total EBID (2/22).

Very few patients continued in the Safety Follow-up Period. Only a total of 14 patients were "excluded" as they had reached their final height, whereas the majority actively declined participation or discontinued for unknown reasons. Thus overall, only 19 patients continued in this follow-up.

Baseline data

The demographic, patient, and baseline disease characteristics were generally balanced between the Total EBID and placebo treatment groups, and were generally representative of the intended adolescent population with type 2 diabetes. Key baseline characteristics of the patient population are summarized below. The pre-existing conditions and concomitant medications were as expected for the study population, and similar between treatment groups (Table 1).

Overall, the study population was consistent with the target patient population, and the characteristics of the treatment groups were similar.

Table 1 Summary of demographic, patient, and disease characteristics (ITT analysis set)

	5 µg EBID (N = 42)	10 µg EBID (N = 38)	Total EBID (N = 80)	Placebo (N = 42)	Total (N = 122)
Mean baseline age (SD); years	13.7 (1.94)	14.0 (1.95)	13.9 (1.94)	14.4 (1.82)	14.0 (1.91)
Sex n (%)					
Male	11 (26.2)	16 (42.1)	27 (33.8)	13 (31.0)	40 (32.8)
Female	31 (73.8)	22 (57.9)	53 (66.3)	29 (69.0)	82 (67.2)
Race					
White	7 (16.7)	5 (13.2)	12 (15.0)	13 (31.0)	25 (20.5)
Black or African American	14 (33.3)	8 (21.1)	22 (27.5)	7 (16.7)	29 (23.8)
Asian	3 (7.1)	2 (5.3)	5 (6.3)	5 (11.9)	10 (8.2)
American Indian or Alaska Native	0	1 (2.6)	1 (1.3)	0	1 (0.8)
Hispanic	18 (42.9)	22 (57.9)	40 (50.0)	17 (40.5)	57 (46.7)
Mean baseline weight (SD); kg	88.29 (21.737)	93.03 (32.017)	90.54 (27.037)	93.40 (30.130)	91.53 (28.049)
Mean body mass index (SD); kg/m^2	33.68 (7.487)	34.87 (11.579)	34.25 (9.604)	34.10 (9.787)	34.19 (9.627)
Mean baseline HbA1c (SD); %	7.55 (1.250)	7.57 (1.267)	7.56 (1.251)	7.65 (1.142)	7.59 (1.210)
Mean baseline diabetes duration (SD); years	1.63 (1.596)	1.63 (1.695)	1.63 (1.633)	1.75 (1.821)	1.67 (1.694)
Background therapy n (%)					
Naïve	10 (23.8)	10 (26.3)	20 (25.0)	10 (23.8)	30 (24.6)
Metformin	26 (61.9)	26 (68.4)	52 (65.0)	25 (59.5)	77 (63.1)
SU	0	0	0	2 (4.8)	2 (1.6)
Metformin + SU	6 (14.3)	2 (5.3)	8 (10.0)	5 (11.9)	13 (10.7)

EBID, exenatide twice daily; HbA1c, glycated hemoglobin A1c; N, Number of patients in Intent-To-Treat analysis set in each treatment group; n, Number of patients included in analysis; SD, standard deviation; SU, sulfonylurea.

Rescue medication

The proportion of patients in the Safety Analysis Set who received rescue medication was similar for the Total EBID and placebo groups (6.4% and 7.1%, respectively). Rescue medication was metformin in all cases but 1, where a patient in the placebo group received glimepiride.

CHMP comment

Demographic, patient, and baseline disease characteristics were balanced between groups, taking into account the small size of the study. Notably, the patients were overweight with a mean BMI of 34. The majority of patients (63%) were treated with metformin and very few were treated with SU as monotherapy (2 patients in the placebo-treated group.

Efficacy results

Primary and secondary endpoint outcomes at Week 28 are summarized in Table 2 below.

Table 2 Summary of primary and secondary efficacy endpoint results

Parameter	Total EBID (N = 78)	Placebo (N = 42)
Change in HbA1c from baseline to Week 28 (%) (Evaluable Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[a]	0.11 (0.215)	0.38 (0.293)
LS mean (SE) difference[a]	-0.28 (0.363)	
95% 2-sided confidence interval for LS mean difference	(-1.01, 0.45)	
P-value	0.444	
Proportion of patients achieving HbA1c goals at Week 28 (%) (Evaluable Analysis Set)		
< 7%		
Number (%) Achieved Goal[b]	26 (33.3)	12 (28.6)
Difference (Total EBID versus Placebo)	4.8	
p-value	0.562	
≤ 6.5%		
Number (%) Achieved Goal[b]	18 (23.1)	8 (19.0)
Difference (Total EBID versus Placebo)	4.0	
p-value	0.621	
< 6.5%		
Number (%) Achieved Goal[b]	18 (23.1)	6 (14.3)
Difference (Total EBID versus Placebo)	8.8	
p-value	0.229	
Change from Baseline in Body Weight (kg) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[c]	-0.81 (0.632)	-0.36 (0.857)
LS mean (SE) difference at Week 28	-0.44 (1.065)	
95% 2-sided confidence interval for LS mean difference	(-2.56, 1.68)	
p-value	0.679	
Change from Baseline to Week 28 in Fasting Serum Glucose (mmol/L) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[d]	0.791 (0.4010)	1.072 (0.5466)
LS mean (SE) difference at Week 28	-0.281 (0.6800)	
95% 2-sided confidence interval for LS mean difference	(-1.614, 1.052)	
p-value	0.679	
Change from Baseline to Week 28 in Fasting Serum Insulin (pmol/L) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[d]	1.67 (25.323)	12.49 (34.825)
LS mean (SE) difference at Week 28	-10.82 (43.187)	
95% 2-sided confidence interval for LS mean difference	(-95.48, 73.84)	
p-value	0.802	

Parameter	Total EBID (N = 78)	Placebo (N = 42)
Change from Baseline to Week 28 in Overall Self-Monitored Blood Glucose (mmol/L) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[d]	-0.877 (0.2468)	-1.193 (0.4117)
LS mean (SE) difference at Week 28	0.316 (0.4749)	
95% 2-sided confidence interval for LS mean difference	(-0.615, 1.248)	
p-value	0.505	
Change from Baseline to Week 28 in Beta-Cell Function (%HOMA-B) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[d]	-25.93 (10.404)	-22.10 (14.885)
LS mean (SE) difference at Week 28	-3.84 (18.542)	
95% 2-sided confidence interval for LS mean difference	(-40.19, 32.51)	
p-value	0.836	
Change from Baseline to Week 28 in Insulin Sensitivity (%HOMA-S) (Full Analysis Set)		
LS mean (SE) adjusted change from baseline to Week 28[d]	-3.18 (2.172)	-2.90 (3.117)
LS mean (SE) difference at Week 28	-0.28 (3.846)	
95% 2-sided confidence interval for LS mean difference	(-7.82, 7.26)	
p-value	0.941	
Total percentage of patients discontinuing study treatment due to failure maintain glycemic control (n [%])[e]	3 (3.8%)	10 (23.8%)

[a] Adjusted LSMean 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.

[b] All patients with missing endpoint data are imputed as non-responders

[c] Adjusted LSMean 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.

[d] Adjusted LSMean and treatment group difference in the change from baseline values at Week 28 are obtained from multiple imputation ANCOVA including treatment, baseline parameter (fasting serum glucose, fasting serum insulin, SMBG, %HOMA-B, or %HOMA-S), screening HbA1c strata and background diabetes therapy strata as fixed effects.

[e] Percentages calculated from total number of patients who discontinued study during treatment period due to failure to maintain glycemic control if either discontinuation reason on SUM CRF form is "Loss of glucose control" or adverse event with lower level MedDRA term "Loss of control of blood sugar" or "Hyperglycaemia" leading to study drug discontinuation, using MedDRA Version 23.0

ANCOVA, analysis of covariance; EBID, twice daily exenatide; HbA1c, glycated hemoglobin A1c; HOMA-B, Homeostasis Model Assessments – Beta-Cell Function; HOMA-S, Homeostasis Model Assessments – Insulin Sensitivity; LS, least square; LSMean, least square mean; MedDRA, Medical Dictionary for Regulatory Activities; SE, standard error.

CHMP comment

No clinically relevant or statistically significant differences were observed for any of the primary or secondary efficacy endpoints. Notably, HbA1c increased in both treatment groups, the increase was however less pronounced in the exenatide treated group. The proportions of patients who achieved treatment goals were numerically higher in the exenatide treated group, the difference was however not statistically significant. Weight decrease was also numerically larger in the exenatide treated group, but again the treatment difference of -0.44 kg was not statistically significant.

Anti-drug antibody results

A total of 61.5% of patients who received EBID had treatment-emergent ADAs. For each of the EBID dose levels, the proportion of patients who were positive for treatment-emergent anti-drug antibodies (ADAs) increased over time from 22.0% at Week 4 to 46.9% at Week 28 for 5 µg EBID, and 40.5% at Week 4 to 56.7% at Week 28 for 10 µg EBID. For those patients with positive results, the majority were low positive (antibody titers < 625) at all visits. The incidence of patients who were high positive (antibody titers ≥ 625) was low, with a maximum of 8.1% of patients in the 5 µg EBID group and 8.3% of patients in the 10 µg EBID group, both at Week 12.

There did not appear to be an impact of ADA on efficacy; however, due to the low sample sizes of patients who were treatment-emergent ADA positive with available HbA1c data at each visit, it is not possible to draw firm conclusions on the overall effect.

Based on the available data, there appeared to be a trend for a greater reduction in HbA1c for the low positive group compared with the negative group for both EBID doses, which was consistent across the 2 dose groups:

- Mean change from baseline of -0.49% (N = 16) versus -0.22% (N = 11) at Week 28 in the 5 µg EBID dose group.
- Mean change from baseline of -0.25% (N = 14) versus +0.63% (N = 3) at Week 28 in the 10 µg EBID dose group.
- Mean change from baseline of -0.38% (N = 30) versus -0.04% (N = 14) at Week 28 in the Total EBID group.

CHMP comment

A relatively high proportion of patients (61.5%) treated with exenatide showed ADAs during the study, the majority had low titers. Since the study is small, interpretation of the data has to be made with caution, but the data provided give no indication of an impact of ADA on efficacy.

Safety results

Extent of exposure

The mean duration of exposure was similar between the Total EBID and placebo groups (174.3 and 170.0 days, respectively). More than half of the patients were exposed to study medication for ≥ 196 days, with a similar proportion between the Total EBID and placebo groups (59.0% and 50.0%, respectively).

In the Safety Follow-up Analysis Set, the mean duration of exposure in the Total EBID groups was 195.3 days (SD: 7.56 days) and 75.0% of patients were exposed to study medication for ≥ 196 days.

CHMP comment

The duration of exposure was comparable between groups and more than 50% of the patients maintained treatment throughout the study duration (≥196 days). Notably, patients continuing in the Safety Follow-up Period showed a higher adherence to treatment than the overall population.

Adverse events

Treatment-emergent AEs are summarized in Table 3 below.

Table 3 Overall summary of Treatment-Emergent Adverse Events at Patient Level (Safety Analysis Set)

	Treatment Period			
	Number (%) of Patients[a]			
Adverse Event Category	5 µg EBID (N = 41)	10 µg EBID (N = 37)	Total EBID (N = 78)	Placebo (N = 42)
Any TEAE	33 (80.5)	30 (81.1)	63 (80.8)	29 (69.0)
Any TEAE with outcome of death	0	0	0	0
Any serious TEAE including events with outcome of death	3 (7.3)	1 (2.7)	4 (5.1)	1 (2.4)
Any TEAE leading to discontinuation from study	2 (4.9)	1 (2.7)	3 (3.8)	0
Any serious TEAE leading to discontinuation from study	0	0	0	0
Any TEAE related to study medication[b]	8 (19.5)	9 (24.3)	17 (21.8)	9 (21.4)
Any TEAE related to study procedure[b]	2 (4.9)	1 (2.7)	3 (3.8)	3 (7.1)
Any TEAE related to study device[b]	1 (2.4)	1 (2.7)	2 (2.6)	1 (2.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Includes possibly related adverse events as judged by the Investigator.

A TEAE is defined as an adverse event starting (or worsening) after the first dose of randomized study medication through the end of treatment + 1 day (+ 30 days for serious AEs and other clinically significant or related AEs), including AEs collected after patients initiate glycemic rescue therapy. For patients who discontinue treatment before Week 28, the end of treatment refers to the date of the early discontinuation visit even if last study medication was before this date.

All percentages are calculated based on the number of patients in the Analysis Set for the study period within each treatment group.

AE, Adverse event; EBID, Exenatide twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, Number of patients in treatment group; TEAE, treatment-emergent adverse event.

MedDRA Version 23.0.

CHMP comment

The reporting of TEAEs was higher in the exenatide treated groups than in the placebo treated group (81% vs 69%), and TEAEs leading to discontinuation were only reported in the exenatide treated group, albeit few (3). Serious TEAEs were rare but slightly more common in the exenatide treated group. No deaths occurred. Notably, the reporting of TEAEs related to study medication, study procedures or to study device did not differ between treatment groups.

Adverse events by system organ class and preferred term

The most common TEAEs by SOC (> 20% of patients in either treatment group) were the same for the Total EBID and placebo groups: infections and infestations (47.4% and 38.1%, respectively), GI

disorders (34.6% and 35.7%, respectively), and nervous system disorders (26.9% and 28.6%, respectively).

The most common TEAEs (≥ 5% in any treatment group) by PT are summarized in Table 4.

Table 4 Most Common Treatment-Emergent Adverse Events (frequency ≥5%) by Preferred Term (Safety Analysis Set)

	Treatment Period			
	Number (%) of Patients[a]			
Preferred Term	5 µg EBID (N = 41)	10 µg EBID (N = 37)	Total EBID (N = 78)	Placebo (N = 42)
Patient with any AE	33 (80.5)	30 (81.1)	63 (80.8)	29 (69.0)
Headache	9 (22.0)	9 (24.3)	18 (23.1)	11 (26.2)
Nausea	4 (9.8)	11 (29.7)	15 (19.2)	7 (16.7)
Nasopharyngitis	8 (19.5)	2 (5.4)	10 (12.8)	3 (7.1)
Vomiting	2 (4.9)	8 (21.6)	10 (12.8)	3 (7.1)
Upper respiratory tract infection	5 (12.2)	3 (8.1)	8 (10.3)	5 (11.9)
Pharyngitis	4 (9.8)	2 (5.4)	6 (7.7)	1 (2.4)
Diarrhoea	2 (4.9)	3 (8.1)	5 (6.4)	5 (11.9)
Dysmenorrhoea	2 (4.9)	3 (8.1)	5 (6.4)	4 (9.5)
Sinusitis	4 (9.8)	1 (2.7)	5 (6.4)	2 (4.8)
Dizziness	2 (4.9)	2 (5.4)	4 (5.1)	2 (4.8)
Ear pain	2 (4.9)	2 (5.4)	4 (5.1)	3 (7.1)
Abdominal pain upper	1 (2.4)	2 (5.4)	3 (3.8)	2 (4.8)
Back pain	1 (2.4)	2 (5.4)	3 (3.8)	2 (4.8)
Influenza	3 (7.3)	0	3 (3.8)	0
Oropharyngeal pain	3 (7.3)	0	3 (3.8)	3 (7.1)
Pyrexia	2 (4.9)	1 (2.7)	3 (3.8)	3 (7.1)
Furuncle	0	2 (5.4)	2 (2.6)	0
Pharyngitis streptococcal	0	2 (5.4)	2 (2.6)	0
Uncoded[b]	1 (2.4)	2 (5.4)	3 (3.8)	1 (2.4)

[a] Number (%) of patients with AEs, sorted by decreasing total frequency of preferred term (sorted by Total EBID column).

[b] For subjects "1041122", "1442320", "1442323" and "1716050" the adverse events were not coded as per MedDRA Version 23.0

Most common is defined as an AE with at least 5% incidence in any treatment.

Patients with multiple events in the same category (ie, same preferred term) are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

A TEAE is defined as an adverse event starting (or worsening) after the first dose of randomized study medication through the end of treatment + 1 day (+ 30 days for serious AEs and other clinically significant or related AEs), including AEs collected after patients initiate glycemic rescue therapy. For patients who discontinue treatment before Week 28, the end of treatment refers to the date of the early discontinuation visit even if last study medication was before this date.

All percentages are calculated based on the number of patients in the Analysis Set for the study period within each treatment group.

MedDRA Version 23.0.

AE, Adverse event; EBID, Exenatide twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, Number of patients in treatment group; PT, Preferred term.

CHMP comment

There were no gross imbalances in the reporting of TEAEs when presented by PT. Infections and infestations were somewhat more common in the exenatide group (47.4% and 38.1%) whereas GI events were slightly more common in the placebo group (34.6% and 35.7%). Nausea and vomiting, which are well-known adverse reactions for exenatide, were somewhat more common in the exenatide treated group. Headache was the most commonly reported TEAE in both groups.

Adverse events by intensity

The majority of TEAEs were mild or moderate in intensity. The proportion of patients with severe TEAEs was low and similar between the Total EBID and placebo groups (3.8% and 4.8%, respectively). At the PT level, none of the severe events were reported by more than 1 patient in either group.

CHMP comment

The majority of events were mild or moderate in intensity and only 4-5% of events were severe in intensity.

Adverse events by Investigator-assessed causality

A similar proportion of patients in the Total EBID and placebo groups experienced TEAEs assessed as possibly related to study medication by the Investigator (21.8% and 21.4%, respectively).

At the PT level, the incidence of TEAEs assessed as possibly related to study medication by the Investigator was generally comparable between the Total EBID and placebo groups. The most common TEAEs by PT (> 3% of patients in either treatment group) were nausea (14.1%), vomiting (7.7%), and diarrhoea (3.8%) for the Total EBID group, and nausea (14.3%), diarrhoea (7.1%), and vomiting and abdominal pain upper (both 4.8%) for the placebo group.

Investigators also assessed relatedness of AEs to study procedures and the study device. Three patients (3.8%) in the Total EBID group and 3 patients in the placebo group (7.1%) had events assessed by the Investigator as related to a study procedure. In the Total EBID group events evaluated by the Investigator as related to a study procedure were urticaria, injection site pain, injection site rash (2 patients), and injection site bruising. In the placebo group events evaluated by the Investigator as related to a study procedure were abdominal pain upper, nausea (2 patients), and injection site pain. All events evaluated as related to a study procedure were of mild intensity and had resolved with the exception of 1 event of nausea for which the outcome was unknown. Overall, the incidence of study procedure-related events was low.

Two patients (2.6%) in the Total EBID group and 1 patient in the placebo group (2.4%) had events assessed by the Investigator as related to the study device. In the Total EBID group the events were injection site pain (2 patients) and injection site rash. In the placebo group the event was injection site pain. All events were of mild intensity with the exception of a moderate event of injection site pain in the Total EBID groups and had resolved.

CHMP comment

When AEs were presented by Investigator-assessed causality, no apparent differences were observed between treatment groups.

Potentially immune-related adverse events

A similar proportion of patients in the Total EBID group who developed ADA antibody (11.8%; 6 patients) and patients who did not (11.1%; 3 patients) had a potentially immune-related TEAE compared with 4.8% of patients in the placebo group. Of the patients who developed positive antibody status, potentially immune-related TEAEs were reported for 2 patients (16.7%) with a higher titer (≥ 625) compared to 4 patients (10.3%) with a low titer (< 625). Potentially immune-related AEs included urticaria, injection site rash, arthralgia, wheezing, asthma, and rash. None of these AEs were considered serious or led to study drug discontinuation.

CHMP comment

Potentially immune-related AEs were reported more frequently in the exenatide treated group than in the placebo treated group, however no difference was observed between ADA-positive and ADA - negative patients in the exenatide treated group. There was a trend towards higher reporting of potentially immune-related events in patients with high ADA titers, however the number of both patients and events are few, thus the observations have to be interpreted with caution.

Deaths, serious adverse events, discontinuation of investigational product due to adverse events, and other significant adverse events

Deaths

No adverse events with fatal outcome were reported in this study, and no patients died of any other cause during the study.

Serious adverse events

The incidence of serious TEAEs was low for both the Total EBID and placebo groups (4 patients [5.1%] and 1 patient [2.4%], respectively) (Table 5). At the PT level, none of the serious events were reported by more than 1 patient in either group.

Table 5 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

	Treatment Period			
	Number (%) of Patients[a]			
System Organ Class/Preferred Term	5 µg EBID (N = 41)	10 µg EBID (N = 37)	Total EBID (N = 78)	Placebo (N = 42)
Patients with any SAE	3 (7.3)	1 (2.7)	4 (5.1)	1 (2.4)
Infections and infestations	2 (4.9)	0	2 (2.6)	1 (2.4)
Cellulitis	1 (2.4)	0	1 (1.3)	0
Gastroenteritis	1 (2.4)	0	1 (1.3)	1 (2.4)
Staphylococcal abscess	1 (2.4)	0	1 (1.3)	0
Gastroenteritis viral	0	0	0	1 (2.4)
Pregnancy, puerperium and perinatal conditions	0	1 (2.7)	1 (1.3)	0
Pregnancy	0	1 (2.7)	1 (1.3)	0
Psychiatric disorders	1 (2.4)	0	1 (1.3)	0
Intentional self-injury	1 (2.4)	0	1 (1.3)	0

[a] Number (%) of patients, sorted for SOC in alphabetical order and for PT by decreasing frequency in Total EBID group. Patients with multiple events in the same category (ie, same system organ class or same preferred term) are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

A serious TEAE is defined as a serious adverse event starting (or worsening) after the first dose of randomized study medication through the end of treatment + 30 days, including SAEs collected after patients initiate glycemic rescue therapy. For patients who discontinue treatment before Week 28, the end of treatment refers to the date of the early discontinuation visit even if last study medication was before this date.

All percentages are calculated based on the number of patients in the Analysis Set for the study period within each treatment group.

MedDRA Version 23.0.

AE, Adverse event; EBID, Exenatide twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, Number of patients in treatment group; PT, Preferred term; SAE, Serious AE; SOC, System organ class; TEAE, treatment-emergent adverse event.

CHMP comment

Serious TEAEs were few, but more often reported in the exenatide treated group. The difference was mainly related to a higher reporting of events in the SOC Infections and infestations. In addition, one pregnancy and one event of intentional self-injury was reported in the exenatide group.

Discontinuations of investigational product due to adverse events

Three patients (3.8%) in the Total EBID group and no patients in the placebo group experienced TEAEs leading to discontinuation from study treatment (Table 6); all of them were considered related to study medication by the Investigator and had resolved by the end of the study. There were no serious events leading to discontinuation from the study.

Table 6 Treatment-Emergent Adverse Events leading to Discontinuation of Investigational Product by System Organ Class and Preferred Term (Safety Analysis Set)

	Treatment Period			
	Number (%) of Patients[a]			
System Organ Class/Preferred Term	5 µg EBID (N = 41)	10 µg EBID (N = 37)	Total EBID (N = 78)	Placebo (N = 42)
Patients with a TEAE leading to discontinuation[b]	2 (4.9)	1 (2.7)	3 (3.8)	0
Gastrointestinal disorders	1 (2.4)	1 (2.7)	2 (2.6)	0
Vomiting	1 (2.4)	1 (2.7)	2 (2.6)	0
Metabolism and nutrition disorders	1 (2.4)	0	1 (1.3)	0
Diabetes mellitus inadequate control	1 (2.4)	0	1 (1.3)	0

[a] Number (%) of patients, sorted for SOC in alphabetical order and for PT by decreasing frequency in Total EBID group. Patients with multiple events in the same category (ie, same system organ class or same preferred term) are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Reason for discontinuation of study is adverse event.

A TEAE is defined as an adverse event starting (or worsening) after the first dose of randomized study medication through the end of treatment + 1 day (+ 30 days for serious AEs and other clinically significant or related AEs), including AEs collected after patients initiate glycemic rescue therapy. For patients who discontinue treatment before Week 28, the end of treatment refers to the date of the early discontinuation visit even if last study medication was before this date.

All percentages are calculated based on the number of patients in the Analysis Set for the study period within each treatment group.

Patient "1061182" had an AE leading to discontinuation starting approx. 5 months before informed consent date and therefore this has been classified as a pre-existing condition and is not presented in any treatment-emergent AE outputs.

MedDRA Version 23.0.

AE, Adverse event; EBID, Exenatide twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, Number of patients in treatment group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

CHMP comment

Three patients in the exenatide treated group and no patients in the placebo treated group discontinued due to adverse events. Two patients discontinued due to GI-events (vomiting) and one patient discontinued due to inadequate metabolic control.

Other significant adverse events

No adverse events were classified as other significant adverse events in this study.

Hypoglycaemia

There were no confirmed major hypoglycaemic events in the study. The proportion of patients with confirmed minor hypoglycaemic events was slightly higher in the Total EBID group (5.1% [4 patients]; a total of 4 events) compared with the placebo group (2.4% [1 patient]; a total of 2 events). The event rate of confirmed minor hypoglycaemia was similar for the Total EBID and placebo groups (10.75 and 10.23 per 100 patient years, respectively).

The proportion of patients with any hypoglycaemic events was slightly higher for the Total EBID group (10.3% [8 patients]; total of 22 events) compared with the placebo group (7.1% [3 patients]; total of 4 events). The proportion of patients with unconfirmed hypoglycaemic events was similar between the 2 groups: 5 patients (6.4%) with a total of 18 events in the Total EBID group compared with 2 patients (4.8%) with a total of 2 events in the placebo group. The event rate for any hypoglycaemic events (including unconfirmed events) was higher in the Total EBID group compared with the placebo group

(59.12 and 20.47 per 100 patient years, respectively). A similar pattern was seen for unconfirmed hypoglycaemic events (48.37 and 10.23 per 100 patient years, respectively).

The greater event rates for any hypoglycaemic event and for unconfirmed hypoglycaemic events in the Total EBID group was due to a single patient (a 12-year-old white female) assigned to 10 µg EBID, who had 15 hypoglycaemic events.

Confirmed minor hypoglycaemic events were reported by 2 of 8 patients with baseline sulfonylurea use in the Total EBID group (25.0%; a total of 2 events and an event rate per of 51.25 per 100 patient years), and 1 of 7 patients with baseline sulfonylurea use in the placebo group (14.3%; a total of 2 events and an event rate of 57.57 per 100 patient years). For patients with no sulfonylurea use at baseline, confirmed minor hypoglycaemic events were reported by 2 of 70 patients in the Total EBID group (2.9%; a total of 2 events and an event rate of 6.00 per 100 patient years) and 0 of 35 placebo patients.

No patients had a serious TEAE of hypoglycaemia.

CHMP comment

Hypoglycaemic events were few but slightly more common in the exenatide treated group. As expected, hypoglycaemias were more common in patients on concomitant SU treatment. No serious events were observed.

Clinical laboratory evaluation

There were no clinically meaningful trends in laboratory parameters over time and no notable differences between treatment groups in laboratory parameters, including carcinoembryonic antigen, and calcitonin.

Vital signs, electrocardiograms, physical findings and other observations related to safety

There were no new safety concerns related to vital signs or ECG. There were no differences in mean blood pressure parameters. A greater proportion of patients aged ≥ 12 years in the Total EBID group had reductions of more than 10 mmHg in diastolic and systolic blood pressure (30.9% and 39.7%, respectively) compared with the placebo group (18.4% and 28.9%, respectively); no TEAEs of hypotension were reported. No other clinically meaningful trends in vital signs were observed over time.

CHMP comment

No clinically meaningful changes were observed with regards to laboratory parameters. A greater proportion of patients ≥ 12 years in the exenatide treated group showed reductions in DBP and SBP, but no adverse events related to hypotension were reported.

Physical findings and other observations related to safety

Height

The mean increase from baseline to Week 28 in height was similar for the Total EBID and placebo groups, with a change of 1.22 cm/4th percentile and 1.21 cm/4th percentile, respectively. A total of 14 patients (8 patients in the Total EBID group and 6 patients in the placebo group) had reached their final height requirement (change of less than 5 mm between baseline and Week 28) and therefore did not enter the Safety Follow-up Period.

Of the 19 patients who entered the Safety Follow-up Period, 9 of the 12 patients in the Total EBID group and all 7 patients in the placebo group completed the Safety Follow-up Period as a result of reaching their final height. The mean increase from baseline in height over the Safety Follow-up Period was higher for the Total EBID group (12 patients) compared with the placebo group (7 patients), with a mean change from baseline to Safety Follow-up Visit 4 of 8.50 cm/21st percentile and 3.50 cm/11th percentile, respectively.

CHMP comment

No difference in the change in height was observed between treatments during the treatment period. Very few patients entered the Safety Follow-up Period (19 in total), therefore the observed higher change in increase in height from baseline observed in the exenatide treated group has to be interpreted with caution, however no safety concern arise from this observation.

Tanner pubertal assessment

Tanner assessment of pubertal development was implemented at the time of Protocol Amendment b [09 February 2011]; and was therefore not determined for all patients.

For those patients that had Tanner data assessments performed, the overall Tanner stage was similar for the Total EBID and placebo groups at Week 28. Most patients in the Total EBID and placebo groups were at either Tanner Stage IV (48.3% and 42.9%, respectively) or Stage V (27.6% and 35.7%, respectively) at Week 28.

CHMP comment

Since assessment of pubertal development was introduced with a protocol amendment in 2011, not all patients had the Tanner stage determined at baseline. The majority of patients were at Tanner stage IV or V at week 28, with no differences observed between groups.

2.3.3. Discussion on clinical aspects

The MAH has submitted a completed paediatric study (H80-MC-GWBQ) for Byetta, in accordance with Article 46 of Regulation (EC) No1901/2006. This study has been conducted as part of a paediatric program based on an agreed PIP, which is ongoing to assess the use of exenatide in the treatment of paediatric patients with type 2 diabetes mellitus.

Exenatide twice daily (Byetta) is administered by subcutaneous injection. It was approved for use in the EU on 20 November 2006. Byetta is indicated for adults who have not achieved adequate glycaemic control on maximally tolerated doses of oral therapies or as an adjunct treatment with insulin glargine.

Study H80-MC-GWBQ was a multicentre, double-blind, placebo-controlled, randomised, parallel, 3-arm study performed in adolescents (aged 10 to 17 years) with T2DM, evaluating the glycaemic control with exenatide compared to placebo. The overall design of the study was adequate as well as the study duration of 28 weeks. The study included an extended safety follow-up period of up to three years. During this period, no study medication was administered, and patients were treated as deemed appropriate by the Investigator or health care provider.

The selection of patients was adequate, in order to recruit a representative study population. The exclusion criteria included concomitant medications and conditions that might have rendered the interpretation of data difficult. Other exclusion criteria were in place to for the safety of the patients.

The original aim of the study was to separately assess 5 µg EBID and 10 µg EBID versus placebo, and 195 patients were to be recruited. However, recruitment to the study was slow, according to the MAH this was probably due to the emergence of other more convenient therapies. It was therefore decided to pool the data for the two EBID arms and to stop recruitment when 122 patients had been randomised. This decision was made with agreement by the EMA and the FDA.

During the treatment period of the study, exenatide was given in accordance with the recommendations in the SmPC for Byetta, which states that treatment should be started with 5 µg exenatide SC twice daily for at least 4 weeks after which the dose may be increased to 10 µg twice daily. Rescue medication was allowed. If prolonged insulin therapy was necessary, the patient was to discontinue from the study.

The primary efficacy endpoint was the change in HbA1c from baseline Visit 3 (Week 0) to Visit 11 (Week 28). The secondary efficacy endpoints were related to other aspects of metabolic control. Both the primary and secondary endpoints were relevant. In addition, relevant safety endpoints were evaluated.

The statistical methods were adequate. As already stated, recruitment was slow with the first patient enrolled in May 2008 and the last patient last visit occurred in April 2020, which resulted in the decision to pool the data for exenatide 5 µg EBID and 10 µg EBID. The difficulty in recruitment is further evidenced by the large proportion of the enrolled patients (110/240) being screen failures. During the study, the drop-out rate was higher in the placebo treated group and the most common reason for discontinuation in this group was loss of glycaemic control (10/17) compared to the exenatide treated group (2/22). Very few patients continued in the Safety Follow-up Period. The majority of patients actively declined participation or discontinued for unknown reasons. Thus overall, only 19 patients continued in this follow-up.

Demographic, patient, and baseline disease characteristics were balanced between groups, taking into account the small size of the study. The mean HbA1c at baseline was 7.59% (range 6.0% to 11.9%) in the overall population and comparable across the study groups. Notably, the patients were overweight with a mean BMI of 34. The majority of patients (63%) were treated with metformin and very few were treated with SU as monotherapy (2 patients in the placebo-treated group).

There were no clinically relevant or statistically significant differences observed for any of the primary or secondary efficacy endpoints. Notably, HbA1c increased slightly in both treatment groups, the increase was however less pronounced in the exenatide treated group (0.11% vs 0.38%). The proportions of patients who achieved treatment goals were numerically higher in the exenatide treated group, the difference was however not statistically significant. Weight decrease was also numerically larger in the exenatide treated group, but again the treatment difference of -0.44 kg was not statistically significant. A relatively high proportion of patients (61.5%) treated with exenatide showed ADAs during the study, the majority had low titers. Since the study is small, interpretation of these data has to be made with caution, but the data provided give no indication of an impact of ADA on efficacy. Thus, no apparent benefit with exenatide treatment could be observed in this small study in obese adolescent with T2DM.

With regards to safety, the duration of exposure was comparable between groups and more than 50% of patients maintained treatment throughout the study duration (≥196 days). Notably, the 19 patients continuing in the Safety Follow-up Period showed a higher adherence to treatment than the overall population.

The reporting of TEAEs was higher in the exenatide treated groups than in the placebo treated group (81% vs 69%), and TEAEs leading to discontinuation were only reported in the exenatide treated group, albeit few (3). Serious TEAEs were rare but slightly more common in the exenatide treated group. No deaths occurred. Notably, the reporting of TEAEs related to study medication, study procedures or to study device did not differ between treatment groups.

There were no gross imbalances in the reporting of TEAEs when presented by PT. PTs in the SOC "Infections and infestations" were somewhat more common in the exenatide group (47.4% and 38.1%) whereas GI events were slightly more common in the placebo group (34.6% and 35.7%). Nausea and vomiting, which are well-known adverse reactions for exenatide, were somewhat more common in the exenatide treated group. Headache was the most commonly reported TEAE in both groups. The majority of events were mild or moderate in intensity and only 4-5% of events were severe in intensity. Serious TEAEs were few (in total 5 patients reporting 7 events), but more often reported in the exenatide treated group. The difference was mainly related to a higher reporting of events in the SOC "Infections and infestations". In addition, one pregnancy and one event of intentional self-injury was reported in the exenatide group. Three patients in the exenatide treated group and no patients in the placebo treated group discontinued due to adverse events. Two patients discontinued due to GI-events (vomiting) and one patient discontinued due to inadequate metabolic control. Hypoglycaemic events were few but slightly more common in the exenatide treated group. As expected, hypoglycaemias were more common in patients on concomitant SU treatment. No serious events were observed.

Potentially immune-related AEs were reported more frequently in the exenatide treated group than in the placebo treated group, however no difference was observed between ADA-positive and ADA-negative patients in the exenatide treated group. There was a trend towards higher reporting of potentially immune-related events in patients with high ADA titers, however the number of both patients and events are few, thus the observations must be interpreted with caution.

No clinically meaningful changes were observed with regards to laboratory parameters. A greater proportion of patients ≥ 12 years in the exenatide treated group showed reductions in diastolic and systolic blood pressure, but no adverse events related to hypotension were reported. No difference in the change in height was observed between treatments during the treatment period. Very few patients entered the Safety Follow-up Period (19 in total), therefore the observed higher change in increase in height from baseline observed in the exenatide treated group should be interpreted with caution. However no safety concern arise from this observation.

Since assessment of pubertal development was introduced with a protocol amendment in 2011, not all patients had the Tanner stage determined at baseline. The majority of patients were at Tanner stage IV or V at week 28, with no differences observed between groups.

In summary, the safety profile does not appear to differ from what is known from the use of exenatide in adults. No new safety concerns arise from the data submitted.

3. Rapporteur's overall conclusion and recommendation

The MAH has submitted a completed paediatric study (H80-MC-GWBQ) for Byetta, in accordance with Article 46 of Regulation (EC) No1901/2006. This study has been conducted as part of a paediatric program based on an agreed PIP, which is ongoing to assess the use of exenatide in the treatment of paediatric patients with type 2 diabetes mellitus.

No clinically relevant or statistically significant effect on metabolic control compared to placebo was observed in the study therefore the study cannot support a paediatric indication for Byetta. The safety profile does not appear to differ from what is known from the use of exenatide in adults and no new safety concerns arise from the data submitted.

Since no safety concerns arise from the data presented, no regulatory action is warranted at this time point. However, the Applicant intends to submit a variation application consisting of the full relevant data package (i.e. containing several studies) concerning the use of Byetta in the paediatric population in order to update the SmPC with relevant information. This variation should be submitted by Q1 2021.

☒ Fulfilled:

No further action required, however further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH should commit to submit this variation application by Q1 2021.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: BYETTA

Active substance: exenatide

Study title	Study number	Date of completion	Date of submission of final study report
A Randomized, Single-Blind, Dose-Rising, Placebo- Controlled, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Tolerability of Exenatide in Adolescent Subjects With Type 2 Diabetes Mellitus	2993-124	February 2007	Compliance check performed on 22 September 2016 (EMEA-C1-000689-PIP01-09-M06)
Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes	H8O-MC-GWBQ	01 April 2020	Included in this Article 46 submission
A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Assess the Safety and Efficacy of **Exenatide Once Weekly** in Adolescents With Type 2 Diabetes	BCB114	06 May 2020	To be submitted via Article 46 in Q4 2020.
Modelling and Simulation study to evaluate the use of **Bydureon** in the treatment of type 2 diabetes mellitus in children from 10 to less than 18 years of age	Study 7	Ongoing	NA