28 June 2018
EMA/700805/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Bydureon

International non-proprietary name: exenatide

Procedure No. EMEA/H/C/002020/ X/0048/G

International non-proprietary name: exenatide

Note

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

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List of abbreviations

AE	Adverse event
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
C_{ss}	Concentration at steady state
$C_{ss, ave}$	Average C_{ss}
CQA	Critical Quality Attribute
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DM-SAT	Diabetes Medications Satisfaction
DTSQ	Diabetes Treatment Satisfaction Questionnaires
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
EC	European Commission
eGFR	Estimated glomerular filtration rate
EQWS	Exenatide once-weekly suspension
EU	European Union
FPG	Fasting plasma glucose
GLM	General linear model
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HOMA	Homeostatic model assessment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IWQOL-Lite	Impact of Weight on Quality of Life Lite
ITT	Intent-to-treat
KF	Karl Fischer titration
LC	Liquid chromatography
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LS	Least squares
max	Maximum
MCT	Medium-chain triglycerides
MDRD	Modification of diet in renal disease
min	Minimum
mITT	Modified Intent-to-Treat
MMRM	Mixed-effect model with repeated measures
NA	Not applicable
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PLG	Poly-(DL-lactide-co-glycolide)
PO	Orally
PPG	Postprandial plasma glucose
PRO	Patient reported outcome
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SCX	Strong cation exchange
SCE	Summary of Clinical Efficacy

SD	Standard deviation
SE	Standard error
SEC	Size exclusion chromatography
SMBG	Self-monitored blood glucose
SmPC	Summary of Product Characteristics
SU	Sulphonylurea
Tg	Glass Transition Temperature
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
US	United States
QW	Once weekly

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 8 September 2017 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Extension application to introduce a new pharmaceutical form (prolonged-release suspension for injection) grouped with type II variation to align the PI for the approved Bydureon products (powder and solvent for prolonged-release suspension for injection, and powder and solvent for prolonged-release suspension for injection in pre-filled pen) with the PI proposed for the Bydureon new pharmaceutical form (prolonged-release suspension for injection in autoinjector). In addition, the MAH took the opportunity to make minor editorial changes throughout the SmPC. Moreover, RMP version 28 has been submitted as part of this application.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0244/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0244/2017 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 19 April 2012. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

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

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	8 September 2017
The procedure started on	28 September 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 December 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 December 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 January 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 March 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	26 April 2018
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation extension to Bydureon on	28 June 2018

2. Scientific discussion

For ease of reading the following terminology is used throughout the overview:

- EQWS - refers to the exenatide prolonged-release, non-aqueous suspension formulation (assessed in this report).
- Bydureon - refers to the exenatide prolonged-release, aqueous suspension formulation.
- Byetta - refers to the exenatide immediate-release aqueous formulation.

2.1. Problem statement

The indications proposed for Bydureon autoinjector is:

"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)."

2.1.1. Epidemiology

For the year 2015, it was estimated that diabetes affected approximately 415 million people worldwide in the age range 20 to 79 years. The majority of patients with diabetes are type 2 diabetes accounting for 87% to 91% in high-income countries; the rest are type 1 and other types of diabetes

Diabetes and its complications are major causes of early death in most countries. People with diabetes have an increased risk of developing a number of serious health problems. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, and nerves. In addition, people with diabetes have a higher risk of developing infections. In almost all high-income countries, diabetes is a leading cause of CVD, blindness, kidney failure, and lower limb amputation.

2.1.2. Aetiology and pathogenesis

Several risk factors have been associated with T2DM and include family history of diabetes, overweight, unhealthy diet, physical inactivity, older age and high blood pressure.

2.1.3. Clinical presentation

Type 2 diabetes is a complex disorder which involves various degrees of decreased beta-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control.

Overweight, hypertension and dyslipidaemia are often associated with diabetes mellitus and multiple cardiovascular risk factor intervention is a key issue in type 2 diabetes.

2.1.4. Management

Initial management includes lifestyle changes such as diet and exercise. Pharmacological treatment includes insulin, biguanides, TZDs, SUs, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1RA. With the exceptions of insulin and GLP-1RA all are administered orally.

Despite combination therapy and/or insulin treatment, a sizeable proportion of patients remain poorly controlled. One important issue is compliance to treatment. Some medicinal products for injection are complicated to administer and there is a need for formulations that are easier to use.

About the product

Type of Application and aspects on development

Exenatide is a synthetic 39 amino acid peptide with partial sequence homology to the naturally occurring human glucagon-like peptide-1 (GLP-1). Exenatide is a GLP-1 receptor agonist that exhibits many of the same glucoregulatory or glucose-lowering actions as the naturally-occurring incretin hormone, but is not substantially degraded by dipeptidyl peptidase-4 (DPP-4), which efficiently degrades native GLP-1 in vivo.

Exenatide was first approved by the European Commission on 20 November 2006 under the name Byetta. Byetta is an immediate-release aqueous formulation. The administration schedule for this formulation is twice daily.

Bydureon, a prolonged-release formulation of exenatide, was approved by the European Commission on 21 June 2011. The drug delivery technology for the Bydureon formulation uses biodegradable polymeric microspheres, which entrap exenatide and provide prolonged release of the peptide over days to months. Once injected subcutaneously, the polymer biodegrades over time, thereby releasing the bioactive peptide for absorption into the systemic circulation. The Bydureon formulation is comprised of a powder that is combined with an aqueous vehicle to form a suspension immediately before injection. It is supplied as a vial and prefilled syringe 'single dose tray' or as a prefilled pen 'dual-chamber pen'.

EQWS is a modified formulation of Bydureon that contains the same drug substance, drug load and prolonged-release microspheres as Bydureon, but with a nonaqueous MCT vehicle. The change from the aqueous vehicle in Bydureon to a nonaqueous MCT vehicle in EQWS was primarily undertaken to develop a formulation that does not require addition of the vehicle immediately before administration and is suitable for use with an autoinjector.

A key factor in the development of the EQWS is the utilisation of the commercially available Bydureon microspheres. No changes were made to the microsphere formulation or the manufacturing process.

The safety and tolerability of exenatide has been documented in the large clinical programmes for Byetta and Bydureon. Over 7,000 patients with T2DM have received the immediate-release formulation of exenatide (Byetta) and over 5,300 patients have received the prolonged-release aqueous formulation of exenatide (Bydureon) in completed clinical trials.

This submission for the non-aqueous formulation of exenatide (EQWS) administered via an autoinjector is supported by data from the Bydureon programme and by 3 completed clinical studies from the EQWS programme: 1 Phase 2 study (BCB110) and 2 Phase 3 studies (BCB118 and BCB120). The commercially representative device and formulation were used in both of the Phase 3 EQWS studies, whereas the Phase 2 EQWS study (BCB110) was performed before development of the autoinjector and optimisation of the associated volume and concentration. The prolonged-release non-aqueous suspension formulation of exenatide for once-weekly administration (EQWS) has been administered to a total of 579 unique subjects in clinical trials.

Guidance was provided by the CHMP in response to a follow-up request for Scientific Advice. The advice given has been adhered to in the design and conduct of the clinical studies.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged-release suspension for injection in pre-filled pen (BCise) containing 2 mg of exenatide as active substance.

Other ingredients are:

Powder: poly (D,L-lactide-co-glycolide), sucrose

Vehicle: medium chain triglycerides

The product is available in a 2-ml Type I glass cartridge, sealed at one end with a (bromobutyl) rubber seal/cap combination (combiseal), and at the other end with a (bromobuty) rubber plunger, the finished medicinal product is comprised of the suspension-filled cartridge assembled into the pen, the pen contains an integrated needle as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used to manufacture the new pharmaceutical form: prolonged-release suspension for injection in pre-filled pen is the same as that used in the manufacture of the currently authorised Bydureon powder and solvent for prolonged release suspension for injection and Bydureon powder and solvent for prolonged release suspension for injection in pre-filled pen (EU/1/11/696/001-004)

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Exenatide prolonged-release suspension for injection in pre-filled pen is presented as a single use, fixed dose pen for subcutaneous injection of 2 mg of exenatide, once weekly. The active substance, exenatide, is a glucagon-like peptide 1 agonist used in the treatment of type 2 diabetes to achieve glycaemic control.

The finished product contains exenatide prolonged-release microspheres that are also components of the already authorised Bydureon authorised products and are used unchanged in the proposed new product.

The exenatide prolonged-release microsphere technology enables patients to achieve continuous glucose control with once weekly injections. The pen is designed to simplify and improve the quality of the patient injection experience versus the existing Bydureon delivery configurations. The ergonomically designed pen utilises a new suspension formulation that eliminates the re-constitution step and enables mixing of the microspheres in up to 15 seconds. In addition, a pre-attached needle is hidden from view by a needle shield and the pen grip makes it easy to hold to enable pressure-activated injection.

Pharmaceutical development focused on two key areas: development of the medium chain triglycerides (MCT) based suspension formulation and pen device development. Formulation development activities involved selection of MCT as an appropriate injection vehicle, understanding the impact of MCT on exenatide microspheres and developing an aseptic manufacturing process.

In case of pen device, design, performance and human factors engineering necessary to demonstrate that the device meet the appropriate device regulatory requirements and standards and it is safe and effective for use by the intended use population has been investigated during the pharmaceutical development.

Exenatide is a white to off-white powder. Exenatide is very soluble in water but much less soluble in organic solvents. Exenatide is slightly soluble in MCT. To ensure stability, exenatide is stored in tightly sealed containers and protected from exposure to excessive humidity by handling and dispensing in a humidity controlled, dry environment.

The finished product consists of exenatide microspheres suspended in a vehicle of medium chain triglycerides (MCT). Exenatide microspheres contain poly-(DL-lactide-co-glycolide) (PLG) and sucrose as excipients. PLG controls release of exenatide from the microspheres and sucrose acts as stabiliser. Full details of the formulation development of the exenatide microspheres for the Bydureon products have previously been submitted and approved.

Compatibility of exenatide with the formulation excipients has been demonstrated in formulation development activities and long term stability studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except MCT which comply with In House quality standards. The MCT used in the finished product complies with pharmacopoeial standards; however MCT is considered a novel excipient when employed for chronic use via subcutaneous injection. MCT has previously been used in commercially available parenteral pharmaceutical products as the fat component of parenteral nutrition emulsions. The suitability of MCT in the finished product has been demonstrated from a safety and tolerability perspective during preclinical and clinical development studies. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

MCT is an injection vehicle, facilitating delivery of the microspheres by the pen device. A non-aqueous vehicle was sought because exenatide microspheres are not stable during long term storage in aqueous media. The formulation of the finished product was determined following screening of a range of potential non-aqueous vehicles with a focus on stability of exenatide and exenatide microspheres within the vehicle. The safety of the MCT when dosed subcutaneously has been demonstrated during the development of the finished product.

In the already authorised finished products, the exenatide microspheres and aqueous suspension vehicle are stored separately. The user combines the two components to produce a suspension immediately prior to dosing. The aqueous vehicle cannot be combined with the microspheres for long term storage because the microspheres are sensitive to water; exenatide release begins after hydration. To enhance the user experience by eliminating the constitution step required, a ready to use suspension formulation was sought and a Quality Target Product Profile (QTPP) was prepared. A pen was selected as the most appropriate device and development of the formulation, container closure and manufacturing process occurred in parallel with device development.

The objective of the formulation development was to identify a non-aqueous vehicle which would be inert with respect to the microspheres and exenatide, facilitating long term storage of the suspension. A key assumption was that the new finished product utilised the commercially available exenatide microspheres and no change to the microsphere composition or manufacturing process was made. An aseptic manufacturing process was developed to combine exenatide microspheres with MCT, producing a bulk suspension that is aseptically filled into cartridges. The filled cartridges are then assembled into pens.

The impact of MCT on microsphere characteristics potentially related to exenatide release was evaluated in formulation development studies. No changes in microsphere morphology, thermal properties or porosity were observed in the presence of MCT and it was selected as a suitable vehicle for the formulation. This was additionally supported by rat PK data, indicating no difference in performance between microspheres suspended in MCT for several weeks (aged) compared with those suspended immediately prior to administration. Subsequently, long term stability studies have supported the suitability of MCT as a suitable injection vehicle.

Formulation performance was first assessed clinically in a 2-Cohort Phase 2 Study. A suitable sustained-release profile of exenatide was observed following a single dose and steady-state plasma concentrations were in the desired therapeutic range. The formulation was therefore progressed to further clinical development. The applicant has applied Quality by design (QbD) principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed. A Quality Target Product Profile (QTPP) for the proposed commercial finished product set out a number of requirements and development studies were carried out to define critical quality attributes (CQAs) to ensure these would be met. The CQAs are related to product performance are: description, pen device functionality, exenatide release, delivered volume, identity, assay, uniformity of content, sterility, impurities, particulate matter, and stability

Two key elements of the finished product design were the selection of the formulation components and the selection of the container closure system, taking into account device considerations. The formulation components of the Phase 3 and proposed commercial formulation are the same as those used in early development/Phase 2 studies. To facilitate dosing via a single use pen in Phase 3/commercial use, the container closure system was selected as a 2 mL Ph. Eur./USP Type 1 glass cartridge sealed at one end with an elastomeric seal/cap combination (Combiseal) and elastomeric plunger at the other. The cartridge, plunger and Combiseal were selected based on their suitability for sterilisation, depyrogenisation and their ability to maintain sterility and stability of the drug product.

The studies showed that the suspension should be only be used if it is evenly mixed, white to off-white and cloudy, with no white medicine seen along the side, bottom or top of the pen window and must be mixed by shaking hard for at least 15 seconds

Injection volume is an important aspect of the QTPP and development studies were carried out to define an injection volume that was acceptable from an injectability and manufacturability perspective.

Exenatide release is controlled by the inherent microsphere characteristics, which are governed by the microsphere formulation and manufacturing process. The microspheres are the same as those used in the commercially available Bydureon products, therefore the *in vitro* release methods and specifications used for Bydureon have also been applied during the development of the prolonged release solution, to confirm that the inherent microsphere release characteristics remained within the acceptable range of performance.

No bioequivalence study has been performed as the commercial product is identical to that used for the pivotal clinical studies.

The manufacturing process development for exenatide suspension is divided into 4 process stages: bulk microsphere manufacture, sieving and dispensing of bulk microspheres, exenatide suspension filled cartridge manufacture, and exenatide suspension pen final assembly. A risk based approach to process development has been followed, focusing on the attributes of the product that are critical to ensuring product quality.

The finished product is manufactured aseptically.

The primary packaging is in a 2-ml Type I glass cartridge, sealed at one end with a (bromobutyl) rubber seal/cap combination (combiseal), and at the other end with a (bromobuty) rubber plunger. The finished medicinal product is comprised of the suspension-filled cartridge assembled into the pen device. The pen contains an integrated needle. All the selected materials are well established in the pharmaceutical industry as suitable for packaging medicinal products. Exenatide suspension stability studies have confirmed the suitability of the contact material. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Stability studies have shown that neither the cartridge nor the elastomer used for both the plunger and the combiseal interacts

either physically or chemically with the product to alter the strength, quality or purity during the finished product shelf life.

Manufacture of the product and process controls

The manufacturing process for exenatide suspension is divided into 4 process stages: bulk microsphere manufacture, exenatide microsphere sieving and dispensing, exenatide suspension filled cartridge manufacture, and exenatide suspension pen final assembly. The process is considered to be a non-standard manufacturing process.

The bulk exenatide microsphere manufacturing process is the same as that used for the already authorised products, except that the bulk microsphere batches may be dispensed into smaller batches after sieving.

The process stages which include aseptic processing have been validated on three batches and process validation details were presented for bulk microsphere manufacture, exenatide microsphere sieving and dispensing, exenatide suspension filled cartridge manufacture, and exenatide suspension final assembly. The pen assembly process does not involve any aseptic processing. Process validation will be completed prior to product launch. This was considered acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (SEC, SCX-LC, mass spectrometry), assay (SEC), uniformity of content (Ph. Eur.), delivered volume (weight), impurities (SCX-LC), water content (KF), particulate matter (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) .

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and identification, uniformity of content, impurities and identification, *in vitro* complete release testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from finished product stored for up to 36 months under long term conditions (5 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same specifications as for release. The analytical procedures used are stability indicating.

There has been no significant change in any of the attributes evaluated under long term and accelerated conditions.

ICH Q1B photostability studies have been carried out to assess the sensitivity of the exenatide suspension to light. Results confirm that the secondary packaging offers adequate protection from light.

Based on available stability data, the proposed shelf-life of 36 months and stored in a refrigerator (2ºC - 8ºC) in the original package to protect from light, the pens may be kept for up to 4 weeks below 30ºC prior to use as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This application is a line extension to Bydureon powder and solvent for prolonged release suspension. The applied product Bydureon prolonged-release suspension for injection in prefilled pen is presented as a single use, fixed dose prefilled pen for subcutaneous injection of 2 mg of exenatide, once weekly. The finished product is an oily suspension of exenatide controlled release microspheres in medium chain triglycerides (MCT). The microspheres are identical to the microspheres of the already approved products. The pen is designed to simplify and improve the quality of the patient injection experience versus the existing Bydureon delivery configurations. The ergonomically designed pen utilises a new suspension formulation that eliminates the re-constitution step and enables mixing of the microspheres in up to 15 seconds.

Information on development, manufacture and control of finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product. However, no design space was claimed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

No new pharmacology studies have been submitted in this application. This is acceptable since EQWS (exenatide once-weekly suspension) uses the same active ingredient as Bydureon and Byetta. The new product, EQWS, contains the same drug substance - exenatide, drug load (5% by weight), and extended-release microspheres as Bydureon (an aqueous formulation), but with a non-aqueous medium chain triglyceride (MCT) vehicle for use

with an autoinjector. The pharmacological profile of exenatide when administered as EQWS is not expected to be significantly altered.

2.3.3. Pharmacokinetics

PK parameters for exenatide from EQWS were determined in both the rat and monkey and showed that exenatide is absorbed over an extended period of time following a SC injection in a similar way as Bydureon (exenatide QW). With the exception of the initial release of exenatide in the first few days following injection. In rats, the exposure to exenatide was lower in the initial period following EQWS administration as compared to that seen with Bydureon (exenatide QW). This difference in the PK profile in rats is not expected to alter the long term pharmacodynamic (PD) or toxicity profiles of exenatide. In monkeys, systemic exposure following single and repeated doses of EQWS was slightly lower than that seen in previous studies conducted with Bydureon (exenatide QW), however at week 13, AUCs were comparable between the two formulations.

Antibodies to exenatide developed over time in rats and monkeys with EQWS and impacted the measured plasma exenatide concentrations in a similar way as seen with both exenatide immediate release and Bydureon (exenatide QW).

Distribution, metabolism, and elimination studies were not conducted for EQWS which is acceptable since these parameters already have been evaluated for exenatide (Byetta).

EQWS uses a non-aqueous MCT vehicle as compared to the aqueous formulation used in Bydueron (exenatide QW). MCTs are found in many foods, such as dairy products, coconut and palm oils and are considered GRAS. As there is limited data available regarding the oral bioavailability of MCTs and PK profile following subcutaneous administration, a single dose (oral and SC) study was conducted in rats. This study showed that the PK profile following oral and SC administration of MCTs were comparable, with SC and oral dosing showing comparable absorption and elimination phases. This suggests that the absorption, distribution, metabolism and excretion profiles of MCTs are comparable following SC and oral dosing.

2.3.4. Toxicology

A complete nonclinical safety program evaluated the safety profile of Byetta in single and repeated dose toxicology, genotoxicity, carcinogenicity, developmental and reproductive toxicology, and special toxicology studies. For Bydureon, nonclinical safety studies including repeated dose toxicology studies in rats and monkeys, in vitro genotoxicity, carcinogenicity, embryo-foetal development and juvenile toxicology studies in rats as well as special toxicology studies were conducted to ascertain that the profile of exposure to exenatide and the established safety profile of Byetta was unaffected by the change in formulation (addition of polylactide-co-glycolide- (PLG-) microspheres).

The only toxicity previously reported for exenatide QW (Bydureon) were injection site reactions which showed partial or complete recovery. Injection site reactions have also been observed in the clinical program. No target organ or dose-limiting toxicity was observed in any of the toxicity studies. NOAEL values were in all cases set to the highest dose tested. Anti-exenatide antibodies were observed in all studies. While there were no toxicological consequences of antibody formation, antibody formation resulted in changes in exenatide exposure. In rats, exenatide antibodies developed in 23-46% of the animals, and presence of antibodies was associated with an increased exenatide exposure. In monkeys, exenatide antibodies developed in 58-75% of the animals. At low titers, exenatide exposure was increased, while at high titers exposure was decreased.

Additional nonclinical safety studies with EQWS were conducted to demonstrate that the safety profile of exenatide QW was unaffected by the addition of MCTs in the formulation. These included additional studies in rats (single dose PK and local tolerance) and monkeys (1- and 3-month repeat dose toxicity studies). As for exenatide QW (Bydureon) the only toxicological findings were injection site reactions and data obtained suggest that the granulomatous inflammation seen in the injection site was primarily a response to the presence of the microspheres, although an increased incidence of lymphocytic infiltration was indicated in EQWS-treated animals. No new toxicological findings were thus seen in the studies performed with EQWS.

MCT is considered a novel excipient when employed for chronic use via subcutaneous injection and in order to evaluate the safety of MCT an single dose PK study with MCTs only in rats was conducted to bridge the available toxicity data following oral administration of MCTs and results obtained support the conclusion that data obtained after oral administration also are relevant for evaluation of safety after subcutaneous administration. A 4 week repeat dose oral toxicity study with MCT was also performed as part of this submission and a non-clinical overview regarding MCTs covering Single and Repeat dose toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental toxicity, Local irritation and Immunotoxicity has also been provided. No safety concerns were identified.

2.3.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment has been performed. This is acceptable and in line with the CHMP guideline which states that peptides are exempted from such assessment.

2.3.6. Discussion on non-clinical aspects

The pharmacological profile of exenatide when administered as EQWS is not expected to be significantly altered. Exenatide EQWS is absorbed over an extended period of time following a SC injection in rat and monkey in a similar way as Bydureon (exenatide QW), except for an initial decrease in the initial release of exenatide in the first few days following injection. The exposure was also found to be slightly lower in both species. However, these differences are not expected to alter the long term pharmacodynamic (PD) or toxicity profiles of exenatide. As for exenatide QW (Bydureon) the only toxicological findings seen were injection site reactions and data obtained suggest that the granulomatous inflammation seen in the injection site was primarily a response to the presence of the microspheres. No new toxicological findings were thus seen in the studies performed with EQWS.

MCT are considered generally recognized as safe (GRAS) but is also considered to be a novel excipient when employed for chronic use via subcutaneous injection. In order to evaluate the safety of MCT the applicant have provided results from two own studies and a literature based non-clinical overview regarding MCTs covering Single and Repeat dose toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental toxicity, Local irritation and Immunotoxicity. No safety concerns were identified.

2.3.7. Conclusion on non-clinical aspects

There are no objections for an approval of Bydureon EQWS from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Overview of Phase 2/3 studies in the clinical development programme for EQWS in subjects with type 2 diabetes mellitus

Study code (Publication reference) CTD location Study period	Design	Primary and secondary efficacy variables	Background treatment	Dose/comparator	Duration of treatment	Number of randomised subjects
Phase 2						
BCB110 (Wysham et al 2016) 5.3.4.2 29-Apr-2009 to 08-Aug-2009	Two-cohort single and repeat dose PK, tolerability, and safety study	Primary: no primary efficacy variable Secondary: HbA1c, FPG, body weight	Cohort 1: None	Cohort 1: EQWS 10 mg in healthy subjects	Single dose	EQWS 10 mg (30)
			Cohort 2: Metformin, TZD or a combination of metformin and a TZD	Cohort 2: EQWS 2 mg/placebo in T2DM	12 weeks	EQWS 2 mg (23) Placebo (12) (2:1 randomisation ratio)
Phase 3						
BCB118 (NA) 5.3.5.1 28-Jan-2013 to 19-Aug-2014	Randomised open-label, parallel-group, comparator-controlled, 2-arm study	Primary: HbA1c Secondary: HbA1c <7%, FPG, body weight, 2-hour postprandial plasma glucose	Diet and exercise alone or with a stable regimen of metformin, SU, pioglitazone, or a combination of any 2 of these agents	Controlled treatment period: EQWS 2 mg /BYETTA 5 µg BID for 4 weeks followed by 10 µg BID for 24 weeks	28 weeks (controlled/ randomised)	EQWS 2 mg (229) BYETTA (148) (3:2 randomisation ratio)
				Extension period: EQWS 2 mg	+ 24 weeks (uncontrolled/ extension)	EQWS 2 mg (375)
BCB120 (NA) 5.3.5.1 08-Feb-2013 to 04-Apr-2014	Randomised open-label, parallel-group, comparator and placebo-controlled 3-arm study	Primary: HbA1c Secondary: HbA1c <7%, FPG, body weight, 2-hour postprandial plasma glucose	Metformin	EQWS 2 mg/ sitagliptin 100 mg orally once daily /placebo orally	28 weeks	EQWS 2 mg (181) Sitagliptin (122) Placebo (61) (3:2:1 randomisation ratio)

BID twice daily; EQWS exenatide once weekly suspension; FPG fasting plasma glucose; HbA1c haemoglobin A1c; NA not applicable; PK pharmacokinetics; SU sulphonylurea; T2DM type 2 diabetes mellitus ; TZD thiazolidinedione
Source: BCB110, BCB118, and BCB120 Clinical Study Reports

2.4.2. Pharmacokinetics

Bioanalysis

A bioanalytical assay for determination of exenatide in plasma has earlier been developed, validated and assessed in the submissions of Byetta (EMEA/H/C698) and Bydureon (EMEA/H/C/2020). The assay was then transferred to Tandem Pharmaceuticals CA, US, where it was revalidated before analysis of samples taken in the current program.

Within study validations, including incurred sample reproducibility in the two phase 3 studies, were performed and met the EMA bioanalytical guideline criteria.

An ELISA for determination of exenatide-antibodies has been developed, validated and assessed in the Bydureon submission (EMEA/H/C/2020). The assay was transferred to Covance Laboratories where it was revalidated before analysis of samples taken in the current program.

Absorption

No bioequivalence study has been performed which is acceptable as the commercial formulation was used in phase 3. A non-final autoinjector was used but the changes are not considered to affect the functionality or the user interface.

Exposure in the target population

Phase 2 (BCB110 [MB001-087])

An extemporaneous non-aqueous suspension was used for administration in both the single and the repeated dosing cohort. Commercially microspheres and MCT suspension vehicle were used but differed from the formulation used in phase 3 in terms of the injection volume, microsphere concentration and administration device (syringe and vial).

Single dose

A supra therapeutic sc single dose 10 mg, dose proportionality has been reported up to at least 10 mg sc (EPAR Bydureon), resulted in a prolonged release of exenatide. An initial increase in exposure was seen during the first week followed by a relatively constant plasma level for ca 4 weeks and then an increase reaching maximum plasma concentration after ca 7 weeks. No initial peak during the first day *post* injection was seen as for Bydureon aqueous formulation.

Repeated dosing once weekly

Steady state was reached after *ca* 8 weeks following once weekly sc injections of 2 mg. The average concentration at steady state ($C_{ss,ave}$) of ca 345 pg/ml is comparable to the average steady state concentration following injection of Bydureon 2 mg aqueous suspension to be reconstituted before injection (EMEA/H/C/2020).

Phase 3 (BCB118 [MB001-003])

Commercial formulation with only minor improvements of the autoinjector *post* phase 3 was used.

Steady state was reached after ca 10 weeks following once weekly sc administration of EQWS 2 mg in T2DM patients. The geometric mean (SE) trough $C_{ss,ave}$ was calculated to 208(9) pg/ml.

Subjects with renal impairment (RI) showed a higher $C_{ss,ave}$ compared to subjects normal renal function. The geometric mean $C_{ss,ave}$ was 172, 220 and 289 pg/ml in normal, mild and moderate renal function, respectively.

Phase 3 (BCB120 [MB001-004])

Sparse trough sampling following repeated sc injection of EQWS 2 mg once weekly in T2DM patients resulted in a geomean(SE) $C_{ss,ave}$ 153(10) pg/ml. The estimated inter-individual variability in $C_{ss,ave}$ was CV 85%. The commercial formulation, with only minor improvements of the autoinjector *post* phase-3 was used.

2.4.3. Pharmacodynamics

Mechanism of action

Exenatide is a GLP-1 receptor agonist that exhibits many of the same glucoregulatory or glucose-lowering actions as the naturally-occurring incretin hormone, but is not substantially degraded by dipeptidyl peptidase-4 (DPP-4), which efficiently degrades native GLP-1 in vivo.

Primary pharmacology

Exenatide has been shown to reduce fasting and postprandial plasma glucose concentrations in nonclinical studies and clinical studies through multiple mechanisms of action and independent of background antihyperglycaemic therapies. These mechanisms of exenatide action include:

- beta cell effects
    - enhancement of glucose-dependent insulin secretion
    - restoration of first phase insulin secretion
    - enhanced insulin synthesis and processing and increased beta cell mass in animals, glucose-dependent suppression of inappropriately elevated glucagon secretion
- slowing the rate of gastric emptying, resulting in slowed absorption of meal-derived glucose
- enhanced splanchnic glucose uptake
- reduction of caloric intake by promoting satiety.

Clinical studies using exenatide have demonstrated that enhancement of insulin secretion and suppression of glucagon secretion are evident during hyperglycaemic and euglycaemic conditions but not under hypoglycaemic conditions. Nonclinical and clinical studies also indicate that the effect of exenatide to slow gastric emptying, which in turn slows the rate of glucose entry into the circulation, is reversed during hypoglycaemia. These glucose-dependent actions of exenatide lead to improvements in glucose control while minimising the risk of hypoglycaemia. In addition, reductions in food intake have been well-documented in nonclinical studies and also reported in a study of healthy volunteers and patients which may partly explain observed reductions in body weight.

Secondary pharmacology

The potential for exenatide to affect the QT interval was studied in both nonclinical models, and in the Byetta and Bydureon clinical development programmes. Exenatide has not been associated with prolongation of the corrected QT interval at therapeutic or supratherapeutic concentrations in clinical studies.

Pharmacodynamic interactions with other medicinal products or substances

Given that exenatide is primarily eliminated by the kidneys, it is not expected to have metabolism-based interactions with concomitantly administered oral medications. However, because it slows gastric emptying, exenatide has the potential to alter the absorption of orally administered drugs.

Relationship between plasma concentration and effect

An exposure-response analysis including data for both prolonged release formulations of exenatide (aqueous and suspension formulations) was performed. The exposure-response analysis included assessments of the effect on HbA1c response relative to predicted exenatide $C_{ss,av}$. The final exenatide population PK model was used to predict exenatide $C_{ss,av}$ corresponding to the different HbA1c measurements.

The estimated EC_{50} of the exenatide systemic exposure-response relationship is 52.1 pg/mL when antibody to exenatide titres are <125 and 85.4 pg/mL when antibody titre levels are ≥125. These values are similar to the empirical estimates of minimal efficacious concentrations defined during the Byetta clinical pharmacology programme based on observations that subcutaneous infusions leading to exenatide $C_{ss,av}$ greater than 50 pg/mL were required to elicit a glucose-lowering response (Taylor et al 2005). Furthermore, these are very similar to the values of 58.2 and 90 pg/mL, previously reported for Bydureon. Most (99%) of the individual median predicted exenatide $C_{ss,av}$ values for EQWS 2 mg exceeded the model predicted EC50, further confirming that EQWS 2 mg would result in a robust clinical response, as observed in studies BCB118 and BCB120.

2.4.4. Discussion on clinical pharmacology

The systemic exposure of exenatide following once sc weekly injection with non-aqueous suspension using autoinjector has been monitored in one phase-2 and two phase-3 studies. Sparse PK samples have been collected, mainly through samples, following repeated dosing.

The formulation used in phase-3 was the commercial formulation with only minor improvements of the autoinjector after the phase-3 studies. No bioequivalence study has been performed which is deemed acceptable.

Following 2 mg once weekly sc injections, the steady state concentration $C_{ss,ave}$ was determined to *ca* 345 pg/ml, using the non-final formulation in phase-2. This is comparable to the steady state level reported for the approved Bydureon aqueous product (EPAR 2011) of *ca* 300 ng/ml.

The concentration-time profile of exenatide following a sc injection with a non-aqueous suspension was characterized after a supra therapeutic dose, 10 mg, using a non-final formulation and device. Dose proportionality has been reported up to at least 10 mg sc (EPAR Bydureon). An initial increase in exposure was seen during the first week followed by a relatively constant plasma level for *ca* 4 weeks and then an increase reaching maximum plasma concentration after *ca* 7 weeks. No initial peak during the first day *post* injection was seen, in contrast to what is known for the Bydureon aqueous formulation.

In the two phase-3 studies $C_{ss,av}$, after 2 mg once weekly sc, lower steady state levels were determined than in the phase 2 study. In study BCB118 and BCB120 the $C_{ss,av}$ was calculated to 208 pg/ml and 153 pg/ml, respectively.

$C_{ss,av}$ of 169 and 151 pg/mL for Bydureon and EQWS, respectively, are reported, from the current popPK analysis, using expanded data sets including two further phase 3 studies with Bydureon (variation II-41 and II-45) and EQWS. The values reported for Bydureon (169 pg/mL) and EQWS (151 pg/mL) using the population PK analysis (including steady-state data from 3 EQWS clinical studies and 8 Bydureon clinical studies) are typical values for a subject having normal renal function, median ideal body weight, and no anti-exenatide antibody titer. For Bydureon, a $C_{ss,av}$ of 300 pg/ml is currently reported in the SmPC section 5.2 while for EQWS, a $C_{ss,av}$ of 208 pg/ml in section 5.2 is proposed by the applicant. Question on if the appropriateness of the $C_{ss,av}$ values in the SmPCs was asked in round 1. The applicant suggests to follow precedent from the previous SmPC to let a single study represent the Css,av for each of the products, Bydureon would be represented as 265 pg/mL from

Study BCB108 and EQWS as 208 pg/mL from Study BCB118. For Bydureon, the $C_{ss,av}$ of 300 pg/mL currently reported in the SmPC, Section 5.2, results from observations in the original clinical trial LAR-105 (DURATION-1) in which non-commercial drug product was used. The CHMP agreed that updating Bydureon $C_{ss,av}$ in the SmPC section 5.2 is necessary since the previous value came from a study using non-commercial drug product. The discussion regarding the typical patient values in the popPK (i.e. normal renal function, body weight and no anti-exenatide antibody titer) is accepted. However it is not understood why only a single study should represent the $C_{ss,av}$ if there are several equally relevant studies using the commercial formulation. In the 3 Phase 3 studies (BCB108, D5553C00002 [DURATION 7], and D5553C00003 [DURATION 8]) that evaluated the pharmacokinetics of exenatide administered as the commercial formulation of exenatide once weekly (BYDUREON), the geometric mean plasma concentration at steady state (Css,av) ranged from 151 to 265 pg/mL. In the 2 studies (BCB118 and BCB120) that evaluated the pharmacokinetics of exenatide administered as the once weekly suspension formulation (BYDUREON BCise), the geometric mean Css,av values were 208 pg/mL and 153 pg/mL, respectively. As requested by the Rapporteur, the proposed SmPC contains Css,av ranges for BYDUREON (single-dose tray and dual chamber pen) (151 to 265 pg/mL) and BYDUREON BCise (153 to 208 pg/mL).

Extrapolation of both efficacy and safety from Bydureon to EQWS, with regards to parts of the indication not covered by the clinical development program for EQWS, is acceptable since the observed $C_{ss,av}$ values for exenatide in the EQWS Phase 3 studies are in a comparable range as that observed for Bydureon. In addition, ninety-nine percent of the individual median predicted exenatide $C_{ss,av}$ values for EQWS exceeded the model predicted half maximal effective concentration (EC50) (52.1 pg/ml). Thus the $C_{ss,\ av}$ values are similar enough and well above the model predicted half maximal effective concentration (EC50) of 52.1 pg/ml and extrapolation of efficacy is appropriate. Since EQWS has a lower $C_{ss,\ av}$ than Bydureon, extrapolation of safety is also accepted.

The increase C_{ss} in patients with mild and moderate RI compared to in subjects with normal renal function is not unexpected for exenatide, a GLP-1 compound eliminated mainly *via* renal excretion. No dose adjustment is recommended patients with mild RI and Bydureon is not recommended in patients with creatinine clearance <50 ml/min. Based on individual subjects, the exposure in mild RI is about 2.5-fold higher than in patients with normal renal function. Comparable effect on HbA1c are reported in the two groups but a slightly higher frequency of GI adverse events are seen in the subjects with mild RI compared to patients with normal renal function.

Exenatide is a synthetic peptide with partial sequence homology to the naturally occurring human glucagon-like peptide-1 (GLP-1). No new data have been submitted with regards to the mechanism of action or the primary and secondary pharmacology of exenatide, but reference is given to data obtained with Byetta and Bydureon. This is acceptable. Adequate preclinical and clinical studies have been performed to investigate any potential of exenatide to prolong QT interval. All these studies have been negative.

No new PD interactions are expected due to the new formulation. The known interactions are adequately reflected in the PI.

Efficacy and safety data are available, from the BCB118, and BCB120 studies, to support the new formulation.

2.4.5. Conclusions on clinical pharmacology

Systemic exposure of exenatide has been monitored following once weekly sc injection with EQWS.

In the SmPCs, the exposure for the new EQWS formulation is reported to be lower than for Bydureon.

Extrapolation of both efficacy and safety from BYDUREON to EQWS, with regards to parts of the indication not covered by the clinical development program for EQWS is accepted. The $C_{ss, av}$ values are similar enough and well above the model predicted half maximal effective concentration (EC50) of 52.1 pg/ml and thus extrapolation of efficacy is appropriate. Since EQWS has a lower $C_{ss, av}$ than Bydureon, extrapolation of safety is also adequate.

The CHMP agreed that updating Bydureon $C_{ss,av}$ in the SmPC section 5.2 is necessary since the previous value came from a study using non-commercial drug product. The updated SmPC contains Css,av ranges for BYDUREON (single-dose tray and dual chamber pen) (151 to 265 pg/mL) and BYDUREON BCise (153 to 208 pg/mL) which is satisfactory.

The pharmacodynamics of EQWS has been adequately investigated and described.

2.5. Clinical efficacy

The EQWS clinical development programme consists of one completed Phase 2 study (BCB110) and two completed Phase 3 studies (BCB118 and BCB120).

Dose-response studies and main clinical studies

Dose selection

Both the EQWS and Bydureon formulations of exenatide employ the same polymeric microspheres containing 5% exenatide and the 2 formulations differ only with regard to the vehicle. Data from study BCB110 provide support for the choice of dose.

Study BCB110 was a Phase 2, 2-cohort, single- and repeat-dose study conducted to assess the pharmacokinetics (PK), tolerability, and safety of EQWS administered as a single dose in Cohort 1 and QW over a 12-week assessment period in Cohort 2. In Cohort 1, healthy subjects received a single SC dose of 10 mg EQWS, and in Cohort 2, subjects with T2DM were randomised to receive 2 mg EQWS or placebo in a 2:1 ratio for 12 weeks.

Efficacy was only assessed in Cohort 2 which included male and nonpregnant female subjects with T2DM, aged 19 to 75 years of age. At screening, subjects were required to have HbA1c of 7.1% to 10.0%, inclusive; body mass index (BMI) of 25 kg/m^2 to 45 kg/m^2, and FPG <260 mg/dL (14.4 mmol/L). Subjects had to be treated with diet and exercise alone or with a stable regimen of metformin, a thiazolidinedione (TZD), or a combination of metformin and a TZD for a minimum of 2 months prior to screening to be eligible to participate.

In Cohort 2, treatment with EQWS for 12 weeks resulted in significant reductions in mean HbA1c (-0.87%), fasting serum glucose (-1.8 mmol/L), and body weight (-1.41 kg).

Pharmacokinetic data from Study BCB110 demonstrated that weekly administration of 2 mg EQWS achieved steady-state exenatide concentrations that were modestly higher compared to 2 mg Bydureon, but well within the range of exenatide systemic exposures previously observed with 2 mg Bydureon. Based on these results, which were confirmed by subsequent PK/pharmacodynamic (PD) modelling and simulations, a 2 mg dose was selected as the EQWS dose for the Phase 3 studies.

Main studies

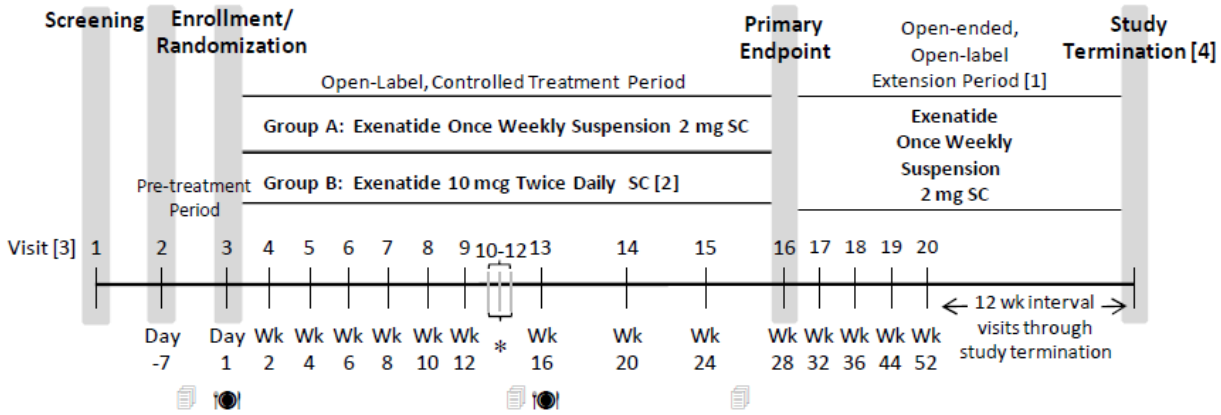
Both Phase 3 studies were randomised, open-label trials of efficacy, safety, and tolerability of EQWS in subjects with T2DM.

Study BCB118

Study BCB118 was a Phase 3, randomised, open-label, long-term, multicentre, comparator-controlled, 2-arm study designed to compare the glycaemic effects, safety, and tolerability of EQWS to Byetta BID over 28 weeks. Subjects with T2DM were randomly assigned to one of the 2 treatment groups in a ratio of 3:2. Randomisation was stratified by diabetes management method at screening, screening glycated HbA1c stratum, and renal function.

Following the 28-week primary assessment period, subjects began an open-ended extension period during which all participating subjects (n=309) were to receive 2 mg EQWS from Week 29 through Week 52.

Figure 1 Study Design BCB118



6 point self-monitored blood glucose profiles performed on any three days in week prior to subsequent visit.

Indicates meal test and postprandial assessments for a subset of subjects at select sites.

* Study site visits for PK assessments for a subset of subjects at select study sites.

[1] For the open-ended extension period, all subjects (Groups A and B) will receive 2 mg exenatide once weekly suspension treatment to Week 52.

[2] Subjects randomized to Group B will receive 4 weeks of 5 mcg exenatide BID followed by 24 weeks of 10 mcg exenatide BID.

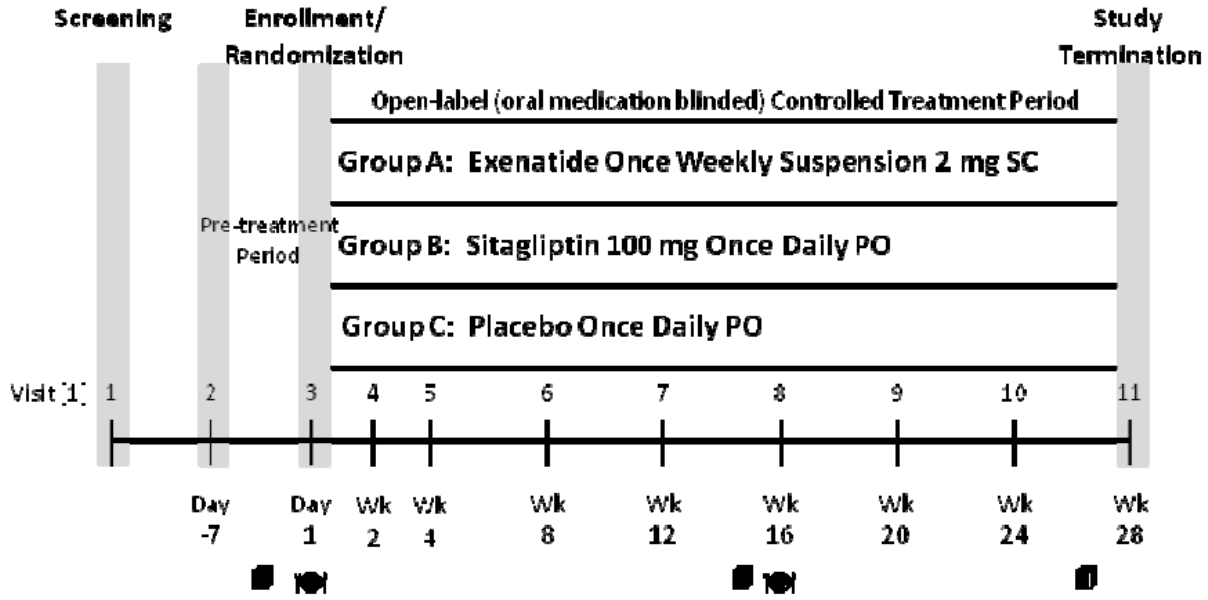
[3] Visit 2 will occur within 14 days following Visit 1. Visit 3 will occur 7 (±2) days following Visit 2. Visits through Visit 20 will occur at the indicated interval (± 2 days), relative to Visit 3. Subsequent visits will occur at the indicated interval (± 3 days), relative to Visit 3.

[4] Subjects must complete a follow-up visit 10 weeks after the final treatment visit (whether the visit occurred during the controlled treatment period or the extension period).

Study BCB120

Study BCB120 was a Phase 3, randomised, open-label (oral agents blinded), long-term, multicentre, comparator- and placebo-controlled, 3-group study designed to compare the efficacy, safety, and tolerability of EQWS to sitagliptin and placebo, and characterise the PK of EQWS over 28 weeks. Subjects were randomly assigned across the 3 treatment groups in a ratio of 3:2:1, with randomisation stratified by screening HbA1c stratum.

Figure 2 Study Design BCB120



6 point self-monitored blood glucose profiles performed on any three days in the week prior to subsequent visit.

Indicates meal test and postprandial assessments for a subset of subjects at select sites.

PO = by mouth, SC = subcutaneous, Wk = week.

[1] Visit 2 will occur within 14 days following Visit 1. Visit 3 will occur 7 (± 2) days following Visit 2. Visits 4 through study termination will occur at the indicated interval (± 2 days), relative to Visit 3.

Subjects will return to the study site for a safety follow up visit 10 weeks after the final treatment visit.

Study participants

Study **BCB118** and Study **BCB120** both included male and nonpregnant female subjects, at least 18 years of age with T2DM. Subjects were required to have HbA1c of 7.1% to 11.0%, inclusive; BMI ≤45 kg/m^2, and FPG concentration <280 mg/dL (15.5 mmol/L). Subjects with any exposure to Byetta, Bydureon, any GLP-1 analogue, or any dipeptidyl peptidase-4 inhibitor within 3 months of screening were excluded, and subjects treated with insulin within 2 weeks prior to screening or for more than 1 week within 3 months of screening were excluded.

In Study **BCB118**, subjects were required to be treated with diet and exercise alone or in combination with a stable regimen of oral antidiabetes medication, and in Study **BCB120**, subjects were required to be treated with a stable regimen of ≥ 1500 mg/day metformin for a minimum of 2 months before screening.

Outcomes/endpoints

The primary efficacy endpoint in Phase 3 Studies **BCB118** and **BCB120** was the change in HbA1c from baseline to Week 28.

Secondary endpoints were the following:

- Proportion of subjects achieving HbA1c target value of <7% at Week 28
- Change in FPG concentrations from baseline to Week 28

- Change in body weight from baseline to Week 28
- Change in 2-hour postprandial plasma glucose concentrations from baseline to Week 16 for subjects in the meal test cohort.

Statistical methods

In both Phase 3 studies, the change in HbA1c from baseline to Week 28 was compared between the EQWS group and the comparator group(s) using a mixed-effect model with repeated measures (MMRM) in the mITT population (observed data) as the primary analysis. No imputation of missing data was performed.

For the analysis of secondary endpoints, namely FPG and weight, the same model as for primary endpoint was used. For analysis of portion of subjects <7% at Week 28, a Cochran- Mantel-Haenszel test was used. A generalised linear model was used for analysis of PPG.

Multiplicity adjustment procedures were used to protect family-wise error rate for the primary endpoint and secondary endpoints.

The data from the open-label extension in Study BCB118 were analysed descriptively using MMRM.

Results

Overall, 742 subjects were randomised to the 2 Phase 3 studies. The proportion of subjects completing each study was similar.

Participant flow

Figure 3 Subject disposition in Study BCB118

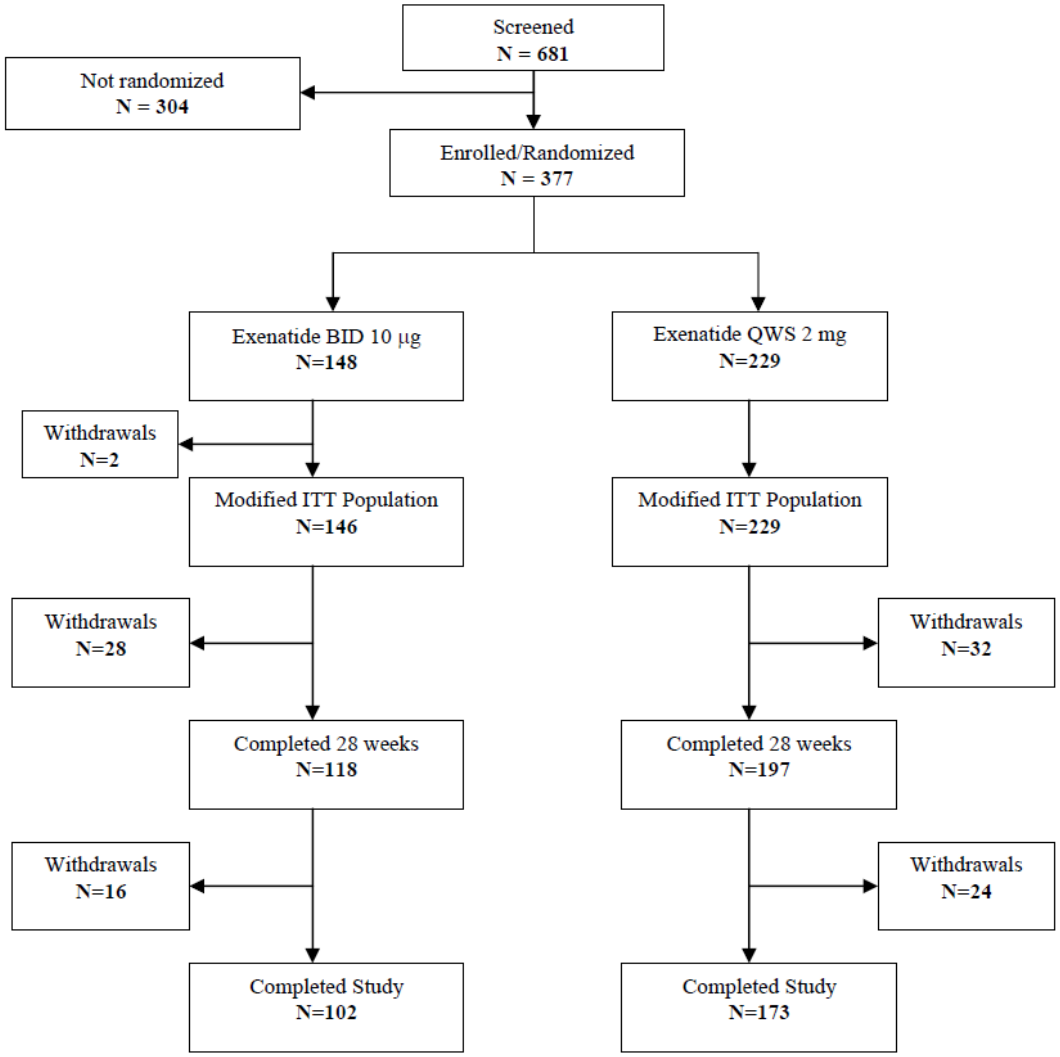


Figure 4 Subject disposition in BCB120

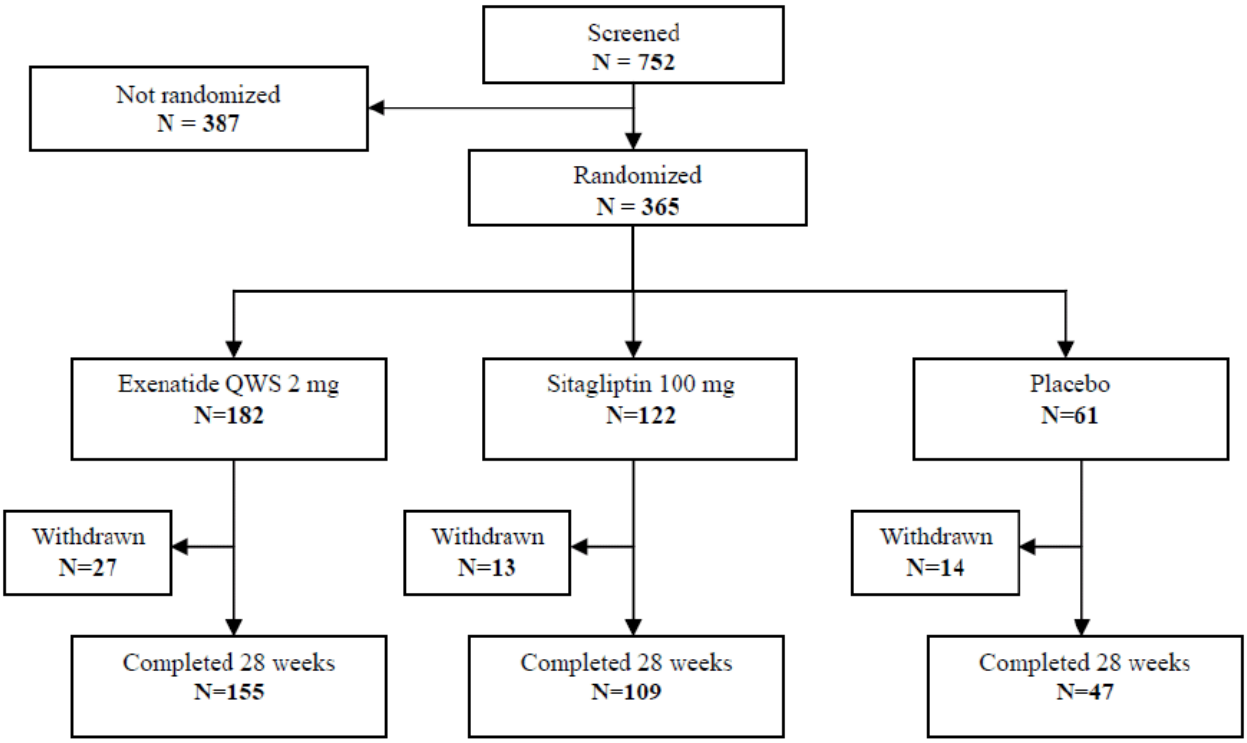


Table 2 Subject disposition by treatment in the Phase 3 studies (All Randomised Subjects)

	Study BCB118		Study BCB120		
Parameter	**EQWS 2 mg (N=229)**	**BYETTA BID 10 µg (N=148)**	**EQWS 2 mg (N=182)**	**Sitagliptin 100 mg (N=122)**	**Placebo (N=61)**
Completed 28-week controlled treatment period	197 (86.0)	118 (79.7)	155 (85.2)	109 (89.3)	47 (77.0)
Completed 52 weeks	173 (75.5)	102 (68.9)	-	-	-
Withdrawal prior to Week 28	32	30	27	13	14
Reason for withdrawal					
Withdrawal by subject	17 (7.4)	11 (7.4)	14 (7.7)	7 (5.7)	7 (11.5)
Adverse event	6 (2.6)	8 (5.4)	4 (2.2)	0	3 (4.9)
Investigator decision	1 (0.4)	1 (0.7)	1 (0.5)	0	1 (1.6)
Protocol violation	2 (0.9)	1 (0.7)	1 (0.5)	0	0
Lost to follow-up	5 (2.2)	7 (4.7)	7 (3.8)	6 (4.9)	3 (4.9)
Administrative	0	2 (1.4)	1 (0.5)	0	0
Loss of glucose control	1 (0.4)	0	0	0	0
All withdrawals on/after Week 28	24	16	-	-	-
Withdrawal by subject	16 (7.0)	7 (4.7)	-	-	-
Adverse event	1 (0.4)	2 (1.4)	-	-	-
Investigator decision	0	3 (2.0)	-	-	-
Protocol violation	0	0	-	-	-
Lost to follow-up	7 (3.1)	4 (2.7)	-	-	-
Administrative	0	0	-	-	-
Loss of glucose control	0	0	-	-	-

BID twice daily; EQWS exenatide once weekly suspension; N number

Baseline data

The demographic and baseline characteristics were generally balanced across the randomised treatment groups in both Phase 3 studies (Table 3)

Table 3 Demographic and baseline characteristics by treatment in the Phase 3 studies (mITT Population), abbreviated

Parameter	Study BCB118		Study BCB120		
	EQWS 2 mg N=229	BYETTA BID 10 µg N=146	EQWS 2 mg N=181	Sitagliptin 100 mg PO N=122	Placebo N=61
Sex, n (%)					
Male	148 (64.6)	92 (63.0)	89 (49.2)	66 (54.1)	37 (60.7)
Female	81 (35.4)	54 (37.0)	92 (50.8)	56 (45.9)	24 (39.3)
Age (years)					
N	229	146	181	122	61
Mean (SD)	55.6 (9.98)	56.5 (9.04)	53.4 (9.82)	54.3 (9.01)	53.4 (9.48)
Median	55.0	58.0	53.0	55.0	54.0
Min, max	30, 80	26, 79	29, 76	31, 73	31, 73
Age category, n (%)					
<65 years	182 (79.5)	118 (80.8)	154 (85.1)	106 (86.9)	54 (88.5)
≥ 65 years [a]	47 (20.5)	28 (19.2)	26 (14.4)	16 (13.1)	7 (11.5)
Body mass index (kg/m^2)					
N	229	146	181	122	61
Mean	33.08 (5.930)	33.38 (5.188)	32.08 (5.423)	31.62 (5.838)	31.51 (5.140)
Median	32.30	32.75	31.70	30.50	30.60
Min, max	18.3, 45.3	21.5, 47.0	21.6, 43.7	21.4, 45.2	19.8, 44.6
Body mass index subgroups, n (%)					
<30 kg/m^2	68 (29.7)	44 (30.1)	74 (40.9)	55 (45.1)	28 (45.9)
≥30 kg/m^2	161 (70.3)	102 (69.9)	107 (59.1)	67 (54.9)	33 (54.1)
HbA1c (%) at baseline					
N	229	146	181	122	61
Mean (SD)	8.46 (1.046)	8.51 (1.004)	8.42 (0.997)	8.50 (1.043)	8.50 (1.043)
Median	8.20	8.45	8.30	8.30	8.30
Min, max	6.7, 11.4	6.6, 11.1	6.8, 10.7	6.7, 10.9	6.6, 10.7
HbA1c stratum at baseline, n (%)					
<9.0	159 (69.4)	97 (66.4)	125 (69.1)	83 (68.0)	42 (68.9)
≥9.0%	68 (29.7)	49 (33.6)	56 (30.9)	39 (32.0)	19 (31.1)

Diabetes management method at screening, n (%)					
Taking SU	89 (38.9)	60 (41.1)	0	1 (0.8)	0
SU + Metformin + TZD	4 (1.7)	2 (1.4)	0	0	0
SU + TZD	1 (0.4)	0	0	0	0
SU + Metformin	76 (33.2)	52 (35.6)	0	1 (0.8)	0
SU	8 (3.5)	6 (4.1)	0	0	0
Not taking SU	140 (61.1)	86 (58.9)	181 (100.0)	121 (99.2)	61 (100.0)
Metformin + TZD	5 (2.2)	4 (2.7)	0	0	0
Metformin	102 (44.5)	65 (44.5)	181 (100.0)	121 (99.2)	61 (100.0)
TZD	2 (0.9)	0	0	0	0
Diet and exercise	31 (13.5)	17 (11.6)	0	0	0
Duration of diabetes (years)					
N	229	146	181	122	61
Mean (SD)	8.34 (6.156)	8.30 (5.868)	8.33 (6.314)	8.00 (4.768)	8.73 (5.758)
Median	7.16	7.92	7.00	7.38	7.64
Min, max	0.1, 35.0	0.0, 29.0	0.2, 37.0	0.4, 26.0	0.2, 25.0
Renal function category [b]					
Normal	85 (37.1)	55 (37.7)	102 (56.4)	64 (52.5)	35 (57.4)
Mild impairment	115 (50.2)	76 (52.1)	78 (43.1)	54 (44.3)	26 (42.6)
Moderate impairment	29 (12.7)	15 (10.3)	1 (0.6)	4 (3.3)	0
Severe impairment	0	0	0	0	0

[a] Including subjects ≥75 years of age

[b] Normal=eGRF ≥90 mL/min/1.73 m^2, mild impairment=eGRF ≥60 to <90 mL/min/1.73 m^2, moderate impairment=eGRF ≥30 to <60 mL/min/1.73 m^2, or severe impairment=eGRF <30 mL/min/1.73 m^2

BID twice daily; BSA body surface area; EQWS exenatide once-weekly suspension; HbA1c haemoglobin A1c; max maximum; MDRD modification of diet in renal disease; min minimum; mITT modified Intent-to-Treat; N number; PO orally; SD standard deviation; SU sulphonylurea; TZD thiazolidinedione

Numbers analysed

Table 4 Subject population by treatment in the Phase 3 studies (All Randomised Subjects)

	Study BCB118		Study BCB120		
Parameter	**EQWS 2 mg (N=229)**	**BYETTA BID 10 µg (N=148)**	**EQWS 2 mg (N=182)**	**Sitagliptin 100 mg (N=122)**	**Placebo (N=61)**
Randomised	229 (100.0)	148 (100.0)	182 (100.0)	122 (100.0)	61 (100.0)
Modified ITT	229 (100.0)	146 (98.6)	181 (99.5)	122 (100.0)	61 (100.0)
Meal Test Subjects	56	43	60	41	20
Meal Test Evaluable	37 (66.1)	31 (72.1)	44 (73.3)	31 (75.6)	15 (75.0)
Week 52 Evaluable	147 (64.2)	68 (45.9)	-	-	-

Modified ITT: Subjects who were randomised and received at least one dose of study drug.
Meal Test Subjects: Subjects who participated in the meal test.
Meal Test Evaluable: Subjects who consumed at least 75% of the standardised meal and had no missing 2-hour postprandial glucose measurements at both baseline and Week 16. Subjects who participated in meal test are used as the denominator.
BID twice daily; EQWS exenatide once weekly suspension; ITT intent to treat; N number

Outcomes and estimation

Primary efficacy variable: Change from baseline in HbA1c at Week 28

In both Phase 3 studies, EQWS demonstrated a significantly larger reduction in HbA1c than the comparators as summarised in Table 5.

Table 5 Change in HbA1c (%) from baseline to Week 28 in the Phase 3 studies (mITT Population)

	Study BCB-118		Study BCB-120		
Visit Statistic	EQWS 2 mg	BYETTA BID 10 µg	EQWS 2 mg	Sitagliptin 100 mg PO	Placebo
Baseline					
N	227	146	181	122	61
Mean (SD)	8.47 (1.047)	8.51 (1.004)	8.42 (0.997)	8.50 (1.043)	8.50 (1.043)
Week 28					
N	175	108	141	98	38
Mean (SD)	7.01 (1.093)	7.37 (1.380)	7.28 (1.306)	7.56 (1.393)	7.74 (1.436)
Mean change from baseline (SD)	-1.44 (1.169)	-1.08 (1.244)	-1.12 (1.209)	-0.87 (0.1360)	-0.64 (1.295)
LS mean change from baseline (SE)	-1.39 (0.093)	-1.02 (0.115)	-1.13 (0.109)	-0.75 (0.1324)	-0.40 (0.195)
95% CI	(-1.57, -1.21)	(-1.25, -0.80)	(-1.34, -0.91)	(-1.01, -0.49)	(-0.79, -0.02)
Difference vs BYETTA (SE)	-0.37 (0.1349)	-	-	-	-
95% CI	(-0.63, -0.10)	-	-	-	-
p-value	0.0072	-	-	-	-
Difference vs sitagliptin (SE)	-	-	-0.38 (0.1638)	-	-
95% CI	-	-	(-0.70, -0.06)	-	-
p-value	-	-	0.0209	-	-
Difference vs placebo (SE)	-	-	-0.72 (0.2167)		-
95% CI	-	-	(-1.15, -0.30)		-
p-value	-	-	0.0010		-

Based on a repeated-measures mixed model including fixed categorical effects of treatment, baseline HbA1c stratum diabetes management method at Screening (for BCB118 only), renal function status at screening, (for BCB118 only), week of visit baseline HbA1c stratum by week interaction and treatment by week interaction as well as the continuous covariates of baseline HbA1c and baseline HbA1c by week interaction.

BID twice daily; CI confidence interval; EQWS exenatide once-weekly suspension; HbA1c haemoglobin A1c; mITT modified intent-to-treat; N number; PO orally; SD standard deviation; SE standard error.

Secondary efficacy variables

For the analysis of secondary endpoints in BCB120, the placebo group was not included in the hierarchical testing strategy.

- *Proportion of subjects with HbA1c <7% at Week 28*

In both Phase 3 studies, a greater proportion of subjects achieved HbA1c of <7% at Week 28 in the EQWS group than in the active comparator groups (Table 6). In both studies, consistent results, with smaller differences between the treatment groups, were observed in a conservative supportive analysis, where subjects with missing values at Week 28 due to early termination or rescue therapy were treated as non-responders.

Table 6 Proportion of subjects achieving HbA1c <7% at Week 28 in the Phase 3 studies (mITT Population)

	Study BCB-118		Study BCB-120		
HbA1c <7% Visit Statistic	EQWS 2 mg (N=229)	BYETTA BID 10 µg (N=146)	EQWS 2 mg (N=181)	Sitagliptin 100 mg PO (N=122)	Placebo (N=61)
Baseline					
Yes	9 (3.9)	2 (1.4)	6 (3.3)	2 (1.6)	2 (3.3)
No	218 (95.2)	144 (98.6)	175 (96.7)	120 (98.4)	59 (96.7)
Week 28					
Yes	113 (49.3)	63 (43.2)	78 (43.1)	39 (32.0)	15 (24.6)
No	114 (49.8)	83 (56.8)	103 (56.9)	83 (68.0)	46 (75.4)
p-value for difference vs BYETTA	0.2247	-	-	-	-
p-value for difference vs sitagliptin	-	-	-	0.0489	-
Nominal p-value for difference vs placebo	-	-	-	-	0.0103

Cochran-Mantel-Haenszel test is stratified by baseline HbA1c stratum.
BID twice daily; EQWS exenatide once-weekly suspension; HbA1c haemoglobin A1c; mITT modified intent-to-treat; N number; PO orally.

- *Change in fasting plasma glucose concentration from baseline to Week 28*

FPG decreased from baseline to Week 28 in all treatment groups, except the placebo group in Study BCB120, where it increased. The reduction in FPG from baseline to Week 28 was numerically greater in the EQWS group than in the active comparator groups in both Phase 3 studies (adjusted p=0.1668 vs Byetta BID in BCB118 and nominal p=0.0931 vs sitagliptin in BCB120). Greater reductions in FPG were observed with EQWS than placebo in BCB120 (nominal p=0.0002).

- *Change in body weight from baseline to Week 28*

Body weight decreased from baseline to Week 28 in all treatment groups, except the placebo group in Study BCB120, where it increased slightly. Reductions in body weight were smaller in the EQWS group than with Byetta BID in BCB118 and with sitagliptin in BCB120. The differences between groups were not statistically significant in either study (nominal p=0.3744 vs Byetta BID in BCB118 and nominal p=0.8625 vs sitagliptin in BCB120). There was a greater reduction in body weight in the EQWS group compared to the placebo group in Study BCB120 (nominal p= 0.0198).

- *Change in 2-hour PPG from baseline to Week 16*

2-hour PPG decreased from baseline to Week 16 in all treatment groups. In Study BCB118, the reduction in 2-hour PPG was greater in the Byetta BID group than in the EQWS group; statistical testing was not performed due to the hierarchical closed testing procedure (nominal p-value=0.0999). In Study BCB120, the reduction in 2-hour PPG was greater in the EQWS group compared with the sitagliptin group; statistical testing was not performed due to the hierarchical closed testing procedure (nominal p=0.0248). The reduction was also numerically greater in the EQWS group compared with the placebo group (nominal p=0.288).

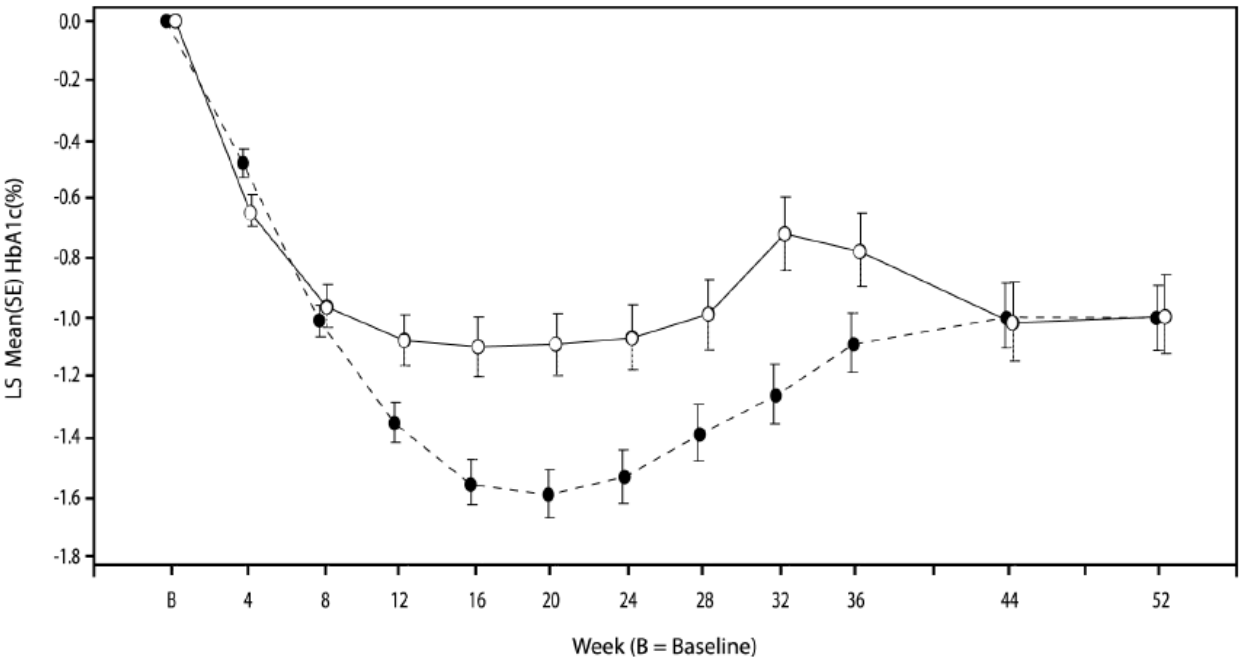
Long-term effect

Study BCB118 included a long-term extension treatment period after the end of the 28-week treatment period through Week 52 during which all subjects received EQWS. The primary purpose of the long-term extension treatment period was to assess the long-term safety of EQWS; exploratory efficacy analyses were also performed during the long-term extension treatment period to assess the long-term durability of treatment effects.

Change from baseline in HbA1c at Week 52

Reductions in HbA1c were observed through 52 weeks of treatment in both treatment groups. Although both groups received EQWS after Week 28, the pattern of HbA1c change over time differed during the long-term extension period between subjects previously randomised to EQWS and those previously randomised to Byetta BID, as shown in Figure 5. The LS mean change (SE) from baseline at Week 52 was -1.00% (0.11%) for subjects previously randomised to the EQWS and -0.99% (0.13%) for those previously randomised to Byetta BID.

Figure 5 Plot of LS mean (SE) change from baseline to Week 52 in HbA1c in Phase 3 Study BCB118 (All mITT Subjects)



Change from baseline in FPG concentrations at Week 52

FPG reductions were observed through 52 weeks of treatment in both groups. At Week 52, the mean change in FPG from baseline was similar in subjects previously randomised to EQWS and those previously randomised to Byetta BID, with LS mean (SE) changes of -26 (4) mg/dL and -31 (5) mg/dL, respectively, and an LS mean (SE) difference between the groups of 5 (6).

Similar to the pattern of change observed in HbA1c over time, FPG gradually increased in subjects who received EQWS throughout the duration of the study, from a nadir achieved at Week 12 through Week 32, at which point FPG reached a plateau. FPG increased from Week 28 to Week 32 in subjects previously randomised to Byetta

BID who were switched to EQWS after completion of the controlled-treatment period. In this group, FPG progressively decreased after Week 32 over the remaining weeks of the study.

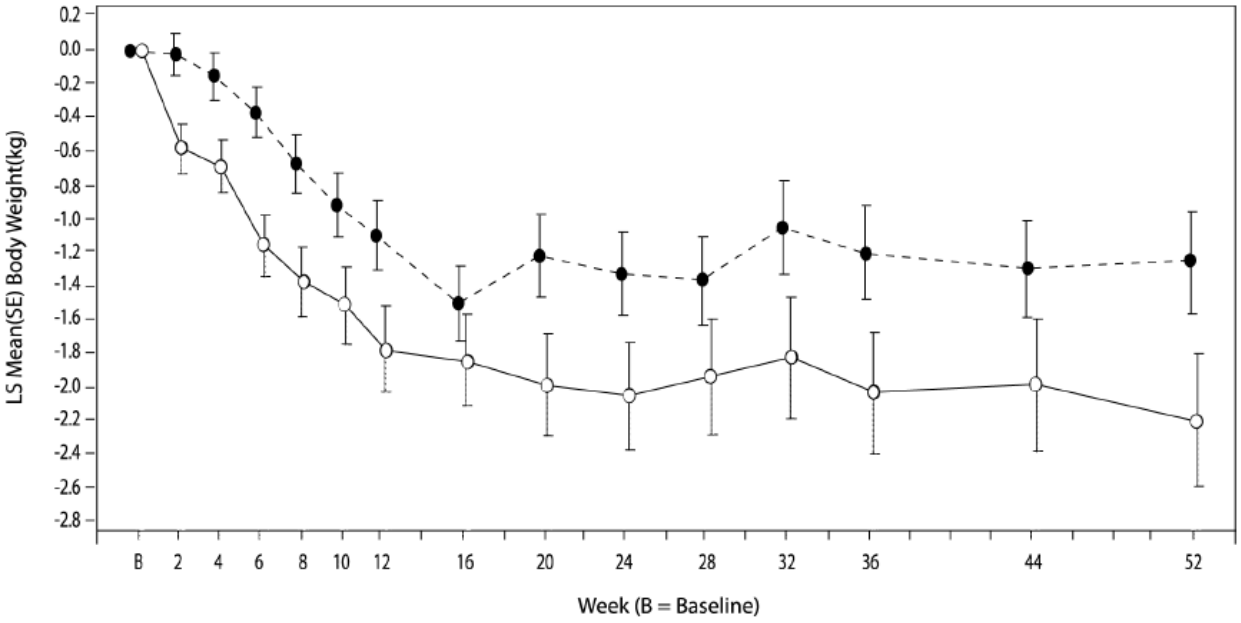
Proportion of subjects achieving HbA1c target value of <7% at Week 52 and up to Study Termination

Increased proportions of subjects achieving HbA1c values of <7% compared to baseline were observed at Week 52 in both treatment groups. At Week 52, the proportions of subjects who achieved an HbA1c of <7% were similar for subjects previously randomised to EQWS and those previously randomised to Byetta BID (38.4% of subjects in each group).

Change in body weight in long-term treatment

Body weight reductions were observed in both treatment groups through Week 52. Body weight appeared to stabilise at approximately Week 16 in subjects who received EQWS throughout the duration of the study while body weight decreased modestly throughout the study in subjects previously randomised to Byetta BID (Figure 6). At Week 52, the LS mean (SE) difference between the groups was 0.9 (0.5) kg.

Figure 6 Plot of LS Mean (SE) change from baseline in body weight from baseline to Week 52 in Study BCB118



Ancillary analyses

Comparison of results in sub-populations

Summary statistics for change from baseline in HbA1c at Week 28 were generated for subgroups defined by gender (male, female), age (<65 years or ≥65 years), and race, and for randomisation strata defined by baseline HbA1c strata (<9.0% or ≥9.0%), diabetes management method at screening (diet/exercise alone, SU use, or non-SU use; for BCB118 only) and renal function status (normal, mild renal impairment, or moderate renal impairment; for BCB118 only) for the mITT population.

Patients who were on diet and exercise at baseline had greater HbA1c reductions at Week 28 in both the EQWS (n=27; -1.73%) and Byetta BID (n=13; -1.38%) groups when compared to the entire study population. Consistent with the entire study population, these reductions were greater for EQWS than Byetta BID.

Larger decreases in HbA1c were achieved in the subgroup of subjects with screening HbA1c ≥9% across treatments in both studies. Otherwise, no interaction by subgroup was observed.

Effect of antibodies to exenatide on efficacy

Amongst EQWS-treated patients evaluable for antibodies at week 28 (n=309), approximately 43.4% of patients had low titre antibodies to exenatide and approximately 13.9% of patients had high titre antibodies.

For Study BCB118, in the EQWS group, the mean (standard deviation [SD]) change from baseline to Week 28 in HbA1c was -1.39% (1.11%) in subjects negative for antibodies (n=101), -1.48% (1.25%) for those with low antibody titres (n=94), and -0.74% (1.33%) in subjects with high antibody titres (n=31).

For Study BCB120, in the EQWS group, the mean (SD) change from baseline to Week 28 in HbA1c was -1.05% (1.15%) in subjects negative for antibodies (n=61), -1.14% (1.30%) for those with low antibody titres (n=79), and -0.58% (1.28%) in subjects with high antibody titres (n=26).

Summary of main efficacy results

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

Table 7 Summary of efficacy for trial BCB118

Title: A Randomized, Open-Label, Long-Term, Parallel-Group, Comparator-Controlled, Multicenter Study To Compare The Glycaemic Effects, Safety, And Tolerability Of Exenatide Once Weekly Suspension To Exenatide Twice Daily In Subjects With Type 2 Diabetes Mellitus			
Study identifier	BCB118		
Design	Randomised, open-label, long-term, multicenter, comparator-controlled, 2-arm study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 weeks not applicable 24 weeks
Hypothesis	Non-inferiority/Superiority vs Exenatide BID		
Treatments groups	Exenatide QWS, 2 mg sc		229
	Exenatide BID, 10 µg BID sc		148
Endpoints and definitions	Primary endpoint	HbA1c (%)	Change in HbA1c from baseline to Week 28
	Secondary endpoint	HbA1c<7%	Proportion of subjects achieving HbA1c target value of <7% at Week 28
	Secondary endpoint	FPG (mmol/L)	Change in fasting plasma glucose concentrations from baseline to Week 28
	Secondary endpoint	BW (kg)	Change in body weight from baseline to Week 28
Database lock	19-Aug-2014 (study completion date)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent to treat		
Descriptive statistics and estimate variability	Treatment group	Exenatide QWS	Exenatide BID
	Number of subject	229	148
	HbA1c (%) (LS mean)	-1.39	-1.02
	95% CI	(-1.57, -1.21)	(-1.25, -0.80)
	HbA1c<7% (n)	113	63
	%	49.3	43.2
	FPG (LS mean)	-1.81	-1.25
	95% CI	(-2.24, -1.39)	(-1.79, -0.71)
	BW (LS mean)	-1.49	-1.89
	95% CI	(-2.05, -0.93)	(-2.61, -1.18)
Effect estimate per comparison	Primary endpoint: Change in HbA1c from baseline to Week 28 (%)	Comparison groups	EQWS vs Exenatide BID
		Difference	-0.37
		95% CI	(-0.63, -0.10)
		P-value	0.0072
	Secondary endpoint: Proportion of subjects achieving HbA1c target value of <7% at Week 28 (%)	Comparison groups	EQWS vs Exenatide BID
		Difference	6.1
		P-value	0.2247
	Secondary endpoint: Change in fasting plasma glucose concentrations from baseline to Week 28 (mmol/L)	Comparison groups	EQWS vs Exenatide BID
		Difference	-0.56
		95% CI	[-1.20, 0. 08]
		P-value	0.1668
	Secondary endpoint: Change in body weight from baseline to Week 28 (kg)	Comparison groups	EQWS vs Exenatide BID
		Difference	0.40
		95% CI	(-0.48, 1.28)
		P-value	0.3744
Notes			
Analysis description			

Table 8 Summary of efficacy for trial BCB120

Title: A Randomized, Long-Term, Open-Label, 3-Arm, Multicenter Study to Compare the Glycaemic Effects, Safety, and Tolerability of Exenatide Once Weekly Suspension to Sitagliptin and Placebo in Subjects with Type 2 Diabetes Mellitus					
Study identifier	BCB120				
Design	Randomised, open-label (oral agents blinded), long-term, multicenter, comparator- and placebo-controlled, 3-group study				
	Duration of main phase:	28 weeks			
	Duration of Run-in phase:	not applicable			
	Duration of Extension phase:	not applicable			
Hypothesis	Superiority vs placebo, Non-inferiority vs sitagliptin				
Treatments groups	Exenatide QWS, 2 mg sc	182			
	Sitagliptin 100 mg OD	122			
	Placebo OD	61			
Endpoints and definitions	Primary endpoint	HbA1c (%)	Change in HbA1c from baseline to Week 28		
	Secondary endpoint	HbA1c<7%	Proportion of subjects achieving HbA1c target value of <7% at Week 28		
	Secondary endpoint	FPG (mmol/L)	Change in fasting plasma glucose concentrations from baseline to Week 28		
	Secondary endpoint	BW (kg)	Change in body weight from baseline to Week 28		
Database lock	04-Apr-2014 (study completion date)				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified intent to treat				
Descriptive statistics and estimate variability	Treatment group		Exenatide QWS	Sitagliptin	Placebo
	Number of subject		181	122	61
	HbA1c (%) (LS mean)		-1.13	-0.75	-0.40
	95% CI		(-1.34, -0.91)	(-1.01, -0.49)	(-0.79, -0.02)
	HbA1c<7% (n)		78	39	15
	%		43.1	32.0	24.6
	FPG (LS mean)		-1.18	-0. 62	0.53
	95% CI		[-1.60, -0.76]	[-1.13, -0.12]	[-0.25, 1.30]

	BW (LS mean)	-1.12	-1.19	0.15
	95% CI	(-1.63, -0.61)	(-1.81, -0.57)	(-0.79, 1.09)

Effect estimate per comparison	Primary endpoint: Change in HbA1c from baseline to Week 28 (%)	Comparison groups	EQWS vs Sitagliptin
		Difference	-0.38
		95% CI	(-0.70, -0.06)
		P-value	0.0209
		Comparison groups	EQWS vs placebo
		Difference	-0.72
		95% CI	(-1.15, -0.30)
		P-value	0.0010
	Secondary endpoint: Proportion of subjects achieving HbA1c target value of <7% at Week 28 (%)	Comparison groups	EQWS vs Sitagliptin
		Difference	11.1
		P-value	0.0489
		Comparison groups	EQWS vs placebo
		Difference	18.5
		P-value	0.0103
	Secondary endpoint: Change in fasting plasma glucose concentrations from baseline to Week 28 (mmol/L)	Comparison groups	EQWS vs Sitagliptin
		Difference	-0.56
		95% CI	[-1.21, 0.09]
		P-value	0.0931
		Comparison groups	EQWS vs placebo
		Difference	-1.71
		95% CI	(-2.59, -0.83)
		P-value	0.0002
	Secondary endpoint: Change in body weight from baseline to Week 28 (kg)	Comparison groups	EQWS vs Sitagliptin
		Difference	0.07
		95% CI	(-0.73, 0.87)
		P-value	0.8625
		Comparison groups	EQWS vs placebo
		Difference	-1.27
		95% CI	(-2.34, -0.20)
		P-value	0.0198
Notes			
Analysis description			

Clinical studies in special populations

No specific studies were performed in special populations.

Of the 410 EQWS-treated subjects in the Phase 3, controlled study periods, 336, 64, 10 and 0 subjects were aged <65, 65 to 74, 75 to 84 and ≥85 years, respectively.

2.5.1. Discussion on clinical efficacy

EQWS is a modified formulation of Bydureon that contains the same drug substance, drug load (5% by mass), and prolonged-release microspheres as Bydureon, but with a nonaqueous MCT vehicle. No changes were made to the microsphere formulation or the manufacturing process.

Design and conduct of clinical studies

The study program includes one Phase 2 study and two Phase 3 studies. Both Phase 3 studies measured the primary endpoint at week 28, and one of the studies includes a 24 week extension during which all patients were treated with EQWS.

The primary objective of the Phase 2 study BCB110 was to investigate PK for the new formulation and to gather safety and efficacy data in support of the selected dose of 2 mg EQWS, i.e. the same dose as in the aqueous formulation. PK data was evaluated for both cohorts whereas efficacy data was only evaluated in Cohort 2 which included patients with T2DM. The inclusion criteria were set to enrol patients largely representative for the target population. Improvements in HbA1c and FPG as well as a decrease in body weight were observed after 12 weeks of treatment. The choice of dose was mainly based on the PK and PK/PD modelling data which bridged to data for the already approved exenatide formulation. The efficacy data provide support that the 2 mg dose is effective.

Both Phase 3 studies (BCB118 and BCB120) were randomised, open-label trials of efficacy, safety, and tolerability of EQWS in subjects with T2DM. The open-label design is acceptable considering that double-dummy injection treatment otherwise have had to be used. In BCB118 EQWS was compared to Byetta BID and in study BCB120, which was a three-armed study, EQWS was compared to both sitagliptin and placebo. Oral treatment was blinded. Both studies measured the primary endpoint at 28 weeks which is adequate, and the extension period in study BCB118 (where all patients received EQWS) provides information both on the switch from Byetta BID to EQWS as well as long-term data (52 weeks). None of the studies had a run-in period which is acceptable since no changes were made to the background medication. In study BCB120, patients were required to be on stable metformin treatment before screening.

The inclusion and exclusion criteria were generally acceptable in both studies. In the scientific advice, concerns were raised regarding the inclusion of patients on diet and exercise alone in study BCB118, as this is not in accordance with EU label. Therefore data from this subgroup is only to be considered supportive.

Both studies included criteria for loss of glucose control, in which case rescue therapy should be initiated. The rescue therapy should be chosen in accordance with local prescribing information and the subject was allowed to continue study participation.

The endpoints chosen were adequate and relevant. PROs were included among tertiary endpoints. The decision not to pool efficacy data is endorsed considering the difference in comparators.

The sample size calculations were adequate. In study BCB118, a non-inferiority margin of 0.4% was applied which may be acceptable for planning purposes but is considered too wide when assessing the outcome.

In both studies, more patients were randomised to EQWS than to comparators. Stratification for previous treatment, glycaemic control and renal function was done in study BCB118, whereas patients were only

stratified by glycaemic control in study BCB120. This is acceptable, taking into account the low number of patients included in the placebo group in study BCB120.

In 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 generally needed. 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. Data after receiving rescue medication are censored and not used in the analysis.

To understand the robustness of the results further data was requested. In study BCB118, only small differences in missing data was observed between treatment groups (24% and 27% for EQWS and Byetta BID, respectively). In study BCB120, the proportion of patients with missing data was considerably higher in the placebo treated group (38%) compared to the groups treated with EQWS (22%) or sitagliptin (20%). This is consistent with a higher drop-out rate in the placebo treated group compared to the groups on active treatment. 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 performed. Also with this conservative analysis EQWS was found superior to Byetta BID and placebo, whereas the treatment difference to sitagliptin was attenuated and did not reach statistical significance. The additional analysis provides further support with regards to the robustness of the results.

The use of hierarchical testing procedure to control the type I-error is endorsed.

With regards to the conduct of the studies, protocol amendments were made in both studies. The amendments made are not considered to affect the outcome of the studies or the interpretation of the data.

Protocol deviations were noted for 36% (BCB118) and 43 % (BCB120) of subjects; the majority of these were classified as "other" (≈30%). Violation of inclusion/exclusion criteria was rather uncommon. Notably two subjects were enrolled twice at different sites in study BCB118. The data from these subjects were treated as if four subjects were enrolled. The Applicant has re-run the analysis excluding the data from the two subjects. The results from the new analysis did not differ from the primary analysis. In study BCB120, one subject was enrolled twice at different sites. The data from this subject was excluded from the last randomisation. Notably, the double enrolment was discovered within a few months for two of the subjects which provide reassurance that the monitoring of the study was adequate. Thus no concerns with regards to the conduct of the study are raised.

Efficacy data and additional analyses

Overall, 742 subjects were randomised to the 2 Phase 3 studies. The completion rate at 28 weeks was comparable for EQWS in both studies (86% and 85%). The highest completion rate was observed in the sitagliptin treated group (89%) and the lowest in the Byetta BID (80%) and placebo treated groups (77%).

"Withdrawal by subject" and "Lost to follow up" were the most common reasons for withdrawal in all treatment groups, these withdrawals were evenly distributed across the treatments. Few patients withdrew due to adverse events, the highest proportion was observed in the Byetta BID treated group (5.4%).

The proportion of patients completing the 52 extension was highest in the EQWS treated group, mainly due to a higher withdrawal rate in the Byetta BID treated groups before week 28.

Demographic and baseline characteristics were generally balanced between treatment groups and comparable between the two studies. In study BCB118, subjects were slightly older and more overweight than in study BCB120. The background treatment differed in line with the differences in inclusion criteria. Notably, in study BCB118, about 12% of patients were on diet and exercise treatment alone. In study BCB120, all patients were on background metformin treatment; whereas about 80% of subjects in study BCB118 were using metformin either as monotherapy or in combination with other OADs.

Patients on EQWS therapy showed a medical history and concomitant medications at baseline as expected in this population. About 47% of EQWS patients had at least 1 concomitant medication added during the 28 weeks of the study. In the extension period, 17% of patients had at least 1 concomitant medication added used in diabetes. In Study BCB118, 13 (5.7%) patients on EQWS and 15 (10.1%) patients on BYETTA received rescue therapy. In Study BCB120, 6 (3.3%) patients on EQWS, 9 (7.4%) patients on sitagliptin, and 9 (14.8%) patients on placebo received rescue therapy. Thus the need for rescue was lowest in the EQWS treated group in both studies.

The mITT includes all patients except for 3 patients in total. The proportion of patients excluded from the evaluable meal test set was generally higher but mostly balanced between groups.

The primary endpoint was met in both studies, where EQWS showed a significantly larger reduction of HbA1c from baseline vs Byetta BID (treatment difference -0.4%; study BCB118) and vs sitagliptin (treatment difference -0.4%) and placebo (treatment difference -0.7%; study BCB120).

The primary endpoint was calculated excluding patients on rescue therapy or terminated early. The proportion of patients included in the analysis was balanced between groups (BCB118: 77% on EQWS vs 74% on Byetta BID; study BCB120: 78% on EQWS vs 80% on sitagliptin). The only exception is the placebo group where only 62% of patients were included in the analysis.

The outcome is largely in line with the outcome observed in comparable studies with the aqueous solution of prolonged-release exenatide.

In both studies, a numerically higher proportion of patients achieved the treatment goal of HbA1c <7% in the EQWS treated groups compared (49% and 43%, BCB118 and BCB120, respectively) to Byetta BID (43%) or sitagliptin (32%). The difference compared to sitagliptin reached statistical significance. The conservative sensitivity analysis showed a similar pattern although no significant differences were observed.

In both studies, a numerically larger reduction in FPG was observed in the EQWS treated groups compared to Byetta BID, sitagliptin or placebo. Statistical significance was only reached when compared to placebo.

The largest reduction in body weight was observed with Byetta BID (-1.9 kg), although not significantly different from EQWS (-1.5 kg; study BCB118). In study BCB120, the weight reduction with EQWS (-1.1 kg) was comparable to that observed with sitagliptin (-1.2 kg) but significantly larger than with placebo (+0.2 kg).

Change in 2-hour PPG was evaluated in a subset of patients after a meal test. The numerically largest effect was observed with Byetta BID (-6.31 mmol/L), although the difference compared to EQWS (-4.83 mmol/L) was not statistically significant (study BCB118). In study BCB120, the decrease in 2-hour PPG was significantly larger with EQWS compared to sitagliptin but only numerically larger than placebo.

Data from the long-term extension show that HbA1c increased from week 20 and onwards in the group treated with EQWS and appeared to reach a plateau after week 44. Patients switching from Byetta BID to EQWS showed a decrease in HbA1c after the switch and at week 52 both treatment arm showed no difference in change from baseline in HbA1c. The FPG showed a similar development as HbA1c, with some increase in the EQWS group

which appeared to plateau. A further decrease in FPG was observed in patients switching from Byetta BID to EQWS and no difference was observed between treatment groups at week 52. The proportion of patients achieving HbA1c <7% decreased over time to 38.4% at week 52 compared to 49.3% at week 28. Body weight remained essentially stable after week 20 in both treatment groups. The larger reduction in body weight observed in patients who started on Byetta BID was maintained throughout the study period.

Subgroup analysis did not reveal any difference in the effect of EQWS on HbA1c reduction in the adequately sized subgroups. Very few patients above the age of 75 years (10 patients) and only 44 patients with moderate/severe renal impairment were included in the studies. As expected, larger decreases in HbA1c was observed in patients with higher HbA1c at baseline. This was observed in all treatment groups. There was no apparent difference in HbA1c reduction between subgroups with normal or impaired renal function. The data for the subgroup only treated with diet and exercise at baseline showed that the mean HbA1c at baseline was slightly lower in this subgroup compared to the mean HbA1c for the total study population. The mean change in HbA1c was also more pronounced in this subgroup, for both treatments, compared to the total study population. The change from baseline in HbA1c was greater with EQWS than with Byetta BID, consistent with the primary outcome. The number of patients per treatment group was however small and the results should be interpreted with caution.

Almost 60% of patients had positive antibody titres at week 28. In both studies, the effect on HbA1c was comparable in antibody-negative patients and patients with low antibody titers, whereas an attenuated but still clinically relevant response was observed in patients with high antibody titers.

2.5.2. Conclusions on clinical efficacy

The efficacy of the new exenatide formulation EQWS has been evaluated in an adequately designed clinical study program, which includes two active comparators (Byetta BID and sitagliptin) as well as placebo. EQWS was found superior to all comparators with regards to the primary endpoint, change from baseline in HbA1c. The outcome of the secondary endpoints was generally supporting the primary outcome, although statistical significance was not always reached. The outcome is in line with previous observations for the aqueous prolonged-release formulation of exenatide.

The efficacy of EQWS has been adequately shown

2.6. Clinical safety

Exenatide once-weekly suspension (EQWS) is a subcutaneously injectable prolonged-release non-aqueous suspension formulation that was developed as extension to Byetta (exenatide twice daily, approved in 2006) and Bydureon (exenatide once weekly aqueous suspension, approved in 2011) for the treatment of patients with type 2 diabetes mellitus (T2DM).

Safety assessments were based on medical review of AEs, laboratory parameters, vital signs measurements, and physical examinations in the 3 clinical studies in the EQWS development programme.

All of the safety analyses were performed using data from the Safety Population, which included all subjects who received at least 1 dose of any randomised study medication. Safety data for the 2 Phase 3 studies (BCB118 and BCB 120) were pooled and summarised. The results of the 28-week controlled periods in the Phase 3 studies constitute the primary safety and tolerability data, with supplemental information provided from the uncontrolled extension period of Study BCB118 and the Phase 2 Study BCB110.

Patient exposure

The 3 EQWS clinical studies enrolled a total of 804 subjects. EQWS was administered to a total of 579 unique subjects in these clinical studies (Table 9).

Table 9 Clinical studies and number of subjects by treatment in the EQWS clinical programme

Study (duration)	Number of subjects	Number of subjects exposed*				
		EQWS		BYETTA	Placebo	Sitagliptin
		10 mg single dose	2 mg once weekly	10 µg BID		100 mg/day PO
Phase 2 study:						
Study BCB110:						
- Cohort 1: Healthy subjects (single dose)	30	30	-	-	-	-
- Cohort 2: T2DM patients (repeated doses)	35	-	23	-	12	-
Phase 3 studies:						
Study BCB118						
- 28-week controlled period	375	-	229	146	-	-
- Uncontrolled extension period: subjects switching from BYETTA to EQWS			116			
Study BCB120	364	-	181	-	61	122
Total (all studies)	**804**	**30**	**549**	**146**	**73**	**122**

*Note: All subjects who received at least one dose of study drug.
BID Twice daily; PO By mouth; T2DM Type 2 diabetes mellitus.

Adverse events

Overall summary of adverse events

In Phase 2 Study BCB110, there were no AEs resulting in discontinuation of study treatment or deaths. One subject in Cohort 2 experienced 2 SAEs during placebo treatment. In Cohort 1, 26 of 30 subjects (86.7%) experienced at least 1 AE and the corresponding values for Cohort 2 were 22 of 23 subjects (95.7%) in the EQWS group and 9 of 12 subjects (75.0%) in the placebo group.

The adverse events for the Phase 3 studies are summarised in Table 10.

Table 10 Overall summary of adverse events by treatment - Phase 3 controlled

	Study BCB118 Controlled Period		Study BCB120 Controlled Period				
Parameter	EQWS N=229 n (%)	Byetta N=146 n (%)	EQWS N=181 n (%)	Sitagliptin N=122 n (%)	Placebo N=61 n (%)	All EQWS[a] N=410 n (%)	All Phase 3 Subjects[b] N=739 n (%)
Subjects with at least one AE	162 (70.7)	110 (75.3)	101 (55.8)	40 (32.8)	29 (47.5)	263 (64.1)	442 (59.8)
Subjects with at least one serious adverse event	5 (2.2)	7 (4.8)	5 (2.8)	0	2 (3.3)	10 (2.4)	19 (2.6)
Subjects with at least one AE leading to discontinuation of study medication	11 (4.8)	11 (7.5)	5 (2.8)	0	3 (4.9)	16 (3.9)	30 (4.1)
Subjects with at least one adverse event leading to death	0	0	0	0	0	0	0

[a] All EQWS subjects in BCB118 (controlled period) + all EQWS subjects in BCB120
[b] All subjects in BCB118 (controlled period) + all subjects in BCB120
Subjects with multiple episodes of a given type of AEs are counted once in each relevant category.
Includes all AEs with onset during the 28-week controlled period, with the exception of hypoglycaemia, which was analysed separately
Abbreviations: AE adverse event; EQWS exenatide once-weekly suspension
MedDRA version 19.0

Common adverse events

Phase 3 controlled period

The most commonly reported AEs (≥5% of subjects) reported in the 410 Phase 3, EQWS-treated subjects during the controlled study periods were under the SOCs Gastrointestinal disorders (nausea, 9.3%), General disorders and administration site conditions (injection site nodule, 12.2%), and Nervous system disorders (headache, 5.1%). Other AEs reported in ≥2% of subjects were diarrhoea (4.1%), upper respiratory tract infection (4.1%), injection site pruritus (3.7%), vomiting (3.4%), dizziness (2.9%), injection site bruising (2.9%) and erythema (2.7%), constipation (2.4%), injection site pain (2.4%), pain in extremity (2.4%), back pain (2.0%), gastroesophageal reflux disease (2.0%), injection site induration (2.0%), and urinary tract infection (2.0%) (Table 11).

As shown in Table 11, gastrointestinal AEs, particularly nausea, vomiting, and diarrhoea, were less frequent in subjects in the EQWS treatment group compared with those in the Byetta group in study BCB118. Conversely, injection site reactions were more frequent amongst EQWS-treated subjects compared with those on Byetta treatment.

Table 11 Adverse events reported in ≥2% of all EQWS subjects by system organ class and preferred term - Phase 3 controlled

	Study BCB118 Controlled Period		Study BCB120 Controlled Period				
System Organ Class Preferred Term	EQWS N = 229 n (%)	Byetta N = 146 n (%)	EQWS N = 181 n (%)	Sitagliptin N = 122 n (%)	Placebo N = 61 n (%)	All EQWS[a] N = 410 n (%)	All Phase 3 Subjects[b] N = 739 n (%)
Subjects with at least one AE during the controlled period	162 (70.7)	110 (75.3)	101 (55.8)	40 (32.8)	29 (47.5)	263 (64.1)	442 (59.8)
General disorders and administration site conditions	70 (30.6)	19 (13.0)	38 (21.0)	1 (0.8)	3 (4.9)	108 (26.3)	131 (17.7)
Injection site nodule	36 (15.7)	1 (0.7)	14 (7.7)	0	0	50 (12.2)	51 (6.9)
Injection site pruritus	10 (4.4)	1 (0.7)	5 (2.8)	0	0	15 (3.7)	16 (2.2)
Injection site bruising	7 (3.1)	0	5 (2.8)	0	0	12 (2.9)	12 (1.6)
Injection site erythema	8 (3.5)	1 (0.7)	3 (1.7)	0	0	11 (2.7)	12 (1.6)
Injection site pain	7 (3.1)	0	3 (1.7)	0	0	10 (2.4)	10 (1.4)
Injection site induration	1 (0.4)	0	7 (3.9)	0	0	8 (2.0)	8 (1.1)
Gastrointestinal disorders	52 (22.7)	54 (37.0)	32 (17.7)	9 (7.4)	2 (3.3)	84 (20.5)	149 (20.2)
Nausea	22 (9.6)	30 (20.5)	16 (8.8)	2 (1.6)	0	38 (9.3)	70 (9.5)
Diarrhoea	12 (5.2)	17 (11.6)	5 (2.8)	2 (1.6)	1 (1.6)	17 (4.1)	37 (5.0)
Vomiting	8 (3.5)	9 (6.2)	6 (3.3)	0	0	14 (3.4)	23 (3.1)
Constipation	8 (3.5)	4 (2.7)	2 (1.1)	1 (0.8)	1 (1.6)	10 (2.4)	16 (2.2)
Gastrooesophageal reflux disease	6 (2.6)	2 (1.4)	2 (1.1)	1 (0.8)	0	8 (2.0)	11 (1.5)
Infections and infestations	52 (22.7)	36 (24.7)	21 (11.6)	7 (5.7)	11 (18.0)	73 (17.8)	127 (17.2)
Upper respiratory tract infection	13 (5.7)	5 (3.4)	4 (2.2)	0	2 (3.3)	17 (4.1)	24 (3.2)
Urinary tract infection	5 (2.2)	3 (2.1)	3 (1.7)	3 (2.5)	2 (3.3)	8 (2.0)	16 (2.2)
Musculoskeletal and connective tissue disorders	29 (12.7)	22 (15.1)	14 (7.7)	5 (4.1)	6 (9.8)	43 (10.5)	76 (10.3)
Pain in extremity	8 (3.5)	5 (3.4)	2 (1.1)	0	1 (1.6)	10 (2.4)	16 (2.2)
Back pain	6 (2.6)	5 (3.4)	2 (1.1)	3 (2.5)	1 (1.6)	8 (2.0)	17 (2.3)
Nervous system disorders	27 (11.8)	20 (13.7)	15 (8.3)	5 (4.1)	3 (4.9)	42 (10.2)	70 (9.5)
Headache	13 (5.7)	9 (6.2)	8 (4.4)	2 (1.6)	1 (1.6)	21 (5.1)	33 (4.5)
Dizziness	8 (3.5)	6 (4.1)	4 (2.2)	1 (0.8)	0	12 (2.9)	19 (2.6)

[a] All EQWS subjects in BCB118 (controlled period) + all EQWS subjects in BCB120
[b] All subjects in BCB118 (controlled period) + all subjects in BCB120
Includes all AEs with onset during the 28-week controlled period, with the exception of hypoglycaemia, which was analysed separately
Abbreviations: AE adverse event; EQWS exenatide once-weekly suspension
MedDRA version 19.0

Phase 3 uncontrolled extension period

In the Phase 3, uncontrolled extension period, AEs reported in ≥2% of all EQWS-treated subjects were nasopharyngitis (3.2%) and influenza (2.3%). The overall AE profile for subjects who switched from Byetta to EQWS was similar to that for subjects who were treated with EQWS throughout both periods of Study BCB118.

The only notable difference in terms of a possible increase in AEs when switching between the 2 formulations of exenatide was for the SOC General disorders and administration site conditions (EQWS to EQWS, 1.6%; Byetta to EQWS, 15.5%), which was mostly attributable to higher incidence rates of injection site AEs in subjects who switched from Byetta to EQWS.

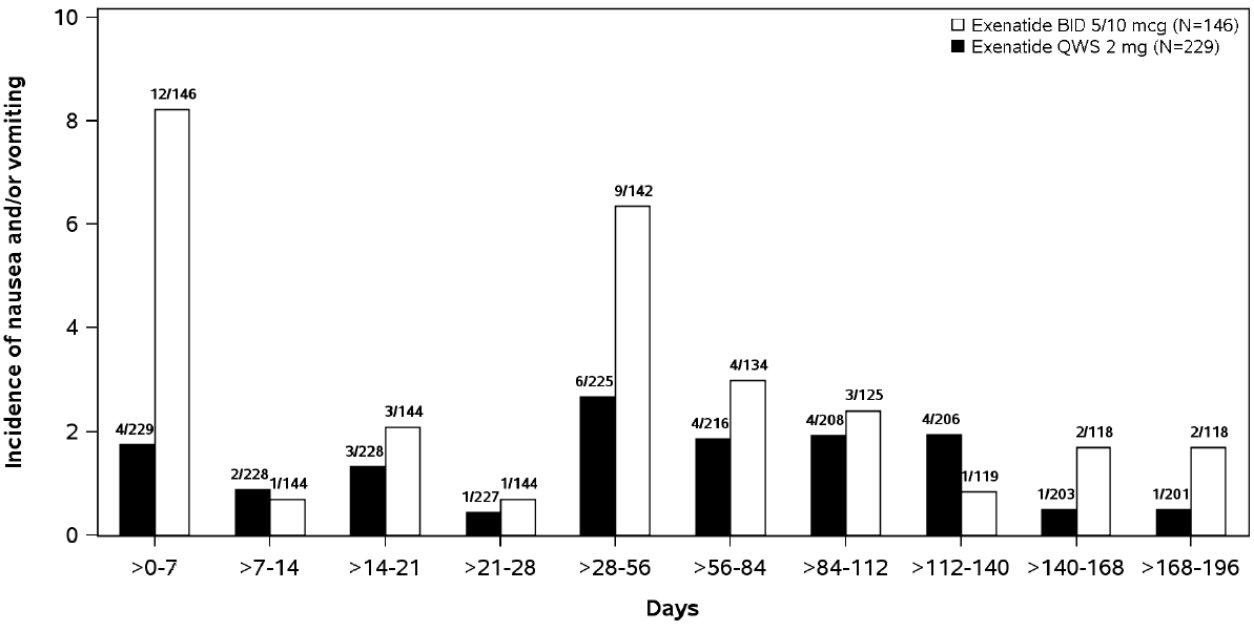
Adverse events of special interest

Gastrointestinal events

Gastrointestinal AEs, especially nausea, diarrhoea, and vomiting, were among the most commonly reported AEs for EQWS-treated subjects; however, the incidence rates for these events were lower compared with Byetta-treated subjects (Figure 7). During the controlled period of study BCB118, nausea was reported in 9.6% of EQWS subjects and 20.5% of Byetta subjects. EQWS appears to have a lower propensity to cause nausea and vomiting than Byetta, particularly upon initiation of treatment, possibly due to a more gradual increase in plasma exenatide levels with EQWS administration relative to Byetta.

In the controlled periods of the Phase 3 studies, the overall incidence of AEs in the SOC Gastrointestinal disorders was 20.5% in the EQWS-treated subjects and the most common events (>1% of subjects) were nausea (9.3%), diarrhoea (4.1%), vomiting (3.4%), constipation (2.4%), abdominal distension (1.7%), and dyspepsia (1.7%).

Figure 7 Incidence (%) of nausea and/or vomiting over time (days) in the EQWS and Byetta treatment groups during the controlled period of Study BCB118



Pancreatitis

Two cases of pancreatitis were reported in EQWS-treated subjects during the Phase 3 studies that were confirmed by an adjudication committee; both cases were SAEs and considered related to study treatment by the investigator.

Hypoglycaemia

One subject in the Byetta group had an event of major hypoglycaemia in Study BCB118. This subject, who received background treatment with a sulphonylurea and was randomized to Byetta, had a hypoglycaemia event and experienced unconsciousness and required assistance. The subject received oral glucose, and recovered from the event. There was no associated blood glucose value.

The overall incidence of minor hypoglycaemia in the 410 EQWS-treated subjects during the controlled period of the Phase 3 studies was low (6.3%). As expected, the incidence of hypoglycaemia was greater in EQWS subjects who were on an SU at baseline (26.1%) than in EQWS subjects who were not taking an SU at baseline (0.9%); appropriate warning has been incorporated into the product label. The incidence was also low in EQWS subjects who were taking metformin only at baseline (0.4%).

Injection site adverse events

Injection site AEs were reported in 23.9% of the 410 EQWS-treated subjects during the Phase 3, controlled study period. The most common injection site events were injection site nodule (12.2%), injection site pruritus (3.7%), injection site bruising (2.9%), injection site erythema (2.7%), injection site pain (2.4%), and injection site induration (2.0%). In the controlled period of study BCB118, injection site nodule AEs were reported in 15.7% of the 229 subjects in the EQWS treatment group versus in 0.7% of subjects in the Byetta group.

Almost all of the injection site AEs that were reported in the EQWS-treated subjects in the Phase 3, controlled study period were mild or moderate in intensity. The only reported severe injection site AE was a case of injection site urticaria in 1 subject. There were no injection site AEs reported as serious during the Phase 3 controlled period or the uncontrolled extension period.

The incidence of injection site AEs in the EQWS-treated subjects declined markedly after the first 3 months of treatment in the Phase 3, controlled study period. Similarly, the numbers of subjects reporting injection site AEs were low during the Phase 3, uncontrolled, extension period.

These observations are suggestive of a localised reaction consistent with the known properties of the polymer microsphere formulation utilised in both EQWS and Bydureon.

Cardiac disorders

For all Phase 3 EQWS-treated subjects, the exposure-adjusted incidence and event rates (95% CI) were calculated as 45.7 (26.1, 70.6) per 1000 patient-years and 53.5 (32.2, 80.1) per 1000 patient-years, respectively.

Among all of the Phase 3 EQWS-treated subjects, there were 2 cases of adjudication-committee confirmed myocardial infarction, 1 each in the controlled and extension study periods; the exposure-adjusted incidence rate (95% CI) for myocardial infarction was calculated as 2.82 (0.07, 10.4) per 1000 patient-years). A case of myocardial infarction was also reported in a subject in the placebo group of study BCB120. The exposure-adjusted subject incidence rate (95% CI) for myocardial infarction amongst EQWS and placebo subjects was 5.65 (0.07, 15.7) and 36.34 (0.92, 134.0) per 1000 patient-years, respectively.

Neoplasms

In the controlled period of the Phase 3 studies, 3 neoplasms were reported in EQWS-treated subjects that were confirmed by the adjudication committee: 1 case each of breast cancer, fibroadenoma of breast, and benign neoplasm of skin. Another 3 confirmed neoplasms were reported during the Phase 3 extension period: 1 case each of malignant melanoma, hepatocellular carcinoma, and basal cell carcinoma. A case of acute myeloid leukaemia was reported during the follow-up period of study BCB118, 10 days after the last dose of EQWS. None of the confirmed neoplasms were judged as related to study treatment by the investigator. No reports of

pancreatic cancer, medullary thyroid carcinoma or any other thyroid malignancies have been received for EQWS subjects.

Acute renal failure

There were no cases of acute renal failure reported in EQWS-treated subjects during the Phase 3 studies. A single case of acute renal failure occurred in a subject on Byetta treatment during the controlled period of study BCB118.

Serious adverse events and deaths

Deaths

There was 1 death in the EQWS clinical programme. During the extension phase of study BCB118, a subject who was originally assigned to treatment with Byetta died during the extension phase because of ascites and hepatocellular carcinoma that were judged as not related to study treatment by the investigator.

Other serious adverse events

During the Phase 3, controlled study period, 2.4% of the 410 EQWS-treated subjects experienced at least 1 SAE compared with 4.8%, 0%, and 3.3% of subjects in the Byetta, sitagliptin, and placebo groups, respectively. For the EQWS-treated subjects, the most common SAEs were Gastrointestinal disorders (0.7%; 1 case each of abdominal hernia obstructive, diarrhoea, and pancreatitis).

During the extension period of study BCB118, 13 (4.2%) of the 309 EQWS-treated subjects experienced at least 1 SAE, most commonly under the SOCs Cardiac disorders and Gastrointestinal disorders (3 subjects each SOC [1.0%]).

Of the 35 events reported in EQWS-treated subjects, 2 events (severe SAEs of ascites and hepatocellular carcinoma) resulted in the death of a subject during the extension period of study BCB118. All events except 2 cases of pancreatitis were considered to be unrelated to study treatment by the investigator.

In Phase 2 study BCB110, there were 2 SAEs reported in the same subject in the placebo group of Cohort 2. Events of infected skin ulcer (recovered/resolved) and wound infection (not recovered/not resolved), both affecting the right foot, were reported in a 66-year-old, white, male.

Laboratory findings

Clinical laboratory evaluations

Potentially clinically significant non-hepatic laboratory abnormalities

The incidence of potentially clinically significant non-hepatic laboratory abnormalities was low (<1%) for most of the non-hepatic parameters in EQWS-treated subjects. The incidence of potentially clinically significant laboratory abnormalities in EQWS-treated subjects was ≥1% and at least twice the rate for placebo only for bicarbonate <18 mmol/L, creatinine ≥1.5 x baseline, and triglycerides >5.65 mmol/L.

Potentially clinically significant hepatic laboratory abnormalities

The incidence of potentially clinically significant hepatic laboratory abnormalities was also low. The only potentially clinically significant hepatic laboratory abnormalities with an incidence at least twice the rate for placebo were alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) (1.0% versus 0%, placebo), ALT >5 x ULN (0.5% versus 0%, placebo), and aspartate aminotransferase >3 x ULN (0.5% versus 0%,

placebo). These transaminase elevations were transient and none were associated with a hepatobiliary AE. No elevations in bilirubin >1.5 x ULN or cases meeting possible Hy's Law criteria were reported in the EQWS clinical studies.

Vital signs

Between baseline and the last on-treatment assessment during the Phase 3, controlled study periods, there were no clinically meaningful effects on heart rate, or systolic and diastolic blood pressure in the EQWS-treated subjects. Heart rate increased by a mean (SD) of 2.4 (9.0) beats per minute. Sitting systolic blood pressure decreased by a mean (SD) of 1.6 mmHg from a baseline value of 128.9 mmHg, and sitting diastolic blood pressure increased by a mean (SD) of 0.14 mmHg from a baseline value of 77.8 mmHg.

Safety in special populations

Effect of age

Of the 410 EQWS-treated subjects in the Phase 3, controlled study periods, 336, 64, and 10 subjects were aged <65, 65 to <75, and ≥75 years, respectively. The small number of subjects aged ≥75 years precludes including this subgroup in comparisons based on age.

Overall adverse events

The overall incidence of AEs was similar in EQWS-treated subjects aged <65 years (63.7%) and those aged ≥65 years (66.2%). At the SOC level, AEs were generally similar between the <65 years and ≥65 years EQWS-treated age groups. The most notable between-group differences for these 2 age groups were higher incidence rates in the ≥65 years age group of Eye disorders (6.8% vs 1.2%), Gastrointestinal disorders (27.0% vs 19.0%), General disorders and administration site conditions (32.4% vs 25.0%), Musculoskeletal and connective tissue disorders (16.2% vs 9.2%), and Skin and subcutaneous tissue disorders (9.5% vs 3.3%). The incidence of AEs in the SOC of Investigations was greater in the <65 years age group (8.0%) than in the ≥65 years age group (4.1%).

Among subjects in the Byetta treatment group in study BCB118, gastrointestinal AEs were reported in 25.0% of subjects aged ≥65 years and in 39.8% of subjects aged <65 years. In the study BCB120 placebo group, gastrointestinal AEs were reported in 0% of subjects aged ≥65 years and in 3.7% of subjects aged <65 years.

The most frequently reported AEs by age group are summarised in Table 12.

Table 12 Adverse events reported in ≥5% of all EQWS-treated subjects by age – Phase 3 controlled

Preferred Term	Number (%) of subjects	
	Age <65 years (N=336)	Age ≥65 years (N=74)
Injection site nodule	36 (10.7)	14 (18.9)
Nausea	29 (8.6%)	9 (12.2)
Headache	17 (5.1)	4 (5.4)
Diarrhoea	11 (3.3)	6 (8.1)
Vomiting	9 (2.7)	5 (6.8)
Dizziness	8 (2.4)	4 (5.4)
Muscle spasms	2 (0.6)	5 (6.8)

Hypoglycaemia

Events of minor hypoglycaemia and symptoms of hypoglycaemia (excluding data after rescue) were evenly balanced between EQWS-treated subjects aged <65 years and those aged ≥65 years.

Antibodies to exenatide

Among the EQWS-treated subjects, 74.8% of subjects aged <65 years and 70.6% of those aged ≥65 years were positive for antibodies to exenatide during the controlled periods of the Phase 3 studies.

Effect of renal function status

Of the 410 EQWS-treated subjects in the Phase 3, controlled study periods, 187 had normal renal function at baseline (eGFR ≥90 mL/min/1.73m^2), 193 had mild impairment (eGFR ≤60 to ≤89 mL/min/1.73m^2), and 30 had moderate impairment (eGFR 30 to ≤59 mL/min/1.73m^2). Because of the relatively low number of subjects with moderate renal impairment, comparisons between this subgroup and the normal renal function and mild renal impairment subgroups should be made with caution.

Overall adverse events

The overall incidence of AEs was very similar in subjects with normal renal function (64.2%), mild renal impairment (64.2%), and moderate renal impairment (63.3%). For most SOCs, the incidence of AEs was balanced across the 3 subgroups. Compared with the subgroups with mild or moderate renal impairment, the incidence of AEs was lower in the normal renal function subgroup for the SOCs Gastrointestinal disorders (16.6% vs 23.8 and 23.3%, respectively), General disorders and administrative site conditions (23.5% vs 28.5% and 30.0%, respectively), and Musculoskeletal and connective tissue disorders (6.4% vs 13.5% and 16.7%, respectively). In subjects with moderate renal impairment, the incidence of Eye disorders was greater than in subjects with normal renal function or mild impairment (6.7% vs 2.1% and 1.6%, respectively). Furthermore, the incidence of AEs was lower in the moderate renal impairment subgroup compared with the normal renal function and mild impairment subgroups for the SOCs Investigations (0% vs 6.4% and 9.3%, respectively) and Nervous system disorders (3.3% vs 9.6% and 11.9%, respectively).

Among subjects in the Byetta treatment group in study BCB118, gastrointestinal AEs were reported in 38.2%, 34.2%, and 46.7% of subjects with normal, mildly impaired, and moderately impaired renal function

respectively. In the study BCB120 placebo group, gastrointestinal AEs were reported in of 2.9%, 3.8%, and 0% subjects with normal, mildly impaired, and moderately impaired renal function respectively.

The most frequently reported AEs by renal function status are summarised in Table 13.

Table 13 Adverse events reported in ≥5% of all EQWS-treated subjects by renal function status – Phase 3 controlled

Preferred Term	Number (%) of subjects		
	Normal renal function (N=187)	Mild renal impairment (N=193)	Moderate renal impairment (N=30)
Injection site nodule	16 (8.6)	30 (15.5)	4 (13.3)
Nausea	14 (7.5)	22 (11.4)	2 (6.7)
Injection site pruritus	3 (1.6)	9 (4.7)	3 (10.0)
Diarrhoea	4 (2.1)	10 (5.2)	3 (10.0)
Upper respiratory tract infection	6 (3.2)	8 (4.1)	3 (10.0)
Vomiting	2 (1.1)	10 (5.2)	2 (6.7)
Injection site bruising	5 (2.7)	5 (2.6)	2 (6.7)
Pain in extremity	3 (1.6)	5 (2.6)	2 (6.7)
Muscle spasms	1 (0.5)	4 (2.1)	2 (6.7)
Cough	2 (1.1)	2 (1.0)	2 (6.7)
Headache	9 (4.8)	11 (5.7)	1 (3.3)

[a] Normal renal function: eGFR ≥90 mL/min/1.73m^2; mild impairment: eGFR ≤60 to ≤89 mL/min/1.73m^2; moderate impairment: eGFR 30 to ≤59 mL/min/1.73m^2

eGFR Estimated glomerular filtration rate.

Hypoglycaemia

Among the controlled study period Phase 3, EQWS-treated subjects, there was a slight trend towards an increased incidence of hypoglycaemia with increasing renal impairment. The respective rates of minor hypoglycaemia and symptoms of hypoglycaemia were 4.8% and 7.5% in subjects with normal renal function, 6.7% and 11.9% in subjects with mild renal impairment, and 13.3% and 13.3% in subjects with moderate renal impairment. The incidence rates of minor hypoglycaemia were markedly higher in subjects taking a sulphonylurea (25.0% to 28.6%) compared with those not taking a sulphonylurea (0% to 0.6%) within each of the renal function subgroups. The incidence rates of hypoglycaemia in subjects who were taking or not taking a sulphonylurea at baseline were generally similar across the 3 renal function subgroups.

Antibodies to exenatide

Among the EQWS-treated subjects, 74.6% of subjects with normal renal function, 74.3% of subjects with mild renal impairment, and 69.0% of those with moderate impairment were positive for antibodies to exenatide during the controlled periods of the Phase 3 studies.

Immunological events

Antibodies to exenatide

Overall, 74.0% of EQWS-treated subjects developed antibodies to exenatide at some point during the Phase 3, controlled period, with 42.2% of EQWS subjects developing low-titre (<625) antibodies and 31.8% developing high-titre (≥625) antibodies. The percentage of antibody-positive subjects reached a peak by about 16 weeks of treatment and then showed a slight reduction during the remainder of the study period.

During the controlled period of study BCB118, the incidence of treatment-emergent antibody-positive subjects was somewhat higher in the EQWS group (76.2%) compared with the Byetta group (50.3%). High-titre antibodies developed in 32.2% and 11.9% of EQWS and Byetta subjects, respectively. During treatment with EQWS in the uncontrolled, extension period, 52.1% of subjects initially randomised to EQWS and 61.8% of subjects initially randomised to Byetta were antibody-positive at Week 52.

Potentially immune-related adverse events by antibody status and titre category

During the Phase 3, controlled period, the overall incidence of potentially immune-related AEs in EQWS-treated subjects was 25.4% in those who were antibody-positive and 17.6% in those who were antibody-negative. For the SOC Skin and subcutaneous tissue disorders, the incidence of potentially immune-related AEs (such as rash, dermatitis, and urticaria) was 3.4% and 0% for antibody-positive and antibody-negative subjects, respectively.

In study BCB118 (controlled period), the incidence of potentially immune-related AEs was greater in subjects in the EQWS treatment group (28.9%, antibody-positive; 27.8%, antibody-negative) than in the Byetta group (11.1%, antibody-positive; 9.9%, antibody–negative).

During the Phase 3, uncontrolled, extension period, the overall incidence of potentially immune-related AEs in EQWS-treated subjects was lower in antibody-positive subjects than in antibody-negative subjects (4.6% versus 7.7%).

In the antibody-positive, EQWS-treated subjects during the Phase 3, controlled period, the overall incidence of potentially immune-related AEs was greater in high-titre (29.6%) versus low-titre (22.3%) subjects.

During the Phase 3, uncontrolled, extension period, the overall incidence of potentially immune-related AEs was 5.8% in the low-titre, antibody-positive, EQWS-treated subjects and 1.7% in subjects in the high-titre category.

Potentially immunogenic injection site-related adverse events by antibody status and titre category

In the EQWS-treated subjects during the Phase 3, controlled period, potentially immunogenic injection site-related AEs under the SOC General disorders and administration site conditions were reported in 21.0% of antibody-positive and 15.7% of antibody-negative subjects.

In the EQWS-treated subjects during the Phase 3, uncontrolled, extension period, the overall incidence of potentially immunogenic injection site-related AEs under the SOC General disorders and administration site conditions was low and similar in antibody-positive (3.1%) and antibody-negative (2.9%) subjects.

In the antibody-positive, EQWS-treated subjects during the Phase 3, controlled period, the overall incidence of potentially immunogenic injection site-related AEs was greater in high-titre (27.2%) versus low-titre (16.3%) subjects. Moreover, the overall incidence of potentially immunogenic injection site-related AEs in low-titre subjects was similar to that in antibody-negative subjects (16.3% versus 15.7%).

During the Phase 3, uncontrolled, extension period, the overall incidence of potentially immunogenic injection site-related AEs was 4.3% in the low-titre, antibody-positive, EQWS-treated subjects and 0% in subjects in the high-titre category.

Safety related to drug-drug interactions and other interactions

Given that exenatide is primarily eliminated by the kidneys, it is not expected to have metabolism-based interactions with concomitantly administered oral medications. However, because it slows gastric emptying, exenatide has the potential to alter the absorption of orally administered drugs.

Although the effect of exenatide on gastric emptying has not been studied with the EQWS formulation, the effects of both Bydureon and Byetta on gastric emptying were assessed in a subset of subjects in study 2993LAR-105. Gastric emptying was assessed by measuring the absorption of acetaminophen (paracetamol) after oral administration. From the results of this study, it was concluded that Bydureon caused a smaller reduction in the rate of acetaminophen absorption than Byetta in both the fed and fasted states. Furthermore, the rate of acetaminophen absorption was marginally lower with Bydureon treatment in the fasted state compared with that in the fed state. During Bydureon and, by extension, EQWS treatment, no adjustment of concomitant oral drug administration is needed, including drugs that must reach threshold levels for efficacy, such as certain antibiotics.

Discontinuation due to AES

During the controlled study period, AEs that led to discontinuation of study treatment occurred in 16 (3.9%) of EQWS-treated subjects, and in 7.5%, 0% and 4.9% of subjects in the Byetta, sitagliptin, and placebo treatment groups, respectively. For the EQWS subjects, the AEs leading to discontinuation of study drug were most commonly under the SOCs Gastrointestinal disorders (8 subjects [2.0%]) and General disorders and administration site conditions (5 subjects [1.2%]).

During the extension period of study BCB118, 4 (1.3%) of the 309 EQWS-treated subjects experienced at least 1 AE that led to discontinuation of study treatment. One subject discontinued because of pancreatitis, 1 discontinued due to visual impairment, and 1 discontinued due to injection site nodule, muscle spasms, and weight increased. The fourth subject discontinued because of ascites and hepatocellular carcinoma and subsequently died.

There were no AEs that led to discontinuation of study treatment in Phase 2 study BCB110.

2.6.1. Discussion on clinical safety

EQWS is a subcutaneously injectable prolonged-release non-aqueous suspension formulation that was developed as extension to Byetta (approved in 2006) and Bydureon (approved in 2011). Thus there is long clinical experience with Byetta and Bydureon and the safety profile is well known.

A total of 549 subjects have been exposed to the new formulation, the majority of these patients were exposed for 28 weeks. In addition, 193 subjects out of the 197 subjects who completed the 28-week controlled period in study BCB118 enrolled in the 24 week extension period and were thus exposed for up to 52 weeks. Considering the previous experience with Byetta and Bydureon, this is considered sufficient.

Adverse events were most commonly reported in patients on Byetta BID treatment (75%) whereas 64% of patients on EQWS reported at least one AE (71% in study BCB118 and 56% in study BCB120). The lowest

reporting of AEs was observed in the sitagliptin treated group (33%). The reporting of SAEs was low and balanced between groups treated with exenatide and placebo, whereas no SAEs were reported in the sitagliptin treated group. Discontinuations due to AEs occurred at a similar rate in patients treated with EQWS (4%) and placebo (5%), whereas the rate of discontinuations due to AE was somewhat more common in the Byetta BID treated group (8%).

The predominating AEs with EQWS treatment were gastrointestinal events and injection site reactions. Gastrointestinal events were less common than with Byetta BID (20.5% vs 37%) but similarly distributed among preferred terms. In line with the mechanism of action for sitagliptin, gastrointestinal events were the most commonly reported AEs also in this group (7.4%). Injection site reactions were more common in EQWS treated subjects than in Byetta BID treated subjects (26% vs 2%).

The overall rate of infections and infestations did not differ from that observed in the placebo treated group whereas musculoskeletal disorders were more commonly reported in the EQWS treated group. Headache and dizziness was also more common in the EQWS treated group than in the placebo treated group. In this context it should be taken into account that the placebo treated group was small (61 subjects).

During the extension period, no apparent differences between patients continuing on EQWS or switching to EQWS were observed apart from a higher reporting of injection site reactions. Notably, the reporting of gastrointestinal events was lower during the extension period than in the controlled period in both groups.

Adverse events of special interest were gastrointestinal events, pancreatitis, hypoglycaemias, injection site reactions, cardiovascular events, neoplasms and renal failure. The selection was based on previous experience with exenatide and is considered adequate.

Gastrointestinal events were commonly reported with EQWS but less common than with Byetta BID. When presented graphically, it is clear that initiation and dose increase of Byetta BID is related to a high reporting of events. The reporting of events in the EQWS treated group slowly increased over time, which may represent the increase in exposure as steady state is reached. However after about four months, the reporting again decreased. The risk of gastrointestinal events is adequately reflected in the PI.

Two cases of pancreatitis were reported in EQWS-treated subjects. The risk of pancreatitis is reflected in the PI. Previously pancreatitis was only described as observed post-marketing with Bydureon. The SmPC, sections 4.4 and 4.8, has been updated to reflect the observed frequency in the studies.

Hypoglycaemic events were collected separately from AEs. Only one major hypoglycaemic event was observed. This event occurred in a patient on concomitant treatment with Byetta and sulphonylurea. Minor events occurred in 6.3% of subjects on EQWS treatment. The highest reporting was observed in patients on concomitant SU treatment where 26% of patients reported an event. The risk of hypoglycaemia is adequately reflected in the PI.

Injection site reactions were common in EQWS treated patients. One reaction (injection site urticaria) was considered severe; otherwise the reactions were mild to moderate. The incidence declined after the first three months of treatment. Localised reactions have also been frequently observed with Bydureon which contains the same polymer microsphere formulation. The risk of injection site reactions is adequately reflected in the PI.

There were few events of cardiac disorder across the phase 3 program and no apparent difference in the incidence across the treatment groups in the controlled periods of the studies. The data does not evoke any new safety concerns with regards to cardiovascular safety.

All neoplasms were reported within one year of exposure to EQWS and the three neoplasms observed in the controlled period of the studies occurred within two months of study start (Day 1, Day 19 and Day 65). None of the confirmed neoplasms were judged as related to study treatment which is endorsed.

One case of acute renal failure in relation to septic shock was reported in a subject treated with Byetta. No cases were observed in subjects treated with EQWS.

Only one death (due to hepatocellular carcinoma) occurred. This event was not considered related to study treatment which is endorsed.

The reporting of SAEs was low during the controlled period of the studies. All events were single events. The same pattern was observed in the open-label extension of study BCB118.

No clinically significant changes in non-hepatic laboratory test were observed. Events of increased liver enzymes were few and no increased bilirubin values were recorded. In line with previous observations, an increase in heart rate of 2.4 beats per minute was observed. There was a slight decrease in SBT of 1.6 mmHg whereas DBT remained essentially unchanged.

When analysed by age, AEs were essentially similar in patients ≥65 years than in patients <65 years (66.2% vs 63.7%). However, injection site nodules and gastrointestinal events (nausea, diarrhoea and vomiting) were more common in the older age group. No relevant difference in the occurrence of hypoglycaemia was observed between age groups. Comparable proportions of patients in both age groups developed antibodies against exenatide. Due to the low number of patients aged ≥75 years (10 patients), further analysis of the safety data in this age group is not considered meaningful.

The overall incidence of AEs was very similar in subjects with normal renal function (64.2%), mild renal impairment (64.2%), and moderate renal impairment (63.3%). For the SOCs Gastrointestinal disorders (nausea, diarrhoea and vomiting), General disorders and administrative site conditions (injections site nodule, injection site pruritus) and Musculoskeletal and connective tissue disorders there was an increase in the reporting by decreasing renal function, although the data in patients with moderate renal impairment has to be interpreted with caution due to the low number of patients (n=30).

The SmPC does not recommend any dosage adjustment of EQWS in patients with mild renal impairment. EQWS is not recommended in patients with moderate to severe renal impairment or end-stage renal disease receiving dialysis. Considering that the exposure of exenatide is increased in patients with impaired renal function and that there appears to be an increase in AEs in this population, this recommendation should be maintained.

A large proportion of patients (74%) had developed antibodies to exenatide by week 16. About 32% of patients had developed high-titre antibodies. After that time-point a slight decline was observed. After 52 weeks of treatment 52% of patients were still antibody-positive. Potentially immune-related AEs were more common in those who were antibody-positive than in those who were antibody-negative (25.4% vs 17.6%). This was mainly due to a higher reporting of injection site reactions. There was a decrease in reporting over time and there was no difference between groups in the extension period of study BCB118. The reporting was also higher in patients with high antibody titres compared to those with low titres. Notably, potentially immune-related events were about three times more common in the EQWS treated patients compared to patients treated with Byetta BID. The most common potentially immunogenic adverse events were different injection site reactions which constituted about 85% of these reactions.

No new data regarding drug interactions have been submitted. Previous data obtained with Bydureon has shown that the delay of gastric emptying does not warrant any adjustments of concomitant oral drug administration. Based on the data on exposure with the new formulation, these data may be extrapolated.

In total 16 patients discontinued due to AEs among EQWS treated patients. The most common reasons for discontinuation were gastrointestinal events and injection site reactions. The discontinuation rate due to GI events was lower than observed in the groups treated with Byetta BID.

No post-marketing data is available for the new formulation. In the postmarketing setting, the total cumulative exposure to Byetta is estimated to be over 3,117,218 patient-years since and the total cumulative exposure to Bydureon is estimated to be over 1,307,511 patient-years since market launch.

2.6.2. Conclusions on clinical safety

The safety data provided with this application is based on the exposure of a total of 549 subjects to the new formulation; the majority of these patients were exposed for 28 weeks. In addition, 193 subjects were exposed for up to 52 weeks. The data provided show that the safety profile of the new formulation is essentially comparable to that previously observed with exenatide. Compared to the immediate release formulation, gastrointestinal events are less prominent whereas injection site reactions are more common with the new formulation. This is in line with the observations made with Bydureon. Considering the previous experience with Byetta BID and exenatide once weekly aqueous suspension, the safety data provided for the new formulation is considered sufficient and no new safety concerns have emerged.

2.7. Risk management plan

The applicant submitted as part of this application the risk management plan (RMP) version 28, dated August 2017. With the responses to the LoQ, a consolidated version of the RMP (version 30 incorporating versions 28 and 29) was submitted. The RMP version 30 contains the following elements:

Safety specification

Summary of safety concerns	
Important identified risks	Pancreatitis Acute renal failure
Important potential risks	Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions) Cardiac events Pancreatic cancer Thyroid neoplasms Administration error (exenatide QW)
Missing information	None

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
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	Medullary thyroid carcinoma	Ongoing	Annual assessment report each Q1 until the end of the study; final report : Q3 2028

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)
	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			
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
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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
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
Missing information		
None		

QW once weekly; PK Pharmacokinetic; SmPC Summary of Product Characteristics

Conclusion

The CHMP and PRAC considered that the RMP version 30 is acceptable.

2.8. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication proposed for Bydureon autoinjector is:

"Bydureon autoinjector 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 when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations)."

The aim of therapy is to improve metabolic control in terms of blood glucose, thereby decreasing the risk of microvascular and macrovascular long-term complications.

3.1.2. Available therapies and unmet medical need

Initial management includes lifestyle changes such as diet and exercise. Pharmacological treatment includes insulin, biguanides, TZDs, SUs, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1RA. With the exceptions of insulin and GLP-1RA all are administered orally.

Despite combination therapy and/or insulin treatment, a sizeable proportion of patients remain poorly controlled. One important issue is compliance to treatment. Some medicinal products for injection are complicated to administer and there is a need for formulations that are easier to use.

3.1.3. Main clinical studies

The study program includes one Phase 2 study and two Phase 3 studies.

Study BCB110 was a Phase 2 study with the primary objective to investigate PK for the new formulation and to gather safety and efficacy data in support of the selected dose of 2 mg EQWS.

Both Phase 3 studies (BCB118 and BCB120) were randomised, open-label trials of efficacy, safety, and tolerability of EQWS in subjects with T2DM.

Study BCB118 included patients required to be treated with diet and exercise alone or in combination with a stable regimen of oral antidiabetes medication and compared EQWS with Byetta BID. The controlled study period was of 28 weeks duration. In the 24 week extension period, all patients were treated with EQWS.

Study BCB120 included patients required to be treated with a stable regimen of ≥ 1500 mg/day metformin. This was a three-armed study of 28 weeks duration in which EQWS was compared to both sitagliptin and placebo.

Overall, 742 subjects were randomised to the 2 Phase 3 studies, 410 were exposed to EQWS, 146 subjects were exposed to Byetta, 122 to sitagliptin and 61 were treated with placebo.

3.2. Favourable effects

The primary endpoint was met in both studies, where EQWS showed a significantly larger reduction of HbA1c from baseline vs Byetta BID (treatment difference -0.4%; study BCB118) and vs sitagliptin (treatment difference -0.4%) and placebo (treatment difference -0.7%; study BCB120).

The primary endpoint was calculated excluding patients on rescue therapy or terminated early. The proportion of patients included in the analysis was balanced between groups (BCB118: 77% on EQWS vs 74% on BIB; study BCB120: 78% on EQWS vs 80% on sitagliptin). The only exception is the placebo group where only 62% of patients were included in the analysis.

In both studies, a numerically higher proportion of patients achieved the treatment goal of HbA1c <7% in the EQWS treated groups compared (49% and 43%, BCB118 and BCB120, respectively) to Byetta BID (43%) or sitagliptin (32%). The difference compared to sitagliptin reached statistical significance. The conservative sensitivity analysis showed a similar pattern although no significant differences were observed.

In both studies, a numerically larger reduction in FPG was observed in the EQWS treated groups compared to Byetta BID, sitagliptin or placebo. Statistical significance was only reached when compared to placebo.

The largest reduction in body weight was observed with Byetta BID (-1.9 kg), although not significantly different from EQWS (-1.5 kg; study BCB118). In study BCB120, the weight reduction with EQWS (-1.1 kg) was comparable to that observed with sitagliptin (-1.2 kg) but significantly larger than with placebo (+0.2 kg).

Change in 2-hour PPG was evaluated in a subset of patients after a meal test. The numerically largest effect was observed with Byetta BID (-6.31 mmol/L), although the difference compared to EQWS (-4.83 mmol/L) was not statistically significant (study BCB118). In study BCB120, the decrease in 2-hour PPG was significantly larger with EQWS compared to sitagliptin but only numerically larger than placebo.

The outcome is largely in line with the outcome observed in comparable studies with Bydureon aqueous suspension.

Data from the long-term extension show that HbA1c increased from week 20 and onwards in the group treated with EQWS and appeared to reach a plateau after week 44. Patients switching from Byetta BID to EQWS showed a decrease in HbA1c after the switch and at week 52 both treatment arm showed no difference in change from baseline in HbA1c. The FPG showed a similar development as HbA1c, with some increase in the EQWS group which appeared to plateau. A further decrease in FPG was observed in patients switching from Byetta BID to EQWS and no difference was observed between treatment groups at week 52. The proportion of patients achieving HbA1c <7% decreased over time to 38.4% at week 52 compared to 49.3% at week 28. Body weight remained essentially stable after week 20 in both treatment groups. The larger reduction in body weight observed in patients who started on Byetta BID was maintained throughout the study period.

Almost 60% of patients had positive antibody titres at week 28. In both studies, the effect on HbA1c was comparable in antibody-negative patients (-1.39% and -1.05%) and patients with low antibody titers (-1.48% and -1.14%), whereas an attenuated response was observed in patients with high antibody titers (-0.74% and -0.58%, study BCB118 and BCB120 respectively).

Subgroup analysis did not reveal any difference in the effect of EQWS on HbA1c reduction in the adequately sized subgroups.

3.3. Uncertainties and limitations about favourable effects

The study program is well designed but has limitations in relation to the proposed indication. However, as the exposure to exenatide with EQWS is comparable to that observed with the Bydureon aqueous formulation, efficacy data obtained with Bydureon can be extrapolated to EQWS.

3.4. Unfavourable effects

A total of 549 subjects have been exposed to the new formulation, the majority of these patients were exposed for 28 weeks. In addition, 193 subjects out of the 197 subjects who completed the 28-week controlled period in study BCB118 enrolled in the 24 week extension period and were thus exposed for up to 52 weeks.

Adverse events were reported by 64% of patients on EQWS (71% in study BCB118 and 56% in study BCB120) to be compared with 75% of patients on Byetta BID treatment. The lowest reporting of AEs was observed in the sitagliptin treated group (33%). The reporting of SAEs was low and balanced between groups treated with exenatide and placebo, whereas no SAEs were reported in the sitagliptin treated group. Discontinuations due to AEs occurred at a similar rate in patients treated with EQWS (4%) and placebo (5%), whereas the rate of discontinuations due to AE was somewhat more common in the Byetta BID treated group (8%).

The predominating AEs with EQWS treatment were gastrointestinal events and injection site reactions. Gastrointestinal events were less common than with Byetta BID (20.5% vs 37%) but similarly distributed among preferred terms (e.g. nausea, diarrhoea and vomiting). The reporting of events in the EQWS treated group slowly increased over time. However after about four months, the reporting again decreased. The risk of gastrointestinal events is adequately reflected in the PI.

Injection site reactions were more common in EQWS treated subjects than in Byetta BID treated subjects (26% vs 2%). One reaction (injection site urticaria) was considered severe; otherwise the reactions were mild to moderate. The incidence declined after the first three months of treatment. Localised reactions have also been frequently observed with the aqueous formulation of Bydureon which contains the same polymer microsphere formulation. The risk of injection site reactions is adequately reflected in the PI.

Two cases of pancreatitis were reported in EQWS-treated subjects. The SmPC, sections 4.4 and 4.8, has been updated to adequately reflect the risk of pancreatitis.

Overall, the reporting of hypoglycaemic events was low. Minor events occurred in 6.3% of subjects on EQWS treatment. The highest reporting was observed in patients on concomitant SU treatment where 26% of patients reported an event. The risk of hypoglycaemia is adequately reflected in the PI.

During the extension period, no apparent differences between patients continuing on EQWS or switching to EQWS were observed apart from a higher reporting of injection site reactions in those switching to EQWS (6.9% vs 0.5%). The reporting of gastrointestinal events was lower during the extension period than in the controlled period in both groups (7.8%).

In line with previous observations with exenatide treatment, an increase in heart rate of 2.4 beats per minute was observed. There was a slight decrease in SBT of 1.6 mmHg whereas DBT remained essentially unchanged.

When analysed by age, AEs were essentially similar in patients ≥65 years than in patients <65 years (66.2% vs 63.7%). However, injection site nodules and gastrointestinal events (nausea, diarrhoea and vomiting) were more common in the older age group. No relevant difference in the occurrence of hypoglycaemia was observed between age groups.

The overall incidence of AEs was very similar in subjects with normal renal function (64.2%), mild renal impairment (64.2%), and moderate renal impairment (63.3%). For the SOCs Gastrointestinal disorders (nausea, diarrhoea and vomiting), General disorders and administrative site conditions (injections site nodule, injection site pruritus) and Musculoskeletal and connective tissue disorders there was an increase in the reporting by decreasing renal function, although the data in patients with moderate renal impairment has to be

interpreted with caution due to the low number of patients (n=30). Adequate recommendations on the use of exenatide in patients with renal impairment are given in the PI.

A large proportion of patients (74%) had developed antibodies to exenatide by week 16. About 32% of patients had developed high-titre antibodies. After that time-point a slight decline was observed. After 52 weeks of treatment 52% of patients were still antibody-positive. Potentially immune-related AEs were more common in those who were antibody-positive than in those who were antibody-negative (25.4% vs 17.6%). This was mainly due to a higher reporting of injection site reactions. The reporting was also higher in patients with high antibody titres compared to those with low titres. Notably, potentially immune-related events were about three times more common in the EQWS treated patients compared to patients treated with Byetta BID.

3.5. Uncertainties and limitations about unfavourable effects

In total 549 patients have been exposed to EQWS, thus the safety database is limited. However, considering the experience with Bydureon aqueous suspension this is deemed sufficient, since the exposure to exenatide is comparable for the two formulations.

3.6. Effects Table

Table 14 Effects Table for Bydureon autoinjector in the treatment of T2DM.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in HbA1c	EQWS vs Byetta BID	% 95%CI	-1.39 (-1.57, -1.21)	-1.02 (-1.25, -0.80)	Treatment diff -0.37 (-0.63, -0.10)	Study BCB118
Change in HbA1c	EQWS vs sitagliptin	% 95%CI	-1.13 (-1.34, -0.91)	-0.75 (-1.01, -0.49)	Treatment diff -0.38 (-0.70, -0.06)	Study BCB120
Change in HbA1c	EQWS vs placebo	% 95%CI	-1.13 (-1.34, -0.91)	-0.40 (0.79, -0.02)	Treatment diff -0.72 (-1.15, -0.30)	Study BCB120
Proportion HbA1c<7	EQWS vs Byetta BID	%	49.3	43.2	p-value 0.22	Study BCB118
Proportion HbA1c<7	EQWS vs sitagliptin	%	43.1	32.0	p-value 0.05	Study BCB120
Proportion HbA1c<7	EQWS vs placebo	%	43.1	24.6	p-value 0.01	Study BCB120
Change in BW	EQWS vs Byetta BID	kg 95%CI	-1.49 (-2.05, -0.93)	-1.89 (-2.61, -1.18)	Treatment diff 0.40 (-0.48, 1.28)	Study BCB118
Change in BW	EQWS vs sitagliptin	kg 95%CI	-1.12 (-1.63, -0.61)	-1.19 (-1.81,-0.57)	Treatment diff 0.07 (-0.73, 0.87)	Study BCB120
Change in BW	EQWS vs placebo	kg 95%CI	-1.12 (-1.63, -0.61)	0.15 (-0.79, 1.09)	Treatment diff -1.27 (-2.34, -0.20)	Study BCB120
Unfavourable Effects						
Nausea	EQWS vs Byetta BID	n (%)	38 (9.3)	54 (37.0)	EQWS N=410 Byetta N=146	Safety pop Week 28

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Nausea	EQWS vs placebo	n (%)	38 (9.3)	0	EQWS N=410 Placebo N=61	Safety pop Week 28
Vomiting	EQWS vs Byetta BID	n (%)	14 (3.4)	9 (6.2)	EQWS N=410 Byetta N=146	Safety pop Week 28
Vomiting	EQWS vs placebo	n (%)	14 (3.4)	0	EQWS N=410 Placebo N=61	Safety pop Week 28
Injection site reactions	EQWS vs Byetta BID	n (%)	98 (23.9)	6 (4.1)	EQWS N=410 Byetta N=146	Safety pop Week 28
Antibodies Week 28	EQWS vs Byetta BID	n (%)	173 (76.2)	72 (50.3)	EQWS N=227 Byetta N=143	Study BCB118

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main objective when treating T2DM is to achieve glycaemic control in order to reduce the risk of long-term complications. Since many patients with T2DM are overweight, it is considered beneficial if weight is reduced by the treatment. The data provided with the clinical program show that EQWS provide clinically relevant effects on glycaemic control in terms of HbA1c reduction and superiority was shown compared to active control (Byetta and sitagliptin). This reduction was achieved with concomitant decrease in body weight of 1 to 1.5 kg. The effect was maintained up to 52 weeks. With the long-term extension, data on the switch from Byetta to EQWS was also provided.

The safety profile of EQWS did not differ significantly from what is already known for the two already approved formulations of the substance. The major adverse reactions were gastrointestinal events which are related to the mechanism of action. Further to this, injection site reactions were common, in line with what is already known for Bydureon aqueous suspension. These adverse events appear to subside over time and are considered manageable.

The current application concerns a line extension to Bydureon aqueous suspension. Extrapolation of both efficacy and safety from Bydureon to EQWS, with regards to parts of the indication not covered by the clinical development program for EQWS, is acceptable since the exposure to exenatide is comparable for the two formulations. Therefore, the same indication as approved for Bydureon is also approvable for EQWS.

3.7.2. Balance of benefits and risks

The effect of EQWS in the treatment of T2DM has been adequately shown and the safety profile is considered acceptable. The benefit risk balance is considered positive

3.8. Conclusions

The overall B/R of Bydureon (including prolonged-release suspension for injection in pre-filled pen (BCise)) is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bydureon new pharmaceutical form is favourable in the following 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).

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Extension application to introduce new pharmaceutical form (prolonged-release suspension for injection in pre-filled pen) grouped with type II variation to align the PI for the approved Bydureon products (powder and solvent for prolonged-release suspension for injection, and powder and solvent for prolonged-release suspension for injection in pre-filled pen) with the PI proposed for the Bydureon new pharmaceutical form (prolonged-release suspension for injection in pre-filled pen). In addition, the MAH took the opportunity to make minor editorial changes through SmPC. Moreover, RMP versions 28 and 30 (incorporating versions 28 and 29) have been submitted as part of this application. RMP version 30 has been approved as part of this application.

The variation leads to amendments to the Summary of Product Characteristics, labelling, Package Leaflet and to the RMP.

The CHMP therefore recommends the extension of the marketing authorisation for Bydureon subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Appendix

1. Product Information (changes highlighted) as adopted by CHMP on 28 June 2018