22 April 2022
EMA/CHMP/644257/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bydureon

International non-proprietary name: exenatide

Procedure No. EMEA/H/C/002020/II/0073

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
$C_{ss,avg}$	Average steady-state concentration
CMH	Cochran–Mantel–Haenszel
CSP	Clinical study protocol
CSR	Clinical study report
CWRES	Conditional weighted residuals
DBP	Diastolic blood pressure
DCP	Dual chamber pen pre filled
EQW	Exenatide 2 mg once-weekly prolonged-release, aqueous formulation
EQWS	Exenatide 2 mg once-weekly prolonged-release, non-aqueous suspension
ER	Exposure-response
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GOF	Goodness-of-fit
HbA1c	Glycated hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HOMA-B	Homeostasis model assessment-beta-cell function
HOMA-S	Homeostasis model assessment-insulin sensitivity
HR	Heart rate
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
LDL-	Low-density lipoprotein cholesterol
LS	Least squares
MAR	Missing at random
MCT	Medium-chain triglyceride
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random

Abbreviation or special term	Explanation
MOA	Mechanism of action
NDA	New Drug Application
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
QC	Quality control
QD	Quaque die, once daily
QW	Once weekly
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SDT	Single-dose tray
SE	Standard error
SI	International system of units
SmPC	Summary of Product Characteristics
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 27 July 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from Study BCB114 (D5551C00002); 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, which was initially submitted and assessed by the CHMP as part of the post-authorisation measure (PAM) P46 028. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated in accordance. Version 35.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0064/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0064/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0064/2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report circulated on:	08 October 2021
PRAC Rapporteur's assessment report circulated on:	08 October 2021
PRAC Outcome:	28 October 2021
Joint Rapporteurs' updated assessment report circulated on:	04 November 2021
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 November 2021
MAH's responses submitted to the CHMP on:	17 February 2022
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	22 March 2022
PRAC outcome:	7 April 2022
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	13 April 2022
CHMP opinion:	22 April 2022

2. Scientific discussion

2.1. Introduction

Exenatide is a GLP-1 receptor agonist that exhibits many of the same glucose-lowering actions as GLP-1, a naturally occurring incretin hormone. Exenatide twice daily (Byetta) is administered by subcutaneous injection. It was approved in the EU on 20 November 2006 for use in adult patients with T2DM. BYDUREON, exenatide 2 mg once weekly prolonged-release aqueous formulation (hereafter referred to as EQW) was first approved for marketing in the EU on 17 June 2011. BYDUREON BCise, exenatide once weekly prolonged-release non-aqueous suspension via autoinjector (referred to as EQWS), was approved in the EU on 27 August 2018.

In the EU, BYDUREON aqueous and non-aqueous formulations are 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.

The purpose of this variation is to provide information to support the efficacy, safety, and PK of BYDUREON (EQW) and BYDUREON BCise (EQWS) in the treatment of adolescents with T2DM. This submission consists of the following study:

- Study BCB114 - 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"

This study is part of a paediatric program based on an agreed Paediatric Investigational Plan (PIP), (PIP number: EMEA-000689-PIP01-09-M10) (EMA Decision: P/0064/2021).

Study BCB114 has previously been assessed within procedure EMEA/H/C/002020/P46/028.

2.1.1. Problem statement

Disease or condition

The proposed extension of the indication in T2DM is:

"Bydureon is indicated in adults***, adolescents and children aged 10 years and above*** with type 2 diabetes mellitus 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."

Epidemiology

The prevalence of T2DM has increased in children and adolescents and has been reported to account for between 8% and 45% of all new cases of diabetes reported in children and adolescents (Temneanu et al 2016). Evidence has shown that a diagnosis of T2DM in childhood, coupled with inadequate glycaemic control, increases the risk of early mortality as well as early end organ damage (Cavallo 2006).

Clinical presentation and prognosis

T2DM is usually diagnosed in the adolescent period with an average age of onset of 13 years (Pulgaron and Delamater 2014). Evidence has shown that a diagnosis of T2DM in childhood coupled with inadequate glycaemic control increases the risk of early end organ damage and mortality (Cavallo 2006, Candler et al 2018).

Management

While multiple medications are available for the treatment of T2DM in the adult population, only insulin, metformin, and, more recently liraglutide QD (a GLP-1 RA administered by injections, approved in 2019 in the US and EU) are approved for use in the paediatric population with T2DM. As there are limited licensed options for the treatment of T2DM in patients 10 to 17 years of age, there is an unmet medical need for additional safe and effective therapies for this age group.

To address this unmet medical need, the efficacy, safety, and PK of BYDUREON, a once-weekly treatment, has been evaluated in the paediatric population with T2DM in the exenatide clinical development program.

2.1.2. About the product

Exenatide is a GLP-1 receptor agonist that exhibits many of the same glucose-lowering actions as GLP-1, a naturally occurring incretin hormone.

Exenatide prolonged release was first approved for use 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 EU on 27 August 2018.

In the EU, Bydureon 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The exenatide Phase IIb/III/IIIb clinical development program established the efficacy and safety of exenatide in lowering glucose levels in adults.

The MAH states that study BCB114 was developed in accordance with the US FDA Guidance for Industry: Diabetes Mellitus — Developing Drugs and Therapeutic Biologics for Treatment and Prevention (FDA February 2008) and is consistent with the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (CPMP/EWP/1080/00, Rev 1, 2012).

The MAH did not seek Scientific advice at the CHMP.

With the finalisation of study BCB114, the MAH has completed the PIP for exenatide which included in total 5 studies.

2.1.4. General comments on compliance with GCP

The MAH has stated that the study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the MAH's policy on Bioethics and Human Biological Samples.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Exenatide is a chemically synthesized 39-amino acid single-chain peptide and, as such, is considered a naturally-occurring product, which is not expected to remain either stable or biologically active in the environment for any significant period of time.

Exenatide is considered to be a non-hazardous, biodegradable product. The environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline (CHMP 2006) ERA studies are not submitted, which is considered acceptable by the CHMP.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. The applicant has previously performed non-clinical juvenile toxicity studies according to the paediatric investigation plan. These studies were assessed in previous procedures and have not been re-assessed for the current application.

The applicant has not submitted an ERA. Given that exenatide is a peptide, this is acceptable.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. Considering the above data, exenatide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The current application is supported by Study BCB114; a multi-centre, randomized, parallel-group, Phase III study in adolescent patients (10 to 17 years of age) with T2DM. The PK data from study BCB114, in combination with PK data from other clinical studies was analysed using population PK (popPK) approach. Full details of the clinical pharmacology properties of exenatide have been previously summarized.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Description of Study BCB114

Study ID	Number of centers[a] Locations	Study start[b]/ completion[c] Total enrolled (n) /randomized (n)	Study objectives	Design and duration	Study medications Background therapy	Patients (n) by treatment: randomized/ completed treatment/ completed study	Gender (M/F) Mean age (range)	Population	Primary endpoint
D5551C00002 (BCB114)	27 centers United States, Mexico, Israel, Hungary, Kuwait, Bulgaria Ukraine	12 May 2016/ 06 May 2020 159/83	Efficacy, safety, PK	Randomized, double-blind, placebo-controlled, multicenter, Phase III 24-week controlled assessment period and 28-week open-label extension	EQW 2 mg (injection) versus Pbo (Patients randomized to Pbo group received EQW 2 mg during extension period)	EQW: 59/44/46 Pbo: 24/18/18	41.5% M 58.5% F 15.1 y (11 to 17 y)	T2DM, 10 to < 18 y	Change from baseline in HbA1c at 24 weeks

[a] Number of centers that randomized patients

[b] First subject enrolled

[c] Last subject last visit

CSR, clinical study report; EQW, exenatide 2 mg once weekly prolonged-release; F, female; HbA1c, glycated hemoglobin A1c; M, male; n, number of patients; Pbo, placebo; PK, pharmacokinetics; T2DM, type 2 diabetes mellitus; y, years.

Source: CSR for Study BCB114

2.3.2. Pharmacokinetics

Analytical Methods

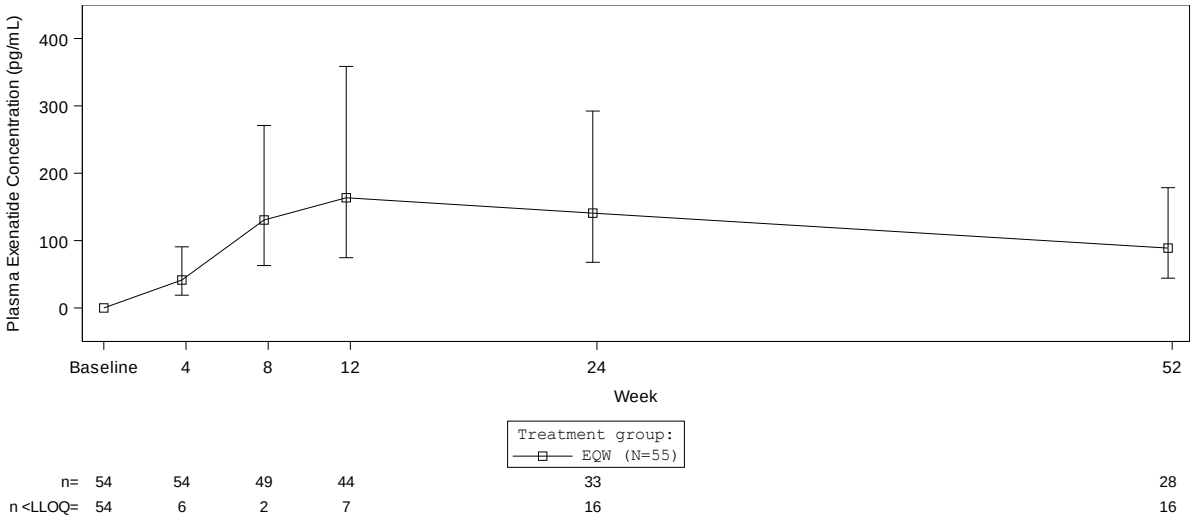
A new bioanalysis method was used for study D5551C00002 (BCB114), TNJS15-094. In the bioanalysis of exenatide at Covance (8328-394, VR 8360-719), QCs and standards performing within pre-set acceptance criteria and satisfactory ISR results (98.3%). All samples were analysed within the above established storage stability duration, as well as established benchtop and freezer thaw stability.

The ligand binding assay for antibodies against exenatide (anti-drug antibodies, ADA) was the same as in the initial application. No data is available on the neutralising potential of the ADAs.

Pharmacokinetic data analysis

In study BCB114 individual samples for analysis of plasma exenatide concentrations were collected from patients pre-dose at Weeks 0, 4, 8, 12, 24, 52, and 62 (Figure 1). No intra-dose PK profiles were recorded.

Figure 1. Study BCB114: Geometric Mean (GSD Interval) Plasma Exenatide Concentrations (pg/mL) by Visit (Pharmacokinetic Analysis Set)



Patients who received placebo during the double-blind controlled assessment period, and went on to enter the open-label extension period and receive open-label EQW, had plasma exenatide concentrations measured at Week 52 only.

The GSD interval was calculated by multiplication/division of the geometric mean.

Concentration values < LLOQ occurring after the first dose, but prior to the first quantifiable value, were imputed to LLOQ/2. Concentration values < LLOQ occurring after the first dose, and after the first quantifiable value, were excluded from the analyses.

EQW, exenatide 2mg once weekly; GSD, geometric standard deviation factor; LLOQ, lower limit of quantification; N, number of patients in the Pharmacokinetic Analysis Set within the treatment group; n, number of patients included in analysis; n < LLOQ, number of concentrations below the lower limit of quantification (both imputed and exduded from analysis).

Source: see CSR Figure 14.2.2.11.

The objective with the popPK analysis was to assess the pharmacokinetics (PK) of exenatide plasma concentrations in adolescents with T2DM from study D5551C00002 at steady state and compare the plasma concentrations to adults with T2DM (Phase 3 studies). Exenatide from once-weekly dosing accumulates in the systemic circulation over only a slightly shorter time scale (8 to 10 weeks).

Data and Methods

The present analysis is based on exenatide plasma concentrations from a study in T2DM patients aged 10 to 17 years (D5551C00002). Overall, 59 patients were randomised to receive EQW. Predose exenatide concentrations were collected at week 4, 8, 12, 24, and 52 (end of treatment). Estimated glomerular filtration rate (eGFR) was derived using the Bedside Schwartz equation (Schwartz et al 2009).

The popPK model was based on steady state data. Therefore, non-steady state concentrations (prior to week 8 and after week 30 for PK) were excluded from the dataset. Further, samples with high antibody titre (> 625) were excluded due to interference in the analytical methods for exenatide. Exenatide concentrations below the lower limit of quantification (LLOQ) were also excluded. Missing covariate values were imputed within a subject, using the last observation carried forward method with the following exception: missing screening/baseline values of covariates were imputed backward (using the first, post-baseline record of the covariate for that subject). If all values for a subject were missing, the mean, median, or mode value (as appropriate for that covariate) for the treatment (or other relevant factor) group was used as the imputed value.

The popPK model utilised in this analysis was developed based on 5 Phase 3 studies using only the 15 kg manufacturing scale exenatide microspheres (earlier studies utilized non-commercial scale manufacturing batches). The popPK model describing Css,avg is shown below:

$$C_{ss,avg,ij} = ((\theta_1 \cdot \left(\frac{baseline\ eGFR_i}{81.6}\right)^{\theta_2} + \theta_3 \cdot (\text{IBW-64.1}) + \theta_4 \cdot T_{125,625,ij}) \cdot F_{rel}) \cdot exp^{\eta_i}$$

Where Css,avg,ij is the individually predicted predose steady-state concentration (pg/mL) for the ith subject at the jth measurement, baseline eGFRi is the baseline eGFR for the ith subject, IBW is the ideal body weight for the ith subject, T125,625,ij is an indicator variable for antibodies to exenatide for the ith subject at the jth measurement (T125,625ij = 1 if antibody titre to exenatide ≥ 125, 0 otherwise), ηi is the inter-individual variability (IIV) estimate for the ith subject. The IIV was modelled using a normal distribution with mean of 0 and variance of ω2. The Frel is the relative bioavailability for the suspension formulation of EQWS relative to EQW. Parameter estimates from the final model is presented in Table 2.

Table 2. Parameter Estimates of the Exenatide Population PK Model Using 15 kg Manufacturing Scale Phase 3 Study Data Only

Parameter	Description	Mean	%RSE
θ_1	Mean $C_{ss,avg}$ for 2 mg dose	161	2.8
θ_2	eGFR effect on $C_{ss,avg}$ as a power model: $(eGFR/81.6)^{\theta 3}$	-0.85	9.2
θ_3	IBW effect on $C_{ss,avg}$ as an additive (shift) model θ_4*(IBW-64.1)	-1.38	14.8
θ_4	Antibody titre ≥ 125 as an additive (shift) effect on $C_{ss,avg}$	39	11.1
θ_5	EQWS as a proportional effect on $C_{ss,avg}$ for autoinjector delivery	1.01	3.8
ω^2	Variance of interindividual variability for $C_{ss,avg}$	0.285	7.5
σ^2	Variance of residual error for Tandem assay	0.284	4.6

Parameter names have been adapted from source to simplify and exclude parameters not needed.
θ, fixed-effects parameter; ω, variance of inter-individual variability; σ, variance of residual variability; $C_{ss,avg}$, average exenatide concentration at steady state; eGFR, estimated glomerular filtration rate; EQWS, exenatide once weekly suspension; IBW, ideal body weight; PK, pharmacokinetic; RSE, relative standard error.
Source: Models\PK\run1.lst.

Results

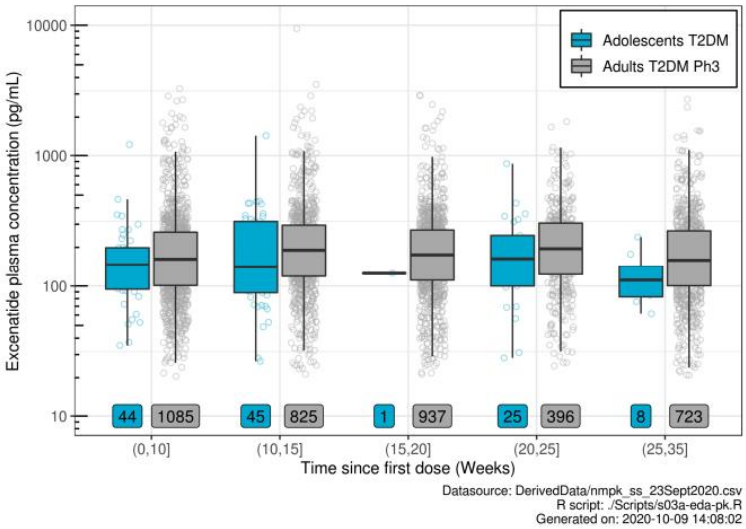
The PopPK and ER models were based on samples from >1000 adults with T2DM. Addition of relatively few data points from study BCB114 was therefore not anticipated to have a major impact on the parameter estimates if re-estimated. Therefore, external model evaluations were performed. A summary of Data Used (34% of all available samples) in the popPK Analysis of Exenatide in Adolescents with T2DM is presented in

Table 3. Summary of Data Used in the PopPK Analysis of Exenatide in Adolescents with T2DM

Type	Subjects [n]	Samples [n (%)]
Below LLOQ	8	8 (2.19)
Antibody titre > 625	12	25 (6.85)
Used in PK analysis	47	123 (33.7)
Non-steady state measurement	58	209 (57.3)
Overall in dataset	58	365 (100)

LLOQ, lower limit of quantification; n, number of subjects; PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.
Datasource: DerivedData/nmpk_ss_23Sept2020.csv. R script: ./Scripts/s03a-eda-pk.R. Generated on: 2020-10-09 14:08:02

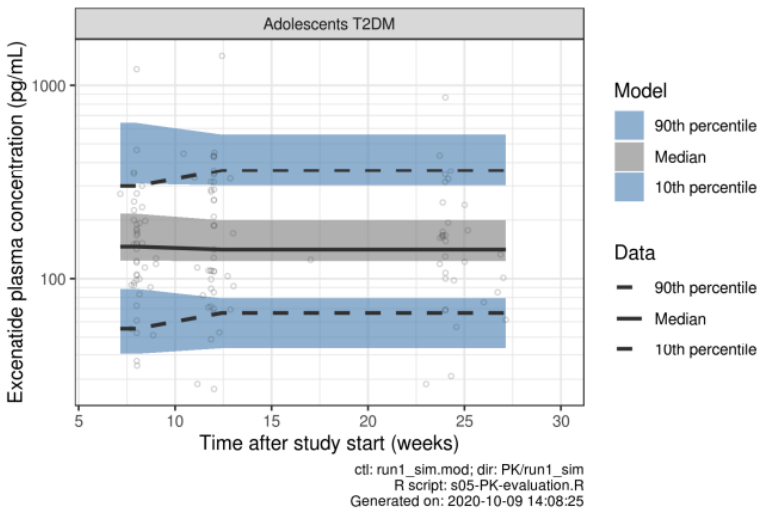
Figure 2. Observed exenatide Plasma Concentrations Versus Time After First Dose at Steady State Stratified by Population (Adolescents (BCB114) and Adult Patients with T2DM)



Open circles: observations, line within box show the median, boxes show IQR and whiskers extend to 1.5*IQR. Data outside whiskers are considered outliers. Time after dose has been lumped into bins of 5 weeks data.
IQR, inter-quartile range; Ph 3, Phase 3; T2DM, type 2 diabetes mellitus.

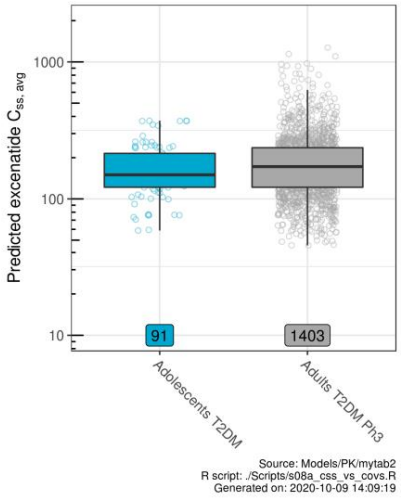
The model predicted concentrations overlaid with the observed concentrations that were not excluded from the analysis is shown in Figure 3, and Figure 4 displays the predicted average exenatide concentration at steady state stratified by population. The plots of the relationship between the predicted average exenatide at steady state versus different continuous and categorical covariates and stratified by population do not show any major trends.

Figure 3. External Evaluation of Adult T2DM Population Pharmacokinetic Ph3 Model for the Use in Adolescents with T2DM Comparing Observed and Predicted Exenatide Plasma Concentrations Versus Time After First Dose



Open circles: observations. Ph 3, Phase 3; T2DM, type 2 diabetes mellitus

Figure 4. Predicted Average Exenatide Concentration at Steady State Stratified by population



Open circles: observations, line within box show the median, boxes show IQR and whiskers extend to 1.5*IQR. Data outside whiskers are considered outliers.
$C_{ss,avg}$, average concentration at steady state; IQR, inter-quartile range; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

2.3.3. Pharmacodynamics

Mechanism of action

Exenatide is a GLP-1 receptor agonist that exhibits many of the same glucose-lowering actions as GLP-1, a naturally occurring incretin hormone.

2.3.4. PK/PD modelling

The ER model utilised in this analysis was developed based on all adult phase 2 and phase 3 study data from studies using EQW and EQWS. The objective with ER analysis was to assess the relationship between predicted average plasma exenatide concentrations at steady state (Css,avg) and glycosylated haemoglobin (HbA1c) at steady state and compare HbA1c in adolescents with T2DM from study BCB114 to adults with T2DM (Phase 3 studies). The PD endpoint, HbA1c, reflects the average blood glucose level over the preceding 90 to 120 days. HbA1c samples were collected at day 1 and week 4, 8, 12, 18, 24, 28, 40, and 52.

The previously developed ER model for EQW and EQWS was estimated based on HbA1c data using an Emax model. Estimates from the ER model can be found in Table 4.

Table 4. Parameter Estimates of the Final EQWS Exenatide Population

Parameter	Description	Mean	%RSE
θ_1	E_{max} at a baseline HbA1c of 8.2%	1.89	6.5
θ_2	EC_{50} for titre < 125 (pg/mL)	52.1	31.3
θ_3	Change in E_{max} for each 1% of deviation of baseline HbA1c from 8.2%	0.67	7.7
θ_4	Increase of EC_{50} for titre ≥ 125 (pg/mL)	33.3	33.7
ω, E_{max}^2	Variance of inter individual variability for E_{max}	0.039	26
ω, EC_{50}^2	Variance of inter individual variability for EC_{50}	2.9	25
σ^2	Variance of residual error for HbA1c	0.0039	8.6

EQWS, Exenatide once weekly suspension; EC_{50}, exenatide concentration generating 50% of E_{max}; E_{max}, maximum effect; HbA1c, glycosylated haemoglobin; RSE, relative standard error.

Results

Table 5 provides a summary of the new data available for ER analysis. Figure 5 shows the observed HbA1c versus time after first dose at steady state for both adults and children. The adolescents had lower age and higher eGFR than adult T2DM patients. Further, they had similar proportion of concomitant metformin, but somewhat smaller proportion with concomitant medication of sulphonamides and thiazolidinediones, and lower fasting plasma glucose. However, body weight, body mass index and HbA1c levels were similar in both groups. Fewer of the adolescents were Caucasian (41% versus 78.7%), whereas more were black (20.5% versus 11.2%) or other ethnicity (25.6% versus 0.8%). The proportion of males/females and different levels of antibody titre were comparable between the 2 populations.

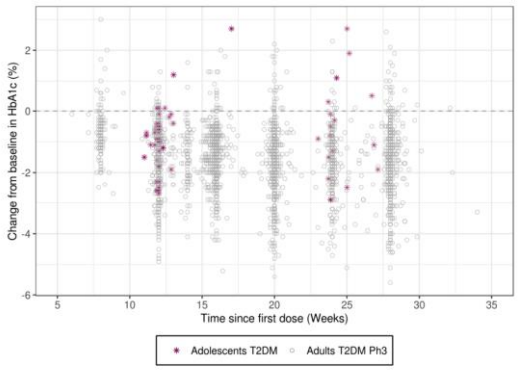
The ER model was based on steady state data. Therefore, non-steady state concentrations (prior to week 12 and after week 30 for HbA1c) were excluded from the dataset. Missing covariate values were imputed within a subject, using the last observation carried forward method with the following exception: missing screening/baseline values of covariates were imputed backward (using the first, post-baseline record of the covariate for that subject). If all values for a subject were missing, the mean, median, or mode value (as appropriate for that covariate) for the treatment (or other relevant factor) group was used as the imputed value.

Table 5. Summary of Data Used in the Exposure-Response Analysis of Exenatide in adolescents with T2DM

Type	Subjects [n]	Samples [n (%)]
Used in HbA1c analysis	39	70 (45.5)
Missing HbA1c	19	32 (20.8)
Non-steady state HbA1c	40	51 (33.1)
Outlier	1	1 (0.649)
Overall in dataset	47	154 (100)

HbA1c, glycosylated haemoglobin; n, number of subjects; T2DM, type 2 diabetes mellitus
Datasource: DerivedData/nmpd_ss_23Sept2020.csv. R script: ./Scripts/s03b-eda-pd.R. Generated on: 2020-10-09 14:08:16

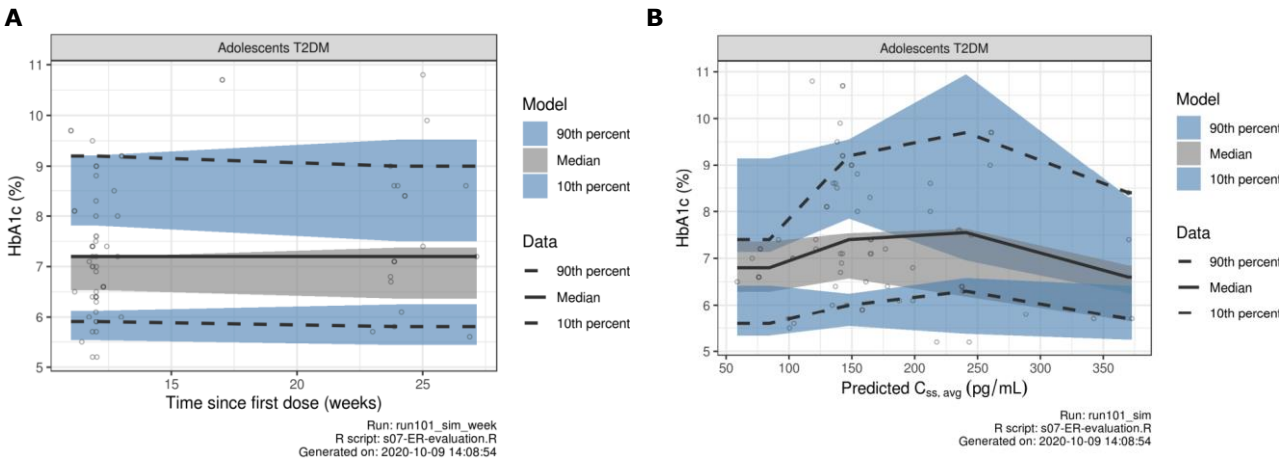
Figure 5. HbA1c Versus Time After First Dose at Steady State Stratified by Population (Adolescents (BCB114) and Adult Patients with T2DM.



Circles and stars: observations. HbA1c, glycosylated haemoglobin; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

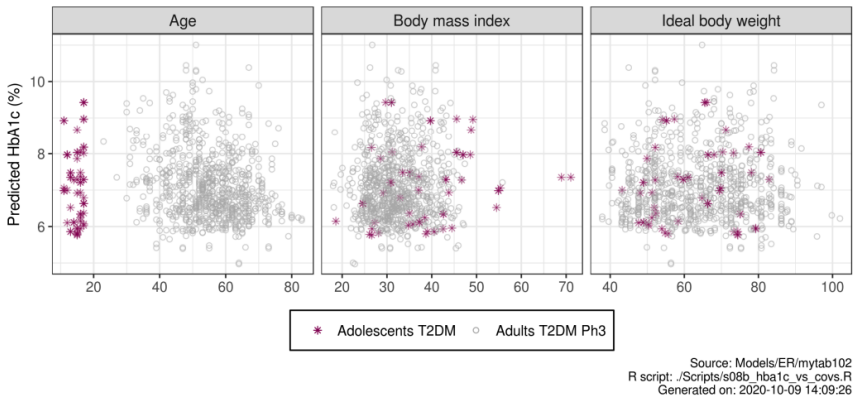
The external evaluation of adult T2DM exposure-response model for the use in adolescents with T2DM comparing observed and predicted HbA1c versus time after first dose and versus predicted average exenatide concentrations at steady state is shown in Figure 6. The relationship between predicted HbA1c at steady state versus different continuous covariates and stratified by population is shown in

Figure 6. External Evaluation of Adult T2DM Exposure-Response Model for the Use in Adolescents with T2DM Comparing Observed and Predicted HbA1c Versus Time After First Dose (A) and Versus Predicted Average Exenatide Concentrations at Steady State (B)



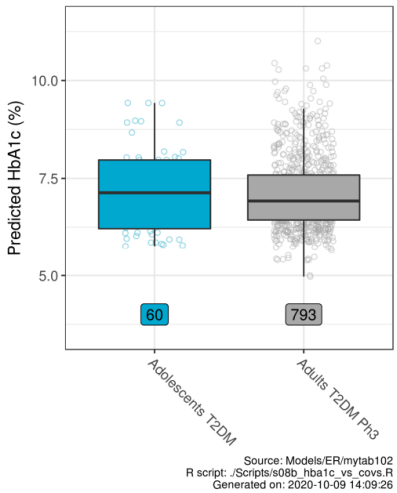
$C_{ss,avg}$, average exenatide concentration at steady state; HbA1c, glycosylated haemoglobin; T2DM, type 2 diabetes mellitus.

Figure 7. Predicted HbA1c at Steady State Versus Different Continuous Covariates and Stratified by Population



HbA1c, glycosylated haemoglobin; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

Figure 8. Predicted HbA1c at Steady State Stratified by Population



Open circles: observations, line within box show the median, boxes show IQR and whiskers extend to 1.5*IQR.
Data outside whiskers are considered outliers.
HbA1c, glycosylated haemoglobin; IQR, inter-quartile range; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

2.3.5. Discussion on clinical pharmacology

The MAH has conducted a randomized, placebo-controlled study (BCB114) including 59 children, where individual samples of plasma exenatide and HbA1c were collected from paediatric patients. No intra-dose PK profiles were recorded.

Bioanalysis of exenatide and anti-exenatide antibodies was conducted. The cross-validation report 8360-719 confirmed the adequacy of the method.

The validation of the ADA method is outdated and incomplete. In particular, data is missing on sensitivity and drug tolerance of the assay. However, updating the assay to meet current requirements would hinder comparability to earlier data in adults. Thus, a new assay is not requested, as comparability is considered more important in this particular case.

Data indicates a higher incidence of ADAs in children compared to adults, which may have an impact both on the PK of exenatide and on the efficacy, in case of high ADA titer or if the ADAs are neutralizing. As noted at the time of MAA, immunogenicity is primarily a concern for efficacy and not safety for this

medicinal product. The impact of ADAs in children may be higher than in adults and children may be exposed to a higher risk of lack of efficacy. See efficacy section for further discussion.

Regarding the neutralising potential of the ADAs, such data would be appreciated. HbA1c data may be indicative of neutralisation, but due to different kinetics of ADA and HbA1c response, a direct conclusive link cannot be established. The applicant clarified that they do not intend to develop an assay to characterize the neutralising potential of anti-exenatide antibodies. It is still considered of importance to get a grasp of the neutralising potential of the ADAs as it potentially affects the benefit/risk balance to a larger extent in this population. The applicant proposed monitoring of Hb1Ac on the individual level, which may serve a similar purpose as a neutralising antibody assay in the clinical practice. The issue is thus not further pursued.

Population PK analysis was used to analyse the data from children in study BCB114. The population PK model used was previously developed based on adult steady-state data from Phase 2 and Phase 3 studies that included adults with T2DM who received the commercial exenatide formulation. Non-steady state concentrations (57%), samples with high antibody titre (7% were > 625) and concentrations below the lower limit of quantification (LLOQ, 2%) were excluded from the BCB114 dataset for this analysis. Only 34% of the total number of available PK samples were used in the analysis, and the exclusions resulted in 11 subjects being completely excluded from the analysis. To discard so much of collected data, that contains considerable amounts of information that would have been useful for both the basic and in-dept understanding of the PK of exenatide in children goes against good modelling practice and ethical principles. The MAH could have e.g. described the relationship between PK and ADA/nAb better as a higher proportion of children have positive ADA response and higher ADA-titres which affects the PK. Currently the model only has a very rough estimate of the ADA impact with a categorical covariate at the cut-off of ADA titre ≥125. The data handling limits the use of the model and the conclusions that can be made. However, given the objective of the population model and that it is not pivotal for this applicant, the issue is not pursued further. The adult model population parameters were not re-estimated. The paediatric data were used as an external validation. The parameter Theta 1, named Css,avg, estimates the concentration measured pre-dose, which is not 'trough' concentration as the value is not the lowest value on the concentration-time interval due to the release characteristics of the product. The model can acceptably describe the observed trough concentration at steady state of exenatide in children that remained after data exclusion. The model can adequately predict the steady state trough exposure at steady state in children with lower ADA-titre, and the concentrations are predicted to be similar to the exposure in adults. No trends are observed for the relationship between the predicted average exenatide at steady state versus different continuous and categorical covariates.

The applicant had a developed **exposure-HbA1c model** based on all adult phase 2 and phase 3 study data from studies using EQW and EQWS. The objective of the steady-state exenatide-HbA1c model was to show that the response at steady state of exenatide is similar in adults and adolescent. The PD endpoint, HbA1c, reflects the average blood glucose level over the preceding 90 to 120 days. Overall, 45% of collected HbA1c samples that were available after the PK dataset exclusions were used in the external validation of the ER model, and only 39 out of the 58 subjects included in the BCB114 study were included in the ER analysis. It is unclear which subjects are represented in the ER analysis, which limits the conclusions that can be made, and the model is therefore less relevant in this application. The model includes the impact of ADA-titre (categorical, if ≥125). The applicant has not characterized the abundance of neutralizing antibodies (nAb) in adults (or children), therefore nAb are not included as a covariate. An adequate characterisation of ADA and nAb is of importance if even younger individuals are going to be included in the indication. A higher proportion of children in BCB114 developed ADA and had higher ADA-titres compared to adults. As ADA affects the effect, a higher proportion of children may have a lower effect than adults, even despite achieving similar plasma concentrations. The relationship between effect and ADA titre may not be properly described in the current model as the abundance ADA is lower in

adults. The relationship may be underestimated. Furthermore, the inclusion of the ADA-titre effect is very crude in the model (categorical, if ≥125). Additional cut-offs in the model would have provided additional information on the impact of ADA-titre, as higher proportion of children have higher titres. Despite the fact that the model can acceptably describe the steady state HbA1c-data in the children that were included in the analysis and that have a lower ADA-titre, no firm conclusions regarding HbA1c can be drawn from this analysis, due to the shortcomings described above.

2.3.6. Conclusions on clinical pharmacology

The applicant used population PK and PKPD analysis to describe the observed concentration of exenatide and HbA1c from study BCB114, however, data handling limits the relevance of the model results. The PK model could describe the trough concentrations at steady state for the children included in the analysis with lower ADA-titres.

2.4. Clinical efficacy

In support of the proposed extension of the indication to include adolescents and children >10 years of age, one clinical study has been submitted.

2.4.1. Main study

Title of 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"

Methods

Overall Study Design

Study BCB114 was Phase III, double-blind, randomized, placebo-controlled, international study that included male and female patients 10 to 17 years of age with T2DM treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening.

The study was designed to recruit a paediatric population representative of that to be treated with EQW and EQWS in clinical practice. Study BCB114 included patients with an HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and with an HbA1c of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Screening, and patients with a C-peptide of > 0.6 ng/mL at Screening.

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

The study duration was 62 weeks (excluding the extended safety follow-up period; see below) and comprised 4 periods (Figure 9):

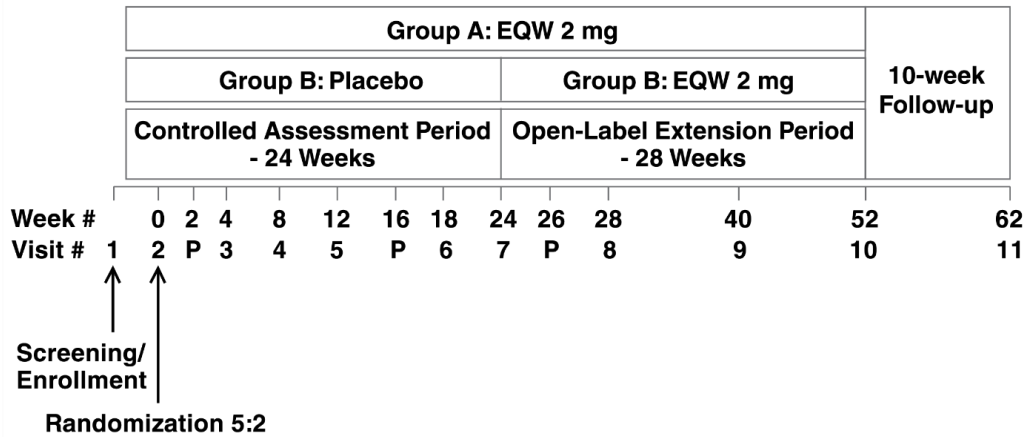
- Screening period (5 weeks)
- Controlled assessment period (24 weeks): double-blind, placebo-controlled period to examine the efficacy and safety of EQW compared with placebo

- Extension period (28 weeks): open-label, uncontrolled period to examine the long-term safety and efficacy of EQW
- Post-treatment follow-up period (10 weeks)

For the controlled assessment period, patients were randomly assigned in a 5:2 ratio to receive either EQW 2 mg (Group A) or placebo (Group B). During the extension period (Week 25 through Week 52), patients assigned to the EQW 2 mg treatment (Group A) continued to be treated with EQW 2 mg, and patients randomized to placebo (Group B) received EQW 2 mg. In addition to receiving study medications, all patients were to participate in a lifestyle intervention program encompassing diet and physical activity modifications.

In addition, an exploratory mixed meal substudy was performed to evaluate the effect of EQW on postprandial beta-cell function after approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of study medication.

Figure 9: Flow Chart of Study Design



All visits scheduled during the controlled assessment period and during the open-label extension period were to occur within ±2 days of the scheduled date, relative to Visit 2 (Week 0).

Visit 11 was to take place at least 10 weeks and no later than 12 weeks after the last dose of EQW.

The investigator and/or qualified study-site personnel was to contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review adverse events.

EQW, exenatide 2 mg once weekly; P, phone call.

Study participants

The patient population included male and females 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 SU) and/or insulin for at least 2 months prior to screening.

The study included patients with an HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at screening, and patients with a C-peptide of > 0.6 ng/mL at screening.

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

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.

The 2 mg weekly dose of BYDUREON used in Study BCB114 was selected based on information from studies with exenatide conducted in adolescents (see Study 2993-124) and with EQW conducted in adults (see Malloy et al 2009). Study BCB114 included patients treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agent (metformin and/or SU) and/or insulin; thus, placebo was an appropriate choice of comparator for Study BCB114.

Rescue Treatment

Patients with a loss of glycaemic 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.

Objectives

The primary efficacy objective of the study was to assess the effect on glycaemic 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.

Outcomes/endpoints

Primary endpoints

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

Secondary endpoints

- 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 glycaemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable

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.

Randomisation

Patients who met all study requirements based on the study inclusion and exclusion criteria were randomized via an interactive voice response system/interactive web response system; patients were assigned to 1 of 2 treatment groups in 5:2 ratio (Group A: Group B, see Figure 9) at Visit 2 (Week 0). Randomization was stratified by screening HbA1c (< 9.0% or ≥ 9.0%) and country.

Blinding

The MAH, the study-site personnel, and patients were blinded to treatment allocation during the double-blind controlled assessment period. Every effort was made to ensure that patients remained blinded to treatment during this period.

Statistical methods

Analysis Populations

The Randomized Analysis Set consisted of all randomized patients.

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

The Evaluable Analysis Set consisted of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and postbaseline HbA1c assessment. Evaluable patients were to be analysed in accordance with their planned treatment group.

The Safety Analysis Set consisted of all patients who received at least 1 dose of study medication. If a patient randomized to the placebo group received at least 1 dose of EQW during the controlled assessment period, their actual group was to be derived as EQW.

Prespecified analyses of the primary efficacy variable were conducted using the Evaluable Analysis Set and analyses of the secondary efficacy variables were to be performed for the ITT Analysis Set, unless otherwise specified. The Evaluable Analysis Set and ITT Analysis Set were identical for this study.

Analysis Methods

In general, prespecified primary and secondary continuous efficacy variables for which multiple postbaseline measurements were collected were to be analysed using an MMRM approach. The statistical analysis of categorical variables was to be conducted using a stratified Cochran-Mantel-Haenszel test. Where applicable, the Early Termination visit were to be included in the analyses.

Primary Analysis

The prespecified primary efficacy analysis compared treatment groups (EQW versus placebo) with respect to change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24) using the MMRM approach. The model included 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. The least squares (LS) mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 7 (Week 24) were provided, as well as the LS mean for each treatment group at Week 24, the SE, and the corresponding 95% CI. The mean (SD) observed HbA1c at baseline and Week 24 was also presented by treatment group.

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

Estimand framework for the primary variable

Variable: Change in HbA1c from baseline to Week 24

Population: Evaluable Analysis Set

Population-level summary: Least squares mean difference in CFBL at W24 between EQW and PBO

Estimand	**Intercurrent event strategy**
Primary	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach due to missing at random (MAR) assumption of MMRM analysis. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.
Sensitivity to primary	All IEs: Data after event excluded. Hypothetical approach using multiple imputation (MI) pattern mixture model imputation.
Supplementary to primary	Rescue and IP discontinuation: Data after event included. Treatment policy approach. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.
Sensitivity to supplementary of primary	Rescue and IP discontinuation: Data after event included. Treatment policy approach.

	Withdrawal from study prior to Week 24: Hypothetical approach using MI pattern mixture model imputation.

Descriptive subgroup analysis was performed for the primary variable.

Sensitivity Analyses of the Primary Endpoint

Several sensitivity analyses were prespecified including an imputation sensitivity analysis using the treatment policy estimand that tested the assumption of MAR made by the MMRM analysis (see table above). For this purpose, a multiple imputation (MI) pattern mixture model that assumed MNAR was implemented whereby assumptions for the missing data were to "stress test" the MAR assumptions of the primary analysis (see Molenberghs and Kenward 2007a, Molenberghs and Kenward 2007b). The proposed MNAR sensitivity analysis assumes that the trajectory after the intercurrent event from the EQW group, regardless of the type of event, can be modelled by that of PBO patients. This assumption tends to result in smaller estimates of difference between the treatment groups, compared to those under the MAR assumption. The patterns here are defined by the time of the intercurrent event, with the imputed values for both treatment groups modelled by observed outcomes from the placebo group only. Note that in this analysis, PBO missing/excluded observations are imputed assuming MAR and here follows the pattern of observed PBO observations, while missing/excluded observations for the EQW group are assumed MNAR. This strategy for imputation is commonly referred to as the copy-reference approach.

Analysis of secondary variables

Similar to the primary analysis, data including the Early Termination visit where applicable were included in the MMRM and CMH analysis for secondary analysis variables. For patients who initiated rescue medication and continued study participation, data collected after the initiation of rescue medication were excluded from analyses. Data collected after discontinuation of IP were excluded from analyses for all secondary efficacy endpoints.

Handling of missing data

Missing data in this study may result from patients discontinuing from the study prematurely or missing intermediate visits or selected assessments while remaining on study. Data collected after the first administration of rescue therapy were excluded from the descriptive statistical summary and inferential statistical analyses for all efficacy endpoints, except the plasma exenatide concentration endpoint. For efficacy analyses, in general, missing observations were not imputed, except those inherited from the mixed model repeated measures (MMRM) which implicitly assumes that data are missing at random (MAR). However, data collected after initiation of rescue medication were included in several sensitivity and supportive analyses for the primary analysis to provide a comprehensive view of the treatment effect.

The pre- and post-withdrawal values were to be assessed to understand the impact of dropouts on the efficacy results. The primary efficacy endpoint of HbA1c data were visually examined to explore the missingness patterns by:

(1) plotting each individual patient's HbA1c change trajectory in completers side-by-side with those who have prematurely discontinued study medication, and by
(2) plotting the last HbA1c change from baseline for those who discontinue study medication prematurely, overlaid with the box plot of change from baseline in HbA1c by visit for completers.

For categorical endpoints HbA1c goals of <6.5%, ≤6.5% and < 7% at 24 weeks, any patient with missing HbA1c value at 24 weeks was considered as non-responder. The same applied for these variables at 52 weeks endpoint. Demographic and baseline characteristics, as well as safety data were analysed based on the observed data only. Data beyond discontinuation of study medication were not included in the analyses.

Hierarchical Testing Strategy

A fixed-sequence procedure hierarchical testing strategy was followed to protect the family-wise error rate for the primary endpoint and secondary endpoints: if superiority for the primary endpoint was established at the 2-sided significance level $\alpha = 0.05$, the same superiority test was to be performed for selected secondary endpoints in the following, prespecified order:

1. Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
2. Change in FPG concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
3. Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
4. Change in fasting insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24)

If the null hypothesis was not rejected for any of the first 4 tests in the hierarchy, a nominal p-value was presented for the remaining endpoints but was to be considered exploratory.

For all other secondary and exploratory endpoints, p-values were to be presented but these were to be considered exploratory in nature with no multiplicity adjustment applied. A nominal level of $\alpha = 0.05$ was to be reported.

Database lock and changes in the analyses

The initial database lock for Study BCB114 occurred on 11 June 2020; however, during the subsequent quality check of ADA data for patients randomized to the EQW group, some errors were noted. The final database lock with the corrected data occurred on 06 August 2020, and the correct ADA data for patients randomized to the EQW group are provided in the BCB114 CSR.

Additionally, it was noted that results for PK and ADA samples collected for patients randomized to the placebo group had not been included in the data transfer. The PK and ADA results for patients randomized to placebo have not been included in this submission and will be summarized in an addendum to the BCB114 CSR.

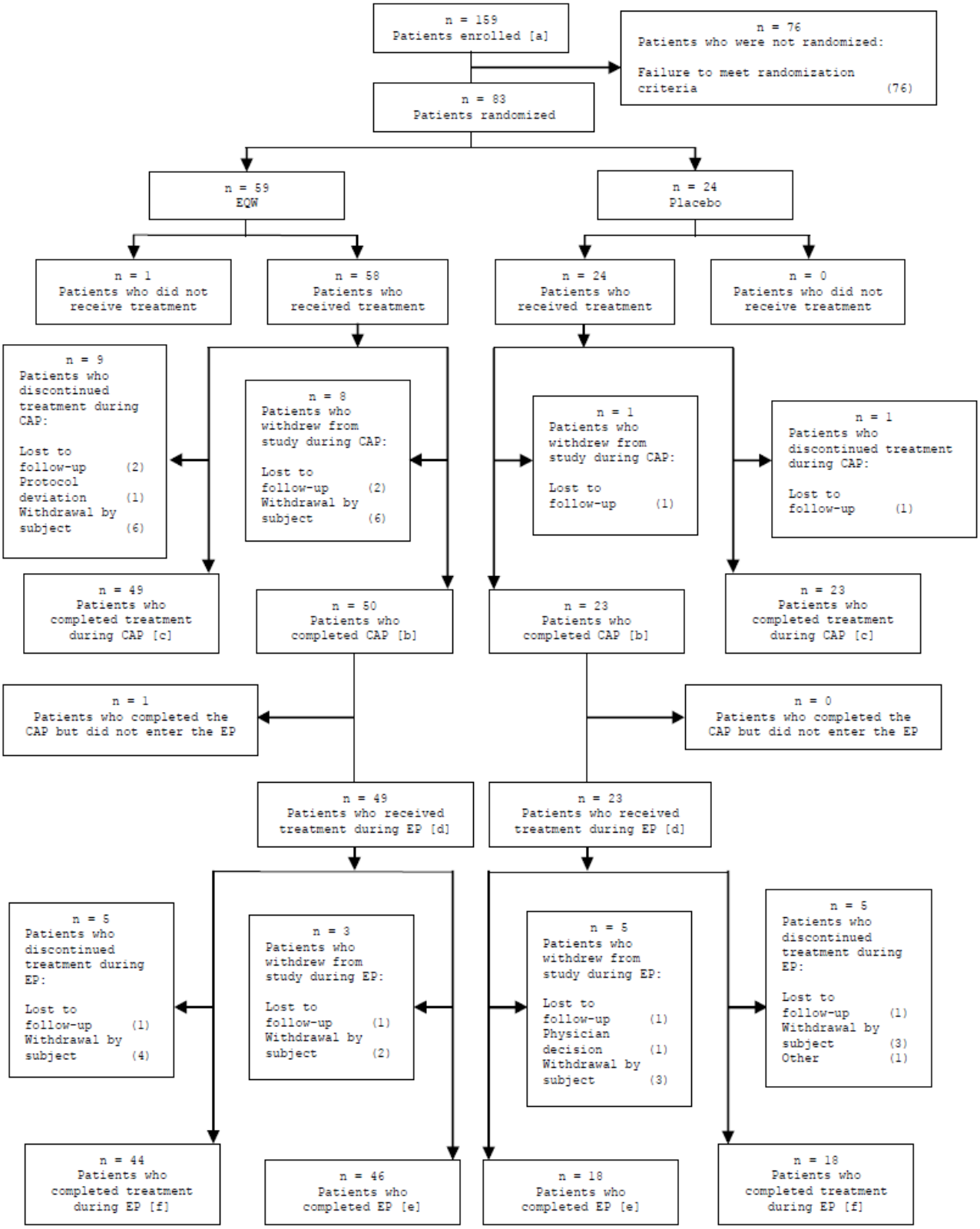
The coronavirus disease 2019 (COVID-19) epidemic is not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

The Statistical Analysis Plan (SAP) was finalised on 21 May 2020 and included several minor changes from the protocol specified analysis.

Results

Participant flow

Figure 10: 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.

CAP controlled assessment period; EQW exenatide 2 mg once weekly; EP extension period; n number of patients.

The disposition of the patients in this study is summarized in Figure 10. A total of 83 patients were randomized (EQW, 59; placebo, 24) and 82 received study treatment during the 24-week controlled assessment period (EQW, 58; placebo, 24). A total of 73 patients (88.0%) (EQW, 50 [84.7%]; placebo, 23 [95.8%]) completed the 24-week controlled assessment period, and 72 patients (86.7%) (EQW, 49 [83.1%]; placebo, 23 [95.8%]) completed treatment during the controlled assessment period. Discontinuation of study treatment was primarily due to withdrawal by patient (EQW, 6/8 patients; placebo, 0/1 patients); no patients discontinued due to AEs.

All patients received EQW during the uncontrolled extension period from Week 24 to Week 52. A total of 72 patients (86.7%) received EQW during the uncontrolled extension period (EQW, 49; placebo, 23). A total of 64 patients (77.1%) (EQW, 46; placebo, 18) completed the uncontrolled extension period, and 62 patients (74.7%) (EQW, 44; placebo, 18) completed EQW treatment during the uncontrolled extension period. Discontinuation of study treatment during the extension period was primarily due to withdrawal by patient (EQW, 4/5 patients; placebo, 3/5 patients); no patients discontinued due to AEs.

Recruitment

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

First subject enrolled: 12 May 2016

Last subject last visit: 06 May 2020

Conduct of the study

Protocol Deviations

The number of patients with important protocol deviations in each treatment group are summarized in Table 6. Important protocol deviations were defined as those that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

The proportion of patients with at least one important protocol deviation was generally balanced between the EQW group and the placebo group (59.3% and 50.0%, respectively). The important protocol deviations recorded during the study were similar between the treatment groups, with the exception of deviations due to patients who did not adhere to the protocol-specified visit schedule, which were reported for a greater proportion of patients in the EQW group than the placebo group (22.0% and 8.3%, respectively).

Table 6: Important Protocol Deviations (Randomized Analysis Set)

	Number (%) of patients		
Important protocol deviations	**EQW (N = 59)**	**Placebo (N = 24)**	**Total (N = 83)**
Total number of important protocol deviations[a]	73	21	94
Number of patients with at least 1 important protocol deviation[a]	35 (59.3)	12 (50.0)	47 (56.6)
Patients who do not meet the inclusion criteria and/or who meet one or more of the exclusion criteria (eligibility and entry criteria) but enter the study and are potentially randomized and treated.	4 (6.8)	0	4 (4.8)
Patients who receive the incorrect randomized study medication at any time during the 24-week double-blind treatment period	0	1 (4.2)	1 (1.2)
Patients who are not compliant with study medication administration requirements (dose, frequency and minimum exposure etc)	9 (15.3)	4 (16.7)	13 (15.7)
Patients taking concomitant medications not complying with the rule specified in IPD number 5 in the PD plan	12 (20.3)	5 (20.8)	17 (20.5)
Patients who do not comply with the protocol-specified assessments criteria (efficacy + safety)	6 (10.2)	2 (8.3)	8 (9.6)
Patients who do not adhere to the protocol-specified visit schedule	13 (22.0)	2 (8.3)	15 (18.1)
Emergency unblinding during the 24-week double-blind treatment period.	1 (1.7)	0	1 (1.2)
Noncompliance with the protocol-specified rescue therapy strategy	1 (1.7)	1 (4.2)	2 (2.4)
Storage temperature excursion of randomized study medication	1 (1.7)	0	1 (1.2)
Patients enrolled into the Mixed-Meal Substudy who do not adhere to the substudy protocol-specified timing schedule for blood collection	2 (3.4)	0	2 (2.4)
Patients enrolled into the Mixed-Meal Substudy taking restricted concomitant medications	1 (1.7)	0	1 (1.2)

[a] The same patient may have had more than 1 important protocol deviation.

Important protocol deviations were defined as those that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Percentages were calculated from the number of patients in the analysis set by treatment group and total.

EQW, exenatide 2 mg once weekly; IPD, important protocol deviation; PD, protocol deviation.

Baseline data

The demographic, patient and baseline disease characteristics were generally representative of the intended adolescent population with T2DM. The demographic characteristics of study patients are summarized in Table 7.

Table 7:Demographic Characteristics (Intent-to-treat Analysis Set)

	EQW	Placebo	Total
Demographic characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
Age (years)[a]			
n	58	24	82
Mean	14.9	15.6	15.1
SD	1.88	1.66	1.84
Median	15.0	16.0	16.0
Min	11	12	11
Max	17	17	17
Age group - 1 (years)[a] n %			
< 10	0	0	0
≥ 10 to ≤ 17	58 (100.0)	24 (100.0)	82 (100.0)
> 17	0	0	0
Total	58 (100.0)	24 (100.0)	82 (100.0)
Age group - 2 (years)[a] n %			
< 10	0	0	0
≥ 10 to ≤ 12	8 (13.8)	3 (12.5)	11 (13.4)
≥ 13 to ≤ 16	36 (62.1)	12 (50.0)	48 (58.5)
> 16	14 (24.1)	9 (37.5)	23 (28.0)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Sex n (%)			
Male	27 (46.6)	7 (29.2)	34 (41.5)
Female	31 (53.4)	17 (70.8)	48 (58.5)
Total	58 (100.0)	24 (100.0)	82 (100.0)
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)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	4 (6.9)	1 (4.2)	5 (6.1)
Other	12 (20.7)	2 (8.3)	14 (17.1)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Ethnic Group n %			
Hispanic or Latino	25 (46.3)	8 (38.1)	33 (44.0)
Not Hispanic or Latino	29 (53.7)	13 (61.9)	42 (56.0)
Total	54 (100.0)	21 (100.0)	75 (100.0)
Missing	4	3	7
Region n %			

	EQW	Placebo	Total
Demographic characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
Europe	8 (13.8)	4 (16.7)	12 (14.6)
Middle East	2 (3.4)	1 (4.2)	3 (3.7)
North America	35 (60.3)	17 (70.8)	52 (63.4)
South America	13 (22.4)	2 (8.3)	15 (18.3)
Total	58 (100.0)	24 (100.0)	82 (100.0)

[a] Age as collected on the demographics eCRF at study entry.

Percentages were calculated from the number of patients in the analysis set with nonmissing data, by treatment group and total.

eCRF, electronic case report form; EQW, exenatide 2 mg once weekly; Max, maximum; Min, minimum; N, number of patients in treatment group; n, number of patients included in analysis; SD, standard deviation.

The patient characteristics of study patients were generally balanced between the EQW and placebo groups (Table 8), with the exception of the weight population percentile, which indicated a somewhat larger proportion of severely obese patients in the EQW group than in the placebo group.

Table 8: Patient Characteristics (Intent-to-treat Analysis Set)

	EQW	Placebo	Total
Patient characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
Baseline height (cm)			
n	58	24	82
Mean	165.74	165.32	165.62
SD	9.610	8.748	9.314
Median	164.75	166.25	165.50
Min	140.0	142.6	140.0
Max	185.3	176.7	185.3
Height population percentile n %			
< 3	0	1 (4.2)	1 (1.2)
≥ 3 to < 85	43 (74.1)	19 (79.2)	62 (75.6)
≥ 85 to < 97	11 (19.0)	2 (8.3)	13 (15.9)
≥ 97	4 (6.9)	2 (8.3)	6 (7.3)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Baseline weight (kg)			
n	58	24	82
Mean	102.18	96.70	100.57
SD	30.108	22.684	28.112
Median	100.30	93.60	95.85
Min	47.0	61.7	47.0
Max	201.4	152.4	201.4
Weight population percentile n %			

	EQW	Placebo	Total
Patient characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
< 3	1 (1.7)	0	1 (1.2)
≥ 3 to < 85	4 (6.9)	1 (4.2)	5 (6.1)
≥ 85 to < 97	11 (19.0)	10 (41.7)	21 (25.6)
≥ 97	42 (72.4)	13 (54.2)	55 (67.1)
Total	58 (100.0)	24 (100.0)	82 (100.0)
Baseline BMI (kg/m^2)			
n	58	24	82
Mean	36.86	35.14	36.36
SD	9.278	6.575	8.572
Median	36.72	33.19	35.40
Min	18.5	25.4	18.5
Max	71.2	50.3	71.2
BMI population percentile n %			
< 3	0	0	0
≥ 3 to < 85	4 (6.9)	0	4 (4.9)
≥ 85 to < 97	9 (15.5)	7 (29.2)	16 (19.5)
≥ 97	45 (77.6)	17 (70.8)	62 (75.6)
Total	58 (100.0)	24 (100.0)	82 (100.0)

Baseline weight, height, and BMI are displayed. BMI = weight (in kilograms)/(height [in $meters^2$]).

Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Percentiles were determined based on the standardized growth chart for boys and girls developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (see CDC 2000).

Percentages were calculated from the number of patients in the analysis set with nonmissing data, by treatment group and total.

BMI, body mass index; EQW, exenatide 2 mg once weekly; Max, maximum; Min, minimum; N, number of patients in treatment group; n, number of patients included in analysis; SD, standard deviation.

A lower proportion of patients in the EQW group were in the ≥ 85 to < 97 percentile for weight compared with the placebo group (19.0% and 41.7%, respectively), while a greater proportion of patients in the EQW were in the ≥ 97 percentile for weight compared with the placebo group (72.4% and 54.2%, respectively).

The mean height of patients at baseline was 165.6 cm (EQW, 165.7 cm; placebo, 165.3 cm) and the mean weight was 100.6 kg (EQW, 102.2 kg; placebo, 96.7 kg). The mean BMI was 36.4 kg/m^2 (EQW, 36.9 kg/m^2; placebo, 35.1 kg/m^2), and, as expected for this study population, the majority of patients (75.6%) were in the ≥ 97 percentile for BMI (EQW, 77.6%; placebo, 70.8%).

Baseline disease characteristics were generally balanced between the EQW and placebo groups (Table 9).

Table 9: 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
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 (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

	EQW	Placebo	Total
Disease characteristic	**(N = 58)**	**(N = 24)**	**(N = 82)**
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)
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. Antidiabetic medication was identified based on medical review of concomitant medications recorded during the study using the WHO-Drug Enhanced plus Herbal 01 Mar 2020 version.

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.

In general, medical and surgical history were generally balanced between the treatment groups, with the exception of obesity which was reported in a greater proportion of patients in the EQW group (32.2%) compared with the placebo group (13.0%). Overall, the most common medical history terms were obesity (26.8%), hypertension (14.6%), and asthma (13.4%). The most common surgical history terms were appendicectomy (4.9%), tonsillectomy (4.9%), esophagogastroduodenoscopy (2.4%), and adenotonsillectomy (2.4%). All other surgical history terms were reported in one patient only.

Pre-treatment medication use was low (20.7% of patients overall) and broadly similar between the EQW and placebo groups. Prior concomitant medication use was broadly similar between the treatment groups and across the treatment periods. Prior concomitant medications were reported in the majority of patients

who entered the controlled assessment period (95.1%), while prior concomitant medications were reported in fewer patients who entered the open-label extension period (37.5%).

For patients entering the controlled assessment period, the most frequently used prior concomitant medications were biguanides (79.3%), long-acting insulins and analogues for injection (37.8%), and fast acting insulins and analogues for injection (28.0%). For patients entering the open-label extension period, the most common prior concomitant medications were fast acting insulins and analogues for injection (9.7%), long-acting insulins and analogues for injection (8.3%), and biguanides (6.9%).

Post-treatment medication use was reported in a low proportion of patients overall (25.6%) and was broadly similar between the EQW and placebo → EQW groups.

Overall, rescue medication use was generally low during the study. One patient in the EQW group (1.7%) reported using both insulin aspart and insulin degludec in the controlled assessment period.

During the open-label extension period, 7 patients (9.7%), including 5 (10.2%) in the EQW group and 2 (8.7%) in the placebo → EQW group, reported use of rescue medication. The 4 reported rescue medications by generic term were insulin glargine, reported in 6.9% of patients (6.1% and 8.7% in the EQW and placebo groups, respectively), insulin lispro, reported in 2.8% of patients (2.0% and 4.3% in the EQW and placebo groups, respectively), and insulin aspart and metformin, both reported in 1.4% of patients (2.0% and 0, in the EQW and placebo groups, respectively).

Study Treatment Compliance

Compliance was generally high and similar between treatment groups in both the 24-week controlled assessment period and 52-week treatment period (defined as the controlled assessment period and open-label extension period combined). During the controlled assessment period, the majority of patients (95.1%) used 80% to < 120% of dispensed study medication: 57 patients (96.6%) in the EQW group and 21 patients (91.3%) in the placebo group. During the treatment period (defined as the controlled assessment period and open-label extension period combined), the majority of patients (95.8%) used 80% to < 120% of dispensed study medication: 49 patients (98.0%) in the EQW group and 20 patients (90.9%) in the placebo group.

Numbers analysed

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 (i.e., 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 post-dose 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.

Outcomes and estimation

Results for the primary and secondary efficacy endpoints in the fixed-sequence procedure hierarchical testing strategy are summarized in the table below (Table 10)

Table 10: Summary of Primary and Secondary Efficacy Endpoint Results in the Fixed-sequence Procedure Hierarchical Testing Strategy

Parameter	EQW	Placebo
Statistic	(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 (mmol/L) (Intent-to-treat Analysis Set)[a,c]		
LS mean (SE) adjusted change from baseline to Week 24	-0.29 (0.424)	0.91 (0.628)
LS mean (SE) difference	-1.20 (0.760)	
95% 2-sided confidence interval for LS mean difference	(-2.72, 0.32)	
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	
Change from Baseline to Week 24 in Fasting Serum Insulin (mIU/L) (Intent-to-treat Analysis Set)[a,e]		
LS mean (SE) adjusted change from baseline to Week 24	11.46 (7.527)	-2.21 (11.302)
LS mean (SE) difference	13.67 (13.716)	
95% 2-sided confidence interval for LS mean difference	(-13.77, 41.11)	
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.

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.

Primary Endpoint:

EQW was superior to placebo in reducing HbA1c over 24 weeks. Estimates from the MMRM analysis from baseline to Week 24 are presented for the Evaluable Analysis Set in Table 11. The LS mean change in HbA1c was -0.36% for the EQW group and 0.49% for the placebo group. The difference in LS mean change between the EQW and placebo groups was -0.85% (p = 0.012).

Table 11: Change in HbA1c (%) from Baseline to Week 24, MMRM Analysis Excluding Measurements After Initiation of Rescue Therapy or Discontinuation of Study Medication (Controlled Assessment Period) (Evaluable Analysis Set)

Measurement: HbA1c	**EQW**	**Placebo**
Unit: %	**(N = 58)**	**(N = 24)**
Observed summary statistics[a]		
n	56	24
Baseline mean (SD)	8.10 (1.201)	8.28 (1.508)
Summary statistics[b]		
n1	48	22
Baseline mean (SD)	8.11 (1.269)	8.22 (1.504)
Week 24 mean (SD)	7.69 (1.511)	8.75 (1.990)
Adjusted change from baseline to Week 24[c]		
LS mean (SE)	-0.36 (0.184)	0.49 (0.273)
95% 2-sided confidence interval	(-0.73, 0.00)	(-0.06, 1.03)
Difference (EQW versus Placebo) at Week 24[c]		
LS mean (SE)	-0.85 (0.330)	
95% 2-sided confidence interval	(-1.51, -0.19)	
2-sided p-value	0.012	

[a] Patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates.

[b] Calculated from observed data for patients with baseline and a Week 24 value.

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

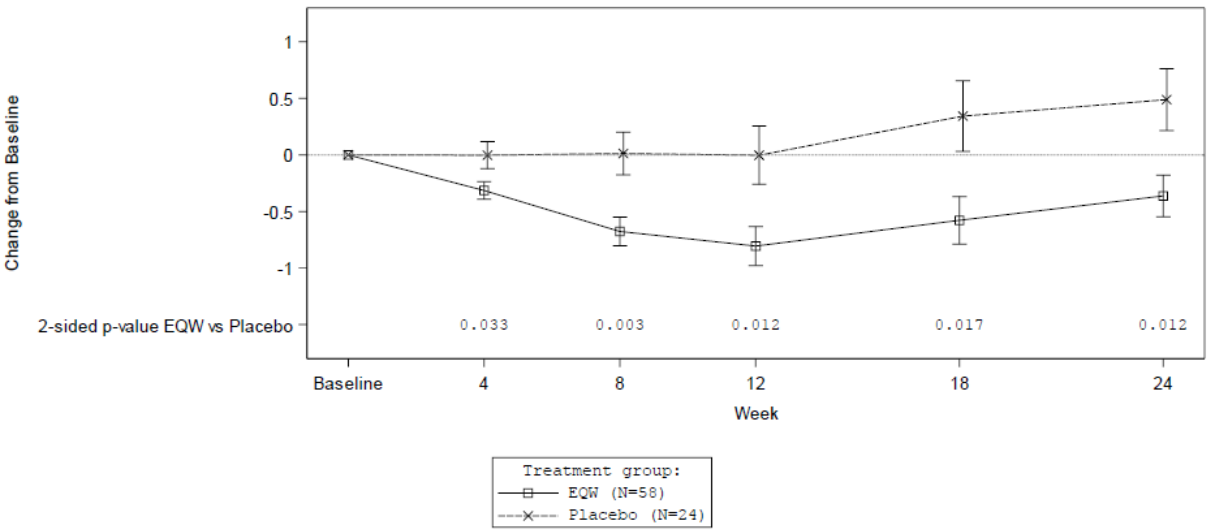
Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.

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 Evaluable Analysis Set within the treatment group; n, number of patients with a baseline assessment, at least one post-baseline assessment, and no missing covariates; n1, number of patients with observed baseline and Week 24 values; SD, standard deviation; SE, standard error.

Estimates from the MMRM analysis of the change in HbA1c over time from baseline to Week 24 and are presented graphically in Figure 11. For the EQW group, mean HbA1c decreased from baseline through Week 12 of the study, and then began to gradually increase through Week 24 (but remained below the baseline level). In the placebo group, mean HbA1c remained stable from baseline through Week 12, and then began to gradually increase through Week 24. The difference between groups was maintained over 24 weeks

Figure 11: Change in HbA1c (%) from Baseline to each Visit between Baseline and Week 24, MMRM Analysis, LS Mean (SE) (Evaluable Analysis Set)



Sensitivity analyses

The following sensitivity analyses were performed to support the primary analyses:

The MMRM analysis of the primary efficacy endpoint was repeated including measurements after initiation of rescue therapy and discontinuation of study medication. Results were consistent with the primary analysis: the LS mean change in HbA1c was -0.37% for the EQW group and 0.49% for the placebo group. The difference in LS mean change between the EQW and placebo groups was -0.86% (p = 0.009).

An imputation sensitivity analysis to test the assumption of MAR that was made by the MMRM analysis was performed. A MI pattern mixture model imputation that assumed MNAR was implemented whereby assumptions for the missing data were to "stress test" the MAR assumptions of the primary analysis. Results were consistent with the primary analysis: the LS mean change in HbA1c was -0.34% for the EQW group and 0.46% for the placebo group. The difference in LS mean change between the EQW and placebo groups was -0.80% (p = 0.021).

The MI pattern mixture model imputation that assumed MNAR was repeated including measurements after initiation of rescue therapy and discontinuation of study medication. Results were consistent with the primary analysis: the LS mean change in HbA1c was -0.36% for the EQW group and 0.46% for the placebo group. The difference in LS mean change between the EQW and placebo groups was -0.81% (p = 0.014).

Secondary Endpoints:

Change in Fasting Plasma Glucose Concentration from Baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to each Intermediate Visit as Applicable

EQW treatment resulted in a numerical decrease from baseline at Week 24 in FPG (nominal p = 0.119) compared to an increase with placebo; however, the difference between groups was not statistically significant. Estimates from the MMRM analysis from baseline to Week 24 are presented for the ITT Analysis Set in Table 12.

The LS mean change in FPG was -5.2 mg/dL (-0.29 mmol/L) for the EQW group and 16.5 mg/dL (0.91 mmol/L) for the placebo group. The difference in LS mean change between the EQW and placebo groups was -21.6 mg/dL (-1.20 mmol/L) (p = 0.119).

There was no statistically significant difference in the FPG change from baseline to Week 24 between the EQW and placebo groups. Therefore, sequential testing to control for multiplicity stopped. All further analyses could not be considered statistically significant after controlling for multiplicity.

Table 12: Change in FPG (mmol/L) from Baseline to Week 24, MMRM Analysis (Intent-to-treat Analysis Set)

Measurement: FPG **Unit: mmol/L**	**EQW** **(N = 58)**	**Placebo** **(N = 24)**
Observed summary statistics[a]		
n	56	24
Baseline mean (SD)	9.17 (3.327)	9.46 (3.349)
Summary statistics[b]		
n1	48	22
Baseline mean (SD)	9.24 (3.416)	9.08 (3.093)
Week 24 mean (SD)	8.87 (3.528)	10.17 (3.702)
Adjusted change from baseline to Week 24[c]		
LS mean (SE)	-0.29 (0.424)	0.91 (0.628)
95% 2-sided confidence interval	(-1.13, 0.56)	(-0.34, 2.17)
Difference (EQW versus Placebo) at Week 24[c]		
LS mean (SE)	-1.20 (0.760)	
95% 2-sided confidence interval	(-2.72, 0.32)	
2-sided p-value	0.119	

[a] Patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates.

[b] Calculated from observed data for patients with baseline and the specific visit value.

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

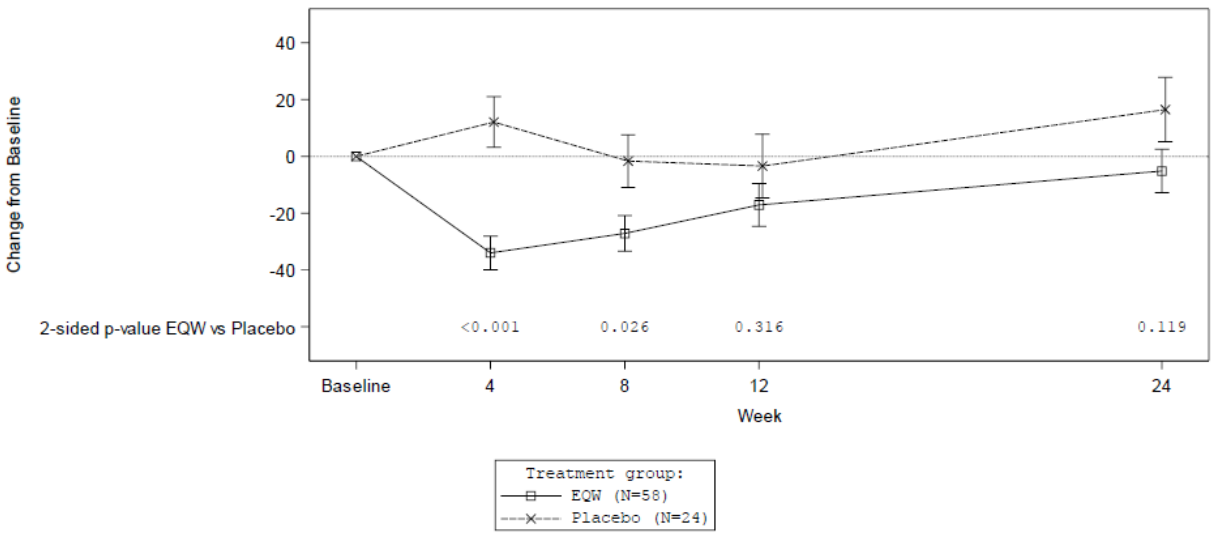
Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.

EQW, exenatide 2 mg once weekly; FPG, fasting plasma glucose; LS, least squares; MMRM, mixed model with repeated measures; N, number of patients in the Intent-to-treat Analysis Set within the treatment group; n, number of patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates; n1, number of patients with observed baseline and Week 24 values; SD, standard deviation; SE, standard error.

Estimates from the MMRM analysis of the change in FPG from baseline to each visit between baseline and Week 24 are presented graphically in Figure 12 (Conventional [US units]). There were numerically greater reductions in FPG at all visits between baseline and Week 24 in the EQW group compared with the placebo group. For the EQW group, mean FPG decreased from baseline through Week 4 of the study, and then began to increase through Week 24. In the placebo group, mean FPG fluctuated from baseline through Week 12, and then began to increase through Week 24. The observed separation between the EQW and placebo groups remained stable from Week 12 through Week 24.

Figure 12: Change in FPG (mg/dL) from Baseline to each Visit between Baseline and Week 24, MMRM Analysis, LS Mean (SE) (Intent-to-treat Analysis Set)



Change in Body Weight from Baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to each Intermediate Visit as Applicable

EQW treatment resulted in a numerical decrease from baseline at Week 24 in body weight, compared to an increase with placebo. Estimates from the MMRM analysis from baseline to Week 24 are presented for the ITT Analysis Set in Table 13; the change in body weight over time is presented graphically in Figure 13. Change in body weight from baseline was the third endpoint in the testing hierarchy (below FPG) and was therefore not formally tested for statistical significance.

The LS mean change in body weight was -0.59 kg for the EQW group and 0.63 kg for the placebo group. The difference in LS mean change between the EQW and placebo groups was -1.22 kg (nominal p = 0.307).

Table 13: Change in Body Weight (kg) from Baseline to Week 24, MMRM Analysis (Intent-to-treat Analysis Set)

Measurement: Body weight **Unit: kg**	**EQW** **(N = 58)**	**Placebo** **(N = 24)**
Observed summary statistics[a]		
n	56	24
Baseline mean (SD)	101.68 (30.508)	96.70 (22.684)
Summary statistics[b]		
n1	48	23
Baseline mean (SD)	100.33 (30.442)	96.96 (23.158)
Week 24 mean (SD)	99.80 (30.367)	97.73 (23.449)
Adjusted change from baseline to Week 24[c]		
LS mean (SE)	-0.59 (0.665)	0.63 (0.982)
95% 2-sided confidence interval	(-1.92, 0.73)	(-1.33, 2.59)
Difference (EQW versus Placebo) at Week 24[c]		
LS mean (SE)	-1.22 (1.189)	
95% 2-sided confidence interval	(-3.59, 1.15)	
2-sided p-value	0.307	

[a] Patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates.

[b] Calculated from observed data for patients with baseline and the specific visit value.

[c] Adjusted LS mean and treatment group difference in the change from baseline values at each visit were 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.

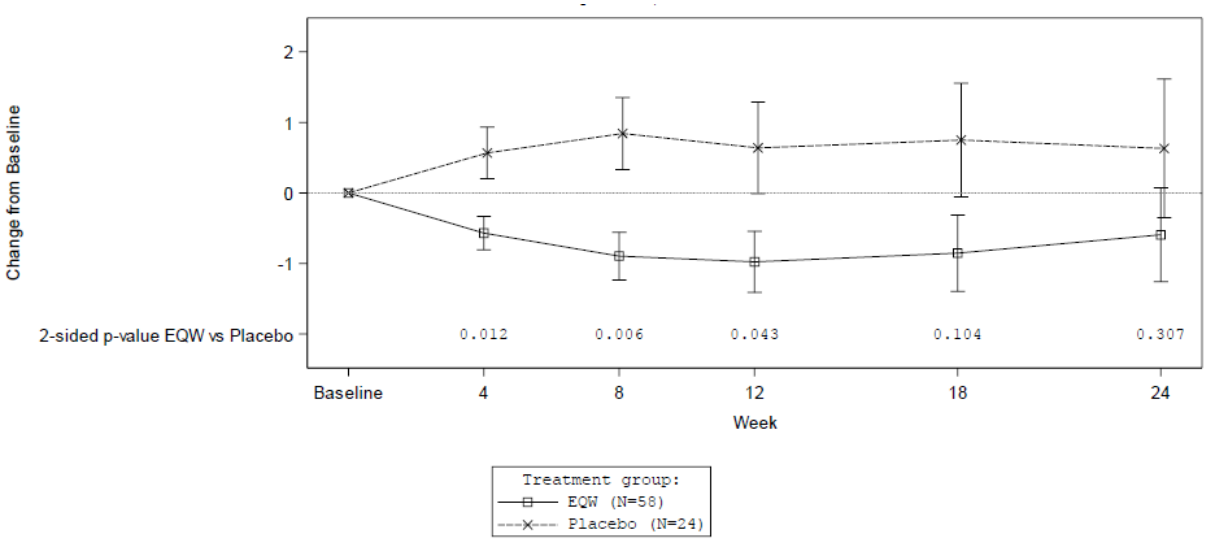
Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.

EQW, exenatide 2 mg once weekly; LS, least squares; MMRM, mixed model with repeated measures; N, number of patients in the Intent-to-treat Analysis Set within the treatment group; n, number of patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates; n1, number of patients with observed baseline and Week 24 values; SD, standard deviation; SE, standard error.

Estimates from the MMRM analysis of the change in body weight from baseline to each visit between baseline and Week 24 for the ITT Analysis Set are presented graphically in Figure 13. There were numerically greater reductions in body weight at all visits between baseline and Week 24 in the EQW group compared with the placebo group. In the EQW group, mean body weight decreased from baseline through Week 12 of the study, and then began to gradually increase slightly through Week 24. In the placebo group, mean body weight increased from baseline through Week 8, and then remained relatively stable until Week 24.

Figure 13: Change in Body Weight (kg) from Baseline to each Visit between Baseline and Week 24, MMRM analysis, LS Mean (SE) (Intent-to-treat Analysis Set)



Change in Fasting Insulin from Baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to each Intermediate Visit as Applicable

There were no meaningful differences between treatments in change from baseline at Week 24 in fasting insulin. Estimates from the MMRM analysis from baseline to Week 24 are presented for the ITT Analysis Set in Table 14(SI units). Change in fasting insulin from baseline was the fourth endpoint in the testing hierarchy and was therefore not formally tested for statistical significance.

The LS mean change in fasting insulin was 79.6 pmol/L for the EQW group and -15.3 pmol/L for the placebo group. The difference in LS mean change between the EQW and placebo groups was 94.9 pmol/L (nominal p = 0.323).

Table 14: Change in Fasting Insulin (mIU/L) from Baseline to each Visit between Baseline and Week 24, MMRM Analysis (Intent-to-treat Analysis Set)

Measurement: Fasting insulin **Unit: pmol/L**	**EQW** **(N = 58)**	**Placebo** **(N = 24)**
Observed summary statistics[a]		
n	56	24
Baseline mean (SD)	56.79 (51.871)	34.87 (19.393)
Summary statistics[b]		
n1	48	22
Baseline mean (SD)	52.19 (50.400)	35.20 (20.182)
Week 24 mean (SD)	55.65 (60.658)	40.56 (37.078)
Adjusted change from baseline to Week 24[c]		
LS mean (SE)	11.46 (7.527)	-2.21 (11.302)
95% 2-sided confidence interval	(-3.60, 26.52)	(-24.82, 20.41)
Difference (EQW versus Placebo) at Week 24[c]		
LS mean (SE)	13.67 (13.716)	
95% 2-sided confidence interval	(-13.77, 41.11)	

Measurement: Fasting insulin Unit: pmol/L	EQW (N = 58)	Placebo (N = 24)
2-sided p-value	0.323	

[d] Patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates.

[e] Calculated from observed data for patients with baseline and the specific visit value.

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

Baseline was defined as the last non-missing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.

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; n, number of patients with a baseline assessment, at least 1 postbaseline assessment and no missing covariates; n1, number of patients with observed baseline and Week 24 values; SE, standard error.

Proportions of Patients Achieving HbA1c Goals at Visit 7 (Week 24), and at each Intermediate Visit as Applicable

Proportion of patients achieving HbA1c goals was not included in the testing hierarchy. Numerically greater proportions of patients in the EQW group, compared with placebo, achieved HbA1c goals of < 6.5%, ≤ 6.5%, and < 7% at Week 24.

The proportion of patients achieving HbA1c < 6.5%, ≤ 6.5%, and < 7.0% at Week 24 is summarized and compared by treatment group using a CMH test with missing data treated as non-responder for the Evaluable Analysis Set in Table 15.

The proportion of patients achieving HbA1c < 6.5% and ≤ 6.5% at Week 24 was 19.0% in the EQW group and 4.2% in the placebo group for both goals; the difference in the proportion of patients who achieved HbA1c < 6.5% and ≤ 6.5% between the EQW group and the placebo group was 14.8% in each case.

The proportion of patients achieving HbA1c < 7% at Week 24 was 31.0% in the EQW group and 8.3% in the placebo group. The difference in the proportion of patients who achieved HbA1c < 7% between the EQW group and the placebo group was 22.7% (nominal p = 0.020).

Table 15: Proportions of Patients achieving HbA1c Goals of < 6.5%, ≤ 6.5% and < 7.0% at Week 24, CMH Analysis with Missing Data treated as Nonresponder (Evaluable Analysis Set)

Analysis visit		EQW (N = 58)	Placebo (N = 24)
HbA1c < 6.5%			
Week 24	n	48	22
	Number (%) achieved goal[a]	11 (22.9)	1 (4.5)
	Percentage achieved goal[b]	19.0	4.2
	95% 2-sided confidence interval[b,c]	(8.9, 29.1)	(0.0, 12.2)
	Difference (EQW versus Placebo)[b]	14.8	
	95% 2-sided CI for difference[b]	(1.9, 27.7)	
	2-sided p-value[b,d]	0.077	
HbA1c ≤ 6.5%			
Week 24	n	48	22
	Number (%) achieved goal[a]	11 (22.9)	1 (4.5)
	Percentage achieved goal[b]	19.0	4.2
	95% 2-sided confidence interval[b,c]	(8.9, 29.1)	(0.0, 12.2)
	Difference (EQW versus Placebo)[b]	14.8	
	95% 2-sided CI for difference[b]	(1.9, 27.7)	
	2-sided p-value[b,d]	0.077	
HbA1c < 7.0%			
Week 24	n	48	22
	Number (%) achieved goal[a]	18 (37.5)	2 (9.1)
	Percentage achieved goal[b]	31.0	8.3
	95% 2-sided confidence interval[b,c]	(19.1, 42.9)	(0.0, 19.4)
	Difference (EQW versus Placebo)[b]	22.7	
	95% 2-sided CI for difference[b]	(6.5, 39.0)	
	2-sided p-value[b,d]	0.020	

g Calculated from observed data.

h Calculated from imputed data.

i 95% CI for the proportion is based on normal approximation to binomial.

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

Difference was the risk difference of the 2 proportions.

Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.

Percentages were calculated from the number of patients with observed/imputed data at the visit by treatment group.

CMH, Cochran-Mantel-Haenszel; EQW, exenatide 2 mg once weekly; HbA1c, glycated hemoglobin A1c; N, number of patients in the Evaluable Analysis Set within the treatment group; n, number of patients with observed value for week.

Change in Lipids (Total Cholesterol, HDL-C, LDL-C, and Triglycerides) from Baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to Each Intermediate Visit as Applicable

There were no meaningful changes in total cholesterol, LDL-C, or HDL-C from baseline to Week 24 in the EQW group or in the placebo group. For triglycerides, there was a numerically greater decrease in triglycerides from baseline to Week 24 in the EQW group of -0.122 mmol/L compared with the placebo group (0.094 mmol/L). This corresponded to median percentage changes from baseline of -13.1% and 5.7%, respectively.

Change in Blood Pressure (Systolic and Diastolic) from Baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to Each Intermediate Visit as Applicable

Systolic Blood Pressure

Treatment with EQW was associated with a numerical decrease from baseline to Week 24 in SBP compared with a numerical increase in the placebo group. The LS mean change in SBP was -0.7 mmHg for the EQW group and 2.2 mmHg for the placebo group. The difference in LS mean change between the EQW and placebo groups was -2.8 mmHg.

Diastolic Blood Pressure

There were no meaningful differences between treatments for change from baseline at Week 24 for DBP. The LS mean change in DBP was 0.2 mmHg for the EQW group and -1.3 mmHg for the placebo group. The difference in LS mean change between the EQW and placebo groups was 1.6 mmHg.

Proportions of Patients Discontinuing the Study and the Proportion of Patients Needing Rescue Due to Failure to Maintain Glycaemic Control at Visit 7 (Week 24), and at each Intermediate Visit as Applicable

The cumulative proportions of patients needing rescue medication due to failure to maintain glycaemic control at Week 24 were low (EQW: 1.7%, placebo: 0%). One of the 58 patients in the EQW group needed rescue medication at Week 18 due to failure to maintain glycaemic control. None of the 24 patients in the placebo group needed rescue medication due to failure to maintain glycaemic control.

Immunogenicity

A summary of the incidence of antibodies to exenatide by visit is presented in Table 16.

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. At Week 52, the percentage of patients positive for antibodies was 31.1% (high positive antibody results) or 40.0% (low positive antibody results). Approximately half of patients (approximately quarter in each category) were positive with any positive result at the 10-week follow-up period.

Table 16: Incidence of Antibodies to Exenatide by Visit (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)

[k] Baseline was the AB measurement at Week 0 (Day 1). A negative or missing AB measurement was considered negative at baseline. A patient was said to have any positive if the AB-confirm test was positive at baseline.

[l] A patient who had a negative result.

[m] High positive = antibody titers ≥ 625, including baseline assessment.

[n] Low positive = antibody titers < 625, including baseline assessment.

[o] A patient was said to have treatment-emergent AB to Exenatide if 1) at any visit the AB test was positive after the first dose of EQW following a negative or missing AB measurement, or 2) the titer at any visit was increased by at least 1 titration category from a detectable measurement prior to first dose of randomized study medication.

[p] A patient's highest AB was obtained based on AB values during 52 weeks of treatment and 10-week follow-up period.

The analysis of ADA data for the placebo → EQW group during the open-label extension period will be reported as an addendum to the clinical study report.

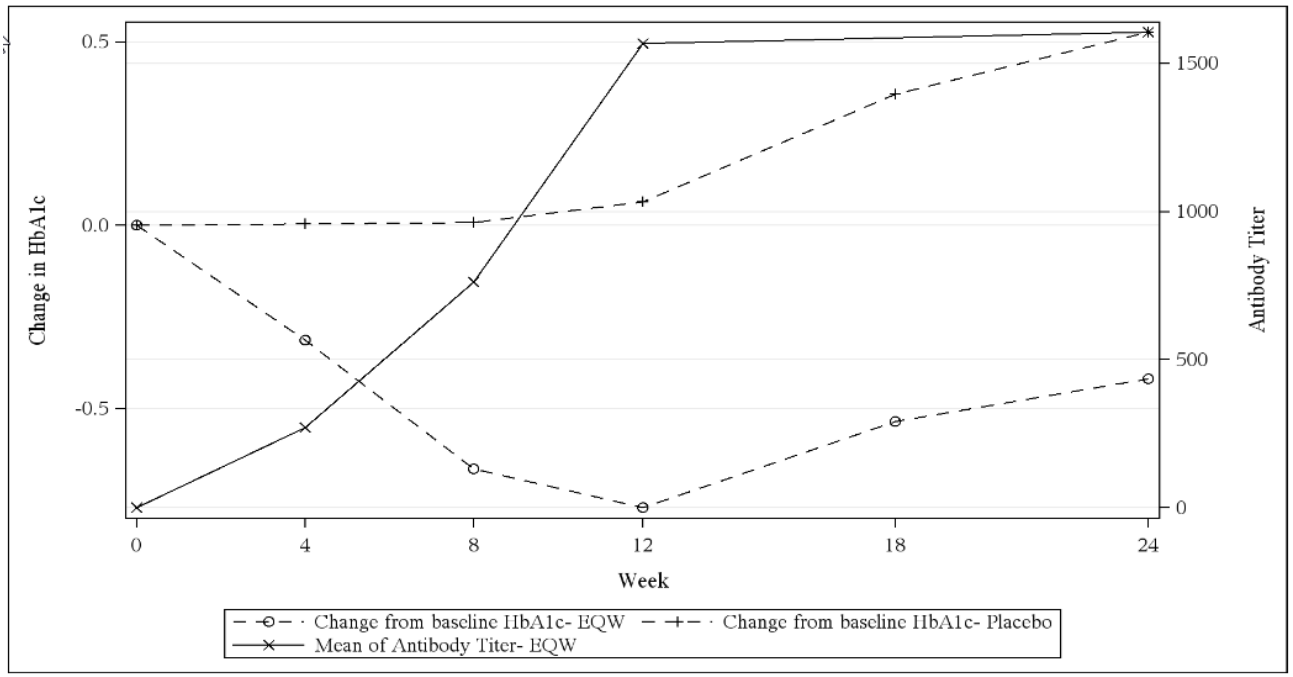
Percentages were calculated from the number of patients with data by treatment group and visit.

Patients randomized to placebo during the controlled assessment period received EQW during the extension period.

AB, antibody; ADA, anti-drug antibody; CSR, clinical study report; EQW, exenatide 2 mg once weekly; N, number of patients in treatment group; n, number of patients included in analysis; NA, not applicable.

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%). In the total placebo group, HbA1c increased from baseline to Week 24, with an LS mean change of 0.49. From Week 4 to Week 12, mean HbA1c in the EQW group 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.

Figure 14: Change in HbA1c (%) from Baseline and Antibody Titres to EQW at each Visit between Baseline and Week 24, by treatment (Controlled Assessment Period) (Evaluable Analysis Set)



EQW, exenatide 2mg once weekly. AB, antibody(ies). HbA1c, glycated haemoglobin A1c,. N, number of patients in the Evaluable Analysis Set within the treatment group.
Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to first dose of randomised study medication.
Data collected after initiation of rescue medication or after premature discontinuation of study medication are excluded.

For the primary outcome, there appears to be a trend showing reduced magnitude of mean changes from baseline in HbA1c with higher anti-drug antibody titre categories. However, there is substantial variability of HbA1c response within each titre category which does not allow for a reliable prediction of the HbA1c response for an individual patient. In the first 12 weeks of Study BCB114, mean change in HbA1c decreases while mean anti-drug antibody titres increase, indicating an accumulation of antibodies (Figure 14). Subsequently, mean HbA1c increases over time and anti-drug antibody titres begin to decrease. The greatest difference in HbA1c response between EQW and placebo was established by Week 12 when antibody titres also reached maximum levels; from this point on, however, a slight decrease in HbA1c response occurred, with a magnitude almost identical in the EQW and placebo groups, suggesting that the decrease in HbA1c response reflects the natural course of the disease rather than the presence of antibodies. HbA1c is an integrated response requiring sustained time of drug exposure (8 to 12 weeks) to manifest changes while changes in anti-drug antibody titre are more immediate. The maximum increase in HbA1c beyond 12 weeks may be a delayed reflection of the peak antibody titre at 12 weeks.

Analysis of efficacy in the open-label extension period

Change in HbA1c from Baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to Each Intermediate Visit as Applicable

In the EQW group, 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. Mean HbA1c decreased from baseline through Week 12 of the study (mean change from baseline of -0.74%), and then began to gradually increase, returning to approximate baseline levels by Week 52 (mean change from baseline of -0.10%).

In the placebo → EQW group, mean HbA1c remained stable from baseline through Week 12 (mean change from baseline of 0.10%), and then began to gradually increase through Week 24 (mean change

from baseline of 0.53%). When the patients were switched to treatment with EQW during the open-label extension period, mean HbA1c decreased through Week 40 (mean change from baseline of 0.00%) and increased through Week 52 (mean change from baseline of 0.53%).

Change in Fasting Plasma Glucose Concentration from Baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to Each Intermediate Visit as Applicable

In the EQW group, the reduction in mean FPG observed with the first 24 weeks gradually diminished over time, returning to approximate baseline levels by Week 52. Mean FPG decreased from baseline through Week 4 of the study (mean change from baseline of -1.97 mol/L), and then began to increase through Week 52 (mean change from baseline of -0.10 mol/L).

In the placebo → EQW group, mean FPG decreased from baseline through Week 12 (mean change from baseline of -0.05 mol/L), and then increased through Week 24 (mean change from baseline of 1.09 mol/L). When the patients were switched to treatment with EQW during the open-label extension period, mean FPG decreased through Week 52 (mean change from baseline of 0.59 mol/L).

Change in Body Weight from Baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each Intermediate Visit as Applicable

In the EQW group, the reduction in mean body weight observed with the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52. Mean body weight decreased from baseline through Week 12 of the study (mean change from baseline of -0.95 kg), and then began to increase through Week 24 (mean change from baseline of -0.53 kg). Mean body weight remained relatively stable through Week 40 (mean change from baseline of -0.45 kg) and had returned to approximate baseline levels by Week 52 (mean change from baseline of 0.04 kg).

In the placebo → EQW group, mean body weight increased from baseline through Week 8 (mean change from baseline of 0.99 kg), and then remained relatively stable until Week 24 (mean change from baseline of 0.77 kg). When the patients were switched to treatment with EQW during the open-label extension period, mean body weight remained stable through Week 28 (mean change from baseline of 0.79 kg) and then decreased to approximate baseline levels by Week 52 (mean change from baseline of -0.04 kg).

Change in Fasting Insulin from Baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each Intermediate Visit as Applicable

In the EQW group, the increase in fasting insulin observed at Week 24 of EQW treatment diminished over time, and a decrease from baseline in fasting insulin was observed through Week 52. Mean fasting insulin fluctuated from baseline through Week 24 (mean change from baseline of 24.0 pmol/L). Levels continued to fluctuate through Week 52 (mean change from baseline of -32.4 pmol/L) but were generally associated with a decrease from baseline.

In the placebo → EQW group, mean fasting insulin fluctuated from baseline through Week 24 (mean change from baseline of 37.3 pmol/L). When patients were switched to treatment with EQW during the open-label extension period, levels continued to fluctuate through Week 52 (mean change from baseline of 121.5 pmol/L) but were generally associated with an increase from baseline.

Proportions of Patients Achieving HbA1c Goals at Visit 10 (Week 52), and at Each Intermediate Visit as Applicable

In the EQW group, the proportions of patients achieving HbA1c goals with the first 24 weeks of EQW treatment were sustained through Week 52. The proportions of patients achieving HbA1c goals at Week 24 (22.9%, 22.9%, and 37.5% of patients achieving HbA1c goals of < 6.5%, ≤ 6.5%, and < 7%, respectively) were maintained through Week 52, with 30.8%, 30.8%, and 35.9% achieving HbA1c goals of < 6.5%, ≤ 6.5%, and < 7%, respectively.

In the placebo → EQW group, the proportion of patients that achieved HbA1c goals of < 6.5%, ≤ 6.5%, and < 7% at Week 24 was 4.5%, 4.5%, and 9.1%, respectively. When patients were switched to treatment with EQW during the open-label extension period, the proportion of patients achieving all 3 HbA1c goals increased at Week 40 through Week 52. At Week 52, the proportion of patients who achieved HbA1c goals of < 6.5%, ≤ 6.5%, and < 7% were 23.5%, 23.5%, and 29.4%.

Change in Blood Pressure (Systolic and Diastolic) from Baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to Each Intermediate Visit as Applicable

Systolic Blood Pressure

In the EQW group, the reduction in mean SBP observed with the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52. Mean SBP decreased from baseline through Week 4 of the study (mean change from baseline of -2.4 mmHg), remained relatively stable from Week 4 through Week 18 (mean change from baseline of -2.3 mmHg), began to increase through Week 40 (mean change from baseline of 1.2 mmHg), and then decreased to approximate baseline levels by Week 52 (mean change from baseline of -0.7 mmHg).

In the placebo → EQW group, mean SBP fluctuated from baseline to Week 12 (mean change from baseline of 0.9 mmHg), then increased to Week 18 and remained stable through Week 24 (mean change from baseline of 2.3 mmHg). When the patients were switched to treatment with EQW during the open-label extension period, mean SBP decreased through Week 40 (mean change from baseline of -1.9 mmHg) and then increased to approximate baseline levels by Week 52 (mean change from baseline of -0.6 mmHg).

Diastolic Blood Pressure

In the EQW group, there were no notable changes in mean DBP from baseline to Week 24. However, from Week 28 through Week 52, there was a predominant increase in mean DBP from baseline (mean change from baseline of 1.1 mmHg at Week 52).

In the placebo → EQW group, there were no notable changes in mean DBP from baseline to Week 24. However, when the patients were switched to treatment with EQW during the open-label extension period, there was a predominant decrease in mean DBP from baseline to Week 52 (mean change from baseline of -2.5 mmHg).

Ancillary analyses

N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial BCB114.

Title: 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			
Study identifier	BCB114		
Design	Phase III, double-blind, randomized, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 5 weeks 28 + 10 weeks
Hypothesis	Superiority		
Treatments groups	EQW		2 mg EQW weekly, 24 weeks, 59 patients
	Placebo		2 mg placebo weekly, 24 weeks, 24 patients
Endpoints and definitions	Primary endpoint	Change HbA[1]c 0-24	Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
	Secondary endpoint	Change HbA[1]c 0-52	Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52)
	Secondary endpoint	Change FPG	Change in fasting plasma glucose from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52)
	Secondary endpoint	Change Body weight	Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52)
	Secondary endpoint	HbA[1]c goals	Proportions of patients achieving HbA1c goals of ≤ 6.5% and < 7.0% at Visit 7 (Week 24), Visit 10 (Week 52)
	Secondary endpoint	PK	Plasma exenatide concentrations at baseline (Visit 2, Week 0), Visit 7 (Week 24), Visit 10 (Week 52)
Database lock	06 August 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The prespecified primary efficacy analysis compared treatment groups (EQW versus placebo) with respect to change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24) using the MMRM approach		
Descriptive statistics and estimate variability	Treatment group	EQW	Placebo
	Number of subject	59	24
	HbA[1]c (%) LS mean- (SE)	-0.36 (0.184)	0.49 (0.273)
	95% CI	(-0.73, 0.00)	(-0.06, 1.03)
	FGP (mmol/L) LS mean- (SE)	-0.29 (0.424)	0.91 (0.628)
	95% CI	(-1.13, 0.56)	(-0.34, 2.17)
	Body weight (kg) LS mean- (SE)	-0.59 (0.665)	0.63 (0.982)
	95% CI	(-1.92, 0.73)	(-1.33, 2.59)
Effect estimate per comparison	Primary endpoint Hb1Ac (%)	Comparison groups	EQW vs Placebo
		LS Mean difference (SE)	-0.85 (0.330)
		95% CI	(-1.51, -0.19)
		P-value	0.012

	Secondary endpoint FPG (mmol/L)	Comparison groups	EQW vs Placebo
		LS Mean difference (SE)	-1.20 (0.760)
		95% CI	(-2.72, 0.32)
		P-value	0.119
	Secondary endpoint Body weight (kg)	Comparison groups	EQW vs Placebo
		LS Mean difference (SE)	-1.22 (1.189)
		95% CI	(-3.59, 1.15)
		P-value	0.307

2.4.2. Discussion on clinical efficacy

This variation concerns the paediatric population and includes data on adolescents and children >10 years of age.

Design and conduct of clinical studies

Study BCB114 was Phase III, double-blind, randomized, placebo-controlled, international study that included male and female patients 10 to 17 years of age with T2DM treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening.

The study duration was 62 weeks (excluding the extended safety follow-up period; see below) and comprised 4 periods: screening period (5 weeks), controlled assessment period (24 weeks): double-blind, placebo-controlled period to examine the efficacy and safety of EQW compared with placebo, extension period (28 weeks): open-label, uncontrolled period to examine the long-term safety and efficacy of EQW and post-treatment follow-up period (10 weeks).

For the controlled assessment period, patients were randomly assigned in a 5:2 ratio to receive either EQW 2 mg (Group A) or placebo (Group B). During the extension period (Week 25 through Week 52), patients assigned to the EQW 2 mg treatment (Group A) continued to be treated with EQW 2 mg, and patients randomized to placebo (Group B) received EQW 2 mg. The trial design is considered adequate. 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 objectives as well as the primary and secondary endpoints were adequate.

The primary endpoint change in HbA1c from baseline to Week 24 was compared between the treatment groups (EQW versus placebo) using the MMRM analysis. The main estimand was based on a hypothetical strategy which excluded observations after intercurrent events defined as receipt of rescue therapy, study medication discontinuation, and study withdrawal. This strategy may have over-estimated the treatment effect, depending on the amount and distribution of missing and/or excluded data. Specifically, a considerably higher treatment discontinuation rate was seen in the EQW treatment group, which is not accounted for in the primary estimand. More emphasis should therefore be given to the sensitivity and supplementary analyses that were based on the treatment policy approach using available data and/or imputation methods that are conservative for the comparison between the treatment groups (such as the applied copy-reference approach).

Missingness patterns were presented for completeness, showing no obvious trends other than several patients with missing data for 3 to 4 consecutive visits in the EQW group while none in the placebo group, which indicates the more pronounced study withdrawals in the EQW group. The Applicant also provided

requested presentation of number of excluded observations due to different reasons, including missing data, in total and per visit for each treatment group in the primary as well as sensitivity and supplementary analysis of the change in HbA1c from baseline to Week 24. Missing data were predominantly missing due to not being available/observed (e.g., lost to follow-up or withdrawal by subject, as shown in the subsection Participant flow) and not due to intercurrent events. There were only few patients excluded due to intercurrent events of treatment discontinuation and rescue intake; at most 2 such observations were reported per visit in the EQW treatment group and none in the placebo group in the primary analysis and sensitivity analysis. Disappointingly, the MAH did not provide the results according to the two methods which were specified in the SAP to examine the missingness patterns by assessing the pre- and post-withdrawal values of HbA1c. The issue will though not be further pursued, considering that the primary endpoint results were supported by sensitivity analysis where missing/excluded observations for the EQW group were assumed to be MNAR and imputed using copy-reference approach (i.e., modelled by observed outcomes from the placebo group).

It is noted that the primary analysis did not include the same stratification factors as used in the randomisation; this will not be pursued.

The hierarchical testing strategy for the primary and secondary variables is endorsed.

Subgroup analysis was performed only in terms of descriptive statistics with no graphical presentation or direct comparison between the treatment groups. For the ease of the assessment and illustration of consistency of the treatment effects across the subgroups, a forest plot for the primary endpoint was provided on request, by subgroups according to sex, age, baseline HbA1c, BMI percentile, region and race. All points estimates are in favour of Bydureon, which is reassuring.

The study appears to be adequately conducted. None of the reported protocol deviations are thought to have significantly affected the results of the study.

The demographic, patient and baseline disease characteristics were representative of the intended population. These parameters were broadly similar between the EQW and placebo groups, taking into account the small size of the study. Minor imbalances were observed for age, sex, race, region, weight population percentile, and baseline diabetes duration.

Notably, study subjects 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. A greater proportion of patients in the EQW were in the ≥ 97 percentile for weight compared with the placebo group. During the assessment of study BCB114 as part of procedure EMEA/H/C/002020/P46, the Applicant was invited to discuss whether the imbalance in weight population percentiles between the study groups may have influenced the study results due to potential differences in exposure to study drug. According to the applicant, the differences in weight population percentiles between the EQW and placebo groups are unlikely to have influenced study results due to differences in study drug exposure. Higher body weight results in lower plasma concentrations of exenatide; however, the PD effect, change in HbA1c, due to lower pharmacokinetics (PK) is minimal (< 0.1%) and not of clinical importance. Thus, the conclusion by the applicant that any minor differences in weight population percentiles between treatment groups would unlikely impact the study results is endorsed, and the issue is not further pursued.

Compliance was generally high and similar between treatment groups in both during the 24-week controlled assessment period and the 52-week open-label treatment period.

Efficacy data and additional analyses

The study BCB114 met the primary endpoint, showing a difference in HbA1c of -0.85% (p = 0.012) in favour of the EQW group after 24 weeks, and the sensitivity analyses support the primary analysis. The difference is considered clinically relevant. The difference in HbA1c between study groups increased gradually until week 12 and was then maintained throughout the rest of the controlled phase (week 24). The LS mean change in HbA1c was -0.36% for the EQW group and 0.49% for the placebo group. Of note, even though the difference in HbA1c was sustained, HbA1c gradually increased in both groups after week 12.

The difference in the secondary endpoint FPG was not statistically significant but still in favour of the EQW group. The reduction in body weight was greater for the EQW group throughout the whole study. A similar trend was seen for BMI. There were no meaningful differences between treatment groups in fasting insulin at week 24.

The proportion of patients achieving HbA1c goals (< 6.5%, ≤ 6.5%, and < 7.0%) was 15 to 23 % higher in the EQW group vs placebo. None of the other secondary and or exploratory endpoints rendered any meaningful difference between study groups (lipids, blood pressure).

Antibodies to exenatide were observed in the majority of patients (93.0%) in the EQW group at any time during the study, and 63% had a high titer. According to the SmPC, approximately 45% of adult patients had low titer antibodies to exenatide at study endpoint, and 12% had high antibody titers. The proportion of adolescents/children with high antibody titers and potentially loss of efficacy is thus higher than in the reference population. According to the MAH, the generally lower anti-drug antibody incidence and titers in adults with T2DM compared with the adolescent patients with T2DM in Study BCB114 may be due to immune aging.

Moreover, study subjects with lower antibody titers had a better outcome at week 24, as 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%). However, no direct correlation between change in HbA1c and antibody titer can be observed, as these parameters evolve in a different time manner.

Even though there seem to be a trend towards reduced magnitude of mean changes from baseline in HbA1c with higher anti-drug antibody titer categories, the high variability of the available data precludes any firm conclusion. Since, according to the MAH, no commercial antibody test for exenatide is available at the moment, testing of anti-drug antibodies is not possible in clinical practice. Indeed, some patients may experience a lower HbA1c decrease due to high antibody titers. Strategies such as a stopping rule could possibly prevent patients with suboptimal treatment responses from unnecessary long treatment duration, taking into account that the HbA1c-lowering effect is relatively modest (-0.36%). The Applicant has further analysed the change in HbA1c by antibody titers during the study. The Applicant concludes that the mean reduction in HbA1c seem decrease with increasing antibody titres. However, no prediction can be done in the individual patient. Because no commercial test for ADA is available, the decision whether to continue treatment with Bydureon should be made by the clinician based on the observed HbA1c reduction and the achievement of the individual HbA1c goal in each patient.

A wording on how to guide the clinician in case lack or loss of efficacy has been included in section 4.4 of the SmPC.

Efficacy outcomes were also evaluated in the open-label extension period. The reduction in mean HbA1c, FPG and body weight observed with the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52. Likewise, the increase in fasting insulin observed at Week 24 of EQW treatment diminished over time, and a decrease from baseline in fasting insulin was

observed through Week 52. On the other hand, the proportions of patients achieving HbA1c goals (<6.5%, ≤6.5%, and <7%) with the first 24 weeks of EQW treatment were sustained through Week 52. The patients that switched from placebo to EQW at week 24 showed an initial decrease in HbA1c up to week 40, but then the HbA1c appeared to increase again. It is, however, noted that the number of patients achieving the treatment goals in this group increased from 4.5-9.1% at week 24 to 23.5-29.4% at week 52. However, as clarified by the Applicant, study BCB114 was not designed to determine the long-term effect of EQW compared to placebo in the paediatric population. Only patients randomised to EQW in the 24-weeks randomized period continued treatment with EQW up to week 52, the latter period without comparator. The return of mean HbA1c towards baseline observed at Week 52 may be due a faster deterioration of β-cell function in paediatric subjects with T2D, following the natural course of the disease, which may have influenced the study result as seen in other paediatric T2D studies. Thus, no firm conclusion can be made on the long-term efficacy of EQW based on data from the current study. There were no consistent changes in SBP or DBP over time, neither in the EQW group or the placebo → EQW group.

2.4.3. Conclusions on the clinical efficacy

Study BCB114 was designed to assess the efficacy and safety of Bydureon in children and adolescents 10 to 17 years of age with T2DM treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin.

The effect of EQW on the primary endpoint was statistically and clinically relevant and the outcome is supported by the secondary endpoints.

2.5. Clinical safety

Introduction

The efficacy and safety of Bydureon adults 18 years and older with T2DM have been documented in the clinical development program for exenatide.

- In paediatric T2DM patients, safety and tolerability data from one clinical study support this submission, Study BCB114, in children with 10 to 17 years of age with T2DM, with a 24-weeks double-blind, placebo-controlled period followed by a 28-weeks open-labelled uncontrolled period to examine the long-term safety and efficacy of EQW.

Patient exposure

A summary of the extent of exposure for the controlled assessment period is presented in Table 17.

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%).

Table 17: Extent of Exposure to Study Medication (Controlled Assessment Period) (Safety Analysis Set)

		EQW (N = 59)	Placebo (N = 23)	Total (N = 82)
Duration of exposure, (days)[a]	n	59	23	82
	Mean	157.3	165.6	159.6
	SD	44.40	18.26	38.94
	Median	170.0	168.0	168.5
	Min	7	92	7
	Max	210	180	210
Exposure category, (days)	1 - 13	1 (1.7)	0	1 (1.2)
	14 - 27	0	0	0
	28 - 55	3 (5.1)	0	3 (3.7)
	56 - 83	3 (5.1)	0	3 (3.7)
	84 - 111	1 (1.7)	1 (4.3)	2 (2.4)
	112 - 139	0	1 (4.3)	1 (1.2)
	140 - 167	5 (8.5)	1 (4.3)	6 (7.3)
	≥ 168	46 (78.0)	20 (87.0)	66 (80.5)

[a] Duration of Exposure = (last dose date - first dose date +7).

Percentages were calculated from the number of patients in the analysis set by treatment group and total.

EQW, exenatide 2 mg once weekly; Max, maximum; Min, minimum; N, number of patients in treatment group; n, number of patients included in analysis; SD, standard deviation.

Adverse events

Treatment-emergent AEs are summarized in the table below (Table 18).

Table 18: 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 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 open-label extension period. For patients not entering the open-label extension period, the period was defined as up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Open-label 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.

Patients randomly assigned to placebo during the controlled assessment period received EQW during the open-label extension period.

AE, adverse event; EQW, exenatide 2 mg once weekly; N, number of patients in treatment group; SAE, serious AE.

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.

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 19). The incidence of AEs overall was generally lower in the open-label extension period than the controlled assessment period.

Table 19: 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)

[a] Number (%) of patients with AEs, sorted in decreasing total frequency for PT (sorted by EQW treatment group during the controlled assessment period).

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

Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than 1 PT were counted once in each of those PTs.

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 open-label extension period. For patients not entering the open-label extension period, the period was defined as up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Open-label 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 randomly assigned to placebo during the controlled assessment period received EQW during the open-label 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; SOC, system organ class.

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).

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:

- Diarrhoea: 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%]).

Hypoglycaemia

A summary of the incidence and frequency of hypoglycaemia by treatment group and by major/minor classification is presented in Table 20 for the controlled assessment period.

Table 20: Number of Patients and Events, Incidence of Hypoglycaemia by Major/Minor Classification (Controlled Assessment Period) (Safety Analysis Set)

	EQW (N = 59)		Placebo (N = 23)	
Hypoglycaemia Intensity	**Number (%) of patients[a]**	**Number of events[b]**	**Number (%) of patients[a]**	**Number of events[b]**
Patients with any hypoglycaemia	8 (13.6)	13	1 (4.3)	7
Any hypoglycaemia				
Major	0	0	0	0
Minor	1 (1.7)	1	1 (4.3)	1
Other	8 (13.6)	12	1 (4.3)	6

[a] Number (%) of patients with hypoglycaemia. Patients with multiple hypoglycaemia events in a single category were counted only once.

[b] Multiple hypoglycaemic events for a patient were considered in the total event calculation.

[c] Major hypoglycaemia = An event that results in loss of consciousness, seizure, or coma (or other mental status change consistent with neuroglycopenia in the judgment of the Investigator or physician), and which resolves after at least 1 item of intervention recorded in the hypoglycaemic event eCRF or an event that required third party assistance and was associated with a plasma or capillary glucose concentration of < 3 mmol/L (54 mg/dL); Minor hypoglycaemia = Nonmajor hypoglycaemia event that had symptoms consistent with hypoglycaemia and had a glucose value of < 3 mmol/L (54 mg/dL) prior to treating the episode. Other = If a hypoglycaemia event does not meet the criteria for a major or minor event.

Controlled assessment period event was defined as an event starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the open-label extension period. For patients not entering the extension period, the period was defined as up to and including last dose of study medication + 7 days.

For patients completing controlled assessment period treatment but not entering the open-label extension period, events were captured up to the later of period definition or Week 24.

Hypoglycaemic events reported from the hypoglycaemic event eCRF.

Percentages were calculated from the number of patients in the analysis set by treatment group.

eCRF, electronic case report form; EQW, exenatide 2 mg once weekly; N, number of patients in treatment group.

During the controlled assessment period, hypoglycaemic 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 hypoglycaemic events. The proportion of patients with minor hypoglycaemic 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 hypoglycaemic 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 hypoglycaemic 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 hypoglycaemic events in the placebo group, insulin use at baseline was reported.

During the open-label extension period, hypoglycaemic 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 hypoglycaemic events.

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

Injection site-related events

A summary of the incidence and frequency of injection site reactions is presented for the controlled assessment period by treatment group in Table 21.

Table 21: Proportions of Patients Reporting Adverse Events of Injection Site Reactions at Week 24 and at Each Intermediate Visit (Controlled Assessment Period) (Safety Analysis Set)

Analysisvisit	EQW (N = 59)		Placebo (N = 23)		Total (N = 82)	
	n	Number (%) of patients	n	Number (%) of patients	n	Number (%) of patients
Week 4	59	5 (8.5)	23	2 (8.7)	82	7 (8.5)
Week 8	57	2 (3.5)	23	1 (4.3)	80	3 (3.8)
Week 12	53	1 (1.9)	23	0	76	1 (1.3)
Week 18	51	0	22	0	73	0
Week 24	51	0	22	0	73	0

Injection site reactions are presented from the AE eCRF, based on the "Injection site reactions" higher level terms.
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 open-label extension period. For patients not entering the open-label extension period, the period was defined as up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).
For patients completing controlled assessment period treatment but not entering the open-label extension period, events were captured up to the later of period definition or Week 24.
Percentages were calculated from the number of patients with data available at the respective visit by treatment group.
MedDRA Version 23.0.

AE, adverse event; eCRF, electronic case report form; EQW, exenatide 2 mg once weekly; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; n, number of patients included in analysis; SAE, serious adverse event.

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.

Potentially immune-related events

A summary of the incidence of potentially immune-related AEs by antibody status is presented by treatment group for the controlled assessment period in Table 22.

Table 22: Number of Patients with Potentially Immune-related Adverse Events by Antibody Status – Positive versus Negative (Controlled Assessment Period) (Safety Analysis Set)

System organ class Preferred term	Number (%) of patients[a]		
	EQW (N = 59)[b]		Placebo (N = 23)
	Positive (N1 = 55)	Negative (N1 = 3)	
Patients with any potentially immune-related AE	6 (10.9)	0	3 (13.0)
Skin and subcutaneous tissue disorders	1 (1.8)	0	0
Urticaria	1 (1.8)	0	0
Musculoskeletal and connective tissue disorders	1 (1.8)	0	1 (4.3)
Arthralgia	1 (1.8)	0	1 (4.3)
General disorders and administration site conditions	5 (9.1)	0	2 (8.7)
Injection site erythema	3 (5.5)	0	1 (4.3)
Injection site induration	1 (1.8)	0	1 (4.3)
Injection site nodule	1 (1.8)	0	0
Injection site pruritus	2 (3.6)	0	1 (4.3)
Injection site swelling	1 (1.8)	0	0

[a] Number (%) of patients who reported at least 1 potentially immune-related AE for a PT, sorted by international order for SOC and alphabetically for PT. A patient could have 1 or more PTs reported under a given SOC.

[b] One patient who was randomly assigned to placebo received a dose of EQW in error and was subsequently reassigned to the EQW group for analyses based on actual treatment (see CSR Section 10.3); however, no antibody result was available for this patient as antibody results were not collected for patients randomly assigned to placebo (see CSR Section 9.9.2).

An antibody was said to be positive if tested positive at any time (pre- and postbaseline). Otherwise, patients who had all available results as negative were categorized as such.

Baseline antibody titer was the measurement at Week 0 (Day 1). A negative or missing measurement was considered negative at baseline.

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 open-label extension period. For patients not entering the open-label extension period, the period was defined as up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

For patients completing controlled assessment period treatment but not entering the open-label extension period, events were captured up to the later of period definition or Week 24.

Percentages were calculated from the number of patients in the analysis set by treatment group by antibody status.

MedDRA Version 23.0.

AE, adverse event; EQW, exenatide 2 mg once weekly; MedDRA, Medical Dictionary for Regulatory Activities; N1, number of patients in treatment group by antibody status; N, number of patients in treatment group; PT, preferred term; SOC, system organ class.

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.

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.

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.

Serious adverse event/deaths/other significant events

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 23). 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 23: Number of Patients with Serious Adverse Events by System Organ Class and Preferred Term – On-treatment (Safety Analysis Set)

System organ class Preferred term	Number (%) of patients[a]					
	Controlled assessment period			Open-label extension period		
	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 open-label extension period. For patients not entering the open-label extension period, the period was defined as up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Open-label 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 randomly assigned to placebo during the controlled assessment period received EQW during the open-label 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.

Laboratory findings

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.

Individual Clinically Important Changes in Clinical Chemistry Variables

Abnormal results were observed in a higher number of patients in the EQW group than the placebo group (between group difference of ≥ 5 patients) for the following parameters:

- AST: high values were reported in 5 patients (9.1%) in the EQW group and 0 patients in the placebo group.

- Creatinine: low values were reported in 7 patients (12.7%) in the EQW group and 2 patients (8.7%) in the placebo group.
- Phosphate: high values were reported in 8 patients (14.5%) in the EQW group and 1 patient (4.3%) in the placebo group.
- Lipase: high values were reported in 9 patients (16.7%) in the EQW group and 0 patients in the placebo group.

Carcinoembryonic Antigen

There were no clinically notable changes in mean values from baseline to Week 12 for carcinoembryonic antigen within the treatment groups (-0.06 µg/L and 0.01 µg/L for the EQW and placebo → EQW groups, respectively). No notable changes in mean values for carcinoembryonic antigen were observed within the treatment groups for the remainder of the treatment period.

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.

Pancreatic amylase

While there was a small numerical increase with EQW versus placebo at Week 12, there were no clinically notable changes in mean values from baseline to Week 12 for pancreatic amylase within the treatment groups (3.6 U/L [0.061 µkat/L] and 0.5 U/L [0.008 µkat/L] for the EQW and placebo → EQW groups, respectively). No notable changes in mean values for pancreatic amylase were observed within the treatment groups for the remainder of the treatment period.

No pancreatic-related AEs were reported for either treatment group.

Discontinuation due to adverse events

No AEs leading to study medication or study discontinuation by the investigator were reported.

Post marketing experience

Cumulatively through 31 March 2020, worldwide post-marketing exposure to EQW for adults is estimated to be 2128373 patient-years and post-marketing exposure to EQWS is estimated to be 149964 patient-years.

Based on a review of the available post-marketing data for adults, the safety profile of EQW/EQWS remains generally similar to the profile established during clinical studies.

2.5.1. Discussion on clinical safety

This variation concerns the paediatric population, i.e., adolescents and children >10 years of age.

The safety database is limited to 59 subjects treated with EQW for a mean of 157.3 days in the controlled assessment period and 72 subjects treated with EQW in the extension period (EQW group and placebo → EQW group). 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.

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. In the controlled assessment period, the incidence of AEs overall was lower in the EQW group vs placebo (61% vs 74%). The incidence of SAEs was also low, with in total 7 events reported for the entire study period. In the controlled assessment period, 2 subjects (3.4%) in the EQW group reported a SAE compared to 3 subjects (4.3%) in the placebo treated group. In the extension period, a total of 4 SAEs were reported. None of the SAEs were considered related to treatment by the Investigator. In the controlled assessment period, the reporting of treatment related AEs was slightly higher in the EQW group (15 subjects; 25.4%) compared to the placebo group (5 subjects; 21.7%).

The most common AE reported in the EQW group were upper respiratory tract infection (10.2%) whereas abdominal pain was the most common AE reported in the placebo group (13.0%). Most AEs were mild or moderate in intensity. The incidence of GI-related AEs was comparable between the EQW and placebo groups (22.0% and 26.1%) during the controlled assessment period. The most frequent gastrointestinal disorder-related AEs were diarrhoea, nausea, vomiting, and upper abdominal pain. These events were more frequently reported in the EQW group.

There were no major hypoglycaemic events reported during the study. The occurrence of any hypoglycaemic event was somewhat higher in the EQW group (8 subjects; 13.6%) than in the placebo group (1 subject; 4.3%), out of which one minor hypoglycaemia was reported in each of the study groups.

The proportions of patients experiencing injection site reactions was low and comparable between the study groups. No injection site reactions were reported after Week 12. Of note, all injection-site reactions were reported among patients using the prefilled syringe device.

Out of 55 patients who were positive (n=55) for exenatide antibodies, 6 patients reported a potentially immune-related AE, compared to no events reported by the 3 patients who were negative. It should also be noted that 3 subjects in the placebo group reported potentially immune-related AEs. The relationship between the timing of the development of ADA and the development of a potentially immune-related AE is however inconsistent, thus there is no clear association between the two.

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

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 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. The safety database is however limited and no data beyond 52 weeks is available. However, there is no scientific rationale for anticipating a different safety profile for long-term use in paediatric patients.

2.5.2. Conclusions on clinical safety

Exenatide was generally well-tolerated in paediatric patients aged 10 to 17 years with T2DM. The safety findings in study BCB114 were consistent with those observed in the adult population with T2DM in the currently approved label. No new safety concerns arise from the data presented. Furthermore, there is no scientific rationale for anticipating a different safety profile for long-term use in paediatric patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 35.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

With this submission, no changes to the safety concerns, PhV activities or RMMs are proposed, which is endorsed. The PRAC considered that the risk management plan version 35.1 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to include information on the paediatric population. The Package Leaflet is updated accordingly.

Please refer to Attachment 1 which includes all changes to the Product Information as adopted by the CHMP

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Only minor changes are proposed for the Package Leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

The indication is extended to include "*adolescents and children aged 10 years and above"*.

3.1.2. Available therapies and unmet medical need

Management of T2DM in children involves lifestyle modifications. Pharmacologic glucose-lowering treatment is often necessary and includes metformin or insulin or a combination of both. Recently, a GPL1-RA (liraglutide) has been approved for the use in children aged 10 or older.

The rapid progression of T2DM in children in terms of beta-cell function deterioration, time to treatment failure and development of complications, with associated poor glycaemic control, calls for an urgent need for additional effective, well tolerated and easily administered treatments to achieve and maintain target HbA1c levels as early as possible in children with T2DM.

3.1.3. Main clinical studies

Study BCB114 was Phase III, double-blind, randomized, placebo-controlled, international study that included male and female patients 10 to 17 years of age with T2DM treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening.

The study included patients with an HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and with an HbA1c of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at screening, and patients with a C-peptide of > 0.6 ng/mL at screening.

The study comprised 4 periods: a screening period (5 weeks); a double-blind, placebo-controlled assessment period (24 weeks); an open-label, uncontrolled extension period (28 weeks); and a post-treatment follow-up period (10 weeks).

The primary efficacy objective of the study was to assess the effect on glycaemic control, as measured by HbA1c, of EQW following 24 weeks of treatment compared with placebo. Secondary endpoints included FPG, body weight, fasting insulin, the percentage of patients requiring rescue treatment and the percentage of patients who achieving HbA1c goals (< 6.5%, ≤ 6.5% and < 7.0%). The primary and secondary efficacy objectives were assessed at Week 24, but also exploratively at Week 52, to assess the long-term trend of glycaemic control.

A total of 83 patients (EQW, 59; placebo, 24) 10 to 17 years of age were randomized and 82 (EQW, 58; placebo, 24) received treatment during the 24-week controlled assessment period. A total of 72 patients (EQW, 49; placebo, 23) received treatment with EQW during the 28-week open-label extension period.

The demographic, patient and baseline disease characteristics were representative of the intended population. Compliance was generally high and similar between treatment groups in both during the 24-week controlled assessment period and the 52-week open-label treatment period.

3.2. Favourable effects

The study BCB114 met the primary endpoint, showing a LS mean difference in change in HbA1c from baseline of -0.85% (95%CI: -1.51, -0.19; p = 0.012) in favour of the EQW group after 24 weeks. The sensitivity analyses support the primary analysis. Treatment with EQW led to an adjusted mean change from baseline (LS mean) in HbA1c of -0.36%, whereas the HbA1c in the placebo treated group increased by 0.49%.

The proportion of patients achieving HbA1c goals (< 6.5%, ≤ 6.5%, and < 7.0%) was 15 to 23 % higher in the EQW group vs placebo.

The LS mean difference in the secondary endpoint FPG (-1.20 mmol/L, 95%CI: -2.72, 0.32) was not statistically significant but numerically in favour of the EQW group.

The reduction in body weight was numerically greater for the EQW group (-0.59 kg vs +0.63 kg in the placebo group) throughout the whole study. A similar trend was seen for BMI.

There were no meaningful differences between treatment groups in fasting insulin at week 24.

None of the other secondary endpoints (lipids, blood pressure) rendered any meaningful difference between study groups.

Efficacy outcomes were also evaluated in the open-label extension period. In the EQW treated group, mean HbA1c decreased from baseline through Week 12 of the study, and then began to gradually increase, returning to approximate baseline levels by Week 52 (mean change from baseline of -0.10%). The reduction in FPG and body weight observed with the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52.

The proportions of patients achieving HbA1c goals (<6.5%, ≤6.5%, and <7%) with the first 24 weeks of EQW treatment were sustained through Week 52.

The patients that switched from placebo to EQW at week 24 showed an initial decrease in HbA1c up to week 40, but then the HbA1c appeared to increase again. The number of patients achieving the treatment goals in this group increased from 4.5-9.1% at week 24 to 23.5-29.4% at week 52.

3.3. Uncertainties and limitations about favourable effects

Antibodies to exenatide were observed in the majority of patients (93.0%) in the EQW group at any time during the study, and 63% had a high titer. The neutralising capacity of these antibodies has not been investigated. According to the SmPC, approximately 45% of adult patients had low titer antibodies to exenatide at study endpoint, and 12% had high antibody titers. The proportion of adolescents/children with high antibody titers and potentially loss of efficacy is thus higher than in the adult population. The mean reduction in HbA1c seem to decrease with increasing antibody titres. However, no prediction can be done in the individual patient. Because no commercial test for ADA is available, the decision whether to continue treatment with Bydureon should be made by the clinician based on the observed HbA1c reduction and the achievement of the individual HbA1c goal in each patient. Warnings and recommendations on the risk of lack of efficacy due to anti-drug antibodies have been included in the SmPC, which is considered sufficient.

There is a lack of data on the persistence of the effect beyond 24 weeks, since the open-label extension of the study did not include a placebo-treated control.

3.4. Unfavourable effects

The safety database is limited to 59 subjects treated with EQW in the 24 Week controlled assessment period and 72 subjects treated with EQW in the extension period (EQW group and placebo → EQW group).

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. In the controlled assessment period, the overall incidence of AEs was lower in the EQW group vs placebo (61% vs 74%). The incidence of SAEs was also low, with in total 7 events reported for the entire study period. In the controlled assessment period, 2 subjects (3.4%) in the EQW group reported a SAE compared to 3 subjects (4.3%) in the placebo treated group. In the extension period, a total of 4 SAEs were reported.

None of the SAEs were considered related to treatment by the Investigator. In the controlled assessment period, the reporting of treatment related AEs was slightly higher in the EQW group (15 subjects; 25.4%) compared to the placebo group (5 subjects; 21.7%). No deaths were reported in the study.

The most common AEs reported in the EQW group were upper respiratory tract infection (10.2%) whereas abdominal pain was the most common AEs reported in the placebo group (13.0%). Most AEs were mild or moderate in intensity. The incidence of GI-related AEs was comparable between the EQW and placebo groups (22.0% and 26.1%) during the controlled assessment period. The most frequent gastrointestinal disorder-related AEs were diarrhoea, nausea, vomiting, and upper abdominal pain. These events were more frequently reported in the EQW group.

There were no major hypoglycaemic events reported during the study. The occurrence of any hypoglycaemic event was somewhat higher in the EQW group (8 subjects; 13.6%) than in the placebo group (1 subject; 4.3%), out of which one minor hypoglycaemia was reported in each of the study groups.

The proportions of patients experiencing injection site reactions was low (8.5%) and comparable between the study groups. No injection site reactions were reported after Week 12. Of note, all injection-site reactions were reported among patients using the prefilled syringe device.

Out of 55 patients who were positive (n=55) for exenatide antibodies, 6 patients reported a potentially immune-related AE compared to no events reported by the 3 patients who were negative for exenatide antibodies. Three subjects in the placebo group reported potentially immune-related AEs. The relationship between the timing of the development of ADA and the development of a potentially immune-related AE is however inconsistent, thus there is no clear association between the two.

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

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 was similar between study groups.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited to 59 subjects treated with EQW in the controlled assessment period and 72 subjects treated with EQW in the extension period (EQW group and placebo → EQW group). Thus, the safety data set is limited. The need for further follow-up of long-term safety in the paediatric population has been discussed with the Applicant within this procedure, coming to the conclusion that no changes to the currently approved RMP are deemed necessary as part of this application, as there is no scientific rationale for anticipating a different safety profile for long-term use in paediatric patients.

3.6. Effects Table

Effects Table for Bydureon in the treatment of children >10 years of age with T2DM (data cut-off: 06 August 2020.)

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Prim end-point	change from baseline in HbA1c (%) at Week 24	LS mean (SE) (95% CI)	-0.36 (0.184) (-0.73, 0.00)	0.49 (0.273) (-0.06, 1.03)	-0.85 (0.330) (-1.51, -0.19) P=0.012	Study BCB 114
Sec end-point	Change from baseline in FPG (mmol/L) at Week 24	LS mean (SE) (95% CI)	-0.29 (0.424) (-1.13, 0.56)	0.91 (0.628) (-0.34, 2.17)	-1.20 (0.760) (-2.72, 0.32) P=0.119	
Sec end-point	Change from baseline in weight (kg) at Week 24	LS mean (SE) (95% CI)	-0.59 (0.665) (-1.92, 0.73)	0.63 (0.982) (-1.33, 2.59)	-1.22 (1.189) (-3.59, 1.15)	
Unfavourable Effects (randomized period – 24 weeks)						
Any AE		n (%)	36 (61.0)	17 (73.9)		
Any SAE including events with outcome of death		n (%)	2 (3.4)	1 (4.3)		
Any AE related to study medication		n (%)	15 (25.4)	5 (21.7)		
GI-disorders (SOC)		n (%)	13 (22.0)	6 (26.3)		
Metabolism and nutrition disorders (SOC)		n (%)	7 (11.9)	2 (8.7)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The incidence of T2DM in children is increasing worldwide, although still relatively rare in Europe, and the main driver is the increased prevalence and degree of childhood obesity. Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

Treatment options are limited in children as currently only metformin, insulin and one GLP-1RA (liraglutide) are approved for the use in paediatric patients.

In study BCB114, a treatment difference in HbA1c of -0.85% was observed between EQW and placebo after 24 weeks. As opposed to what is often observed in studies with adult patients with T2DM, the HbA1c increased in the placebo treated group during the controlled assessment period of 24 weeks. A similar pattern was observed in the study supporting the paediatric indication for liraglutide QD and this gives some indication on the difficulties in treating the paediatric population with T2DM. The secondary endpoints, FPG and body weight, did not reach statistical significance but were in favour of EQW and the proportion of patients achieving HbA1c goals (< 6.5%, ≤ 6.5%, and < 7.0%) was 15 to 23 % higher in the EQW group vs placebo. Thus, a clinically relevant and statistically significant effect of EQW on glycaemic control, as reflected by the change in HbA1c, has been shown.

Antibodies to exenatide were observed in the majority of patients (93.0%) in the EQW group at any time during the study, and 63% had a high titer. The proportion of adolescents/children with high antibody titers and potential loss of efficacy is higher than reported in the adult population. The mean reduction in HbA1c seem to decrease with increasing antibody titres. However, no prediction can be done in the individual patient. Because no commercial test for ADA is available, the decision whether to continue treatment with Bydureon should be made by the clinician based on the observed HbA1c reduction and the achievement of the individual HbA1c goal in each patient. Warnings and recommendations on the risk of lack of efficacy due to anti-drug antibodies have been included in the SmPC, which is considered sufficient.

There is a lack of data on the persistence of the effect beyond 24 weeks, since the open-label extension of the study did not include a placebo-treated control.

The safety database is limited to 59 subjects treated with EQW for 24 weeks in the controlled assessment period and 72 subjects treated with EQW in the extension period.

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 GI-related AEs was comparable between the EQW and placebo groups (22.0% and 26.1%) during the controlled assessment period. There were no major hypoglycaemic events reported during the study.

Potentially immune-related AEs were only reported by EQW treated subjects who were positive for exenatide antibodies, however, 3 subjects in the placebo group also reported potentially immune-related AEs. Thus, there is no clear relationship between ADAs and the development of a potentially immune-related AEs.

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. The safety database is however limited and no data beyond 52 weeks is available. However, as there is no scientific rationale for anticipating a different safety profile for long-term use in paediatric patients, no changes to the safety specification are warranted as part of this application.

3.7.2. Balance of benefits and risks

Exenatide prolonged release showed a clinically relevant and statistically significant effect on metabolic control compared to placebo after 24 weeks of treatment. The treatment seems to be well tolerated in this age group. 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.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The benefit risk balance for Bydureon in the treatment of adolescent and children aged 10 years and above is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from Study BCB114 (D5551C00002); 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, which was initially submitted and assessed by the CHMP as part of the post-authorisation measure (PAM) P46 028. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet. Version 35.1 of the RMP was agreed during the procedure.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0064/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.