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Human Medicines Division

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

Bydureon

exenatide

Procedure no: EMEA/H/C/002020/P46/028

Note

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

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1. Introduction

On 15 Oct 2020, the MAH submitted a completed a paediatric study for Bydureon, 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.

Of note, the MAH has communicated the intention to submit a type II variation to update the Bydureon SmPC in Q4 2021 with a paediatric indication.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study BCB114 (Study code D5551C00002) is 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 (T2DM) 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 supports the use of Bydureon in paediatric patients (from 10 years to less than 18 years). The MAH has the intention to submit a type II variation to update the Bydureon with the proposed indication: "*BYDUREON is indicated for use in patients 10 years and older with T2DM to improve glycaemic control in combination with other glucose- lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control*."

The variation application consisting of the full relevant data package is expected to be submitted by Q4 2021. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Exenatide prolonged release was first approved for use in the US on the 27 January 2012 and in the EU on 17 June 2011. It is currently available as either as a vial and prefilled syringe single dose tray (SDT) or in a prefilled dual chamber pen (DCP), administered by subcutaneous injection. In order to avoid the need for recombination prior to administration, exenatide prolonged-release non-aqueous suspension via autoinjector was developed (Bydureon BCise; hereafter referred to as EQW). It was approved in the US on 20 October 2017 and in the EU on 27 August 2018. In the EU is approved for use in adults 18 years and older with T2DM to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study D5551C00002 (hereafter referred to as study BCB114): a phase 3, double-blind, placebo- controlled, randomized, multicenter study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes"

Clinical study

Study BCB114: "A phase 3, double-blind, placebo- controlled, randomized, multicenter study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes"

Description

This was a randomised, double-blind, placebo-controlled study in paediatric and adolescent patients 10 to 17 years of age with T2DM evaluating the glycemic control with exenatide extended release vs placebo. This study has been conducted as part of a paediatric program based on an agreed Paediatric Investigation Plan (number: EMEA-000689-PIP01-09-M10), which assessed the potential therapeutic benefits of exenatide once-weekly in paediatric patients with type 2 diabetes mellitus.

Methods

Objective(s)

The primary efficacy objective of the study was to assess the effect on glycemic control, as measured by HbA1c, of EQW following 24 weeks of treatment compared with placebo in children and adolescents with T2DM.

The primary safety objective was to evaluate the safety and tolerability of EQW compared with placebo following 24 weeks of treatment in children and adolescents with T2DM.

Study design

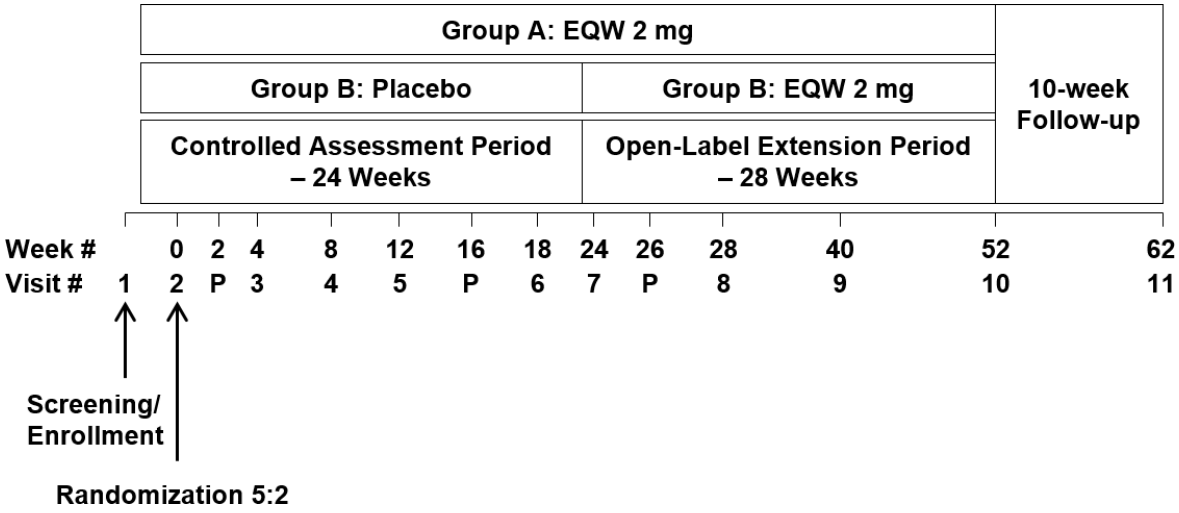
This was a multicenter, randomized, parallel-group, Phase III study in adolescent patients with type 2 diabetes mellitus (T2DM) treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin. In addition to receiving study medications, all patients were to participate in a lifestyle intervention program encompassing diet and physical activity modifications.

The total study duration was to be approximately 67 weeks. The study was divided in 4 periods (Figure 1):

- Screening period (5 weeks)
- Controlled assessment period (24 weeks): double-blind, placebo-controlled period to examine the efficacy and safety of exenatide once weekly (EQW) compared with placebo. Approximately 77 patients were to be randomly assigned in a 5:2 ratio to receive either EQW 2 mg (Group A) or placebo (Group B).
- Open-label extension period (28 weeks): open-label, uncontrolled period to examine the long-term safety and efficacy of EQW. Patients assigned to the EQW 2 mg treatment (Group A) were to continue to be treated with EQW 2 mg during the open-label extension period (through Week 52). Patients randomized to placebo (Group B) were to receive EQW 2 mg beginning at the start of the open-label extension period through Week 52.

- Post-treatment follow-up period (10 weeks).

Figure 1 Flow chart of study design



An exploratory mixed meal substudy was performed in approximately 20 patients to evaluate the effect of EQW on postprandial beta-cell function (as assessed by C-peptide secretion) and postprandial glucose and glucagon responses during a mixed meal test (MMTT).

All visits up to Week 62 (the end of the post-treatment follow-up period; last patient last visit: 06 May 2020) took place in accordance with the CSP. Therefore, the coronavirus disease 2019 (COVID-19) epidemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

CHMP comment:

The overall design of the study as well as the study duration was adequate.

Study population /Sample size

The study population consisted of male or female children and adolescents of 10 to < 18 years of age, diagnosed with T2DM, and treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (metformin and/or sulfonylurea [SU]) and/or insulin for at least 2 months prior to screening).

Target Sample Size

Approximately 77 patients were to be randomized into this study to yield 70 evaluable patients. This was estimated to provide an overall power of 74% to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for glycosylated haemoglobin (HbA1c) (%), with a common standard deviation of 1.0% and a 2-sided significance level of 0.05.

At least 40% and not more than 60% of the randomized patients were to be females. At least 40% of patients were to be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.

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.

Treatments

Caregivers were to administer study medication (2 mg EQW or matching placebo) subcutaneously to the patient (or the patient self-administered, if deemed appropriate) once weekly (± 2 days) relative to the date of the first dose of study medication (Visit 2 [Week 0]), for the duration of the study, as applicable. Adjustments to dosing regimens were not permitted.

Rescue Treatment

Patients with a loss of glycemic control, defined as either an increase from baseline in HbA1c values by ≥ 1.0% at 2 consecutive clinic visits that were at least 1 month apart, or a fasting plasma glucose value ≥ 250 mg/dL or random blood glucose value > 300 mg/dL for 4 days during a 7-day period, were to receive rescue treatment. Patients who required rescue therapy were to receive antihyperglycemic therapy (e.g., insulin) by the Investigator. Patients receiving rescue therapy were to remain in the study and continue receiving study medication, at the discretion of the Investigator. The temporary use of insulin to treat acute decompensation due to an intercurrent illness was permitted for up to 2 weeks. Extended use of insulin in this manner was to be considered as rescue treatment.

CHMP comment:

Exenatide prolonged release was given in accordance with the recommendations in the SmPC for Bydureon. Rescue medication was allowed. If prolonged insulin therapy was necessary, the patient was to discontinue from the study.

Outcomes/endpoints

Primary endpoints (efficacy)

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)

Primary endpoints (safety)

- Treatment-emergent AEs
- Antibodies to exenatide
- Physical examinations
- Laboratory measurements (clinical, chemistry/haematology)
- Vital signs

Secondary endpoints (efficacy/safety)

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in fasting plasma glucose, body weight, lipids and blood pressure from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

- Proportions of patients achieving HbA1c goals of ≤ 6.5% and < 7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable
- Change in fasting insulin and C-peptide from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Proportions of patients discontinuing the study and the proportion of patients needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable
- Proportions of patients reporting different injection site reactions

Secondary endpoints (PK)

- Plasma exenatide concentrations at baseline (Visit 2, Week 0), Visit 7 (Week 24), Visit 10 (Week 52), and each intermediate visit as applicable

Secondary endpoints (safety)

- Incidence of treatment-emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical chemistry/haematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)
- Change in thyroid-stimulating hormone, thyroxine, prolactin, cortisol, insulin-like growth factor 1, and dehydroepiandrosterone from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)
- Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)

CHMP comment:

Primary and secondary endpoints were adequate.

Statistical Methods

In general, primary and secondary continuous efficacy variables for which multiple postbaseline measurements were collected were to be analysed using a mixed model with repeated measures (MMRM) approach. The statistical analysis of categorical variables was to be conducted using a stratified Cochran-Mantel-Haenszel test. If data has been collected at the Early Termination visit, it were to be included in the analyses.

Intercurrent events that may have occurred during the study were defined as receipt of rescue therapy, study medication discontinuation, and study withdrawal. Efficacy data collected after the initiation of rescue medication or following discontinuation of study medication were to be excluded from the analyses, except for select sensitivity analyses and plasma EQW concentration endpoints, where data after rescue were included.

The primary efficacy analysis was to compare treatment groups (EQW versus placebo) with respect to change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24) using MMRM. The model was to include change in HbA1c as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects.

A fixed-sequence procedure hierarchical testing strategy was to be followed for the primary endpoint and secondary endpoints in order to protect the family wise error rate. Endpoints were to be tested in order from HbA1c, fasting plasma glucose (FPG), body weight to fasting insulin.

All safety and tolerability variables (including examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide) were to be summarized descriptively by visit to Week 52, and where applicable also for the 10-week follow-up, by treatment groups. Observations post rescue were to be included for safety analyses.

CHMP comment:

Statistical methods were adequate.

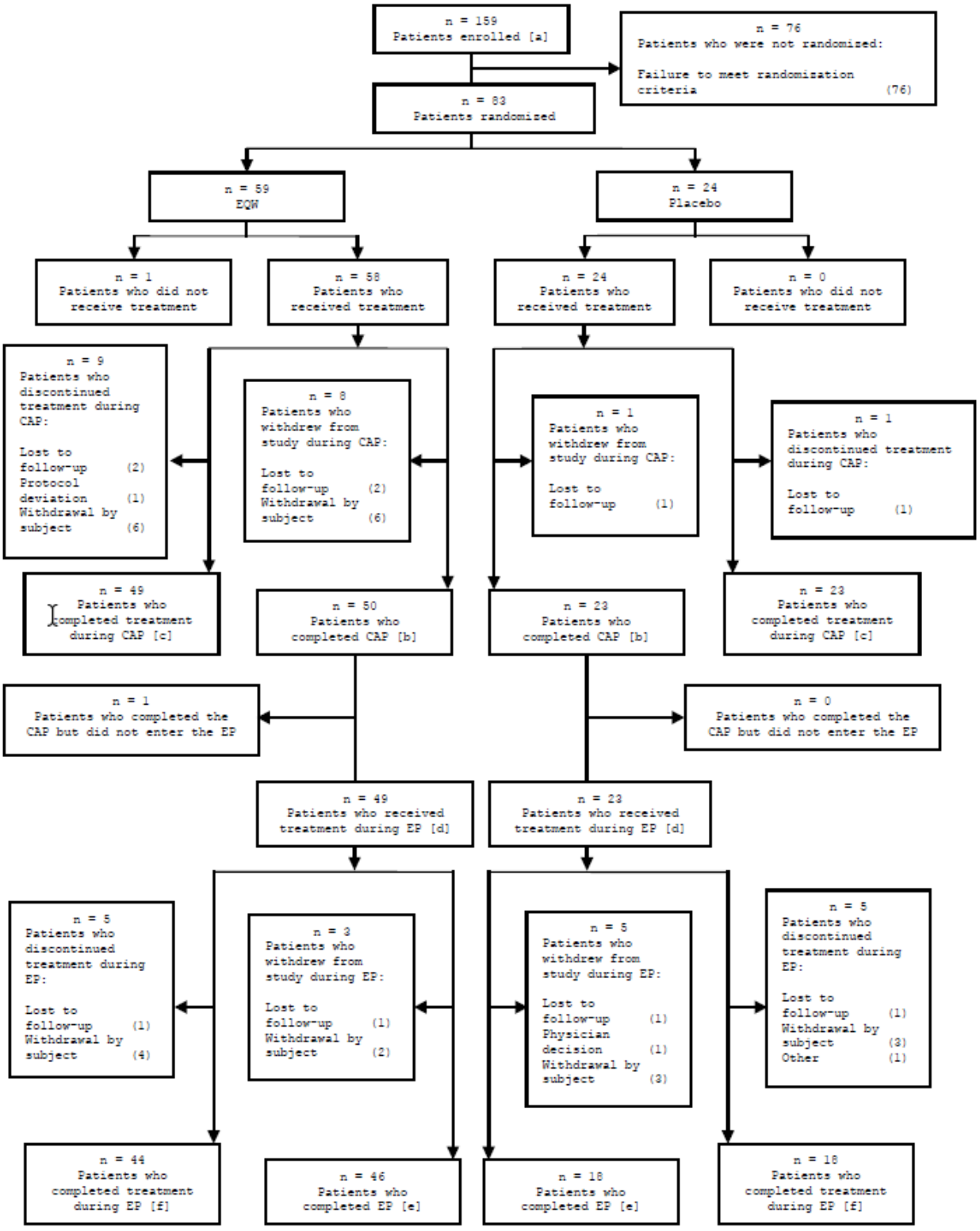
Results

Recruitment/ Number analysed

A total of 159 patients enrolled in this study from 36 centers; 27 study centers randomized patients during the study (Figure 2).

A total of 83 patients were randomized and entered the double-blind controlled assessment period: 59 patients randomized to EQW and 24 patients randomized to placebo. Of the 83 randomized patients, 82 (98.8%) received EQW/placebo treatment, 73 (88.0%) completed the controlled assessment period, and 72 (86.7%) completed treatment during the controlled assessment period. Of the 73 patients who completed the controlled assessment period, all but 1 patient (randomized to EQW) entered the open-label extension period and received open-label EQW treatment. Of these patients, 64 (77.1% of all randomized patients) completed the open-label extension period and 62 (74.7% of all randomized patients) completed treatment during the open-label extension period. No patients discontinued treatment during the controlled assessment period or the open-label extension period due to an AE.

Figure 2: Patient Disposition (All Patients)



[a] Informed consent/assent received.

[b] Patients who received at least one dose of study medication, did not prematurely withdraw from study prior to Week 24 and had a Week 24 assessment regardless of randomized treatment status at the visit.

[c] Patients who did not prematurely discontinue EQW/Placebo prior to Week 24.

[d] All patients who completed the controlled assessment period and received open-label EQW during the extension period.

[e] Patients who did not prematurely withdraw from study prior to Week 52.

[f] Patients who did not prematurely discontinue EQW prior to Week 52.

Note: E-codes E7812001 and E7812003 were captured in interactive voice response system twice for the same patient. E-code E7812001 was incorrectly randomized and screen failed, while E7812003 was captured as a screen failure. E-codes E4907002 and E4907004 were captured in interactive voice response system twice for the same patient. E-code E4907002 was captured as a screen failure, while E4907004 was screened, randomized and treated.

CAP Controlled assessment period; EQW Exenatide 2 mg once weekly; EP Extension period; n Number of patients.

Data Source: Figure 14.1.1.

Subjects Analysed (Analysis Sets)

The Randomized Analysis Set, which included all randomized patients, consisted of 59 patients in the EQW group and 24 patients in the placebo group. One patient who was randomized to EQW did not receive any study medication and was excluded from the ITT, Evaluable, and Safety Analysis Sets. In addition, 1 patient who was randomized to placebo received a dose of EQW in error and was subsequently reassigned to the EQW group for analyses based on actual treatment (ie, for analyses based on the Safety and PK Analysis Sets).

Of the patients who received at least 1 dose of randomized study medication, 55 patients in the EQW group and 0 patients in the placebo group had at least 1 postdose PK concentration assessment available and were included in the PK Analysis Set. A further 6 patients in the EQW group and 3 patients in the placebo group also provided informed consent/assent for the substudy, participated in the standardized mixed meal test, completed study procedures in compliance with the main CSP and the substudy, and had valid and adequate pharmacodynamic measurements, and were included in the Standardized Mixed Meal Test Evaluable Analysis Set. Approximately 20 patients provided informed consent for the substudy; however, a high proportion of these patients failed screening. Therefore, the actual number of patients that participated in the mixed meal substudy was low.

Baseline data

The demographic, patient and baseline disease characteristics were generally representative of the intended adolescent population with T2DM. Demographic, patient, and baseline disease characteristics were broadly similar between the EQW and placebo groups, with the exception of minor imbalances in age, race, region, weight population percentile, and baseline diabetes duration; however, these imbalances would not be expected to affect the interpretation of the primary efficacy analysis. The pre-existing conditions and concomitant medications were as expected for the study population, and similar between treatment groups (Table 1).

Table 1: Summary of Demographic, Patient, and Disease Characteristics (Intent-To-Treat Analysis Set)

	EQW	**Placebo**	**Total**
	(N = 58)	**(N = 24)**	**(N = 82)**
Mean baseline age (SD); years[a]	14.9 (1.88)	15.6 (1.66)	15.1 (1.84)
Sex n (%)			
Male	27 (46.6)	7 (29.2)	34 (41.5)
Female	31 (53.4)	17 (70.8)	48 (58.5)
Race n %			

White	23 (39.7)	12 (50.0)	35 (42.7)
Black or African American	17 (29.3)	8 (33.3)	25 (30.5)
Asian	2 (3.4)	1 (4.2)	3 (3.7)
American Indian or Alaska Native	4 (6.9)	1 (4.2)	5 (6.1)
Other	12 (20.7)	2 (8.3)	14 (17.1)
Hispanic or Latino n (%)	25 (46.3)	8 (38.1)	33 (44.0)
Mean baseline weight (SD); kg	102.18 (30.108)	96.70 (22.684)	100.57 (28.112)
Mean body mass index (SD); kg/m^2	36.86 (9.278)	35.14 (6.575)	36.36 (8.572)
Mean baseline HbA1c (SD); %	8.13 (1.215)	8.28 (1.508)	8.17 (1.300)
Mean baseline diabetes duration (SD); years	2.2359 (2.17477)	2.5105 (1.96478)	2.3163 (2.10718)

The mean baseline HbA1c was 8.17% and the mean duration of type 2 diabetes was 2.3 years. The mean baseline FPG was 166 mg/dL (9.2462 mmol/L) and the mean baseline eGFR was 107 mL/min/1.73 m^2. Prior to randomization, the most common antidiabetic medication was metformin alone, reported in 40.2% of patients, followed by insulin plus metformin, reported in 37.8% of patients. The majority of patients were Tanner stage 5 (69.5%), followed by Tanner stage 4 (17.1%), as expected based on the age of the study population.

The baseline disease characteristics were generally balanced between the EQW and placebo groups, with the exception of diabetes duration: a higher proportion of patients in the EQW group had a duration of diabetes of < 1 year compared with the placebo group (31.0% and 12.5%, respectively), while a lower proportion of patients in the EQW group had a duration of diabetes of ≥ 1 and ≤ 5 years compared with the placebo group (58.6% and 83.3%, respectively) (Table 2). This imbalance would not be expected to affect the interpretation of the primary efficacy results.

Table 2: Baseline Disease Characteristics (Intent-to-Treat Analysis Set)

	EQW	**Placebo**	**Total**
Disease characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
Baseline HbA1c (%)			
n	58	24	82
Mean	8.13	8.28	8.17
SD	1.215	1.508	1.300
Median	8.00	7.60	8.00
Min	6.3	6.6	6.3
Max	11.2	11.2	11.2
Baseline HbA1c (%) n (%)			
< 9	44 (75.9)	17 (70.8)	61 (74.4)
≥ 9	14 (24.1)	7 (29.2)	21 (25.6)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Diabetes duration (years)			
n	58	24	82
Mean	2.2359	2.5105	2.3163

	EQW	Placebo	Total
Disease characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
SD	2.17477	1.96478	2.10718
Median	1.3662	1.9890	1.7659
Min	0.041	0.241	0.041
Max	10.357	9.604	10.357
Diabetes duration (years) n (%)			
< 1	18 (31.0)	3 (12.5)	21 (25.6)
≥ 1 and ≤ 5	34 (58.6)	20 (83.3)	54 (65.9)
> 5	6 (10.3)	1 (4.2)	7 (8.5)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Baseline FPG (mg/dL)			
n	58	24	82
Mean	165.0014	170.4561	166.5979
SD	59.33635	60.34979	59.31284
Median	147.0000	144.0000	146.0000
Min	71.000	90.090	71.000
Max	342.000	301.000	342.000
Baseline FPG (mmol/L)			
n	58	24	82
Mean	9.1576	9.4603	9.2462
SD	3.29317	3.34941	3.29186
Median	8.1585	7.9920	8.1030
Min	3.941	5.000	3.941
Max	18.981	16.706	18.981
Baseline eGFR (mL/min/1.73 m^2)			
n	58	24	82
Mean	108.8139	105.2594	107.7736
SD	21.58758	23.33613	22.02777
Median	108.4738	103.9276	107.2790
Min	68.489	57.361	57.361
Max	149.833	145.987	149.833
Baseline eGFR (mL/min/1.73 m^2)			
≥ 125	16 (27.6)	5 (20.8)	21 (25.6)
< 125	42 (72.4)	19 (79.2)	61 (74.4)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Prior antidiabetic medication use n (%)[a]			
Metformin only	22 (37.9)	11 (45.8)	33 (40.2)
Insulin only	6 (10.3)	1 (4.2)	7 (8.5)

	EQW	Placebo	Total
Disease characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
Insulin and metformin	21 (36.2)	10 (41.7)	31 (37.8)
Metformin and sulfonylurea	1 (1.7)	0	1 (1.2)
Baseline Tanner stage n (%)			
Stage 1	1 (1.7)	0	1 (1.2)
Stage 2	2 (3.4)	1 (4.2)	3 (3.7)
Stage 3	7 (12.1)	0	7 (8.5)
Stage 4	9 (15.5)	5 (20.8)	14 (17.1)
Stage 5	39 (67.2)	18 (75.0)	57 (69.5)
Total	58 (100.0)	24 (100.0)	82 (100.0)

[a] For the controlled assessment period.

eGFR was derived based on the Bedside Schwartz formula: eGFR (unit = mL/min/1.73 m^2) = 41.3 × (Height in meters/Serum creatinine in mg/dL).

Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication. Percentages were calculated from the number of patients in the analysis set with nonmissing data, by treatment group and total.

Duration of Diabetes (years) = (Date of screening − Date of diabetes diagnosis + 1) / 365.25.

Prior antidiabetic medications were defined as antidiabetic medications that started prior to and continued past the first dose of randomized study medication. Anti-diabetic medication was identified based on medical review of concomitant medications recorded during the study using the WHO-Drug Enhanced plus Herbal 01Mar2020 version.

This table was derived from Table 14.1.10 and Table 14.1.18. Please see source tables for full information.
eGFR Estimated glomerular filtration rate; EQW Exenatide 2 mg once weekly; FPG Fasting plasma glucose; HbA1c Glycated hemoglobin A1c; Max Maximum; Min Minimum; N Number of patients in treatment group;

n Number of patients included in analysis; SD Standard deviation.

Data Source: Table 14.1.10 and Table 14.1.18.

CHMP comment:

The demographic, patient and baseline disease characteristics were representative of the intended population. Notably, the patients were overweight with a mean weight of 100 kg and mean BMI of 36 kg/m^2. No difference was observed in terms of pre-existing conditions and concomitant medications between study groups but there were minor imbalances in age, race, region, weight population percentile, and baseline diabetes duration. It is agreed that these imbalances are generally not expected to affect the interpretation of the primary efficacy analysis.

Efficacy results

Results for the primary and secondary efficacy endpoints in the fixed-sequence procedure hierarchical testing strategy are summarized in the table below (Table 3).

Table 3: Summary of Primary and Secondary Efficacy Endpoint Results in the Fixed-sequence Procedure Hierarchical Testing Strategy

	EQW	**Placebo**
	(N = 58)	**(N = 24)**
Primary Endpoint: Change in HbA1c from baseline to Week 24 (%) (Evaluable Analysis Set)[a,b]		
LS mean (SE) adjusted change from baseline to Week 24	-0.36 (0.184)	0.49 (0.273)
LS mean (SE) difference	-0.85 (0.330)	
95% 2-sided confidence interval for LS mean difference	(-1.51, -0.19)	
2-sided p-value	0.012	
Change from Baseline to Week 24 in Fasting Plasma Glucose (mg/dL) (Intent-to-Treat Analysis Set)[a,c]		
LS mean (SE) adjusted change from baseline to Week 24	-5.2 (7.65)	16.5 (11.32)
LS mean (SE) difference	-21.6 (13.70)	
95% 2-sided confidence interval for LS mean difference	(-49.0, 5.7)	
2-sided p-value	0.119	
Change from Baseline in Body Weight (kg) (Intent-to-Treat Analysis Set)[a,d]		
LS mean (SE) adjusted change from baseline to Week 24	-0.59 (0.665)	0.63 (0.982)
LS mean (SE) difference	-1.22 (1.189)	
95% 2-sided confidence interval for LS mean difference	(-3.59, 1.15)	
2-sided p-value	0.307	
Change from Baseline to Week 24 in Fasting Serum Insulin (pmol/L) (Intent-to-Treat Analysis Set)[a,e]		
LS mean (SE) adjusted change from baseline to Week 24	79.6 (52.28)	-15.3 (78.49)
LS mean (SE) difference	94.9 (95.26)	
95% 2-sided confidence interval for LS mean difference	(-95.6, 285.5)	
2-sided p-value	0.323	

[a] Excluding measurements after initiation of rescue therapy or discontinuation of study medication.

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

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

[d] Adjusted LS mean and treatment group difference in the change from baseline values at each visit are modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline body weight, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline body weight by visit interaction as fixed effects, using an unstructured covariance matrix.

[e] Adjusted LS mean and treatment group difference in the change from baseline values at each visit are modeled using a MMRM including treatment group, region, visit, treatment group by visit

interaction, baseline fasting insulin, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline fasting insulin by visit interaction as fixed effects, using an unstructured covariance matrix.

This table was derived from Table 14.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1. Please see source tables for full information.

EQW Exenatide 2 mg once weekly; HbA1c Glycated hemoglobin A1c; LS Least-squares; MMRM Mixed model with repeated measures; N Number of patients in the Intent-to-Treat Analysis Set within the treatment group; SE Standard error.

Data Source: Table 14.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1.

Primary Endpoints:

EQW was statistically superior to placebo in reducing HbA1c at Week 24 (p = 0.012). Sensitivity analyses of the primary endpoint were consistent with the primary analysis.

Secondary Endpoints:

The reduction in mean HbA1c observed within the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52.

There were no significant differences between treatment groups in change from baseline at Week 24 in FPG, body weight, or fasting insulin. However, for patients in the EQW group numerical decreases in FPG and body weight, and numerical increases in fasting insulin were observed during the controlled assessment period.

At Week 24, numerically higher proportions of patients achieved HbA1c goals of < 6.5%, ≤ 6.5%, and < 7% in the EQW group compared with the placebo group.

At Week 24, there was a numerical decrease from baseline in mean triglycerides in the EQW group compared with a numerical increase in the placebo group. There were no notable differences between treatment groups in total cholesterol, low-density lipoprotein cholesterol, or high-density lipoprotein cholesterol.

There were no significant differences between treatment groups in change from baseline at Week 24 in systolic or diastolic blood pressure.

The cumulative proportion of patients needing rescue medication due to failure to maintain glycemic control at Week 24 was low (EQW: 1.7%, placebo: 0%).

Reductions in HbA1c were observed among patients who were switched from placebo to open-label EQW treatment, consistent with observations among patients treated with EQW during the controlled assessment period.

For the EQW group, exenatide plasma concentration reached steady state by Week 8 and was stable over time (Weeks 12 to 52).

CHMP comment:

The study met the primary endpoint, as the difference in HbA1c was statistically significant lower in the EQW group vs placebo. The decrease in HbA1c was clinically relevant. However, HbA1c returned to baseline at week 52.

The reason why the effect on HbA1c decreases over time is unclear, as the effect in adult patients in the pivotal study was maintained up to 52 weeks.

Although no significant differences were observed in secondary endpoints, there was a trend towards lower FPG and body weight in the EQW group. During the open-label phase of the study, patients switched from placebo to EQW treatment experienced also a reduction in HbA1c.

PK analysis in paediatric patients shows a similar pharmacokinetic profile as compared to adults, where a stable exenatide plasma concentration was achieved by week 7-8.

A mixed-meal substudy was originally planned as to assess the effect of EQW on beta-cell function, but no conclusion has been drawn from it due to the low number (n=9) of patients included.

Anti-drug antibody results

The primary endpoint is summarized descriptively by antibody status and by visit for the Evaluable Analysis Set in Table 4 and Table 5.

Antibodies to exenatide were observed in the majority of patients (93.0%) in the EQW group at any time during the study, with more patients having high positive results (63.2%) compared with low positive results (29.8%). After an initial increase in positive antibody levels, with the percentage of patients positive for antibodies peaking at Week 12 (for high positive antibody results [58.8%]) or Week 24 (for low positive antibody results [55.1%]), antibody positivity decreased over the remaining time period to approximately half of patients (approximately quarter in each category) with any positive result at the 10-week follow-up period (Table 6).

The primary endpoint was also summarized descriptively by antibody status and by visit for the Evaluable Analysis Set in Table 4 and Table 5. At Week 24, the mean change from baseline in HbA1c in the EQW group was greater in patients with low positive antibodies (-0.73%) compared with those with high positive antibodies (+ 0.07%). From Week 4 to Week 12, mean HbA1c decreased over time for the low positive group and remained relatively stable for the high positive group. Due to the low number of patients in the EQW group with negative antibody results, no further comparisons could be made.

Table 4: Change from Baseline in HbA1c (%) to Week 24, Summary Statistics by Antibody Status (Controlled Assessment Period) (Evaluable Analysis Set)

		EQW (N=58)			
Analysis visit	HbA1c summary statistics	Negative [a]	High Positive [b]	Low Positive [c]	Treatment Emergent ADA Positive [d]
Week 4	n	28	9	16	24
	Mean	-0.21	-0.53	-0.38	-0.48
	SD	0.526	0.412	0.836	0.681
	Min	-1.1	-1.2	-1.7	-1.7
	Median	-0.20	-0.50	-0.10	-0.35
	Max	1.8	0.0	0.7	0.6
Week 8	n	4	28	19	47
	Mean	-1.03	-0.51	-0.82	-0.63
	SD	0.568	1.235	0.779	1.076
	Min	-1.8	-2.4	-2.6	-2.6
	Median	-0.85	-0.45	-0.60	-0.50
	Max	-0.6	4.8	0.4	4.8
Week 12	n	2	29	19	48
	Mean	-1.10	-0.55	-1.07	-0.76
	SD	0.141	1.687	1.028	1.472
	Min	-1.2	-2.6	-2.7	-2.7
	Median	-1.10	-0.60	-0.90	-0.75
	Max	-1.0	7.1	1.2	7.1

Table 5:Change from Baseline in HbA1c (%) to Week 24, Summary Statistics by Antibody Status (Controlled Assessment Period) (Evaluable Analysis Set)

		EQW (N=58)			
Analysis visit	HbA1c summary statistics	Negative [a]	High Positive [b]	Low Positive [c]	Treatment Emergent ADA Positive [d]
Week 24	n	2	20	26	46
	Mean	-1.15	0.07	-0.73	-0.39
	SD	0.071	1.097	1.226	1.227
	Min	-1.2	-1.4	-2.9	-2.9
	Median	-1.15	-0.05	-0.75	-0.55
	Max	-1.1	2.5	2.7	2.7

Table 6: Incidence of Antibodies to Exenatide by Visit (Treatment Period) (Safety Analysis Set)

Analysis Visit	EQW (N = 59)			
	Negative [b] n (%)	High positive [c] n (%)	Low positive [d] n (%)	Any positive [e] n (%)
Baseline [a] (n = 58)	57 (98.3)	0	1 (1.7)	NA
Week 4 (n = 55)	30 (54.5)	9 (16.4)	16 (29.1)	24 (43.6)
Week 8 (n = 52)	4 (7.7)	28 (53.8)	20 (38.5)	48 (92.3)
Week 12 (n = 51)	2 (3.9)	30 (58.8)	19 (37.3)	49 (96.1)
Week 24 (n = 49)	2 (4.1)	20 (40.8)	27 (55.1)	47 (95.9)
Week 52 (n = 45)	13 (28.9)	14 (31.1)	18 (40.0)	32 (71.1)
10-week Follow-up (n = 44)	21 (47.7)	11 (25.0)	12 (27.3)	23 (52.3)
Highest over 52 weeks and Follow-up [f] (n = 57)	4 (7.0)	36 (63.2)	17 (29.8)	53 (93.0)

CHMP comment:

Almost all treated patients developed anti-drug antibodies throughout the study, whereof 60% developed high titres, as compared to 32% in in phase 3 studies in adults. Of note, HbA1c mean change from baseline was lower in patients with high antibody titres vs those patients with low levels, even though there are responders in both groups. At week 52, mean HbA1c has returned to baseline level in the group with high antibody titres, whereas a reduction of ca 0,7% still remain in group with low antibody levels. The reduction was greater in patients without antibodies, but no conclusion can be made due to the low number of patients.

Safety results

Extent of exposure

In the controlled assessment period, the mean duration of EQW/placebo exposure was similar between the EQW and placebo groups (157.3 and 165.6 days, respectively). For the whole study period, the mean duration of EQW exposure was longer in the EQW group (356.7 days) than the placebo → EQW group (161.1 days), as expected. The majority of patients in the EQW group were exposed to exenatide for ≥ 364 days (76.0%), while the majority of patients in the placebo → EQW group were exposed to exenatide for 168 to 223 days (72.7%).

CHMP comment:

The duration of exposure was similar for both study groups during the controlled assessment period but taking into account the open-label extension phase period the exposure was longer in the EQW group as compared to the placebo → EQW group. 76 % of patients were treated for more than 365 days.

Adverse events

Treatment-emergent AEs are summarized in the table below (Table 7).

Table 7: Overall Summary of Adverse Events - On-Treatment (Safety Analysis Set)

	Number (%) of Patients[a]			
	Controlled Assessment Period		Extension Period	
Patients with AE category	**EQW (N = 59)**	**Placebo (N = 23)**	**EQW (N = 50)**	**Placebo → EQW (N = 22)**
Any AE	36 (61.0)	17 (73.9)	27 (54.0)	11 (50.0)
Any AE with outcome of death	0	0	0	0
Any SAE including events with outcome of death	2 (3.4)	1 (4.3)	3 (6.0)	1 (4.5)
Any AE leading to discontinuation of treatment	0	0	0	0
Any SAE leading to discontinuation of treatment	0	0	0	0
Any AE leading to discontinuation from study	0	0	0	0
Any SAE leading to discontinuation from study	0	0	0	0
Any AE related to treatment[b]	15 (25.4)	5 (21.7)	5 (10.0)	2 (9.1)

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

[b] Included causally related AEs as judged by the Investigator.

Controlled assessment period AE is defined as an AE starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the extension period. For patients not entering extension period, the period is defined up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs). Extension period AE was defined as an AE starting on or after day of first dose of open-label EQW through Week 52 or last dose + 7 days for patients who discontinued open-label EQW prematurely (+ 90 days for SAEs and other clinically significant or related AEs). Events are captured up to the later of period definition or Week 52, where patients completed treatment. Percentages were calculated from the number of patients in the analysis set for the study period by treatment group. Patients randomized to placebo during the controlled assessment period received EQW during the extension period. AE Adverse event; EQW Exenatide 2 mg once weekly; N Number of patients in treatment group; SAE Serious AE.
Data source: Table 14.3.2.1.1.

Exenatide was generally well-tolerated in adolescents with T2DM and safety findings in this study were consistent with the known safety profile of the product. There were no AEs with an outcome of death or AEs leading to treatment or study discontinuation reported during the study.

The incidence of AEs overall was generally lower in the EQW group (61.0%) than the placebo group (73.9%) during the controlled assessment period. The majority of AEs were mild or moderate in intensity throughout the whole study.

CHMP comment:

During the controlled assessment period, adverse events related to treatment occurred in a higher proportion of patients in the EQW compared with the placebo group. During the open-label extension period, the reporting of AEs and SAEs was similar in both study groups. No deaths occurred during the study and the majority of AEs were mild or moderate in intensity.

Adverse events by system organ class and preferred term

The most common AEs were upper respiratory tract infection and abdominal pain in the EQW and placebo groups, respectively (Table 8). The incidence of AEs overall was generally lower in the open-label extension period than the controlled assessment period.

Table 8: Number of Patients with Adverse Events, Most Common (Frequency ⩾ 5%), by Preferred Term (Safety Analysis Set)

	Number (%) of Patients[a]					
	Controlled Assessment Period			Extension Period		
Preferred Term	**EQW (N = 59)**	**Placebo (N = 23)**	**Total (N = 82)**	**EQW (N = 50)**	**Placebo →EQW (N = 22)**	**Total (N = 72)**
Patient with any AE	36 (61.0)	17 (73.9)	53 (64.6)	27 (54.0)	11 (50.0)	38 (52.8)
Upper respiratory tract infection	6 (10.2)	0	6 (7.3)	2 (4.0)	0	2 (2.8)
Diarrhoea	5 (8.5)	1 (4.3)	6 (7.3)	1 (2.0)	0	1 (1.4)
Cough	4 (6.8)	1 (4.3)	5 (6.1)	0	2 (9.1)	2 (2.8)
Headache	4 (6.8)	2 (8.7)	6 (7.3)	2 (4.0)	1 (4.5)	3 (4.2)
Nasopharyngitis	4 (6.8)	2 (8.7)	6 (7.3)	1 (2.0)	1 (4.5)	2 (2.8)
Nausea	4 (6.8)	1 (4.3)	5 (6.1)	0	1 (4.5)	1 (1.4)
Abdominal pain upper	3 (5.1)	0	3 (3.7)	1 (2.0)	0	1 (1.4)
Hypoglycaemia	3 (5.1)	0	3 (3.7)	1 (2.0)	0	1 (1.4)
Injection site erythema	3 (5.1)	1 (4.3)	4 (4.9)	0	0	0
Pain in extremity	3 (5.1)	0	3 (3.7)	0	0	0
Urinary tract infection	3 (5.1)	2 (8.7)	5 (6.1)	0	0	0
Vomiting	3 (5.1)	0	3 (3.7)	2 (4.0)	0	2 (2.8)
Abdominal pain	2 (3.4)	3 (13.0)	5 (6.1)	1 (2.0)	0	1 (1.4)
Hyperglycaemia	1 (1.7)	1 (4.3)	2 (2.4)	0	2 (9.1)	2 (2.8)

During the controlled assessment period, the most common AEs by SOC in both the EQW and placebo groups were: infections and infestations (16 patients [27.1%] and 5 patients [21.7%], respectively), gastrointestinal disorders (13 patients [22.0%] and 6 patients [26.1%], respectively), and metabolism and nutrition disorders (7 patients [11.9%] and 2 patients [8.7%], respectively).

During the open-label extension period, the most common AEs by SOC in both the EQW and placebo → EQW groups were infections and infestations (10 patients [20.0%] and 6 patients [27.3%], respectively) and gastrointestinal disorders (6 patients [12.0%] and 3 patients [13.6%], respectively).

Adverse events by intensity

During the controlled assessment period, the majority of AEs were mild or moderate in intensity. One patient (1.7%) in the EQW group and 2 patients (8.7%) in the placebo group reported at least 1 severe AE. Of the severe AEs reported, 1 event of major depression in the EQW group

and 1 event of irritable bowel syndrome in the placebo group were considered serious but neither led to treatment or study discontinuation.

There were no deaths reported during the study. No discontinuations of study treatment due to an AE were reported during the study.

The incidence of serious AEs (SAEs) was low and comparable between the EQW and placebo groups during the controlled assessment period (Table 9). No SAEs were reported by more than 1 patient in the EQW or placebo groups and none were considered related to study medication by the Investigator. Similar results were observed for patients with SAEs during the open-label extension period.

Table 9: Number of Patients with Serious Adverse Events by System Organ Class and Preferred Term – On-treatment (Safety Analysis Set)

	Number (%) of patients[a]					
	Controlled assessment period			Extension period		
System organ class / Preferred term	EQW (N = 59)	Placebo (N = 23)	Total (N = 82)	EQW (N = 50)	Placebo → EQW (N = 22)	Total (N = 72)
Patients with any SAE	2 (3.4)	1 (4.3)	3 (3.7)	3 (6.0)	1 (4.5)	4 (5.6)
Infections and infestations	1 (1.7)	0	1 (1.2)	2 (4.0)	0	2 (2.8)
Abscess limb	1 (1.7)	0	1 (1.2)	0	0	0
Cellulitis	0	0	0	1 (2.0)	0	1 (1.4)
Pneumonia	0	0	0	1 (2.0)	0	1 (1.4)
Psychiatric disorders	1 (1.7)	0	1 (1.2)	1 (2.0)	1 (4.5)	2 (2.8)
Major depression	1 (1.7)	0	1 (1.2)	0	0	0
Suicidal ideation	0	0	0	1 (2.0)	1 (4.5)	2 (2.8)
Gastrointestinal disorders	0	1 (4.3)	1 (1.2)	1 (2.0)	0	1 (1.4)
Gastritis	0	0	0	1 (2.0)	0	1 (1.4)
Irritable bowel syndrome	0	1 (4.3)	1 (1.2)	0	0	0

[a] Number (%) of patients were sorted by international order for SOC and alphabetical order for PT. Patients with multiple events in the same category (ie, same SOC or same PT) were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

Controlled assessment period AE was defined as an AE starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the extension period. For patients not entering the extension period, the period was defined up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Extension Period AE was defined as an AE starting on or after day of first dose of open-label EQW to last dose + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Events were captured up to the later of period definition or Week 52, where patients completed treatment.

Percentages were calculated from the number of patients in the analysis set for the study period by treatment group and total.Patients randomized to placebo during the controlled assessment period received EQW during the extension period.

MedDRA version 23.0.

AE Adverse event; EQW Exenatide 2 mg once weekly; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients in treatment group; PT Preferred term; SAE Serious adverse event; SOC System organ class.

Data source: Table 14.3.4.1.1.

CHMP comment:

The majority of events were mild or moderate in intensity and only 4-6% of events were severe in intensity.

Gastrointestinal disorders

During the controlled assessment period, the proportions of patients with gastrointestinal disorder-related AEs overall were slightly lower in the EQW group than the placebo group (13 patients [22.0%]) and 6 patients [26.1%], respectively).

The following gastrointestinal disorder PTs were reported in a higher proportion of patients in the EQW group compared with the placebo group:

- Diarrhea: 5 patients (8.5%) versus 1 patient (4.3%), respectively
- Nausea: 4 patients (6.8%) versus 1 patient (4.3%), respectively
- Vomiting: 3 patients (5.1%) versus 0 patients, respectively
- Upper abdominal pain: 3 patients (5.1%) versus 0 patients, respectively

None of the gastrointestinal disorder-related AEs in the EQW group led to study drug discontinuation and the majority were mild or moderate in intensity with most resolving during the study. Only the severe event of irritable bowel syndrome reported in the placebo group during the controlled assessment period was considered serious.

During the open-label extension period, the proportions of patients with gastrointestinal disorder-related AEs overall in both the EQW and placebo → EQW groups (6 patients [12.0%] and 3 patients [13.6%], respectively) were lower than those observed for the EQW group during the controlled assessment period (13 patients [22.0%]).

CHMP comment:

The incidence of GI AEs was low and comparable between the EQW and placebo groups during the controlled assessment period. The most frequent gastrointestinal disorder-related AEs were diarrhoea, nausea, vomiting, and upper abdominal pain.

Hypoglycaemia

During the controlled assessment period, hypoglycemic events were reported in 8 patients (13.6%) and 1 patient (4.3%) in the EQW and placebo groups, respectively. Of the events reported, there were no major hypoglycemic events. The proportion of patients with minor hypoglycemic events was low and similar between the treatment groups: 1 patient (1.7%) with 1 event in the EQW group compared with 1 patient (4.3%) with 1 event in the placebo group.

Other hypoglycemic events (which did not meet the criteria for major or minor episodes) were reported in 8 patients (13.6%), with a total of 12 events, in the EQW group and 1 patient (4.3%), with a total of 6 events, in the placebo group.

Among the 8 patients with hypoglycemic events in the EQW group, insulin use at baseline was reported for the majority of patients (6 of 8 patients), while no insulin or SU use at baseline was

reported for the remaining patients (2 of 8 patients). For the 1 patient with hypoglycemic events in the placebo group, insulin use at baseline was reported.

During the open-label extension period, hypoglycemic events were reported in 4 patients (8.0%) in the EQW group and 1 patient (4.5%) in the placebo → EQW group. Of the events reported, there were no major hypoglycemic events.

In the EQW group, the incidence of patients with minor hypoglycemia was similar between the treatment periods.

CHMP comment:

No major hypoglycaemic events were reported during the study. The occurrence of minor hypoglycaemic events was low and comparable between the study groups. Most of patients with hypoglycaemia events reported insulin and concomitant medication use at baseline.

Injection site-related events

During the controlled assessment period, the proportions of patients with AEs of injection site reactions were generally low and comparable between the EQW and placebo group. In both the EQW and placebo groups, injection site reactions occurred most frequently at Week 4 (5 patients [8.5%] and 2 patients [8.7%], respectively), then gradually diminished over time. No injection site reactions were reported after Week 12 in either treatment group.

During the open-label phase of the treatment period, the incidence of AEs of injection site reactions was low (2 patients [4.0%] in the EQW group only).

All AEs of injection site reactions were reported in patients using the prefilled syringe device (no injection site reactions were reported in patients using the dual chamber pen device) and were mild in intensity; none met the criteria for a SAE.

CHMP comment:

Injection site reactions were few and comparable between the EQW and placebo groups during both the controlled assessment period and open-label period. Of note, all injection-site reactions were reported among patients using the prefilled syringe device (none were reported among patients using the dual chamber pen device).

The proportions of patients experiencing injection site reactions was low and comparable between the EQW and placebo groups during the controlled assessment period. Similar results were observed for patients who received open-label EQW during the treatment period. All injection-site reactions were reported among patients using the prefilled syringe device (none were reported among patients using the dual chamber pen device).

Potentially immune-related events

During the controlled assessment period for the EQW group, potentially immune-related AEs were more common among patients who were positive for exenatide antibodies (10.9%) compared with patients who were negative (0%).

Of the patients who developed positive antibody status, potentially immune-related AEs were reported for a similar proportion of patients with a higher titer (10.8%) and with a low titer (11.1%). The most common potentially immune-related AEs were injection site erythema,

reported in 3 EQW patients (8.1%) with a higher titer, and injection site pruritus, reported for 1 EQW patient (2.7%) with a higher titer and 1 EQW patient (5.6%) with a low titer.

During the open-label extension period, potentially immune-related AEs were reported for 4 patients (8.2%) in the EQW group who were all positive for exenatide antibodies. No patients were negative for exenatide antibodies and, therefore, no comparison could be made.

Of the patients who developed positive antibody status, potentially immune-related AEs were reported for a similar proportion of patients with a higher titer (8.6%) and with a low titer (7.1%). At the PT level, none of the potentially immune-related AEs were reported by more than 1 patient.

None of the potentially immune-related AEs were considered serious or led to study drug discontinuation.

CHMP comment:

In the EQW group, there was a trend towards a higher incidence of potentially immune-related AEs among patients who were positive for exenatide antibodies compared with patients who were negative. This trend is consistent with an immune mediated mechanism for some of these events.

Because the number of patients with negative antibodies at any time during the study were small, these results should be interpreted with caution.

Clinical laboratory evaluation

There were no clinically meaningful trends in laboratory parameters over time and no notable differences between treatment groups in laboratory parameters. No patients met the criteria for a potential Hy's Law case.

One patient in the EQW group reported an AE of carcinoembryonic antigen increased during the off-treatment period. Serum calcitonin levels were undetectable (< 2 ng/L) throughout the study, and per the Investigator, the patient had no evidence of any medical condition that would result in elevated carcinoembryonic antigen.

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

Treatment with EQW was associated with a small but notable reduction in systolic blood pressure and a small increase in heart rate. Of note, there were no AEs of hypotension or tachycardia reported during the study. No other clinically meaningful trends in vital signs over time or notable differences between treatment groups in vital sign parameters were observed. There were no new safety concerns related to vital signs.

CHMP comment:

No clinically meaningful changes were observed with regards to laboratory parameters other than a small but notable reduction in systolic blood pressure and a small increase in heart rate in the EQW group. No adverse events related to hypotension were reported. This is in line with short acting exenatide studies the paediatric population.

Tanner Pubertal Stage

Development and growth assessed by Tanner staging resulted in comparable results for patients treated with EQW and placebo during the controlled assessment period.

At Week 24, an overall Tanner stage of V was reported for the majority of patients treated with EQW or placebo (71.7% and 76.2%, respectively). Overall Tanner stage results at Week 52 were consistent with those observed at Week 24 for the treatment groups.

CHMP comment:

Development and growth assessed by Tanner staging resulted was similar between study groups.

2.3.2. Discussion on clinical aspects

The MAH has submitted the results of Study BCB114 as part of the agreed PIP and subsequently plans to submit a type II variation by Q4 2021 to update the Bydureon SmPC with the proposed indication: "BYDUREON is indicated for use in patients 10 years and older with T2DM to improve glycaemic control in combination with other glucose- lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control."

Exenatide prolonged-release non-aqueous suspension via autoinjector (Bydureon BCise) is administered by subcutaneous injection. This formulation was developed to simplify the administration of exenatide once weekly and was approved in the EU in 2018 for the use in adults 18 years and older with T2DM. This device was used by study subjects recruited from August 2018 and onwards whereas subjects recruited prior to this date used the prefilled syringe.

Study BCB114 was a phase 3, double-blind, placebo- controlled, randomized, multicenter study to assess the safety and efficacy of exenatide once weekly in adolescents (10 to 17 years of age) with type 2 diabetes. The overall design of the study was adequate as well as the study duration of 24 weeks, with a follow-up period up to 67 weeks. The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results since the last patient visit occurred in May 2020.

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.

During the treatment period of the study exenatide prolonged release was given in accordance with the recommendations in the SmPC for Bydureon. 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 2 (Week 0) to Visit 7 (Week 24). The secondary efficacy endpoints were related to other relevant variables of metabolic control. Both the primary and secondary endpoints in terms of efficacy and safety were relevant, including Tanner pubertal stage.

In addition, plasma exenatide concentration as well as several PD endpoints in the Exploratory Mixed Meal Substudy were to be evaluated. Approximately 20 patients provided informed consent for the mixed meal substudy; however, a high proportion of these patients failed screening. Therefore, the actual number of patients that participated in the mixed meal sub-study was too low for any conclusions to be drawn.

The statistical methods were adequate. A total of 159 patients enrolled in this study from 27 study centres. A total of 83 patients were randomized and entered the double-blind controlled assessment period: 59 patients randomized to EQW and 24 patients randomized to placebo. The dropout rate was low, and no patients discontinued treatment during the controlled assessment period or the open-label extension period due to an AE.

The demographic, patient and baseline disease characteristics were representative of the intended population. Notably, the patients were overweight with a mean weight of 100 kg and mean BMI of 36 kg/m^2. No difference was observed in terms of pre-existing conditions and concomitant medications between study groups. However, there were minor imbalances in age, race, region, weight population percentile, and baseline diabetes duration. Although it is agreed that these imbalances are generally not expected to affect the interpretation of the primary efficacy analysis, the applicant is invited to discuss within the submission of the type II variation whether the imbalance in weight population percentiles between the study groups may have influenced the study results due to potential differences in study drug exposure.

The study met the primary endpoint, as the difference in HbA1c was statistically significant lower in the EQW group vs placebo. The decrease in HbA1c was clinically relevant. However, HbA1c returned to baseline at week 52.

The reason why the effect on HbA1c decreases over time is unclear, as the effect in adult patients in the pivotal study was maintained up to 52 weeks. The MAH is invited to discuss on the difference in long term effect between adult and paediatric patients within the submission of the type II variation.

Although no significant differences were observed in secondary endpoints, there was a trend towards lower FPG and body weight in the EQW group. During the open-label phase of the study, patients switched from placebo to EQW treatment experienced also a reduction in HbA1c.

Almost all treated patients developed anti-drug antibodies throughout the study, whereof 60% developed high titres, as compared to about 30% in in phase 3 studies in adults. Of note, HbA1c mean change from baseline was lower in patients with high antibody titres vs those patients with low levels, even though there are responders in both groups. At week 52, mean HbA1c has returned to baseline level in the group with high antibody titres, whereas a reduction of ca 0,7% still remain in group with low antibody levels. The reduction was greater in patients without antibodies, but no conclusion can be made due to the low number of patients. The MAH is invited to discuss within the coming type II variation on the relevance of anti-drug antibody development in the primary and secondary outcomes and whether (a lack of) HbA1c change from baseline could be used to identify patients with an inadequate treatment response, possibly due to the development of antibodies, in order to identify patients who will not benefit from treatment.

With regards to safety, exenatide prolonged release was generally well-tolerated in adolescents with T2DM. Safety findings in this study were consistent with the known safety profile of the drug in the adult population. The incidence of AEs overall was generally lower in the EQW group vs placebo. The incidence of SAEs was also low, in total 7 events but with a higher reporting in the EQW group. None of the SAEs were considered related to treatment by the Investigator. The most common AEs were upper respiratory tract infection and abdominal pain in the EQW and placebo groups, respectively. Most AEs were mild or moderate in intensity. The incidence of GI-related AEs was low and comparable between the EQW and placebo groups during the controlled assessment period. There were no major hypoglycaemic events reported during the study. The occurrence of minor hypoglycaemic events was low and comparable between study groups. The proportions of patients experiencing injection site reactions was low and comparable between the study groups. Of note, all injection-site reactions were reported among patients using the prefilled syringe device. Furthermore, there was a trend towards a

higher incidence of potentially immune-related AEs among patients who were positive for exenatide antibodies compared with patients who were negative.

Treatment with EQW was associated with a small but notable reduction in systolic blood pressure and a small increase in heart rate but here were no AEs of hypotension or tachycardia reported during the study. Development and growth assessed by Tanner staging resulted was similar between study 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 (BCB114) for Bydureon, 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 prolonged release showed a clinically relevant and statistically significant effect on metabolic control compared to placebo after 24 weeks of treatment and the MAH intend to submit a variation to update the SmPC of Bydureon in Q4 2021 with a paediatric indication. The safety profile does not appear to differ from what is known from the use of exenatide prolonged release in adults and no new safety concerns arise from the data submitted.

No further regulatory action is warranted at this time point, however a variation application consisting of the full relevant data package (i.e. containing several studies) concerning the use of Bydureon in the paediatric population should be submitted by Q4 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: BYDUREON, Bydureon

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	Submitted via Article 46 on 28 September 2020.
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	Submitted via Article 46 in this submission.
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