12 October 2017
EMA/717429/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bydureon

International non-proprietary name: exenatide

Procedure No. EMEA/H/C/002020/II/0045

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

ADA	American Diabetes Association
AE	Adverse event
BMI	Body mass index
BP	Blood pressure
BOCF	Baseline Observation Carried Forward
CSR	Clinical study report
CR	Copy reference
CV	Cardiovascular
DBP	Diastolic blood pressure
DCP	Dual chamber pen
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EQW	Exenatide once weekly
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Hemoglobin A1c
ITT	Intent-to-treat
LS	Least-squares
MTT	Meal tolerance test
MMRM	Mixed model with repeated measures
MNAR	Missing not at Random
NDA	New Drug Application
PI	Prescribing Information
PPG	Postprandial glucose
SAE	Serious adverse event
SBP	Systolic blood pressure
SDT	Single dose tray
sNDA	Supplemental New Drug Application
SOC	System organ class
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione

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 31 May 2017 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 treatment in combination with basal insulin for Bydureon; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on the study D5553C00002 (Duration 7 study) which evaluated safety and efficacy of exenatide once weekly therapy added to titrated basal insulin in patients with type 2 diabetes who have inadequate glycaemic control on basal insulin with or without metformin. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in sections 4.8 and 5.1 of the SmPC. Furthermore, the updated RMP version 26 has been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0130/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0130/2016) was not yet completed as some measures were deferred.

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 applicant 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
Rapporteur's preliminary assessment report circulated on:	11 August 2017
PRAC Rapporteur Assessment Report circulated on:	11 August 2017
PRAC Outcome	1 September 2017
Request for supplementary information adopted by the CHMP on:	14 September 2017
MAH's responses submitted to the CHMP on:	18 September 2017
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 September 2017
CHMP opinion:	12 October 2017

2. Scientific discussion

2.1. Introduction

The purpose of this application is to provide information on the efficacy and safety of concomitant add-on treatment with exenatide once weekly (prolonged-release exanatide) to titrated basal insulin with or without metformin, supporting addition of new study data to the Summary of Product Characteristics (SmPC), section 5.1.

As combination with insulin is not covered by the current indication, SmPC, section 4.1 has been updated. The MAH proposes to simplify the wording to be in line with more recently approved glucose-lowering agents including other glucagon-like peptide-1 receptor agonists (GLP-1RAs).

It should be noted that the wording of the indication was updated within procedure EMEA/H/C/2020/II/41, which got a positive opinion by the CHMP in July 2017. Thus with this procedure, the indication is only updated to include "basal insulin".

Proposed indication:

Bydureon is indicated in adults 18 years and older 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 (see section 4.4, 4.5 and 5.1 for available data on different combinations).

Exenatide once weekly (prolonged-release exanatide)

Exenatide, a GLP-1RA, exerts its glycaemic-lowering effect by enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying. In addition, it lowers weight by inducing satiety through central mechanisms.

Rationale for combination therapy with exenatide and basal insulin

Type 2 diabetes is a progressive disease that is characterised by defects in multiple organ systems and usually requires combination therapy with agents that target different pathways. Because physiological defects may be manifested differently in individual patients, and patients differ in their care needs due to differences in demographics, comorbidities, individual preferences and other factors, individualisation of diabetes management is emphasised in international guidelines as essential for successful diabetes care.

The availability of various types and combinations of diabetes therapy is consistent with this emphasis on patient-centered care.

Because of their differing and complimentary mechanisms of action, the combination of exenatide and basal insulin glargine was expected to be a more effective treatment strategy than intensification of basal insulin therapy alone. Basal insulin treatment primarily improves FPG, and exenatide has a significant effect on PPG via its postprandial effects. The body weight loss associated with exenatide was expected to mitigate the weight gain associated with insulin, and the gradual onset of action and glucose-dependent mechanism of action of exenatide were not expected to exacerbate the risk of hypoglycaemia associated with insulin. Additionally, the weekly administration of EQW and the lack of a requirement for monitoring would not add significantly to the patient burden associated with insulin therapy.

The clinical programme for this submission consists of a single Phase 3 study, Study D5553C00002. A 28-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 3 trial to evaluate the safety and efficacy of once weekly exenatide therapy added to titrated basal insulin glargine compared to placebo added to titrated basal insulin glargine in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control on basal insulin glargine with or without metformin.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

No environmental risk assessment was performed because exenatide, as a moderately sized naturally-occuring peptide, is unlikely to result in significant risk to the environment, in line with the current ERA guideline (CPMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Study ID	Objectives of the study	Design and duration	Study drugs Background therapy Route of administration	Number of subjects randomized/ treated	Gender (M/F) Mean age (range)	Population
D5553C00002	Efficacy and safety	Randomized, double-blind, active-controlled, multi-center, Phase 3 Duration: 28 weeks	EQW 2 mg (injection) versus EQW Placebo (injection) Background: Basal insulin ≥ 20 units/day with or without Metformin (≥1500 mg/day)	EQW: 233/232 Placebo: 231/231	48% M 52% F 58 yrs (20 to 80 yrs)	T2DM, ≥18 years, HbA1c ≥7,5% to ≤12%, CrCl ≥30 mL/min

2.3.2. Pharmacokinetics

An exploratory object was to characterize the pharmacokinetic (PK) of exenatide following 2 mg subcutaneous injections once weekly.

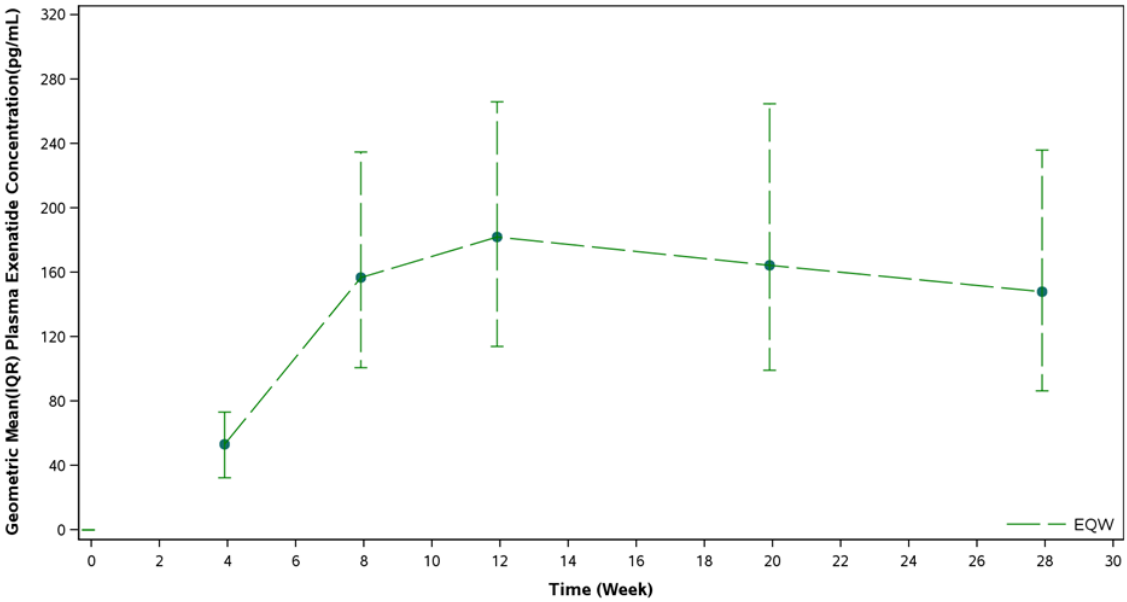
Sparse PK samples were taken regularly and plasma concentrations of exenatide were determined by the use of a validated ligand binding assay. The presences of anti-drug antibodies (ADA) was also determined.

All together 214 patients were included in the PK evaluation.

Historically plasma concentrations of exenatide associated with high titers of ADA >625, have been excluded from the PK analyses which were also done in the current study.

Below figure shows the plasma concentration-time profile of exenatide in patients with ADA ≤625. Steady state was reached after about eight weeks treatment. Geometric mean (SE) steady state was calculated to 161(8) pg/ml.

Geometric mean plasma concentration *versus* time of exenatide following 2mg sc once weekly, ADA titer ≤625



Higher steady state levels were determined in subjects diagnosed with renal impairment (Table 1).

Table 1 Geometric mean (SE) steady state levels of exenatide following 2mg sc once weekly (ADA titer ≤625) in subjects diagnosed with renal impairment

Renal function	Steady state (pg/ml)
Normal (n=85)	139 (9)
Mild (n=93)	160 (12)
Moderate (n=15)	397 (87)

Patients with BMI ≥30 kg/m2 had similar steady state levels 158 (9) pg/ml to those with BMI >25 and <30 kg/m2 162 (19) pg/ml. Only nine patients included had a BMI of <25 kg/m2, with a steady state calculated to 223 (6) pg/ml.

2.3.3. Conclusions on clinical pharmacology

Descriptive PK shows a steady state after about eight weeks treatment. Higher steady state levels were seen in subjects with decreased renal function. Patients with BMI ≥30 kg/m^2 had comparable steady state concentrations as subjects with a BMI of >25 and <30 kg/m^2.

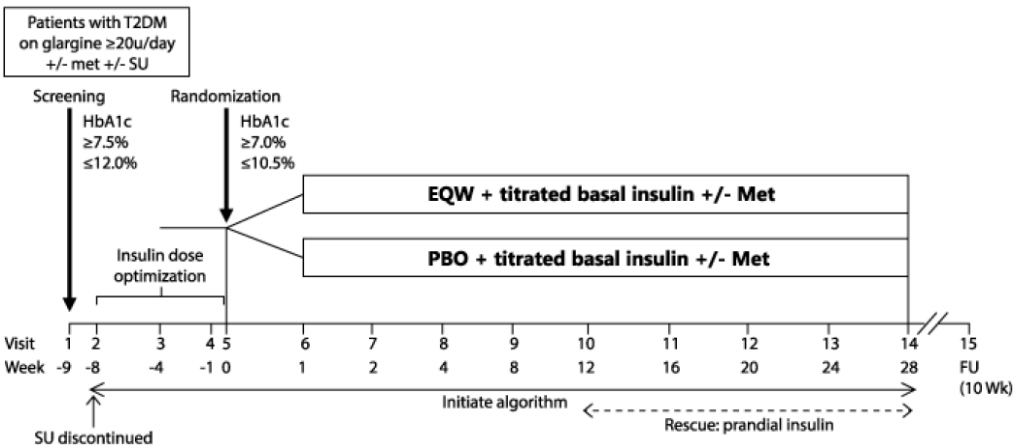
2.4. Clinical efficacy

2.4.1. Main study

Study D5553C00002. A 28-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 3 trial to evaluate the safety and efficacy of once weekly exenatide therapy added to titrated basal insulin glargine compared to placebo added to titrated basal insulin glargine in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on basal insulin glargine with or without metformin.

Methods

Study D5553C00002 was a 28-week, randomized, double-blind, active-controlled, multicentre, Phase III efficacy and safety study of EQW 2 mg versus placebo as add-on treatment to titrated basal insulin in patients with T2DM who had inadequate glycaemic control on titrated basal insulin with or without metformin, and with or without an SU (discontinued at Week -8).



EQW=exenatide once weekly; HbA1c=glycated hemoglobin A1c; Met=metformin; PBO=placebo; SU=sulfonylurea; T2DM=Type 2 diabetes mellitus.

Study participants

Inclusion / exclusion criteria

Patients were included in the study if they were treated with basal insulin glargine at a dose of ≥20 units/day once daily for at least 6 weeks prior to Screening, in combination with diet and exercise alone or in combination with:

- a stable dose of metformin (≥1500 mg/day) for at least 8 weeks prior to Visit 1 (Screening)
- a stable dose of metformin (≥1500 mg/day) for at least 8 weeks prior to Visit 1 (Screening) and a stable dose of SU for at least 8 weeks prior to the Screening visit.

Exclusion criterias included administration of any antihyperglycaemic therapy, other than SU, insulin, or metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to Visit 1 (Screening). In addition, administration of any antihyperglycaemic therapy, other than SU, insulin, or metformin, at any dose, at any time during the 4 weeks prior to Visit 1 (Screening).

Also excluded were patients who had been treated, were currently being treated, or were expected to require or undergo treatment with any of the following treatment-excluded medications:

- any DPP-4 inhibitor within 3 months prior to Visit 1 (Screening)

- systemic corticosteroids within 3 months prior to Visit 1 (Screening) by oral, intravenous, intra-articular, or intramuscular route; or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption.
- prescription or over-the-counter weight loss medications within 3 months prior to Visit 1 (Screening).

Background therapy

Patients were treated with basal insulin glargine at a dose of ≥20 units/day once daily for at least 6 weeks prior to screening. Insulin glargine dose was optimized according to the INITIATE algorithm during the insulin dose optimization phase and throughout the treatment phase of the study. The Investigator could have deviated from this algorithm if necessary according to his/her clinical judgment. Glucose control was optimized by (further) titrating the insulin glargine dose, aiming to achieve a fasting plasma glucose (FPG) of 4,0–5,5 mmol/l without hypoglycaemia. Adjustments were made at scheduled visits and in between visits by both Investigators and patients. Dose changes (if any), were based on the average of 3 consecutive measurements (on different days) of fasting blood glucose levels.

The INITIATE algorithm

Fasting[a] glucose mmol/L	(mg/dL)	Dose change of glargine (units)
<4.0	(<72)	-2[b]
4.0-5.5	(72-99)	0
5.6-8.5	(100-153)	+2
>8.5	(>153)	+4

[a] Fasting means before breakfast.
[b] Decrease the dose of insulin glargine by 2 units if fasting blood glucose is lower than 4.0 mmol/L (<72 mg/dL) and symptomatic hypoglycemia occurs without reason.

A majority of patients (84% in EQW group, 81% in placebo group) were treated with a stable dose of metformin (≥1500 mg/day) for at least 8 weeks prior to screening. Up to week 28, patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Metformin is recommended as the initial pharmacological therapy in both the United States (US) and the European Union (EU).

Exenatide

The 2 mg dose was used for this study as it is the dose that was studied in the Phase III program, and is the only approved dose of exenatide once weekly.

Rescue

During 28-Week randomised treatment period, patients with inadequate glycaemic control based on progressively stricter glycaemic criteria (table below) remained in the study and received open-label rescue therapy with prandial insulin while they continued receiving study medication.

Period	Central laboratory FPG
From Week 12 to Week 18 (excluding Week 18)	FPG >270 mg/dL (15 mmol/L)
From Week 18 to Week 24 (excluding Week 24)	FPG >240 mg/dL (13.2 mmol/L)
From Week 24 to Week 28 (including Week 28)	FPG >200 mg/dL (11.1 mmol/L)

FPG=fasting plasma glucose.

Patients who met rescue criteria in the double-blind Treatment Period first completed the Rescue Visit procedures (equivalent to the Week 28 assessments) before receiving open-label rescue therapy, to ensure that important study endpoint measurements were collected.

Objectives

Primary objective

To compare the change from baseline in haemoglobin A1c (HbA1c) achieved with EQW added to titrated basal insulin glargine to placebo added to titrated basal insulin glargine, with or without metformin, after 28 weeks of double-blind treatment.

Secondary objectives

To compare the effect of EQW added to titrated basal insulin glargine, with or without metformin, to placebo added to titrated basal insulin glargine, with or without metformin, on changes in glycaemic control and anthropometric measures.

Outcomes / endpoints

Primary endpoint

The primary endpoint was change in HbA1c from baseline to Week 28.

Secondary endpoints

Glycaemic

- Change in 2-hour PPG after a standard meal tolerance test (MTT) at Week 28.
- Proportion of patients achieving HbA1c <7.0% at Week 28.
- Change in total mean daily insulin dose from baseline to Week 28.
- Proportion of patients with HbA1c <7.0% at Week 28 with no body weight gain at Week 28 and no major hypoglycaemia over 28 weeks.

Body weight

- Change in body weight from baseline to Week 28.

Blood pressure

- Change in SBP from baseline to Week 28.

Sample size

Sample size was estimated to be 209 patients per treatment group, assuming:

- Mean difference of 0.35% in HbA1c change from baseline
- Standard deviation of 1.1%
- Testing at 2-sided α=0.05
- 90% power to detect treatment differences.

Assuming a 5% dropout rate prior to Week 4 (Visit 8), the first visit where HbA1c was tested, 220 patients per treatment arm (a total of 440 patients) would have had post-baseline measurements of HbA1c and thus would have been included in the ITT analysis of the primary objective. Assuming 40% of screened patients failed to meet enrolment criteria and 25% of the patients who met enrolment criteria

failed to meet the randomization criterion after the dose optimization phase, approximately 978 patients were to be screened.

Randomisation

Patients who meet all criteria for this study were randomized to double-blind treatment at Visit 5. Assignment to treatment groups were determined by a computer-generated random sequence using an IVRS.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization; patients will be randomized to 1 of the 2 treatment groups in a 1:1 ratio. If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence. Random assignment to study treatment were stratified by HbA1c stratum (<9.0% or ≥9.0%), and diabetes management method (SU use or non-SU use).

Blinding (masking)

This was a double-blind study. Patients, the investigator, study site personnel, and sponsor personnel involved with data review and analysis will remain blinded to study treatment throughout the study. To preserve the blinding, access to the treatment codes will be limited to personnel not involved in the daily conduct of the study or data review and analysis.

The results central laboratory for FPG and HbA1c are blinded to the Investigator for all visits except Visits 1-5. FPG values are blinded to the investigator site until the unblinding criteria for rescue therapy are met. If the criteria for rescue therapy are met, a report will be sent to the site for an individual subject. Previous values will remain blinded and the site will only receive the values going forward from the point the criteria were met.

Statistical methods

Different analysis sets were defined:

The Randomized analysis set consisted of all patients who signed informed consent and who were randomized to a treatment group. Analysis performed for this Randomized population was according to the treatment group to which patients were assigned (regardless of whether or not they receive study drug).

The Intention to treat (ITT) analysis set, the primary efficacy analysis set, included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment, with patients being analyzed as randomized, rather than as treated.

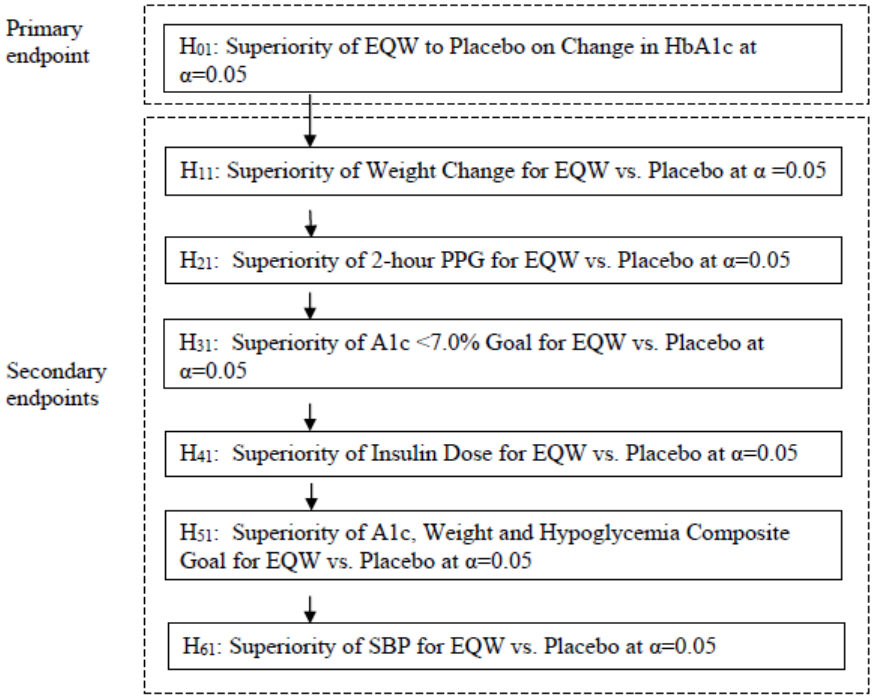
The Per-protocol (PP), the secondary efficacy analysis set, was a subset of the ITT without important protocol violations. Patients excluded from the PP analysis were identified prior to database lock and treatment unblinding.

All statistical tests were conducted at a 2-sided significance level of 5% unless otherwise specified. Where appropriate, model-based point estimates, together with their 95% confidence intervals (CIs), were presented along with the 2-sided p-values for the tests.

The multiplicity adjustment procedures to protect the family-wise type I error rate for the primary endpoint and secondary endpoints are described in Figure 1. Each hypothesis test served as a serial gatekeeper for the tests placed later in the sequence, i.e., the null hypothesis for no treatment difference must have been rejected in order to proceed to the next hypotheses. If a null hypothesis for no treatment difference could not be rejected, all subsequent hypothesis testing stopped. All nominal p-values for the

secondary analysis are presented. All other analyses for exploratory efficacy endpoints were evaluated at a 2-sided significance level of 5% without multiplicity adjustment.

Figure 1. Hypothesis testing procedure



The primary efficacy analysis was to compare treatment arms with respect to change from baseline in HbA1c at Week 28 for the intent-to-treat (ITT) analysis set. The difference between treatment groups was estimated using an MMRM. Factors in the MMRM model included treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), baseline SU-use stratum (yes vs. no in prior SU usage), week, and treatment-by-week interaction as fixed effects. Baseline measurement of HbA1c was included as a continuous covariate for primary efficacy analysis.

An unstructured covariance structure was used to model the within-patient errors, unless the model did not converge, in which case the covariance matrix was to be decided upon model convergence status and the Akaike information criterion. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

The least-squares (LS) means for change from baseline by visit and treatment, the SEs, and the corresponding 95% CIs, as well as the LS mean treatment differences, SEs for the LS mean treatment differences, the 95% CIs around the LS mean treatment differences, and the p-values for between treatment group comparisons, were derived from the MMRM.

If a patient's last available measurement during the 28-week assessment period was from an unscheduled visit or Early Termination visit, the value was programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. No other missing data imputation was performed.

Data collected after the initiation of the glycaemic rescue therapy or at the post-treatment Follow-up visits after a premature treatment discontinuation, were excluded from the analysis.

For all secondary continuous variables for which multiple post-baseline measurements were collected, the MMRM model was applied as the main analysis. Data collected after the initiation of the glycaemic rescue therapy or at the post-treatment Follow-up visits after a premature treatment discontinuation were excluded, except for blood pressure-related endpoints, where data after rescue were included.

Change from baseline in postprandial glucose (PPG) was analysed by an ANCOVA model. The observed value and change in 2-hour PPG from baseline to Week 28 was also summarized descriptively by treatment for the ITT analysis set. The ANCOVA model included treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), and baseline SU-use stratum (yes vs. no in prior SU usage) as fixed effects and the baseline value of 2-hour PPG as a covariate. The LS mean in each treatment group at Week 28, the SE, and the corresponding 95% CI, as well as the LS mean difference between treatment groups, the SE, the 95% CI, and the p-value, were derived and presented from the ANCOVA model.

Proportions of patients achieving HbA1c target values of <7.0% at Week 28 were summarized and compared by treatment using a CMH test stratified by baseline HbA1c stratum (<9.0% or ≥9.0%) and baseline SU-use stratum for ITT analysis set. The general association statistics were provided. All patients with missing endpoint data were treated as non-responders.

Supportive analyses

For the primary endpoint, supportive analyses were done using the same MMRM model as in the primary analysis but based on the PP analysis set and the Randomized analysis set.

To further support the primary endpoint analysis, an ANCOVA examining the last available observation prior to receiving rescue therapy in ITT analysis set was conducted. The model specification is the same as the ANCOVA described above.

In addition, to provide a comprehensive view of the treatment effect in accordance with the ITT principle, data collected post rescue therapy and post discontinuation of study medication were included in the following sensitivity analyses:

1. HbA1c measurements collected during the study period, including those collected after the initiation of rescue medication or after discontinuation of study medication, were analysed using the same MMRM model as that for the primary efficacy analysis in HbA1c.
2. HbA1c measurements collected during the study period, including those collected after the initiation of rescue medication, but excluding data collected after discontinuation of study medication, were analysed using the same MMRM model as that for the primary efficacy analysis.

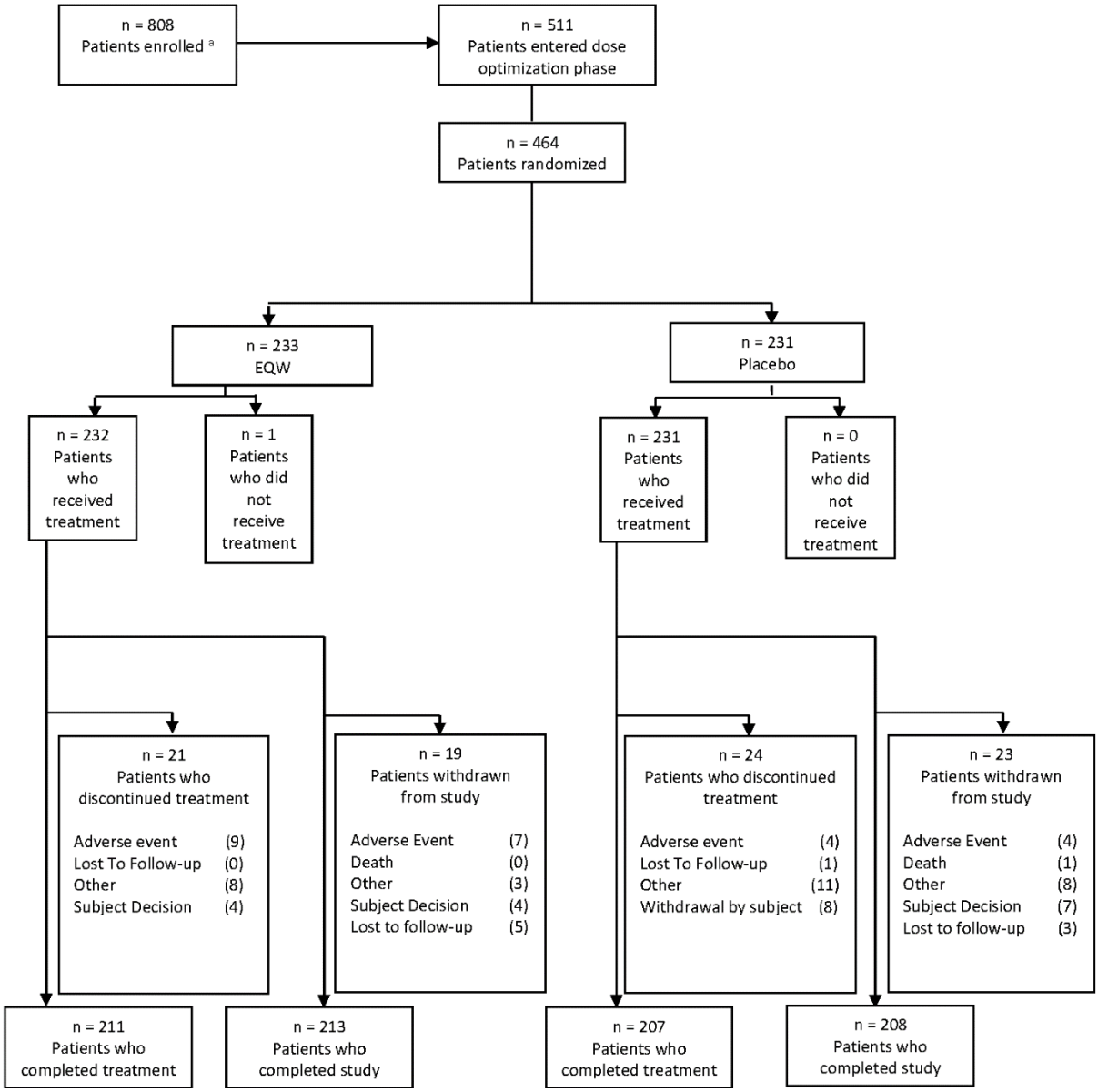
To address the possible violations of the missing at random (MAR) assumption, 2 additional methods of sensitivity analyses based on missing not at random (MNAR) assumption were conducted. The first method was the copy reference (CR) analysis and the second method was the tipping point analysis.

The CR method assumes that patients from the experimental treatment arm who discontinue the study treatment early or initiate a rescue therapy will follow the trajectory of outcomes in the control arm after treatment discontinuation/initiation of rescue therapy. The tipping point method considers an MNAR mechanism that patients from the experimental treatment arm who discontinue study treatment prematurely or who initiate a rescue therapy would have, on average, their efficacy values post rescue/post treatment discontinuation worse by some amount delta compared to efficacy values of similar patients who continue with the study treatment and do not require rescue therapy. The aim of the tipping point analysis is to find a “tipping point” corresponding to a value of delta where the study conclusion of a significant treatment effect would no longer hold. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided.

Additional sensitivity analyses for HbA1c were also performed to exclude patients who were screened or randomized multiple times. Such patients to be excluded from the analysis were identified by clinical operations with reason of exclusion prior to database lock.

Results

Participant flow



Recruitment

A total of 808 patients enrolled in this study from 126 centers in Hungary, Poland, Romania, Slovakia, South Africa and the US. The first subject was enrolled 06 September 2014 and the last subject last visit for 28-week Treatment Period was 29 August 2016.

Conduct of the study

Changes in the conduct of the study

There were two amendments to the protocol dated 3 Oct 2014 and 20 Feb 2015. All amendments concerned clarifications on study procedures and are not considered to affect the outcome or interpretation of data.

Protocol deviations

A total of 15 patients (3.3%) had important protocol deviations: 8 patients (3.5%) in the EQW group and 7 patients (3.0%) in the placebo group.

Important Protocol Violations	Number (%) of patients EQW (N=231)	Placebo (N=230)	Total (N=461)
Total number of important protocol violations[a]	8	7	15
Number of patients with at least 1 important protocol violation	8 (3.5)	7 (3.0)	15 (3.3)
Systemic corticosteroids within 3 months prior to Screening (Visit 1); or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption prior to V1	1 (0.4)	2 (0.9)	3 (0.7)
Dispensed EQW used <70% or >130%	7 (3.0)	5 (2.2)	12 (2.6)

EQW=Exenatide once weekly + titrated basal insulin +/- metformin; N=number of patients in treatment group;
Placebo=Placebo + titrated basal insulin +/- metformin.
[a] The same patient may have had more than 1 important protocol violation.
Percentages are calculated from the number of patients in the ITT Analysis Set.

Baseline data

In general, baseline demographic characteristics were similar across the treatment groups. Overall, most patients randomized in this study were white (87.0%) The majority of patients in the ITT analysis set were from the United States (54.2%); approximately 41.0% were from Europe and the remainder was from South Africa (4.8%).

The mean age of patients in the study was 58 years and 48% of the patients were female. The mean height of patients in the study was 167.0 cm, and the mean weight was 94.02 kg. The mean BMI was 33.66 kg/m2, and most patients were in the obese (≥30 kg/m2) BMI group (70.1%).

In general, baseline disease characteristics were similar across the treatment groups. The mean baseline HbA1c was 8.5%. The mean duration of diabetes was 11 years. Sulfonylurea use at screening was reported by 34.9% of patients overall, with metformin use at baseline reported by 82.6% of patients overall. The mean glargine dose at Screening was 38.7 units/day in the EQW group and 39.0 units/day in the placebo group. After the insulin dose optimization phase, the mean glargine dose at baseline was 50.1 units/day in the EQW group and 52.0 units/day in the placebo group.

The mean baseline eGFR calculated by the Modification of Diet in Renal Disease (MDRD) method was 90.5 mL/min/1.73m2, and the result was similar when the CKD-EPI calculation method was used. Most patients had baseline eGFR (MDRD) ≥60 mL/min/1.73m2, with no patients having eGFR <30 mL/min/1.73m2.

In general, medical and surgical history was similar across the treatment groups. The most commonly reported medical history terms were hypertension (79.7%), hyperlipidaemia (36.7%), diabetic neuropathy (24.6%), and obesity (23.8%).The most commonly reported surgical history terms were hysterectomy (15.6%), cholecystectomy (9.9%), appendectomy (7.3%), and tonsillectomy (5.2%).

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarized below:

Table 2

	Number (%) of patients		
	EQW (N=233)	Placebo (N=231)	Total (N=464)
Patients included in safety analysis set	232 (99.6)	231 (100.0)	463 (99.8)
Patients included in ITT analysis set	231 (99.1)	230 (99.6)	461 (99.4)
Patients excluded from ITT analysis set	1 (0.4)	1 (0.4)	2 (0.4)
Missing required efficacy assessments	1 (0.4)	1 (0.4)	2 (0.4)
Patients included in Per-protocol analysis set	223 (95.7)	223 (96.5)	446 (96.1)
Patients excluded from Per-protocol analysis set	9 (3.9)	8 (3.5)	17 (3.7)
Important Protocol Violation	8 (3.4)	7 (3.0)	15 (3.2)
Missing required efficacy assessments	1 (0.4)	1 (0.4)	2 (0.4)

EQW=Exenatide once weekly + titrated basal insulin +/- metformin; Placebo=Placebo + titrated basal insulin +/- metformin.
Randomized analysis set includes all patients who signed informed consent and who are randomized to a treatment group.
Safety analysis set includes all patients who receive at least 1 dose of randomized study medication.
ITT analysis set includes all randomized patients who received at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.
Per-protocol analysis set is a subset of the ITT without important protocol violations.
All percentages are calculated based on the number of patients in the Randomized analysis set within each treatment group.

Outcomes and estimation

Primary efficacy endpoint

Change in HbA1c from Baseline to Week 28

Mean HbA1c decreased from baseline to Week 28 in both treatment groups. The least squares (LS) mean change in HbA1c was -0.96% for the EQW group and -0.23% for the placebo group. The difference in LS mean change between the EQW group and the placebo group was -0.73% ($p<0.001$)

Table 3 Change in HbA1c from baseline to Week 28 (ITT analysis set)[a]

	EQW (N=231)	Placebo (N=230)
n	206	207
Baseline mean (% [SD])	8.51 (0.917)	8.50 (0.903)
Week 28 mean (%[SD])	7.55 (1.195)	8.24 (1.103)
LS mean change (% [SE])	-0.96 (0.079)	-0.23 (0.079)
95% 2-sided confidence interval	(-1.11, -0.80)	(-0.38, -0.07)
LS mean difference from placebo (% [SE])	-0.73 (0.101)	
95% 2-sided confidence interval	(-0.93, -0.53)	
p-value[b]	<0.001	

Baseline is defined as the last non-missing assessment prior to first dose.
This analysis excludes measurements post rescue therapy and post premature discontinuation of study medication.

[a] Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 were modeled using a MMRM including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), baseline SU-use stratum (yes vs. no), week, and treatment by week interaction as fixed factors, and baseline value as a covariate. All Intent-to-treat patients are included in the MMRM analysis.

[b] p-values are based on a gatekeeping procedure using a hierarchical testing strategy.

EQW Exenatide once weekly + titrated basal insulin +/- metformin; HbA1c Hemoglobin A1c; ITT Intent-to-treat; LS mean Least squares mean; MMRM Mixed model with repeated measures; N Number of patients in treatment group; n Number of patients with observed baseline and week-28 values; Placebo Placebo + titrated basal insulin +/- metformin; SD Standard deviation; SE Standard error; SU Sulfonylurea.

Supportive analyses of the primary endpoint

The results for each of the planned supportive and sensitivity analyses were consistent with those of the primary analysis.

To provide a comprehensive view of the treatment effect in accordance with the pure ITT principle, data collected post rescue therapy or treatment discontinuation and post rescue therapy were included as additional supportive analyses using the same MMRM model as that for the primary efficacy analysis of HbA1c. Including measurements post rescue therapy or treatment discontinuation, the LS mean change in HbA1c was -0.94% for the EQW group and -0.24% for the placebo group. The difference in LS mean change between the EQW group and the placebo group was -0.70% ($p<0.001$).

These results are consistent with the primary MMRM analysis which was analysed without data collected post rescue therapy or treatment discontinuation.

Table 4

Final

Table 11.2.1.4 MMRM Analysis of Change in HbA1c from Baseline to Week 28 -Including Measurements after Initiation of Rescue Therapy or Treatment Discontinuation (Intent-to-treat Analysis Set)

Measurement: HbA1c Unit: %	EQW (N=231)	Placebo (N=230)
Summary Statistics		
n	212	213
Baseline Mean (SD)	8.50 (0.912)	8.51 (0.908)
Week 28 Mean (SD)	7.57 (1.217)	8.25 (1.090)
Adjusted Change from Baseline to Week 28 [a]		
LSMean (SE)	-0.94 (0.078)	-0.24 (0.078)
95% two-sided confidence interval	(-1.09, -0.79)	(-0.39, -0.08)
Difference from Placebo at Week 28 [a]		
LSMean (SE)	-0.70 (0.099)	
95% two-sided confidence interval	(-0.90, -0.51)	
P-value	<0.001	

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EQW=Exenatide once weekly + titrated basal insulin +/- metformin; Placebo=Placebo + titrated basal insulin +/- metformin.
HbA1c=hemoglobin A1c; LSMean=least squares means; MMRM=mixed model with repeated measures; N=Number of patients in treatment group; n=Number of patients with observed baseline and week-28 values; SD=Standard deviation; SE=Standard error; SU=sulfonylurea.
[a] Adjusted LSMean and treatment group differences in the change from baseline values at Week 28 are modeled using a MMRM including treatment, region, baseline HbA1c stratum (<9.0% or >=9.0%), baseline SU-use stratum (yes vs. no), week, and treatment by week interaction as fixed factors and baseline value as a covariate. All Intent-to-treat patients are included in the MMRM analysis. Baseline is defined as the last non-missing assessment prior to first dose.
This analysis includes measurements post rescue or after premature discontinuation of study medication.

Table 5

Table 11.2.4.4 ANCOVA Analysis of Change in HbA1c from Baseline to Week 28 (Intent-to-treat Analysis Set)

Measurement: HbA1c Unit: %	EQW (N=231)	Placebo (N=230)
Summary Statistics		
n	227	230
Baseline mean (SD)	8.54 (0.911)	8.53 (0.917)
Week 28 mean (SD)	7.59 (1.219)	8.30 (1.113)
Mean Change from baseline (SD)	-0.95 (1.116)	-0.23 (1.067)
Adjusted change from baseline to Week 28[a]		
LSMean (SE)	-1.01 (0.099)	-0.29 (0.099)
95% two-sided confidence interval	(-1.20, -0.81)	(-0.49, -0.10)
Difference from Placebo at Week 28[a]		
LSMean (SE)	-0.71 (0.096)	
95% two-sided confidence interval	(-0.90, -0.53)	
p-value	<0.001	

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EQW=Exenatide once weekly + titrated basal insulin +/- metformin; Placebo=Placebo + titrated basal insulin +/- metformin.
ANCOVA=Analysis of Covariance; HbA1c=hemoglobin A1c; LOCF=Last Observation Carried Forward; LSMean=least squares means; N=Number of patients in treatment group; n=Number of patients with observed baseline and week-28 values; SD=Standard deviation; SE=Standard error; SU=sulfonylurea.
[a] Adjusted LSMean and treatment group differences in the change from baseline values at Week 28 are modeled using ANCOVA including treatment, region, baseline HbA1c stratum (<9.0% or >=9.0%), baseline SU-use stratum (yes vs. no) as fixed factors and baseline value as a covariate.
Baseline is defined as the last non-missing assessment prior to first dose.
In this analysis missing values are imputed using LOCF.
This analysis excludes measurements post rescue therapy and post premature discontinuation of study medication.

The use of rescue medication was similar over the 2 treatment groups.

Table 6

Final

Table 11.1.22 Rescue Medications (Safety Analysis Set)

ATC classification/ Generic term	Number (%) of patients [a] EQW (N=232)		Placebo (N=231)		Total (N=463)	
Patients with any medication	4	(1.7)	4	(1.7)	8	(1.7)
INSULINS AND ANALOGUES FOR INJ,INTERMEDIATE-ACTING	1	(0.4)	1	(0.4)	2	(0.4)
INSULIN ASPART	1	(0.4)	1	(0.4)	2	(0.4)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	3	(1.3)	2	(0.9)	5	(1.1)
INSULIN ASPART	1	(0.4)	0		1	(0.2)
INSULIN GLULISINE	2	(0.9)	1	(0.4)	3	(0.6)
INSULIN LISPRO	0		1	(0.4)	1	(0.2)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	0		1	(0.4)	1	(0.2)
INSULIN GLARGINE	0		1	(0.4)	1	(0.2)

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EQW=Exenatide once weekly + titrated basal insulin +/- metformin; Placebo=Placebo + titrated basal insulin +/- metformin.
ATC=Anatomical Therapeutic Chemical; FPG=Fasting Plasma Glucose.
[a] Number (%) of patients with rescue medication, sorted alphabetically by ATC code and Generic term. A patient can have one or more Generic terms reported under a given ATC. If a Patient has more than one record under the same ATC/Generic term, then they are counted only once.
Rescue medications are defined as medication prescribed by the Investigator for patients who required rescue therapy (i.e., FPG rescue criteria met).
All percentages are calculated based on the number of patients in the analysis set within each treatment group.
AZ Drug Dictionary version 16.1.

Subgroup analyses of the primary endpoint

The following subgroups were tested for treatment-by-subgroup interactions for the primary endpoint (HbA1c): age group, sex, region, ethnic group, baseline BMI, baseline HbA1c, duration of T2DM, race, eGFR, and country. A potential subgroup-by-treatment interaction, based on a p-value of <0.1, was not observed for any of the pre-specified subgroups.

Secondary efficacy endpoints

Table 7

	EQW (N=231)	Placebo (N=230)
Glycaemic endpoints		
2-hour postprandial glucose (mmol/L)		
LS mean change (SE)[c]	-1.58 (0.318)	-0.06 (0.323)
95% 2-sided confidence interval	(-2.21, -0.96)	(-0.69, 0.58)
LS mean difference from placebo (SE)[c]	-1.52 (0.319)	
95% 2-sided confidence interval	(-2.15, -0.90)	
p-value[b]	<0.001	
HbA1c <7%		
Number (%) achieved HbA1c <7%[d]	75 (32.5)	17 (7.4)
95% 2-sided confidence interval[e]	(26.4, 38.5)	(4.0, 10.8)
Difference[f]	25.1	
p-value[b,g]	<0.001	
Insulin dose (units/day)[h]		
LS mean change (SE)[c]	1.6 (0.77)	3.6 (0.77)
95% 2-sided confidence interval	(0.1, 3.1)	(2.0, 5.1)
LS mean difference from placebo (SE)[c]	-2.0 (1.07)	
95% 2-sided confidence interval	(-4.1, 0.1)	
p-value[b]	0.068	
HbA1c <7% with no weight gain and no major hypoglycemia		
Number (%) achieved goal[d]	51 (22.1)	6 (2.6)
95% 2-sided confidence interval[e]	(16.7, 27.4)	(0.6, 4.7)
Difference[f]	19.5	
Nominal p-value[g,i]	<0.001	
Body weight endpoints		
Body weight (kg)		
LS mean change (SE)[a]	-1.04 (0.256)	0.46 (0.254)
95% 2-sided confidence interval	(-1.54, -0.54)	(-0.03, 0.96)
LS mean difference from placebo (SE)[a]	-1.50 (0.340)	
95% 2-sided confidence interval	(-2.17, -0.8477)	
p-value[b]	<0.001	

Blood pressure

Systolic blood pressure (mmHg)		
LS mean change (SE)[c]	-2.6 (0.93)	-0.7 (0.93)
95% 2-sided confidence interval	(-4.4, -0.7)	(-2.6, 1.1)
LS mean difference from placebo (SE)[c]	-1.8 (1.12)	
95% 2-sided confidence interval	(-4.0, 0.4)	
Nominal p-value[i]	0.105	

Baseline is defined as the last non-missing assessment prior to first dose.
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication.
Only the systolic blood pressure analysis includes measurements post rescue therapy but excludes data post premature discontinuation of study medication.

[a] Adjusted LS Mean and treatment group difference in the change from baseline values at Week 28 are modeled using a MMRM including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%) and baseline SU-use stratum (yes versus no) as fixed factors, and baseline value as a covariate. All Intent-to-treat patients are included in the MMRM analysis.

[b] p-value based on a gatekeeping procedure using a hierarchical testing strategy.

[c] Adjusted LS Mean and treatment group difference in the absolute change in 2-hour postprandial glucose at Week 28 are modeled using analysis of covariance including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), baseline SU-use stratum (yes versus no), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[d] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders.

[e] 95% confidence interval for the proportion is based on normal approximation to Binomial.

[f] Difference is the risk difference between the 2 proportions calculated separately from the Cochran-Mantel-Haenszel test.

[g] Treatment comparison is based on Cochran-Mantel- Haenszel test stratified by baseline HbA1c (<9.0% or ≥9.0%) and baseline SU-use (yes versus no). P-value is from the general association statistics.

[h] Daily insulin dose is the current value recorded on the case report form for each patient at baseline and at Week 28 (or last week while on study medication).

[i] Considered to be a nominal p-value because of the failure of the previous endpoint in hierarchical testing.

EQW Exenatide once weekly + titrated basal insulin +/- metformin; HbA1c Hemoglobin A1c; ITT Intent-to-treat; LS Least squares; MMRM Mixed model with repeated measures; Placebo Placebo + titrated basal insulin +/- metformin; SE Standard error; SU Sulfonylurea.

Glycaemic endpoints:

EQW was superior to placebo in reducing 2-hour PPG after a standard MTT at Week 28.

The difference between EQW and placebo for change from baseline to Week 28 in mean daily insulin dose was not statistically significant.

A larger proportion of patients in the EQW group (22.1%) achieved HbA1c <7.0% at week 28 with no weight gain and no major hypoglycaemia over 28 weeks than in the placebo group (2.6%). However, the comparison of proportions between treatments was not tested for statistical significance because the comparison of treatments for the previous secondary endpoint in the hierarchy of statistical analyses (i.e., change in daily insulin dose) was not statistically significant.

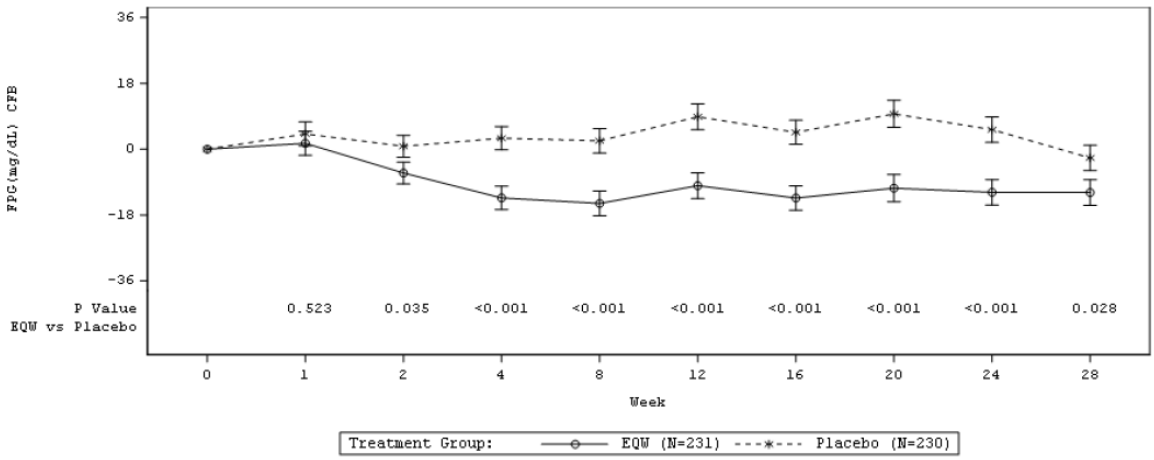
Fasting plasma glucose (FPG)

FPG was an exploratory end-point in the study. Basal insulin was titrated throughout the study in order to achieve the treatment target of FPG 4.0-5.5 mmol/L. There was a greater change in FPG from baseline to Week 28 in the EQW group compared to the placebo group.

The change in FPG over time from baseline to Week 28 is presented graphically in Figure 2. Mean FPG decreased from Week 1 to Week 4 and then remained stable over time for the EQW group; there were no relevant changes in FPG over time for the placebo group.

Figure 1

Change in Fasting Plasma Glucose (FPG) Over Time, LSMean (SE) – 28-Week Treatment Period- Conventional (US) Units (Intent-to-treat analysis Set)



EQW=Exenatide once weekly + titrated basal insulin +/- metformin; Placebo=Placebo + titrated basal insulin +/- metformin.
CFB=Change from baseline.
Baseline is defined as Week 0.

Body weight endpoints

Mean body weight decreased from baseline to Week 28 by 1.04 kg in the EQW group and increased by 0.46 kg in the placebo group. The difference in LS mean change between treatment groups was 1.50 kg ($p<0.001$).

Blood pressure

There was a numerical decrease in SBP in the EQW group compared with baseline; however, there was no difference in SBP compared with placebo (nominal $p=0.129$).

Summary of main study

The following table summarises the efficacy results from the main studie supporting the present application. This summary 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 D5553C00002

Title: A 28-week, randomized, double-blind, active-controlled, multicentre, Phase III efficacy and safety study of EQW 2 mg versus placebo as add-on treatment to titrated basal insulin in patients with T2DM who had inadequate glycaemic control on titrated basal insulin with or without metformin, and with or without an SU (discontinued at Week -8).		
Study identifier	Study D5553C00002	
Design	Randomised, double-blind, active-controlled, multicentre, Phase 3 efficacy and safety study	
	Duration of main phase: Duration of Run-in phase:	28 weeks
Hypothesis	Superiority	
Treatments groups	EQW	Exenatide QW 2mg add on

	placebo		Placebo add on
Endpoints and definitions*	Primary endpoint	HbA1c	Change in HbA1c from Baseline to Week 28
	Secondary endpoint*	HbA1c<7%	Patients achieving HbA1c<7% at Week 28
	Secondary endpoint*	Body weight	Change in body weight from Baseline to Week 28

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Week 28			
Descriptive statistics and estimate variability	Treatment group	EQW	placebo	
	Number of subject	206	207	
	HbA1c (LS Mean)	-0.96	-0.23	
	(SE)	0.079	0.079	
	HbA1c<7% (n)	75	17	
	%	32.5	7.4	
	Body weight (LS Mean)	-1.04	0.46	
	(SE)	0.256	0.254	

Effect estimate per comparison	Primary endpoint HbA1c	Comparison groups	EQW vs placebo
		LS Mean Differences (SE)	-0.73 (0.101)
		95% CI	(-0.93, -0.53)
		P-value	< 0.001
	Secondary endpoint HbA1c<7%	Comparison groups	EQW vs placebo
		% Difference	25.1%
		P-value	<0.001
	Secondary endpoint Body weight	Comparison groups	EQW vs placebo
		LS Mean Differences (SE)	-1.50 (0.340)
		95% CI	(-2.17, -0.848)
		P-value	<0.001

Notes	* For additional secondary endpoints, see further tables in the efficacy section

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study D5553C00002 was a 28-week, randomised, double-blind, placebo-controlled, multicentre, Phase 3 efficacy and safety study of once weekly exenatide therapy added to titrated basal insulin glargine compared to placebo added to titrated basal insulin glargine in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control on basal insulin glargine with or without metformin.

Overall the study population is adequate for the purpose of the study and the study duration is sufficient to allow assessment of the short-term effect on HbA1c.

A double-blinded study design was chosen, which is acknowledged considering that EQW is to be injected subcutaneously.

The overall approach to the statistical analysis and sensitivity analyses are acceptable and covering the various aspects that should be addressed. There is however some comments on the choice of the primary analysis method and data set.

The definition of the ITT data set excludes patients without post-baseline HbA1c assessment. These subjects should preferably be included in the primary analysis set; however, in this study only 1 patient in each treatment group was excluded hence similar results would be expected with an all randomised analysis set.

The primary analysis model, a mixed model repeated measures model, no explicit imputation of missing assessments is performed. Considering that missing at random (MAR) seldom is a plausible assumption the planned sensitivity analyses to assess the robustness of the primary analysis to departures from the MAR assumption is endorsed. Generally, the preferred analysis is one with which a continued treatment benefit after study treatment discontinuation is avoided. Given the model used, of importance for the credibility of the estimated primary outcome is to what extent subjects stayed in a study and contributed with data.

The n presented in the table of the results of the primary analysis are the number of patients with observed baseline and week-28 values. The descriptive statistics presented are based on 206 and 207 patients in the respective treatments groups. However, it is understood that all Intent-to-treat patients (231 and 230 patients) are included in the MMRM analysis. There is a discrepancy in number of patients between the analyses using different statistical models, i.e. MMRM and ANCOVA, due to difference in available data and imputed data for a particular analysis. For the primary endpoint 206 and 207 patients have available data and 25 and 23 with missing data, in the respective treatment groups. The analysis based on ANCOVA included 227 in active treatment group and 230 patients in the placebo group with observed baseline and week-28 values, which is understood to include imputed values.

A sensitivity analyses of the primary endpoint based on all randomised patients using a conservative imputation approach in case data is missing (e.g. ANCOVA with BOCF) was provided as requested. Analyses should be performed both with and without censoring of post rescue therapy and post study treatment discontinuation. In at least one analysis patients with missing endpoint data, patients in need of rescue therapy and patients who discontinued the study and/or study treatment should be handled as treatment failures using baseline observation carried forward (BOCF).

The relevance of why data collected while subjects where on rescue were to be treated as missing can

further be discussed. With the primary approach excluding data after rescue, used for analyses of primary and secondary efficacy endpoints, only data collected up to the time-point for when a subject needed rescue was used to estimate treatment efficacy. Hence, what will further have an impact on the primary outcome is to what extent subjects were in need of rescue. What is to be considered the most appropriate approach may (at the planning stage) depend on study design and objective. In a superiority study versus placebo, in theory, if the experimental treatment works, the approach where including data collected after starting on rescue treatment should result in a more conservative estimate.

The sensitivity approach using the CR approach is considered a reasonably conservative method for handling of missing data that is not considered missing at random. Patients in the active treatment group are assigned a placebo-like value and the placebo treated patients are assigned a value that does not punish the placebo treatment. The tipping point analysis is also supported as a useful way to assess MNAR data.

Efficacy data and additional analyses

Efficacy data with regard to the primary endpoint, reduction in HbA1c, supports the use of exenatide as an add-on treatment to insulin therapy. Secondary endpoints are consistent with this view.

In the exenatide treated group the mean change from baseline in HbA1c was -0.96% compared to the placebo group which had a reduction of -0.23% from the baseline levels of 8.5% in both groups (estimated treatment difference -0.73% (95% CI: -0.93, -0.53; p<0.001). It is noted that during the eight week insulin dose optimization phase prior to study start, mean HbA1c decreased on average 0.6%. Relative to this effect, HbA1c decrease during the 28 week long study suggests that insulin optimization therapy was less aggressive once the study was initiated.

The most conservative sensitivity analysis using baseline observation carried forward imputation for missing data after excluding data post-rescue and post-premature treatment discontinuation alters the estimated difference between treatments to -0.62 with a 95% 2-sided CI (-0.80, -0.44).

The change in FPG over time showed a significant reduction in the exenatide group from week 2 and onwards throughout the study, whereas FPG did not change over time in the placebo group. The relatively flat FPG curve in the placebo group may further indicate that the insulin therapy was not optimized, i.e. more insulin could perhaps have been administered. At each visit during the study (week 1, 2, 4, 8, 12, 16, 20 and 24) before the final visit week 28, FPG was measured and insulin dosage should be adjusted according to the INITIATE algorithm. However, at each of the eight visits, mean FPG in the placebo group was higher than the baseline value of 8.0 mmol/l. Target FPG levels were thus not reached in the insulin treated placebo group. The MAH acknowledges that insulin titration did not occur to the extent that was expected and that insulin titration plateaued after randomisation to study drug. However, insulin titration was not significantly different between the two groups over 28 weeks. Two explanations for the sub-optimal insulin titration are presented by the MAH; concerns about hypoglycaemia, and clinical inertia. Both explanations appear reasonable. The MAH claims that in this regard, study results are more consistent with real world clinical practice, in which the dose of insulin often remains unchanged despite poor glycaemic control. This may be true but it is important that the study is adequately reflected in section 5.1 of the SmPC. The wording is considered acceptable.

2.4.3. Conclusions on the clinical efficacy

The study D5553C00002 provided supports the use of EQW in combination with basal insulin. In this study exenatide treatment led to a slight reduction in body weight. Basal insulin treatment on the contrary led to a small increase in body weight. In this regard the combination of basal insulin and

exenatide could be a rational option for T2D patients where weight gain should be minimised and when there is a need for improvement of the metabolic control.

2.5. Clinical safety

Introduction

The safety and tolerability of exenatide as both single agent therapy and in combination with other therapies for T2DM, including metformin, were thoroughly documented and evaluated in the clinical development programme for BYDUREON.

The most frequent adverse reactions reported with EQW were mainly gastrointestinal related (nausea which was the most frequent reaction and associated with the initiation of treatment and decreased over time, and diarrhoea). In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with prolonged-release exenatide were mild to moderate in intensity. The risk of hypoglycaemia is low and dependent on the background therapy used.

Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly.

Patient exposure

Both the mean duration of exposure to study medication and the proportion of patients in the exposure categories were similar across treatment groups in Study D5553C00002. The mean duration of exenatide/placebo exposure was 189.7 days in the EQW group and 191.4 days in the placebo group.

Adverse events

Hypoglycaemia was recorded on a separate CRF throughout the study, separate from other AEs.

Adverse events and SAEs were reported by similar numbers of patients in both treatment groups (Table 8).

Table 8

	Number (%) of patients[a]		
	EQW (N=232)	**Placebo (N=231)**	**Total (N=463)**
Any AE	125 (53.9)	133 (57.6)	258 (55.7)
Any AE with outcome of death	0	1 (0.4)	1 (0.2)
Any SAE including events with outcome of death	11 (4.7)	11 (4.8)	22 (4.8)
Any AE leading to discontinuation of EQW or placebo[b]	9 (3.9)	4 (1.7)	13 (2.8)
Any SAE leading to discontinuation of EQW or placebo	1 (0.4)	0	1 (0.2)
Any AE related to EQW or placebo[c]	41 (17.7)	27 (11.7)	68 (14.7)

A 28-week Treatment Period adverse event is defined as an adverse event occurring on or after the day of the first dose of randomized study drug EOT. EOT refers to Week 28 visit. For patients who discontinued early, the EOT refers to the period after the last dose + 7 days for all treatment groups.

All percentages are calculated based on the number of patients in the analysis set within each treatment group.

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

[b] For 1 patient in the EQW group who experienced an event of pancreatitis chronic, EQW was noted as drug interrupted on the AE page of the eCRF, and was subsequently not restarted. For 1 patient in the EQW group who experienced an AE of intense diarrhea, the AE date entered on the AE page of the eCRF was later than the drug discontinuation date and therefore the AE was not counted as an AE leading to discontinuation of study medication.

[c] Includes causally related adverse events as judged by the Investigator.

AE Adverse event; eCRF Electronic case report form; EOT End of the treatment; EQW Exenatide once weekly + titrated basal insulin +/- metformin; Placebo Placebo + titrated basal insulin +/- metformin; SAE Serious adverse event.

Common adverse events

The most commonly reported AEs (frequency ≥5% in any treatment group) by preferred term (PT) were urinary tract infection, nausea, blood creatine phosphokinase increased, and injection site nodule. Events of blood creatine phosphokinase increased were more common in the placebo group and injection site nodules were more common in the EQW group (Table 9).

Table 9

Preferred term	Number (%) of patients	
	EQW (N=232)	Placebo (N=231)
Patients with any adverse event	125 (53.9)	133 (57.6)
Urinary tract infection	18 (7.8)	15 (6.5)
Nausea	12 (5.2)	9 (3.9)
Blood creatine phosphokinase increased	5 (2.2)	13 (5.6)
Injection site nodule	12 (5.2)	1 (0.4)

Most common is defined as an AE with at least 5% incidence in any treatment group.
Patients with multiple events in the same category (ie, same preferred term) are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
A 28-week treatment period adverse event is defined as an adverse event occurring on or after the day of the first dose of randomized study drug through the end of the treatment (EOT). EOT refers to the Week 28 visit. For patients who discontinued early, the EOT refers to the period after the last dose + 7 days for all treatment groups.
All percentages are calculated based on the number of patients within that treatment group.
MedDRA version 19.0.
[a] Number (%) of patients with AEs, sorted in decreasing total frequency of Preferred Term (sorted by total column even when not reported).
AE Adverse event; EOT End of treatment; EQW Exenatide once weekly + titrated basal insulin +/- metformin; MedRA Medical Dictionary for Regulatory Activities; Placebo Placebo + titrated basal insulin +/- metformin.

All adverse events

There was a >1% difference in the proportion of patients in the EQW group compared with the placebo group reported AEs in the following SOCs: gastrointestinal disorders (EQW, 15.1%; placebo, 10.8%); general disorders and administration site conditions (EQW, 12.1%; placebo, 6.1%); vascular disorders (EQW, 4.3%; placebo, 2.6%); skin and subcutaneous tissue disorders (EQW, 3%; placebo, 1.7%); and psychiatric disorders (EQW, 2.2%; placebo, 0.4%).

Adverse events of nausea, diarrhoea, and dyspepsia were more common in the EQW group (5.2%, 4.7%, and 2.2%, respectively) compared with the placebo group (3.9%, 3.5%, and 0%, respectively).

No malignancies were reported during the study other than one event of malignant skin neoplasms (PT: squamous cell carcinoma) in the EQW group.

Adverse events reported as related to study drug

Adverse events reported as related to study medication (EQW or placebo) as judged by the investigator were reported more frequently in the EQW group than in the placebo group.

Adverse events related to study medication (EQW or placebo) were reported by 41 patients (17.7%) in the EQW group and 27 patients (11.7%) in the placebo group. The most common AEs related to study medication or titrated basal insulin were injection site nodule (EQW, 5.2%; placebo, 0.4%), nausea (3.0% and 2.6%, respectively), diarrhoea (2.2% and 1.3%, respectively), and injection site pruritus (1.7% and 1.3%, respectively).

Serious adverse event / deaths / other significant events

The frequency and types of SAEs during the 28-week treatment period were low and similar across treatment groups. Serious AEs were reported by 11 patients (4.7%) in the EQW group and 11 patients (4.8%) in the placebo group. More SAEs were reported in the SOC of psychiatric disorders for the EQW group (1.3%) compared with the placebo group (0%). At the PT level, no SAE was reported by more than 1 patient (0.4%) per treatment group, with the exception of cardiac failure congestive and musculoskeletal chest pain, each reported by 2 patients (0.9%) in the placebo group.

One patient in the placebo group died during the study. The patient experienced an SAE of pneumonia and the cause of death was adjudicated as undetermined.

Adverse events of special interest

Incidence of hypoglycaemia

There were no events of major hypoglycaemia. Events of minor and other hypoglycaemia occurred in a similar number of patients in each treatment group. Events of minor hypoglycaemia were reported in 13 patients (5.6%) in both the EQW (31 events) and placebo (28 events) groups. Events of other hypoglycaemia (defined as not meeting the criteria for major or minor hypoglycaemia) were reported in 68 patients (29.3%; 331 events) in the EQW group and 64 patients (27.7%; 311 events) in the placebo group.

Adjudicated CV events

There were 3 confirmed adjudicated CV events in the study (cardiac failure congestive, myocardial infarction and ventricular fibrillation), all in the placebo group.

Pancreatic carcinoma related- or thyroid neoplasm-related events

No pancreatic carcinoma-related events or thyroid neoplasm-related events were reported during the study.

Injection site-related events

Injection site-related events were reported in 18 patients (7.8%) in the EQW group and 7 patients (3.0%) in the placebo group. All events were mild or moderate in intensity and most were considered related to study medication by the investigator. Adverse events of injection site nodule and injection site erythema were more common in the EQW group (5.2% and 1.3%, respectively) compared with placebo group (0.4% and 0%, respectively).

Gastrointestinal-related events

Gastrointestinal-related events were reported in 35 patients (15.1%) in the EQW group and 25 patients (10.8%) in the placebo group, and these events were mostly mild or moderate in intensity. The most commonly reported gastrointestinal-related AEs were nausea (EQW, 5.2%; placebo, 3.9%) and diarrhoea (EQW, 4.7%; placebo, 3.5%), none of which were reported as SAEs.

Vital signs

Pulse rate increased from baseline to Week 28 by 2.5 beats/min in the EQW group and remained unchanged in the placebo group (mean change from baseline, 0.2 beats/min).

Laboratory findings

Creatinine elevations 1.5x higher than pre-treatment creatinine were greater in the EQW group (20 patients [8.6%]) compared with the placebo group (12 patients [5.2%]). In the EQW group, 14 of the 20 patients had one-time elevations in creatinine. Despite being >1.5x higher than pre-treatment values, the creatinine values remained within the normal range in 11 of the 20 EQW patients. Of these 20 EQW patients, 16 had normal creatinine values and 4 had high values at the last collection; of the 4 high values, 3 were less than 1.5x the pre-treatment value. None of the creatinine elevations in the EQW group were reported as AEs.

Creatine kinase elevations of >10x ULN were reported for more patients in the placebo group (4 patients; 1.7%) compared to the EQW group (no patients).

Anti-exenatide antibodies

Anti-exenatide antibodies were observed in 76.0% of patients in the EQW group at any time during the study. The mean proportion of patients positive for anti-exenatide antibodies plateaued at Week 8 and remained stable through the end of treatment period. The proportion of patients with high positive antibody titer (≥625) peaked at Week 8 (27.0%) and then decreased over time to the lowest proportion at Week 28 (12.9%). At Week 28, the mean change from baseline HbA1c in the EQW group was similar in patients with any positive antibodies (-1.05%) compared with patients who were antibody negative (-0.88%), and greater in patients who were low-titer antibody positive (-1.19%) compared with patients who were high-titer antibody positive (-0.48%). As observed in previous EQW clinical studies, injection site-related AEs were more common among patients who were antibody positive (7.3%) than those who were antibody negative (0.4%).

Discontinuation due to adverse events

Greater proportions of patients discontinued study treatment because of an AE and had an AE that was considered to be related to study treatment in the EQW group compared with placebo.

Discontinuation of study medication (EQW or placebo) because of an AE was reported for 9 patients (3.9%) in the EQW group and 4 patients (1.7%) in the placebo group. More patients in the EQW group (4 patients [1.7%]) discontinued due to AEs in the SOC of gastrointestinal disorders compared with the placebo group (1 patient [0.4%]). At the PT level, no AE leading to discontinuation was reported by more than 1 patient per treatment group.

Post marketing experience

Limited data are available from post-marketing reports of concomitant use of EQW and titrated basal insulin. Given the cumulative exposure estimate for the exenatide twice daily and EQW formulations (over 3,117,218 and 1,307,511 patient-years, respectively), the overall patient-years of exposure for exenatide is estimated to be over 4.4 million patient-years for the cumulative period ending 31 March 2017.

The important identified risks with EQW (pancreatitis, acute renal failure, rapid weight loss, and injection site reactions) and important potential risks (risks associated with anti-exenatide antibodies [focus on anaphylactic-type reactions], cardiac events, pancreatic cancer, thyroid neoplasms, administration error, malignant neoplasm following combination treatment with insulin [this risk is an imposition in the EU Risk Management Plan; ie, not the Company position]) for exenatide are described in the EU Risk Management Plans for BYETTA and BYDUREON, 13 January 2016.

2.5.1. Discussion on clinical safety

With study D5553C00002, 28 week data on the concomitant treatment with exenatide and insulin has been provided. A total of 463 patients were included in the safety data set out of which 232 received exenatide. The mean duration of exposure to exenatide was about 190 days. The overall reporting of AEs was fairly balanced between the EQW group (54%) compared to the placebo group (58%). Treatment related AEs were more common in the EQW treated group (18%) than in the placebo group (12%).

GI events were more common with EQW (15%) than with placebo (11%). AEs judged as drug related were mainly GI events and injection site reactions, in line with the known safety profile for exenatide.

The frequency and types of SAEs during the 28-week treatment period were low and similar across treatment groups. Serious AEs were reported by 11 patients (4.7%) in the EQW group and 11 patients (4.8%) in the placebo group. At the PT level, no SAE was reported by more than 1 patient (0.4%) per treatment group, with the exception of cardiac failure congestive and musculoskeletal chest pain, each reported by 2 patients (0.9%) in the placebo group.

No malignancies were reported during the study other than one event of squamous cell carcinoma in the EQW group.

One patient in the placebo group died during the study. The patient experienced an SAE of pneumonia and the cause of death was adjudicated as undetermined.

Hypoglycaemia was an AE of special interest in the study. There were no events of major hypoglycaemia. Events of minor (13 patients, 5.6% in each group) and other (68 patients (29%; 331 events) EQW, 64 patients (27.7%; 311 events) placebo) hypoglycaemia occurred in a similar number of patients in each treatment group. Hypoglycaemia (with insulin) is proposed to be added as an adverse event in SmPC section 4.8, with the frequency common based on the observed frequency of minor events. This is endorsed.

An increase in heart rate (2.5 bpm) was observed in the EQW group at week 28. These findings are consistent with results observed in other EQW studies. No increase was observed in the placebo group.

Anti-exenatide antibodies were observed in 76.0% of patients in the EQW group at any time during the study. At Week 28, the mean change from baseline HbA1c in the EQW group was similar in patients with any positive antibodies (-1.05%) compared with patients who were antibody negative (-0.88%). Patients who were high-titer antibody positive seem to have a reduced effect (-0.48%). This is in line with previous observations.

Injection site-related events were more common in patients with ADA. Increased injection site related AEs in patients with positive antibodies have also been observed in previous EQW studies.

2.5.2. Conclusions on clinical safety

No new important safety issues have been brought forward from the current study. A combination treatment with insulin means that there will be risk for hypoglycaemia. The data does not indicate that the add-on treatment with exenatide will increase this risk compared to insulin treatment alone. Hypoglycaemia (with insulin) is proposed to be included in the SmPC, section 4.8, which is endorsed.

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 updated RMP version 26 was initially submitted as part of this application. A consolidated updated version of the RMP, version 29, was subsequently submitted and assessed within the procedure.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 29 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the RMP version 29 with the following content:

Safety concerns

Important identified risks	• Pancreatitis • Acute renal failure • Rapid weight loss • Injection site reactions (exenatide QW)
Important potential risks	• Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions) • Cardiac events • Pancreatic cancer • Thyroid neoplasms • Administration error (exenatide QW) • Malignant neoplasm following combination treatment with insulin
Missing information	• Adolescents • Pregnant women • Very elderly (≥75 years old) • Patients using exenatide in combination with other agents (TZDs and insulins) • Severe gastrointestinal disease (exenatide QW) • Various degrees of impaired renal function (exenatide QW) • Hepatic impairment (exenatide QW)

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
H8O-MC-GWDQ/ D5551C00003 (BCB109; EXSCEL) (CV) Category 3	The primary objective of EXSCEL will be to evaluate the effect of exenatide QW, used in conjunction with the current usual care for glycaemic control, on major macrovascular events when administered to patients with T2DM	Cardiac events Pancreatitis Acute renal failure Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions) Pancreatic cancer Thyroid neoplasms	Ongoing	Final report (CSR) Q4 2018
H8O-JE-EX01/D5550C00001:Byetta post-marketing surveillance study/Prospective patient cohort Category 3	To assess primarily the occurrence of acute pancreatitis and major adverse CV events in relation to the exposure to exenatide BID	Pancreatitis, CV events	Ongoing	Final report Q3 2020
H8O-MC-B016/ D5551N00006: An Observational Post-Authorisation Modified Prescription-Event Monitoring Safety Study to Monitor the Safety and Utilization of Exenatide Once Weekly (Bydureon®) in the Primary Care Setting In England Category 3	To study the utilisation and safety of exenatide QW to treat T2DM in new user patients (exenatide naïve) and switchers (past exenatide BID users) under normal conditions of use in primary care in England. The objective is to quantify the incidence rate of the important identified risk of acute pancreatitis in the first 12 months after starting treatment	Pancreatitis	Ongoing	Interim report was conducted in Q4 2015 with 2538 exenatide QW users Final report when 5000 patients are available: Dependent upon enrolment

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
H8O-MC-B017: Incidence of Thyroid Neoplasm and Pancreatic Cancer in T2DM Patients who Initiate Bydureon® Compared to Other Antihyperglycaemic Drugs (UK study) Category 3	The objective of this study is to estimate and compare the incidence of thyroid neoplasm and pancreatic cancer among initiators of exenatide QW compared to other antidiabetes agents. Primary Objectives are: (1) to estimate the absolute and relative incidence of newly diagnosed thyroid cancer among initiators of exenatide QW compared to matched initiators of other antidiabetes drugs – assessing events 1-year post drug initiation by duration of follow-up and drug exposure; (2) to estimate the absolute and relative incidence of newly diagnosed pancreas cancer among initiators of exenatide QW compared to matched initiators of other antidiabetes drugs – assessing events 1-year post drug initiation by duration of follow-up and drug exposure.	Pancreatic cancer Thyroid neoplasms	Ongoing	Risk assessment: Every two years until study ends Interim report (when 20000 exenatide QW users are available): years (dependent upon enrolment) Final analysis will be performed after 55000 exenatide QW users: years depending on enrolment

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
BCB402/ D5551R00001: MTC Surveillance Study: A Case Series Registry/Registry Category 3	The objectives of this prospective active surveillance program are: (1)To establish a multicentre registry of incident cases of MTC in adults in the US in order to characterize their medical histories and possible risk factors, including history of treatment with EQW and other long-acting GLP-1RAs; (2) To systematically monitor the annual incidence of MTC in the US through the NAACCR to identify any possible increase related to the introduction of EQW and other long-acting GLP-1RAs into the US market	Medullary thyroid carcinoma	Ongoing	Annual assessment report each Q1 until the end of the study; final report : Q3 2028
H8O-MC-GWBQ (Adolescent) (Byetta®) Category 3	The primary objective of this study is to test the hypothesis that glycaemic control, as measured by change in HbA1c from baseline to endpoint, with exenatide BID daily is superior (in at least 1 of the exenatide treatment arms) to that of placebo after 28 weeks of treatment in adolescent patients with T2DM who are naïve to antidiabetes agents, or patients who are being treated with metformin, an SU, or a combination of metformin and an SU.	Adolescents	Ongoing	Final report: Q2 2019

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
BCB114/D5551C00002 (Adolescent) Category 3	Primary objectives: To assess the effect on glycaemic control, as measured by HbA1c, of exenatide QW following 14 weeks of treatment compared to placebo in adolescents with T2DM; to evaluate the safety and tolerability of exenatide QW compared to placebo following 14 weeks of treatment in adolescents with T2DM	Adolescents	Ongoing	Final report: Q1 2019
H8O-MC-B015 extension (D5550R00003) Category 3	To estimate the absolute and relative incidence of pancreatic cancer and thyroid neoplasm among exenatide initiators relative to initiators of OADs.	Pancreatic cancer Thyroid neoplasms	Ongoing	Final Report: 2018

BID twice daily; CSR clinical study report; CV cardiovascular; EQW exenatide once weekly; GLP-1RA glucagon-like peptide 1 receptor agonist; HbA1c haemoglobin A1c; MTC medullary thyroid carcinoma; NAACCR North American Association of Central Cancer Registries; OAD oral antidiabetes drug; PhV pharmacovigilance; Q1 first quarter; Q3 third quarter; Q4 fourth quarter; QW once weekly; SU sulphonylurea; T2DM type 2 diabetes mellitus; UK United Kingdom; US United States.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Pancreatitis	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Acute renal failure	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Rapid weight loss	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Injection site reactions (exenatide QW)	Product information such as product labelling and medication guide	None
Important potential risks		
Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions)	Statements within Sections 4.3 (Contraindications), and 4.8 (Undesirable effects) of the SmPC.	None
Cardiac events	No association identified between exenatide and cardiac events to date.	None
Pancreatic cancer	No association identified between exenatide and pancreatic cancer to date.	None
Thyroid neoplasms	None. Section 5.3 Preclinical safety data of the SmPC describes the thyroid cancer incidence observed in rats. No reasonable causal association between exenatide and thyroid neoplasm in humans has been identified to date.	None
Administration error (exenatide QW)	Product information such as product labelling and user manual	None
Malignant neoplasm following combination treatment with insulin	No association identified between exenatide and combination insulin use to date.	None
Missing information		
Adolescents	Statements within Sections 4.4 (Special warnings and precautions for use) and 5.2 (Pharmacokinetic properties) of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pregnant women	Statements within Section 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Very elderly (≥75 years of age)	Statements within Sections 5.2 (PK properties) of the SmPC.	None
Use of Exenatide in Combination with Other Agents (TZDs and insulins)	No differential adverse event profile has been found for patients taking exenatide in combination with other agents (TZDs and insulins).	None
Severe Gastrointestinal Disease (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration) and 5.2 (PK properties) of the SmPC	None
Various Degrees of Impaired Renal Function (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration), 4.4 (Special warnings and precautions for use) and 5.2 (PK properties) of the SmPC.	None
Hepatic Impairment (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration) and 5.2 (PK properties) of the SmPC.	None

QW once weekly; PK Pharmacokinetic; SmPC Summary of Product Characteristics; TZD thiazolidinedione.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to hypoglycaemia (with insulin) has been added to the product information. The Package Leaflet has been updated accordingly. The changes are as follows:

4.1 Therapeutic indications

Bydureon is indicated in adults 18 years and older 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 (see section 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

. . .
When used with insulin, prolonged-release exenatide and insulin must be administered as two separate injections.

. . .

4.4 Special warnings and precautions for use

. . .
Concomitant medicinal products
The concurrent use of prolonged-release exenatide with ~~insulin,~~ D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied. The concurrent use of prolonged-release and immediate-release exenatide has not been studied and is not recommended.

. . .

For changes in subsequent sections of the SmPC, including section **5.1 Pharmacodynamic properties**, and consequential changes in the patient leaflet, see complete PI in attachment.

Minor editorial changes were also made to the PI and accepted by the CHMP.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Favourable effects

Study D5553C00002 was a 28-week, randomized, double-blind, active-controlled, multicentre, Phase III efficacy and safety study of prolonged-release exanatide (exenatide once weekly; EQW 2 mg) versus placebo as add-on treatment to titrated basal insulin in patients with T2DM who had inadequate glycaemic control on titrated basal insulin with or without metformin.

The primary objective of the study was met. The mean HbA1c decreased from baseline to Week 28 in both treatment groups. The least squares (LS) mean change in HbA1c was -0.96% for the EQW group and -0.23% for the placebo group. The difference in LS mean change between the EQW group and the placebo group was -0.73% ($p<0.001$). A larger proportion of patients treated with exenatide also reached $HbA_{1c} \leq 7\%$ at the end of the study (active 33%, placebo 7%, $p<0.001$). The study also reported a significant reduction in bodyweight compared to the placebo group (-1.5 95% CI -2.17, -0.84, $p<0.001$). These finding supports the proposed updated indication with concomitant insulin treatment.

3.2. Uncertainties and limitations about favourable effects

The change in FPG during the study showed a significant reduction in the exenatide group from week 2 and onwards throughout the study, whereas FPG did not change over time in the placebo group. The relatively flat FPG curve in the placebo group could indicate that the insulin therapy was not optimized. In fact, at each of the eight study visits, FPG in the placebo group was on average increased from the baseline value of 8.0 mmol/l. Therefore the size of the beneficial add-on effect of exenatide to optimised basal insulin therapy cannot be determined from the presented data. The study data however show that exenatide, when added to basal insulin treatment, provides a significant additional effect on metabolic control.

3.3. Unfavourable effects

With study D5553C00002, 28 week data on the concomitant treatment with exenatide and insulin has been provided. A total of 463 patients were included in the safety data set out of which 232 received exenatide. The mean duration of exposure to exenatide was about 190 days. The overall reporting of AEs was fairly balanced between the EQW group (54%) compared to the placebo group (58%). Treatment related AEs were more common in the EQW treated group (18%) than in the placebo group (12%). AEs judged as drug related were mainly GI events and injection site reactions, in line with the known safety profile for exenatide. Because of the established risk profile of insulin, hypoglycaemia was an AE of special interest in the study. There were no events of major hypoglycaemia. Events of minor (13 patients, 5.6% in each group) and other hypoglycaemias occurred in a similar number of patients in each treatment group (68 patients (29%; 331 events) EQW, 64 patients (27.7%; 311 events) placebo). Hypoglycaemia (with insulin) is added as an adverse event in SmPC section 4.8. Overall in this study no new serious risks have been discovered for exenatide.

3.4. Uncertainties and limitations about unfavourable effects

Only short-term data (28 weeks) of the treatment combination is yet available.

3.5. Effects Table

Effects Table for exenatide once weekly (prolonged-release exenatide; Bydureon) in the treatment of T2DM, combination with basal insulin

Effect	Short Description	Unit	EQW + basal insulin	Basal insulin	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in HbA1c	Estimated treatment difference -0.73% (95% CI: -0.93, -0.53; p<0.001)	%	-1.0±0.1	-0.2±0.1	Patients in the placebo group appear not to have been titrated to target.	
Patients achieving HbA1c<7%		%	33	7		
Change in mean body weight	Estimated treatment difference -1.5 kg (95% CI: -2.17, -0.84; p<0.001)	kg	-1.0±0.3	0.5±0.3		

Effect	Short Description	Unit	EQW + basal insulin	Basal insulin	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Hypo-glycaemia	Minor events (patients)	N (%)	13 (5.6)	13 (5.6)	No major events observed	

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

When EQW was added to basal insulin treatment, a clinically relevant reduction of HbA1c was observed in combination with a slight reduction in body weight. This is considered of benefit, especially as this was shown in an over-weight, and difficult to treat, population of patients with T2DM.

The safety data provided does not indicate that there is any additive toxicity or change in the safety profile, with the important exception of insulin related hypoglycaemia when exenatide is used concomitantly with insulin.

3.6.2. Balance of benefits and risks

T2DM is a progressive disease where metabolic control is often difficult to achieve. Once life style changes are insufficient to maintain metabolic control, metformin remains the first step in pharmaceutical treatment. Upon failure on metformin, current treatment guidelines recommend individualised treatment, combining existing treatment options based on the patient's needs. A majority of T2DM patients is overweight and hypertensive, thus there is a need for treatment options which at least not aggravate these conditions.

In this study exenatide once weekly treatment as add-on to basal insulin resulted in improved metabolic control in combination with a slight reduction in body weight. Basal insulin treatment alone on the contrary led to a small increase in body weight. Thus the combination of basal insulin and exenatide could be a rational option for T2D patients where weight gain should be minimised and when there is a need for improvement of the metabolic control. Exenatide add-on treatment with basal insulin could also be an option for patients that are prone to hypoglycaemic events, since exenatide do not seem to increase the risk for hypoglycaemia compared to intensified basal insulin therapy alone.

3.7. Conclusions

The overall B/R of Bydureon (prolonged-release exenatide), including the combined use with basal insulin, 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 treatment in combination with basal insulin for Bydureon; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on the study D5553C00002 (Duration 7 study) which evaluated safety and efficacy of exenatide once weekly therapy added to titrated basal insulin in patients with type 2 diabetes who have inadequate glycemic control on basal insulin with or without metformin. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in sections 4.8 and 5.1 of the SmPC. Furthermore, the consolidated RMP version 29 has been agreed.